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OBESITY AND CANCER

by

Laura Healy

A Thesis for the degree of Doctor of Philosophy (Ph.D)

at

University of Dublin, Trinity College

Departments of Clinical Nutrition & Surgery
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DECLARATION

This thesis is submitted by the undersigned to Trinity College, University of Dublin for the examination of the degree of Ph.D. I certify that none of the work in this thesis has been submitted for any degree or diploma at this, or any other university, and that all the work in this thesis is entirely my own. I agree that the Library may lend or copy this thesis upon request.

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SUMMARY

Cancer rates are increasing with predictions of incidence rates doubling between 2000 and 2020. Although several factors are contributory, the rising incidence of overweight and obesity is currently thought to be fuelling cancer rates and has also been linked with pre cancerous lesions. The World Cancer Research Fund (WCRF) now considers that diet and obesity account for 35% of cancer-related deaths, as compared to smoking accounting for 30%. Obesity is an important modifiable risk factor for cancer. At present the strongest support for mechanisms to link obesity and cancer risk involves the metabolic and endocrine effects of obesity and the alterations they induces. This thesis describes several studies of the impact of obesity on different cancers – oesophageal, breast and colorectal cancer - from its' aetiology, factors linked to progression of cancer and treatment outcomes.

Chapter 3 of this thesis examines the nutritional epidemiology of breast cancer, a case control study of 200 cancer cases and 519 healthy controls showed that obesity was an independent risk factor for post-menopausal breast cancer. Obesity doubled the risk in obese women compared to healthy controls. This was the first Irish study on obesity and postmenopausal breast cancer.

Chapter 4 and Chapter 5 of this thesis examine the effect of metabolic syndrome on tumour features in postmenopausal breast cancer and colorectal cancer. **Chapter 4** Metabolic syndrome was diagnosed in 39% of patients, its presence was associated with central obesity ($p<0.005$) and increased inflammation. Metabolic syndrome was also associated with more aggressive tumour biology; patients with more advanced cancer (pathological stage II-IV) were significantly more likely to be obese, centrally obese, hyperglycaemic, hyperinsulinaemia and 51% had metabolic syndrome compared with 12% for early stage disease. Hyperinsulinaemia and metabolic syndrome were both significantly associated with node positive disease. **Chapter 5** Metabolic syndrome was diagnosed in 38% patients, which exceeds the reported population norms of 21%. Males had significantly ($p < 0.05$) greater visceral fat area compared with females. Metabolic syndrome and plasma leptin are associated with a more aggressive tumour phenotype in males only in respect of nodal status, microvascular invasion, pathological stage, while no significant association was observed in females. The implications of these studies with respect to prevention and treatment require further study. Chapter 6 and 7 establishes oesophagectomy as a severe operation associated with higher post operative morbidity and mortality, compared to colorectal cancer surgery. Traditionally obesity was considered to increase operative risk, this question was addressed separately in the treatment of both oesophageal and colorectal cancer.

Chapter 6 examines the effect of obesity on postoperative morbidity, mortality and overall survival following the management of localised adenocarcinoma, which had not been addressed in the literature before. We compared of 150 obese and non obese patients undergoing

neoadjuvant therapy or surgery alone, and report that obesity was associated with increased respiratory complications, anastomotic leaks and a longer length of stay with no difference in mortality or major complications or survival, suggesting that obesity should not independently have a significant impact on risk assessment in oesophageal cancer management. **Chapter 7** we compared BMI categories to investigate the effect of under nutrition and obesity on tumour pathology as well as standard outcomes following resection of colorectal cancer. Analysis by cancer site as well as by gender was also possible. Obesity was associated with more advanced tumours (advanced pathological stage, node positivity, and degree of nodal involvement) in males and in colon cancer patients only, and with a higher risk of postoperative pelvic abscesses, but no significant differences with non-obese cohorts in the main outcome measures of in-hospital mortality, major morbidity, and survival. Conversely, the adverse consequences of under-nutrition in relation to major complications and post operative death were highlighted in this study.

Chapter 8 this unit has already reported obesity as an independent risk factor for adenocarcinoma of the oesophagus and the metabolic syndrome as a potential factor involved in the progression of Barrett's metaplasia. Although the mechanism is unclear, a pathway from reflux to inflammation through metaplasia is the dominant hypothesis. In short, little is known regarding why only some people with GORD develop Barrett's oesophagus. In a follow up to the earlier studies we compared patients with Barrett's oesophagus to age and sex matched GORD patients and found the incidence of central obesity and the metabolic syndrome are common in both cohorts, but not significantly different suggesting that central obesity and the metabolic syndrome does not per se impact on the development of Barrett's oesophagus in a reflux population.

Chapter 9 These studies on obesity and cancer add to our understanding of obesity's aetiological role, and its clear association with central obesity, (WC, percent body fat, visceral fat area) and metabolic abnormalities (hyperglycaemia, hyperinsulinaemia, hyperleptinaemia low HDL cholesterol and high triglycerides) highlighting potential mechanisms whereby obesity and the metabolic syndrome may effect cancer initiation or cancer progression. The association of metabolic syndrome and some individual features of the metabolic syndrome deserve further investigation with special focus on progression of pre cancerous lesions, and how we can intervene in these pathways by use of pharmacological inhibitors, behaviour modification or gene therapy. These results may have treatment implications for many other solid tumours.

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LIST OF ABBREVIATIONS

AdipoR1	Adiponectin Receptor 1
AdipoR2	Adiponectin Receptor 2
AICR	American Institute for Cancer Research
ATP III	Adult Treatment Panel
BAPEN	British Association of Parenteral and Enteral Nutrition
BCDDP	Breast Cancer Detection Demonstration Project
BMI	Body Mass Index
BO	Barretts Oesophagus
BP	Blood Pressure;
CABG	Coronary Artery Bypass Graft
CI	Confidence Interval
COX-2	Cyclooxygenase -2
CRC	colorectal cancer
CRP	C- reactive protein
CT	Computerised Tomography
DBP	Systolic Bood pressure
DBP	Diastolic blood pressure
DECODE	Diabetes Epidemiology Collaborative Analysis of diagnostic Criteria in Europe
EGIR	European Group for the study of Insulin Resisitance
EPIC	European Prospective Investigation into Cancer and Nutrition
ER	Oestrogen Receptor
et al	and others
GOJ	Gastro Oesophageal Junction
GORD	Gastro Oesophageal Reflux Disease
H PYLORI	*Helicobacter Pylori*
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
HER-2	Human Epidermal Growth Factor Receptor 2
HRT	Hormone Replacement Therapy
HTN	Hypertension
IDF	International Diabetes Federation

IGF	Insulin Like Growth Factor alpha
IGFBPS	Insulin Like Growth Factor Binding Proteins
IL-6	Interleukin 6
IR	Insulin Receptor
IR-A	Insulin Receptor A isoform
IRS-1	Insulin receptor substrate 1
MAPK	Mitogen-activated Protein Kinase
MetS	Metabolic Syndrome
MNA	Mini Nutritional Assessment
MUST	Malnutrition Universal Screening Tool
NCEP	National Cholesterol Education Program
NHANES	National Health and Nutrition Examination Survey
NIH	National Institute for Health
OB-R	Leptin Receptor
OR	Odds Ratio
PR	Progesterone Receptor
RR	Relative Risk
SEER	Surveillance, Epidemiology and End Results program
SGA	Subjective Global Assessment
SHBG	Sex Hormone Binding Globulin
T2DM	Type 2 Diabetes Mellitus
TAG	Triacylglycerol
TNF-α	TNF
UK	United Kingdom
VAT	Visceral Adipose Tissue
VEGF	Vascular Endothelial Growth Factor
WC	Waist Circumference
WCRF	World Cancer Research Fund
WHI	Womens Health Initiative
WHO	World-Health-Organisation
WHR	Waist Hip Ratio

LIST OF PUBLICATIONS ARISING FROM THIS WORK

"Impact of obesity on outcomes in the management of localized adenocarcinoma of the esophagus and esophagogastric junction."

Laura A Healy, Aoife M Ryan, Gopinath Bussa, Suzanne Rowley, Patick J Byrne, John V Reynolds. Journal of Thoracic Cardiovascular Surgery. 2007; 134(5): 1284-91.

"Obesity increases the risk of postmenopausal breast cancer and is associated with more advanced stage at presentation but no impact on survival."

Laura A Healy, Aoife M Ryan, Suzanne Rowley, Terence Boyle, Elizabeth Connolly, Michael J Kennedy, John V Reynolds. *Breast Journal* 2010; 16(1): 95-7.

"Lack of differential pattern in central adiposity and metabolic syndrome in Barrett's esophagus and gastroesophageal reflux disease."

Laura A Healy, Aoife M Ryan, Graham Pidgeon, Narayanasami Ravi, John V Reynolds. *Diseases of Esophagus*. 2010; 23(5): 386-91.

"Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer."

Laura A Healy, Aoife M Ryan, Paul Carroll, Darren Ennis, Vivienne Crowley, Terence Boyle, Michael J Kennedy, Elizabeth Connolly, John V Reynolds. *Clinical Oncology (R Coll Radiol).* 2010; 22(4): 281-8.

"Impact of obesity on surgical and oncological outcomes in the management of colorectal cancer."

Laura A Healy, Aoife M Ryan, Eillis Sutton, Kate Younger, Brian Mehigan, Richard Stephens, John V Reynolds. *International Journal of Colorectal Disease* 2010; 25(11): 1293-9.

"Metabolic syndrome and Leptin are Associated with Adverse Pathological Features in Male Colorectal Cancer Patients"

Laura A Healy, Julia M Howard, Aoife M Ryan, Peter Beddy, Brian Mehigan, Richard Stephens, John V Reynolds.

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OTHER RELEVANT PUBLICATIONS :

"Prevalence of Central Adiposity, Metabolic Syndrome, and a Pro-inflammatory state in Barrett's Esophagus"

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"Obesity, The Metabolic Syndrome and Cancer."

Laura A Healy *Nutritionwise*, Vol 2;1: Spring 2008

"Obesity, Metabolic Syndrome and Oesophageal Adenocarcinoma: Epidemiology, Aetiology & New Targets"

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Paul A Carroll **Laura A Healy**, Joanne Lysaght , Terence Boyle, John V Reynolds, Michael J Kennedy , Graham Pidgeon, Elizabeth M Connolly.

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ORAL AND POSTER PRESENTATIONS

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Gastro 2009 (Poster Presentation X3)

ASPEN 2010 (Oral Presentation X1)

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AWARDS

ESPEN 2009: Best poster presentation

Cancer 2009: Best poster presentation

INDI Research Day: Highly Commended Poster

Recipient of Tanita Grant in Aid 2009

CHAPTER 1: LITERATURE REVIEW AND INTRODUCTION: OBESITY AND CANCER

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1.1 Obesity in general

Obesity has reached epidemic proportions globally, with more than 1.7 billion adults overweight and 300 million clinically obese (World-Health-Organisation 2000). Data from two U.S. National Health and Nutrition Examination Survey surveys show that the prevalence of obesity more than doubled in 30 years (15% in 1976-1980 - 33.8% in 2007-2008 (Flegal *et al*, 2010). Currently 68% of U.S. adults aged 20 years or over are overweight or obese with half (34%) obese (Flegal *et al*, 2010). In the World Health Organization (WHO) European Region, it is estimated that 30-80% of adults are currently overweight, and the WHO predicts that by 2010 there will be 150 million obese adults and 15 million obese children (Branca *et al*, 2007). Obesity is diagnosed using Body Mass Index (BMI): weight in kilograms divided by height in meters squared. The WHO divides BMI into three broad categories: normal: 20-25 kg/m^2, overweight: 25-29.9 kg/m^2, and obese >30 kg/m^2 (World-Health-Organisation 2000). The increasing prevalence of obesity is a worldwide phenomenon affecting both children and adults. In Ireland over 60 per cent of the adult population are overweight or obese, with about 25% obese (McCarthy *et al*, 2002), and the dramatic rise in the incidence of obesity is concerning for future health risks.

1.2 Obesity, Cancer Incidence & Cancer Mortality

While the association between obesity, diabetes and cardiovascular disease are well documented, the relationship of obesity with cancer has only been examined in the last 30 years. Obesity is one of the strongest emerging risk factors for many cancers in Western countries (Bergstrom *et al*, 2001; Parkin *et al*, 2005). The American Institute for Cancer Research (AICR) and the World Cancer Research Fund (WCRF) now consider that diet and obesity account for 35% of cancer-related deaths, as a comparison smoking accounts for 30% (WCRF/AICR 2007). There is a very strong association between obesity and cancer especially cancer of the oesophagus (adenocarcinoma), cancer of the uterus, breast cancer (after the menopause), and kidney cancer, and a real but lesser association with some types of lung cancer, colon cancer, prostate cancer, and pancreas cancer. The WCRF/AICR estimates of cancer preventability through good nutrition, exercise and tackling obesity are, as examples, 60% for oesophageal cancer, 70% for uterine womb cancer, 40% for breast cancer, 45% for colon cancer, 20% for prostate cancer, with a

combined estimate of 25% of all cancers that could be prevented through these approaches (WCRF/AICR 2007).

The relationship between excess body weight and overall mortality has long been recognized (Calle *et al*, 1999; Kopelman 2000; Manson *et al*, 1995; Stevens *et al*, 1998; Bianchini *et al*, 2002; Calle *et al*, 2003). In the largest prospective cohort investigation of the role of obesity and cancer mortality, over 900,000 American adults were followed for 16 years (Calle *et al*, 2003), with analyses adjusted for many potential confounders. Compared with individuals with a normal BMI, obesity was associated with significant increases in cancer mortality from colorectal, liver, gallbladder, pancreatic, prostate, non Hodgkin's lymphoma, multiple myeloma, oesophageal, breast (post-menopausal), uterine, cervical, and ovarian cancers. Compared to normal weight individuals, the heaviest members of the cohort (BMI>40 kg/m^2) had death rates from all cancers that was 52% higher for men and 62% higher for women (Calle *et al*, 2003). Taken together, the authors estimate that obesity is responsible for up to 14% and 20% of all cancer deaths in men and women respectively, amounting to 90,000 annual deaths that are potentially avoidable if BMI was kept below 25 kg/m^2 (Calle *et al*, 2003). In Europe it is estimated that 36,000 cancer cases could be avoided by halving the prevalence of overweight & obesity (Bergstrom *et al*, 2001).

Obesity is an important modifiable risk factor for cancer, with many cancers being linked to excess weight. However the effect of obesity may differ depending on the site of cancer, it is unlikely that there is a 'one system fits all mechanism' (Roberts *et al*, 2010). This thesis is mainly concerned with the impact of obesity and its associated metabolic abnormalities on adenocarcinoma of the oesophagus, postmenopausal breast cancer and colorectal cancer, whose cancer incidence and the epidemiological studies linking increased risk with obesity will be reviewed next.

1.2.1 Breast Cancer

1.2.1.1 Breast Cancer Incidence

Breast cancer is the second most common cancer diagnosis in the world (Ferlay *et al*, 2010; Parkin *et al*, 2005), the most common diagnosis in women with more than a million women diagnosed with breast cancer every year, accounting for 13% of all new cancers and 28% of all female cancer cases (Ferlay *et al*, 2010). Breast cancer is also the leading

cause of cancer death in women in Ireland (18% of deaths), at almost 700 deaths per year (Cancer in Ireland 1994-2007). The risk of women developing breast cancer continues to rise to the order of 3-5% per annum (Women and Cancer in Ireland). In the UK, it has been estimated that the lifetime risk of developing breast cancer is 1 in 1,014 for men and 1 in 9 for women (Cancer Research UK, 2010).

Breast cancer incidence varies considerably by world region. In general, the incidence is high (greater than 80 per 100,000) in developed regions of the world and low (less than 30 per 100,000), though increasing, in developing regions (Parkin *et al*, 2006). This unfavorable trend is due in part to increases in risk factors (decreased childbearing and breast-feeding, increased exogenous hormone exposure, and detrimental dietary and lifestyle changes, including obesity and less physical activity). The risk typically increases for women who migrate from low to high risk countries, further supporting the strong effect for lifestyle or environmental factors (Ziegler *et al*, 1993; Deapen *et al*, 2002).

During the 1990s the increase in the use of hormone replacement therapy (HRT) is thought to have also contributed to the increase in incidence (Beral *et al*, 1997). A steep decrease in incidence since 2002 for women aged 50 or older has been noted in the US (Ravdin *et al*,2007) and other countries (Kumle *et al*, 2008) and linked to the sudden drop in HRT use following publication of the Women's Health Initiative (WHI) (Rossouw *et al*, 2002; Chlebowski *et al*, 2009).On the other hand, mortality is now decreasing in many high-risk countries due to a combination of intensified early detection efforts and the introduction of mammographic screening, resulting in the diagnosis of more small, early stage tumours, and advances in treatment. In Ireland, the proportion of late stage "distant" tumours decreased during 2000-2005 compared to 1994-1999, and this was accompanied by an increase in the proportion 'in situ' and earlier stage tumours in breast cancer reflecting the effects of organised screening (Cancer in Ireland 1994-2005).

1.2.1.2 Breast Cancer, Obesity and Epidemiology Evidence

Most large epidemiological studies have found that overweight or obese women are at increased risk of developing postmenopausal breast cancer, when compared to normal weight women, reporting an increased risk of 8-18% with a $5kg/m^2$ increase in BMI. A pooled analysis of seven prospective cohort studies involving 337,819 women and 4,385 invasive breast cancers showed an 8% increased risk per added $5kg/m^2$ in postmenopausal women (van der Brandt *et al*, 2000). The WCRF found a similar increase in risk from a

meta analysis on 17 cohort studies which gave a summary effect estimate of 1.03 (95% CI's: 1.01-1.04) per 2kg/m^2, which produce an increased risk of 8% for each 5 kg/m^2 (WCRF/AICR 2007). The WCRF also performed a further meta-analysis on 48 case control studies and gave a summary effect estimate of 1.05 (95% CI's: 1.05-1.06) per kg/m^2 which would produce an increased risk of 13% for each 5 kg/m^2 (WCRF/AICR 2007). Another pooled analysis based on 8 case control studies with 642 cases and 1,669 controls, showed a higher increase in risk, estimated at 18% increased risk per 5kg/m^2 for postmenopausal breast cancer (Key *et al*, 2003). Three major studies (Feigelson *et al*, 2004; Lahmann et al, 2003; Morimoto et al, 2002) that reported results stratified for HRT status all found statistically significant increased risk with increasing body fatness only in women not taking HRT (WCRF/AICR 2007). In the UK Reeves et al performed a prospective cohort study of 1.2 million women (50-64 years) during 1996 – 2001 and followed for cancer incidence for on average, 5.4 years. During this period 5,629 cases of postmenopausal breast cancer cases were identified and BMI ≥30 kg/m^2 was associated with increased risk [Odds ratio (OR): 1.40 (95% confidence interval (CI): 1.31 - 1.49] (Reeves *et al*, 2007).

Adult weight gain is an established risk factor for breast cancer in postmenopausal women (Carmichael 2006, Huang *et al*, 1997; Magnusson *et al*, 1998). Risk appears to increase with degree of weight gain. Lahmann estimated the pooled relative risk (RR) of developing breast cancer for a weight gain of 5 kg is 1.08 (95% CI's: 1.04–1.12) and a weight gain of 15–20 kg is associated with 1.5 times increased risk of developing breast cancer (95% CI's: 1.06–2.13) as compared with women of stable weight (+/-2kg) (Lahmann *et al*, 2005). Women with weight gain >21 kg have a relative risk of developing breast cancer of 1.75 (95% CI's: 1.11–2.77) compared with women with more modest weight gain (5 - 9.9 kg) (Lahmann *et al*, 2003).

The evidence for anthropometric factors influencing breast cancer risk and mortality is equally strong. Hip circumference was positively associated with breast cancer risk at 5 years of follow up among non-users of hormone replacement therapy in a study of 73,542 premenopausal and 103,344 postmenopausal (1879 incident invasive breast cancers) women from nine European countries taking part in the European Prospective Investigation into Cancer and Nutrition (EPIC) Study (Lahmann *et al*, 2004). A meta-analysis of the published literature on Waist Hip Ratio (WHR) and breast cancer risk

reported that the overall risk for developing breast cancer in women with a high WHR was 1.62 (95% CI's: 1.28–2.04). The summary risks were 1.79 (95% CI's: 1.22–2.62) for premenopausal women and 1.50 (95% CI's: 1.10–2.04) for postmenopausal women respectively (Connolly *et al*, 2002).

Together with BMI, weight gain and anthropometric measurements, percent body fat is also positively associated with risk of breast cancer as shown in the Malmo Diet and Cancer Study (Lahmann *et al*, 2003). In this prospective cohort study of 12,159 postmenopausal women (246 breast cancer), the percent body fat showed the strongest association with breast cancer (RR: 2.01; 95% CI's: 1.26–3.21). Authors concluded that percent body fat is a more discriminating risk factor for breast cancer risk than the commonly used BMI (Lahmann *et al*, 2003). There is also evidence to suggest that obesity can further increase the risk of women developing postmenopausal breast cancer who are genetically susceptible (Carpenter *et al*, 2003).

1.2.2 Colorectal Cancer

1.2.2.1 Colorectal Cancer Incidence

Colorectal cancer is the third most common cancer worldwide after lung and breast with two-thirds of all colorectal cancers occurring in more developed regions. A million new cases are diagnosed annually, accounting for more than 9% of all new cancer cases, with 0.5 million deaths from the disease in the same time period (Ferlay *et al*, 2010; Parkin *et al*, 2005). In 2006 there were an estimated 307,432 new cases of colorectal cancer in the European Union (Ferlay *et al*, 2007). At present in Ireland, colorectal cancer is the second most common cancer in women and in men after breast and prostrate cancer respectively. In the UK lifetime risk for men of being diagnosed with colorectal cancer is estimated to be 1 in 16 for men and for women 1 in 20 (Cancer Researrch UK).

There are striking variations in the risk of different cancers by geographic area. Most of the international variation is due to exposure to known or suspected risk factors related to lifestyle or environment. A recent study examined international changes in the incidence rate of colorectal cancer over the past 20 years. Analysis was performed on 51 cancer registries from Cancer Incidence in Five Continents (CI5) and the ratio of the incidence rates in 1998-2002 to that in 1983-87 was calculated. The main finding was that colorectal cancer incidence rates increased for both males and females in 27 of the 51 cancer

registries analysed, especially in economically transitioning countries like Eastern European countries, most parts of Asia, and select countries of South America (Center *et al*, 2009). These high rates are most likely the result of "Westernization," where traditional risk factors such as obesity and physical inactivity increased during this time (Center *et al*, 2009, Marchand 1999; Koyama *et al*, 1997). Modest increases or stabilisation of incidence rates were reported in economically developed countries like Western Europe, Australia, Canada and New Zealand. In the US, incidence rates rose until the mid-1980s, but in the last two decades decreased for both men and women (Altekruse *et al*, 2010). Factors that may have contributed to the worldwide variation in colorectal cancer incidence patterns include differences in the prevalence of risk factors and screening practices.

1.2.2.2 Colorectal Cancer, Obesity and Epidemiology Evidence

The WCRF reviewed evidence for obesity and cancers of the colon and rectum. Fifty one out of 60 cohort studies reviewed showed an increased risk with increasing obesity and over half of these were statistically significant. Five studies showed a lower risk with increasing obesity, 4 of these non-significant, and a further four found no association. A clear dose-response relationship with increasing obesity was apparent from cohort data for colorectal cancer. A meta-analysis of 28 cohort studies gave a summary effect estimate of 1.03 (95% CI's: 1.02-1.04) per kg/m^2, this is equivalent to a 15% increased risk for each $5kg/m^2$. It has been estimated that 455 cases of colon cancer treated in Ireland in 2003 were directly attributable to obesity (National Taskforce on Obesity Report 2005). When stratified according to cancer site, a larger more consistent increased risk was found for colon cancer than for rectal cancer (WCRF/AICR 2007). Similar relationships are seen for increasing BMI and colorectal adenomas, a well-recognised pre-cancerous lesion of the colon (Giovanucci *et al.* 1995). Gender differences have been reported, with the association of obesity and risk of colorectal cancer stronger and more pronounced in men compared to women. Harriss et al performed a meta analysis of 28 studies including 67,361 incident cases and reported that high BMI was associated with both colon (relative risk;RR 1.24, 95% CI's: 1.20–1.28) and rectal (RR 1.09, 95% CI's: 1.05–1.14) cancers in men, but only colon cancer (RR 1.09, 95% CI's: 1.04–1.12) in women (Harriss *et al*, 2009). Other meta analyses found broadly similar results (Larssone *et al*, 2007; Dai *et al*, 2007; Bergstrom *et al*, 2001). One hypothesis is that central adiposity, which is strongly related to metabolic abnormalities occurs more frequently in men, and is a stronger risk

factor for colorectal cancer than general overweight (Schoen *et al.* 1999, Frezza *et al.* 2006 Pischon *et al.* 2006).

In a large prospective cohort study performed by Reeves et al, 1.2 million women aged between 50-64 years were followed for 5.4 years and 4,008 cases of colorectal cancer cases were identified. Individuals with a BMI ≥30 kg/m^2 had a modest increase in risk (RR 1.01 95% CI's: (0.94 to 1.09) (Reeves et al, 2007). The effect of increasing BMI on risk appears to be different for premenopausal and postmenopausal women (P value for heterogeneity=0.03), with a significant increase in risk with increasing BMI among premenopausal women (RR 1.61, 95% CI's: 1.05 - 2.48) but not amongst postmenopausal women (RR 0.99, 95% CI's: 0.88 - 1.12) (Reeves *et al*, 2007). This apparent interaction between adiposity and menopausal status may explain, at least in part, the variability in published results on the relation between BMI and colorectal cancer in women. In postmenopausal women, the potential adverse effects of obesity may be offset by the ameliorative effects of increased endogenous oestrogen levels, which have been associated with a lower risk of colorectal cancer in adults.

Adipose tissue distribution may be another important mediating factor in the association between BMI and colorectal cancer. In a random-effects meta-analyses involving 70,000 cases of incident colorectal cancer from 31 studies, of which 23 were cohort studies and 8 were case-control studies, the estimated relative risk of colorectal cancer was stronger for central obesity 1.45 (95% CI's: 1.31-1.61), comparing to a relative risk of 1.19 (95% CI's: 1.11-1.29), comparing obese (BMI >30 kg/m2) with normal weight (BMI <25 kg/m2) people (Moghaddam et al 2007). There was evidence of a dose-response relationship between BMI and colorectal cancer: for a 2 kg/m^2 increase in BMI, the risk of colorectal cancer increased by 7% (4-10%) For a 2-cm increase in waist circumference, the risk increased by 4% (2-5%) (Moghaddam *et al*, 2007). In the Cardiovascular Health Study cohort with 5849 participants and 102 incident cases of colorectal cancer identified, a larger waist circumference was statistically significantly associated with colorectal cancer (RR 1.9; 95% CI's: 1.1–3.3; *P*=0.02) (Schoen *et al.* 1999). In the Health Professionals Follow-up Cohort Study of more than 31,000 men, both waist circumference and waist-to-hip ratio, demonstrated a strong relationship with the subsequent development of colorectal cancer, the relative risk in relation to WHR was 3.41 (95% CI's: 1.52–7.66) and for waist circumference it was 2.56 (95% CI's: 1.33–4.96) comparing those in the highest to the lowest quintile (Giovannucci 2001). An elevated waist-to-hip

ratio was also associated with incident colorectal adenomas of at least 1 cm in size, which are considered at high risk for subsequent development of colorectal cancer, but not with small adenomas, which are less likely to progress (Atkin *et al*, 1992; MacInis *et al.* 2006).

As well as increasing the risk of developing colorectal cancer, obesity also appears to negatively influence cancer recurrence and survival in patients with established colon cancer (Meyerhardt *et al,* 2003, Calle *et al,* 2003, Dignam *et al,* 2006). Haydon examined the effect of body size on survival and found that an increased waist circumference and greater percentage body fat were associated with increased mortality after diagnosis of colon cancer. For every 10% increase in body fat a 33% decrease in disease specific survival was observed, while a 10cm increase in waist circumference resulted in a 20% reduction in disease specific survival (Haydon *et al,* 2006).

1.2.3 Oesophageal Cancer

1.2.3.1 Oesophageal Cancer Incidence

Oesophageal cancer is the eighth most common cancer worldwide, responsible for 462,000 new cases in 2002 (4.2% of the total), and represents the sixth most common cause of cancer death (386,000; 5.7% of the total) (Brown *et al*, 2008). Although not as common as other malignancies, the probability that an individual with cancer will die (case fatality ratio) is much higher at 83% compared to colorectal (52%), and breast cancer (36%) (Parkin *et al*, 2005). Worldwide, the incidence of oesophageal adenocarcinoma is increasing (Bird-Lieberman & Fitzgearld 2009), with increases of 500% reported in some countries over the last three decades (Edelstein *et al*, 2007). In the US, from 1975-2001 the incidence of distal and junctional oesophageal adenocarcinoma rose approximately six-fold (from 4 to 23 cases per million), strongly indicating a true increase in disease burden, that is not explained by over-diagnosis or reclassification (Edelstein *et al*, 2007). Data from the Surveillance, Epidemiology and End Results program (SEER) program, 1975-2007, confirm this dramatic increase in adenocarcinoma is predominantly, but not exclusively, in white men and women in all age groups (SEER Fast Stats), and that this cancer constitutes the fastest rising malignancy in the US (Brown *et al*,1995). The risk of developing the disease increases with age with very few cases diagnosed in people aged less than 40 years. The male/female ratio reported for adenocarcinomas is generally around 5-10-fold higher in males, which makes it one of the

highest sex differentials of any non-occupational cancer (Wild *et al*, 2003). Adenocarcinoma now accounts for at least half of all oesophageal cancers in the West (Chow *et al*, 1998), which has overtaken squamous cell carcinoma previously the commonest histology. Lifestyle changes may contribute to this change, with increases in obesity rates, (Engel *et al*, 2003) decrease in smoking, (Chow *et al*, 1998) and increases in Barrett's Oesophagus (BO) incidence rates (Brown *et al*, 1995).

1.2.3.2 Epidemiology: Obesity and Oesophageal Cancer

Epidemiological evidence strongly links obesity with up to 40% of adenocarcinoma cases (Calle *et al*, 2003; Brown *et al*, 1995; Chow *et al*, 1998; Engel *et al*, 2003; Lagergren *et al*, 1999; Vaughan *et al*, 1995). A recent meta-analysis pooled data from 14 studies (2 cohort and 12 case control) with 2,488 cases of oesophageal carcinoma and reported a positive association between increased BMI (overweight and obese) and adenocarcinoma for both males and females, with the strength of the association increasing with increasing BMI. The pooled risk for obese males was 2.4 (95% CI's: 1.9-3.2) and 2.1 (95% CI's: 1.4-3.2) for females (Kubo & Corley 2006).

Further studies published since the meta-analysis in 2006 confirm obesity's relationship to oesophageal adenocarcinoma. Abnet et al prospectively examined the association between BMI and adenocarcinoma in 480,475 participants in the National Institute for Health (NIH) American Association for Retired Persons Diet and Health study cohort described by Schatzkin (Schatzkin *et al*, 2001). During an 8 year follow up period 371 cases of adenocarcinoma were identified and those individuals with a BMI in the highest category (>35 kg/m2) were at increased risk (Abnet *et al*, 2008). In the United States (US) a nested case control study with 94 cancer cases in 206,974 participants, found an increased risk for individuals with a BMI ≥30, with abdominal obesity an independent risk factor after adjustment for BMI - individuals with a diameter ≥25cm had an estimated odds ratio (OR of 4.67 (95%CI: 1.14-20.11), suggesting that abdominal obesity increases the risk of adenocarcinoma independent of BMI (Corley *et al*, 2008). In the UK Reeves et al performed a prospective cohort study of 1.2 million women (50-64 years) during 1996 – 2001 and followed for cancer incidence for on average, 5.4 years. During this period 150 cases of adenocarcinoma were identified and individuals with a BMI ≥30 were at increased risk (Reeves *et al*, 2007). In Ireland, Ryan and colleagues conducted a case-control study of 508 adenocarcinoma cases and 893 controls. A dose-dependent

relationship between pre-illness BMI and adenocarcinoma was observed for males (OR 4.3, 95% CI's: 2.3-7.9) in the highest BMI quartile versus the lowest. For specifically the lower oesophagus, an OR of 11.3 (95% CI's: 3.5 - 36.4) was observed and for the gastro-oesophageal junction (GOJ) the OR was 3.4 (95% CI's: 1.4-8.7) (Ryan *et al*, 2006). Another Irish case-control study examining BMI and adenocarcinoma risk reported a similar association with increased BMI (Anderson *et al*, 2007).

Like breast cancer and colorectal cancer, central obesity may also be a more important risk factor than BMI alone. In EPIC study, Steffen et al followed 346,544 adults for 8.9 years. BMI, waist circumference and waist-hip ratio were all positively associated with EA (RR 2.60 (95% CI's: 1.23-5.51; RR 3.07; 95% CI's: 1.35-6.98; and RR 2.12; 95% CI's: 0.98-4.57, respectively) (Steffen *et al*, 2009). In a prospective cohort study MacInnis et al followed 41,295 subjects for 11 years. Detailed body composition information from bioelectrical impedance analysis was performed at baseline. The odds ratio of adenocarcinoma of the lower oesophagus for individuals with a BMI > 30 versus <25 was 3.7 (95% CI's: 1.1-12.4). For every 10cm increase in waist circumference the OR was 1.46 (95% CI's:1.0 –2.04) and for every 10kg increase in fat mass the OR was 1.48 (95% CI's:0.98-2.23) (MacInnis *et al*, 2006). Whiteman et al conducted a population-based case-control study of 367 cases of adenocarcinoma and 426 cases of GOJ adenocarcinoma and 1580 controls. Morbidly obese individuals (BMI >40) had a significantly elevated risk of adenocarcinoma, OR 6.1 (95% CI's: 2.7-13.6). The authors reported that the risk was significantly higher for males versus females, and for obese people with reflux (OR 16.5, 95% CI's: 8.9-30.6) compared to obese people without reflux (OR 2.2, 95% CI's: 1.1-4.3) suggesting a synergistic interaction between these factors (Whiteman *et al*, 2008).

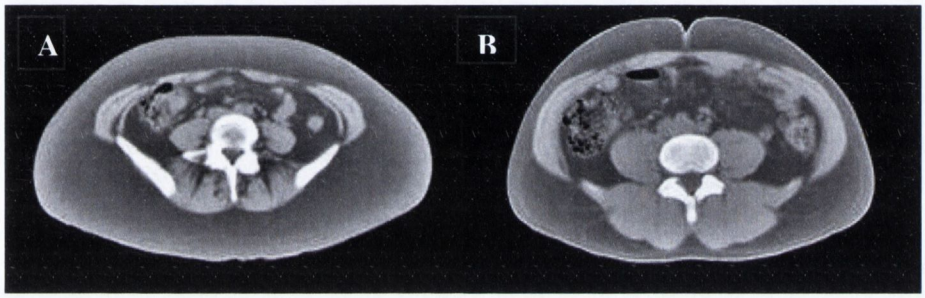
1.3 Mechanism of Obesity's Altered Cancer Risk

1.3.1 Abdominal Adiposity

Despite epidemiological evidence, the precise biological mechanism by which obesity increases the risk of cancer remains unknown, there is an intriguing potential link relating to altered metabolic, endocrine and immuno-inflammatory responses that are common to obesity and better described in association with type 2 diabetes and cardiovascular disease. The general consensus is that the influence of obesity on cancer risk and outcomes applies specifically to upper body obesity (Vona Davis *et al*, 2007). As reviewed earlier, studies

using anthropometric measures of adipose distribution (waist circumference, WHR in addition to BMI found a stronger or independent association to cancer risk with site specific anthropometry than with BMI alone (Schoen *et al*, 1999; Giovannucci *et al*, 1995; Frezza *et al*, 2006; Pischon *et al*, 2006; Steffan *et al*, 2009; Corley *et al*, 2008; Moghaddam *et al*, 2007; Martinez *et al*, 1997; Russo *et al*, 1998).

Figure 1.1: CT scans showing high level of subcutaneous fat (A) and visceral fat (B)

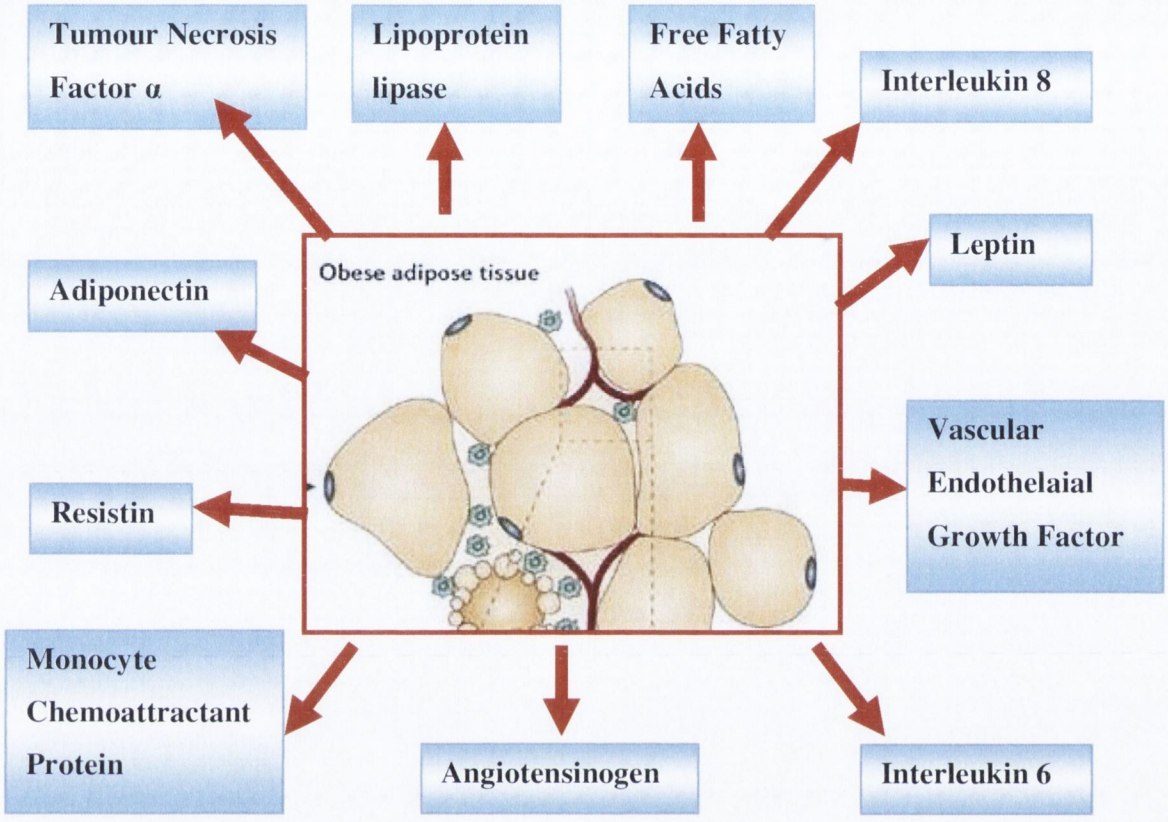


CT scans reveals whether abdominal fat is stored under the skin in a region called the hypodermis (subcutaneous fat) or has accumulated around the internal organs (visceral fat). This is important as adipose tissue in different parts of the body have different biochemical profiles. Excess visceral fat is associated with diabetes, insulin resistance, inflammatory diseases and other obesity related diseases, while subcutaneous fat is not related to many of the classic obesity-related pathologies. Gender differences in body fat distribution are influenced by sex hormones, with the typical female (or gynecoid) pattern of body fat distribution around the hips, thighs, and buttocks mostly subcutaneous fat and male abdominal obesity is more visceral fat, and therefore poses different health risks.

Adipose tissue has long been considered to be metabolically inactive and primarily responsible for energy storage. However, recent scientific advances have dramatically altered our understanding of this tissue's function. Abdominal adiposity consists of different stores which differ in their metabolic activity and contribute in varying degrees to the hormonal milieu (Vona Davis *et al*, 2007).Visceral Adipose Tissue (VAT) (Figure 1.1), is the most metabolically active. Waist circumference alone is a better indicator of VAT than WHR (Carr *et al*, 2004; Raikkonen *et al*, 1999) but the gold standard for measurement of visceral fat is Computerised Tomography (CT). As reviewed earlier, studies using measurements of percent body fat, and CT measured visceral fat area found a stronger or independent association to cancer risk compared with BMI alone (Giovanucci *et al*, 1995; Lahmann *et al*, 2003; Haydon *et al*, 2006; MacInnis *et al*, 2006). CT assessments show individuals with excess VAT are characterised by the most substantial adverse alterations in metabolic risk profile (Fox et al 2007).VAT secretes a variety of biologically active substances (Figure 1.2) important in the pathogenesis of insulin resistance, dyslipidemia, glucose intolerance, hypertension, features of the metabolic syndrome (Cowey & Hardy 2006; MacInnis *et al*, 2006; Bray 1998; Fontana & Klein 2007; Giovannucci *et al*, 1995; Rexrode *et al*, 1998; Misra & Vicram 2003).

The specific molecular mechanisms underlying the relationship between obesity and cancer remain to be elucidated but the aetiology is likely to be multifactorial involving many factors like chronic inflammation, hyperinsulinaemia, and altered hormone levels. The presence of metabolic syndrome represents the co-existance of many of these altered factors in individuals and may be linked to cancer incidence or progression. Before reviewing the current evidence to support this link, we must first consider the different defnintions that have been used to define the presence of the metabolic syndrome and their effect on the reported prevelance.

Figure 1.2 Adipose Tissue as an Endocrine Organ



Adipose tissue is metabolically active and is one of the body's most important endocrine organs. Adipose tissue expresses and secretes a variety of bioactive peptides known as adipokines. Among the wide variety of adipokines, adipocytes synthesize and secrete proteins such as classical cytokines - tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), growth factors (transforming growth factor-β). Adipocytes also secrete proteins that participate in lipid transport lipoprotein lipase, cholesterol ester transfer protein (CETP), retinol-binding protein (RBP) - vascular haemostasis (plasminogen activator inhibitor-1 (PAI-1), regulation of blood pressure (angiotensinogen) angiogenesis (VEGF), and glucose homeostasis (adiponectin, resistin).

1.3.2 Metabolic Syndrome

1.3.2.1 Definition of Metabolic Syndrome

This combination of metabolic disturbances now known as the metabolic syndrome was first described by Kylin in the 1920s as the clustering of hypertension, hyperglycaemia, and gout and formally labelled in 1988 by Gerald Reaven (Reaven 1988). Over the last 50 years the metabolic syndrome has had many names (e.g. "Syndrome X", "The deadly quartet", and "The insulin resistance syndrome" (Deedwania 1998) and different definitions used to determine the presence of the metabolic syndrome. General features of metabolic syndrome include: central adiposity or obesity, insulin resistance or impaired glucose tolerance, dyslipidaemia (increased Triacylglycerol TAG, and reduced high density lipoprotein HDL cholesterol), hypertension, and a pro-inflammatory and pro-thrombotic state. Table 1.1 highlights the differences and similarities between the most widely used definitions. The main differences include different essential criteria and different cut offs for abnormal features, also a different emphasis on adiposity and insulin resistance and priority of assignment. The International Diabetes Federation (IDF) definition takes into account lower cut offs for waist circumference with an ethnic specific adjustment, and lower cut offs for glucose intolerance in line with the American Diabetes Association (ADA); (Expert Committee on the Diagnosis and Classification of Diabetes Mellitus 1997). In 2009 several global organisations including the International Diabetes Federation (IDF), American Heart Association, and International Association for the Study of Obesity and the National Heart, Lung and Blood Institute published a consensus definition requiring 3 of 5 risk factors to diagnose the metabolic syndrome. These include elevated waist circumference, reduced HDL and elevated triglycerides, blood pressure, or blood glucose, or drug treatment for any of these (Alberti *et al*, 2009) (Table 1.1). The definition has come under some criticism, it has been questioned whether the IDF set their cut offs too low and if it labels low risk individuals in already economically challenged health systems (Zimmet & Alberti, 2005).

1.3.2.2 Prevalence of Metabolic Syndrome

The prevalence of metabolic syndrome varies according to the definition (Table 1.1) used and also on the characteristics of the population being studied. In the National Health and Nutrition Examination Survey (NHANES) 1999-2000 27% of participants had the metabolic syndrome assessed by the National Cholesterol Education Program Adult

Treatment Panel (NCEP ATP) III definition (Ford *et al*, 2004), which represents an increase from 24% in the NHANES III (Ford *et al*, 2002). The prevalence in European studies ranges from 7% to 36% in men and 5% to 22% in women using the WHO definition (Balkau *et al*, 2002). The Diabetes Epidemiology Collaborative Analysis of diagnostic Citeria in Europe (DECODE) study determined the presence of metabolic syndrome using a modification of the WHO definition for 11 European cohorts and showed that 15.7% of non diabetic men and 14.2% of non diabetic women had the metabolic syndrome (Hu *et al*, 2004). In Europe, the age- and sex-adjusted prevalence of metabolic syndrome was 24.6% using the 2005 ATP definition and 30.9% using the International Diabetes Federation definition, according to the Madrid Risego Cardiovascular Study (MADRIC) study performed on 1344 participants (Martinez *et al*, 2008).

Prevalence in Ireland in largely unknown, although small population studies have estimated a prevalence of 21% using the WHO definition and 20.7% using the NCEP ATP III definition in 1,018 middle aged Irish men and women (Villeagas *et al*, 2004). A more recent study on 1,716 participants found metabolic syndrome in 13.2% using ATP III definition and 21.4% using IDF definition (Waterhouse *et al*, 2009). These studies include populations from small areas with different socioeconomic statuses and are perhaps not representative of the national prevalence, but again highlight some of the difficulties in estimating prevalence.

The prevalence of metabolic syndrome increases with age, rising steeply after the third decade and reaching a peak in men aged 50-70 years and in women aged 60- 80 yrs, age also increases the risk of cancer which may have some impact on prevalence of metabolic syndrome in cancer population (Park *et al*, 2003). Education and socioeconomic status also impact on prevalence similar to incidence of obesity (Yuseuf *et al*, 2004, Churilla *et al*, 2007). The prevalence of the metabolic syndrome also increases with obesity as assessed by BMI or waist circumference (Park *et al*, 2003, Janssen *et al*, 2004), but not all obese persons have features of the metabolic syndrome.

Table 1.1 Definitions of Metabolic Syndrome

Definition *	WHO 1998	EGIR 1999	NCEP ATPIII 2001	IDF 2005	Consensus 2009
Reference	Alberti 1998	Balkau 2002	NCEP 2001	Alberti 2006	Alberti 2009
Criteria	Impaired glucose regulation or hyperinsulinaemia and more than two factors	Insulin resistance and two of:	3 or more of:	WC and two or more risk factors	3 or more of:
Abdominal Obesity	Waist : hip ratio ≥0·85 or BMI ≥30 kg/m2	Men: WC ≥94 cm Women: WC ≥80 cm	Men: WC>102cm Women WC>88cm	Men: WC* ≥94cm Women: WC*≥80cm	Increased WC*
Impaired glucose Tolerance (IGT)	Fasting plasma ≥6·1mmol/l or 2h postglucose load ≥7·8 mmol/l	Fasting plasma ≥6·1 mmol/l	6·1–7·0 mmol/l	Fasting plasma ≥5·6 mmol/l or T2DM	Fasting plasma ≥5·6 mmol/l or T2DM
Hyperinsulinaemia	Fasting serum insulin >1/3rd quartile for control group	Fasting serum insulin >1/3rd quartile for non-diabetic control group	Not included	Not included	Not included
HDL cholesterol	Not included	HDL <1·0 mmol/l and/or treatment for dyslipidaemia	Men: <1·03 mmol/l Women: <1·3 mmol/l	Men: <1·03 mmol/l Women: <1·3 mmol/l	Men: <1·03 mmol/l Women:<1·3 mmol/l
Triglycerides (TAG)	≥1·7 mmol/l	≥2·0 mmol/l and/or treatment for dyslipidaemia	≥1·7 mmol/l	≥1·7 mmol/l	≥1·7 mmol/l
Hypertension	≥140/90 mmHg	≥140/≥90 mmHg or treatment for HTN	≥130/≥80 mmHg	≥130/≥85 mmHg or treatment for HTN	≥130/≥85 mmHg or Treatment for HTN
Microalbuminuria	Albumin/creatinine ratio >30 mg/g	Not included	Not included	Not included	Not included

** WHO: World Health Organisation; EGIR: European Group for the study of Insulin Resisitance; NCEPATPIII: Adult Treatment Panel III; IDF: International Diabetes Federation; WC: Waist circumference; T2DM: Type 2 Diabetes Mellitus; HDL: High Density Lipoprotein cholesterol; TAG: Triglycerides; HTN: Hypertension*

The different definitions used to diagnose metabolic syndrome are presented above along with the cut-offs used for each individual feature. The main differences include different essential criteria and different cut-offs for abnormal features, also a different emphasis on adiposity and insulin resistance and priority of assignment.

1.3.3 Metabolic syndrome and cancer

The pathogenesis of metabolic syndrome is complex and so far incompletely understood. Until now the most recognised effect of metabolic syndrome was its association with the increased risk of developing cardiovascular disease and type 2 diabetes (Ford, 2005). Individuals with metabolic syndrome are twice as likely to die from, and have a three fold higher risk of developing, heart attack or stroke compared with people without the syndrome, with a 5 fold higher risk of developing type 2 diabetes (Isomaa *et al*, 2001).

The metabolic syndrome has more recently been proposed as a high risk state for cancer (Cowey & Hardy 2006). Individual components of metabolic syndrome have been linked to several processes including insulin resistance, aromatase activity, adipokine production, angiogenesis, elevated C - reactive protein (CRP), glucose utilisation, and oxidative stress/DNA damage, which together can increase cancer risk beyond that of individual components alone. Recent epidemiological evidence has emerged indicating that clustering of components of metabolic syndrome increase the risk of many common cancers for example breast (Vona Davis *et al*, 2007; Rose *et al*, 2007), endometrial (Bjorge *et al*, 2010) colorectal (Giovanucci *et al*, 2007), and prostate cancer (BeebeDimmer *et al*, 2009, Hsing *et al*, 2007). To date no studies have been published linking metabolic syndrome to oesophageal adenocarcinoma, but an intriguing link between metabolic syndrome and its precursor lesion Barrett's oesophagus has recently been published which we will review in more depth later. Although the link between metabolic syndrome and colorectal and breast cancer is not as well studied as BMI or obesity, we will review all the available evidence for each cancer separately, before examining more closely the individual features of the metabolic syndrome and its potential to influence the cancer process.

1.3.3.1 Metabolic Syndrome & Colorectal Cancer

Despite the use of different definitions of the metabolic syndrome most studies that examined the presence of metabolic syndrome have shown an increased risk of colorectal cancer incidence or increased cancer mortality (Table 1.2). Subjects with metabolic syndrome (HTN, elevated cholesterol, diabetes) in the US National Health Interview Survey 2002-2003 (n=58,000) were almost twice as likely to have colorectal cancer (Garrow *et al*, 2008). After controlling for age, race, gender, obesity, smoking and alcohol use, individuals with metabolic syndrome had a 75% increased risk for colon or rectal

cancer (Garrow *et al*, 2008). Stocks et al evaluated the presence of metabolic syndrome components as well as other markers of obesity (C-peptide, HbA1c, leptin, adiponectin, BMI, hypertension and fasting glucose) in 306 individuals with known colorectal cancer. The presence of hypertension, obesity and hyperglycaemia, correlated with a RR for three vs null factors of 2.57 (95% CI: 1.20-5.52, P<0.001) (Stocks *et al*, 2008).

Other studies provide information concerning the association of colorectal cancer incidence and mortality with the increasing number of metabolic syndrome components, suggesting an additive effect of the individual components. In an analysis of 14,109 participants from the ARIC study (Atherosclerosis Risk in Communities), baseline metabolic syndrome (> 3 components vs 0 components) had a positive association with age and gender adjusted colorectal cancer incidence (RR: 1.49, 95% CI's: 1.0-2.4). There was a dose-response association between colorectal cancer incidence and the number of metabolic syndrome components present at baseline (P for trend =0.006) after multivariate adjustment (Ahmed *et al*, 2006). In an analysis of 20,433 men and 15,149 women, metabolic syndrome was defined as having at least 3 of the following components (glucose levels, systolic blood pressure, body mass index, or resting heart rate) in the highest quartile. They reported an increased risk of colorectal cancer associated with high blood pressure and hyperglycaemia and confirmed that the clustering of metabolic syndrome components significantly increased the risk of associated colorectal cancer (Colangelo *et al, 2002*). Trevisan et al, pooled data from nine epidemiological studies (n=21,311 men and 15,991 women) and used low HDL and high triglyceride levels, hypertension and high glucose levels as individual components of the metabolic syndrome. The presence of the cluster of metabolic abnormalities was associated with a 3 fold increased risk of colorectal cancer mortality (OR 2.99 CI: 1.27-7.01). When analyzing the individual components, only glucose levels were associated with an increased risk of death from colorectal cancer (OR: 1.8, CI: 1.05-3.09). The results of this study suggest that the effects of the individual components of metabolic syndrome are additive, because the RR of death from colorectal cancer was increased in cluster analysis compared with glucose alone (Trevisan *et al*, 2001).

Table 1.2: Summary of studies on Metabolic Syndrome and Colorectal Cancer

Author	N	MetS Definition	Results	Significance
Garrow et al, 2008 United States	1200 MetS (350 CRC)	3 common chronic medical conditions: hypertension, diabetes and elevated cholesterol	MetS resulted in a 75% increased risk for colon or rectal cancer	MetS associated with increased risk of CRC
Stocks et al, 2008 United States	306 CRC and 595 matched controls	Modified WHO definition BMI >30 kg/m2; BP > 140 or >90mmHg, or anti HTN drugs; Gluc >6.1 mmol/L or post-load gluc >8.9 mmol/l MetS >3 vs 0 factors	Gluc: 1.7 (1.1 - 2.6) BMI: 1.8 (1.1 - 2.8) HTN: 1.3 (0.9 - 1.9) NS MetS: 2.6 (1.2 - 5.5)	Components of the MetS increase the risk of CRC, and clustering further increases the risk of CRC
Strumer et al 2006, United States	22,071 healthy male physicians	Self Reported BMI >27 kg; BP >130/85mmHg or Anti HTN drugs; Diabetes; Cholesterol >6.2 mmol/l or lipid-lowering drugs MetS >3 vs 0 factors	MetS: 1.4 (0.9 - 2.1) Each abnormality 1.2 (1.1 - 1.3) BMI >27 kg/m2: 1.4 (1.1 - 1.7) Diabetes: 1.5 (1.1 - 2.0) BP: 1.1 (0.9 - 1.3) High Cholesterol: 0.9 (0.7 - 1.1)	Model assessing clustering metabolic abnormalities was more predictive for colorectal cancer than a model based on the number of abnormalities
Bowers et al, 2006 Finland	28,983 Finnish male smokers	BMI >25 kgm; BP > 140 or 90mmHg; HDL cholesterol <1.55 mmol/l MetS: 3 vs 0 factors	CRC 1.40, (1.12, 1.74) Colon only 1.58 (1.18- 2.10) Rectal only 1.20 (0.9-1.7) NS	MetS is associated with increased CRC but primarily associated with colon cancer in males but not rectal cancer

BP: blood pressure; CRC: colorectal cancer; F: female; Gluc: glucose; HDL: high density lipoprotein; HTN: Hypertension; IRS: Insulin Resistance Syndrome; M: male; MetS: metabolic syndrome; MF: male and female; NS: non siificant; OR: odds ratio; TAG: triglycerides; WC: waist circumference.

This table presents a summary of the different studies assessing the metabolic syndrome and colorectal caner mortality. It describes how metabolic syndrome was defined in each study, significant results and the significance of these findings.

Author	N	MetS Definition	Results	Significance
Ahmed et al, 2006 United States	14,109 men and women 194 incident cases CRC	WC: M>102cm F> 88cm BP >130/85mmHg Gluc> 5.5 mmol/l or diabetes TAG >1.7 mmol/l HDL M < 0.9; F<1.15 mmol/l MetS: >3 vs 0 factors	M: 1.8 (1.0 - 3.6) F: 1.2 (0.6 - 2.2) NS MF: 1.4 (0.9 - 2.2)	Metabolic syndrome was a risk factor for incident CRC in men but not women.
Colangelo et al, 2002 United States	20,433 men and 15,149 women 217 CRC deaths	Highest quartile of the sex-specific distribution for Gluc, SBP,BMI or resting heart rate MetS: >3 vs 0 factors	Gluc F:1.94 (1.04–3.60) M: 1.48 (0.93–2.35) NS MF: 1.64 (1.13–2.37) IRS M :1.67 (1.04-2.70) F: 1.29 (0.70 –2.37) MF: 1.50 (1.03-2.19)	Adjusted for categories of age, race, education, and each of the other factors listed. Plasma glluc and MetS are associated with CRC mortality, providing evidence for the insulin hypothesis
Trevisan et al, 2001 Italy	21,311 men and 15,991 women 54 cases of CRC Mortality	Higest quartile TAG, GLUC, Lowest quartile of HDL BP >140 or >90 mmHg	Gluc M: 1.83 (1.0 – 3.4); F: 1.73 (0.6 - 5.2); MF: 1.8 (1.1 – 3.1) IRS: M: 3.0 (1.1 – 8.3); F: 2.7 (0.6 – 12.5); MF: 3.0 (1.3-7) NS: TAG,HDL, BP	Glucose was the only significant individual feature and Met S clusrtering associated with increased risk CRC mortality

BP: blood pressure; CRC: colorectal cancer; F: female; Gluc: glucose; HDL: high density lipoprotein; IRS: Insulin Resistance Syndrome; M: male; MetS: metabolic syndrome; MF: male and female; NS: non siificant; OR: odds ratio; TAG: triglycerides; WC: waist circumference.

This table presents a summary of the different studies assessing the metabolic syndrome and colorectal caner mortality. It describes how metabolic syndrome was defined in each study, significant results and the significance of these findings.

Table 1.3: Summary of studies on Metabolic Syndrome and Breast Cancer

Author	N	MetS Definition	Results	Significance
Agnoli et al, 2010 Italy	163 breast Cancer pts 652 Controls	Highest teritles of WC >86 cm; TAG >1.43 mmol/l; HDL <1.42 mmol/l; Gluc >4.9 mmol/l (or diabetes); and BP >106.5 mmHg or Anti HTN drugs and NCEP ATP III MetS: >3 vs 0 factors	MetS (Tertiles): 1.6 (1.1 - 2.3) MetS (NCEP): 2.6 (1.5 - 4.6)	MetS is a risk factor for breast cancer in postmenopausal women. HDL & TAG had the strongest association with breast cancer, but all components may contribute to increased risk by multiple interacting mechanisms
Kabut et al, 2009 United States	4,888 women with postmenopausal breast cancer	NCEP ATP III defined as having 3+ features	MetS: 1.1 (0.8 - 1.6) NS Time-dependent analysis (MetS 3-5yr pre-diagnosis) Gluc: 1.6 (0.9 - 2.9) TAG: 1.8 (1.0 - 3.0)	MetS not association with increased risk but presence of MetS prior to diagnosis indicated an increased risk, highlighting importance of longitudinal studies
Pasanisi et al, 2006 Italy	110 postmenopausal breast cancer patients	WC >88 cm; GLUC> 6.1 mmol/l; TAG >1.7 mmol/l; HDL <1.29 mmol/l; SBP>130 mmHg; DBP>85 mmHg Testosterone > 0.4ng/l MetS: >3 vs 0 factors	MetS: 3.0 (1.2 - 1.7) MetS + testosterone: 6.7 (2.3 - 19.8)	MetS is an important prognostic factor for breast cancer recurrences, especially if associated with high serum levels of testosterone

BP: blood pressure; CRC: colorectal cancer; F: female; GLUC: glucose; HDL: high density lipoprotein; IRS: insulin resistance syndrome; M: male; MetS: metabolic syndrome; MF: male and female; NS: non siificant; OR: odds ratio; TAG: triglycerides; WC: waist circumference;

This table presents a summary of the different studies assessing the metabolic syndrome and breast cancer. It describes definition metabolic syndrome used in each study, significant results and the significance of these findings.

1.3.3.2 Metabolic Syndrome & Breast Cancer

The metabolic syndrome has recently been suggested to play a role in breast carcinogenesis (Xue & Michels 2007; Goodwin *et al*, 2009; Vona Davis *et al*, 2007). Several studies have associated the individual components of metabolic syndrome (high serum glucose and triglycerides, low HDL-cholesterol, high blood pressure, and abdominal obesity) with breast cancer risk, but very few prospective studies have investigated risk in relation to the presence of explicitly defined metabolic syndrome. One nested case control study on postmenopausal women (n= 3,966), found 163 women developed invasive breast cancer and metabolic syndrome (as defined by the highest or lowest tertiles (HDL) of individual features of metabolic syndrome among controls) was present in 29.8%. Metabolic syndrome (i.e. presence of three or more metabolic syndrome components) was significantly associated with breast cancer risk (OR: 1.58; 95% CI's: 1.07-2.33), with a significant increase in risk with increasing number of components. Among the individual metabolic syndrome components, only low serum HDL-cholesterol and high triglycerides were significantly associated with increased risk (Agnoli *et al*, 2010).

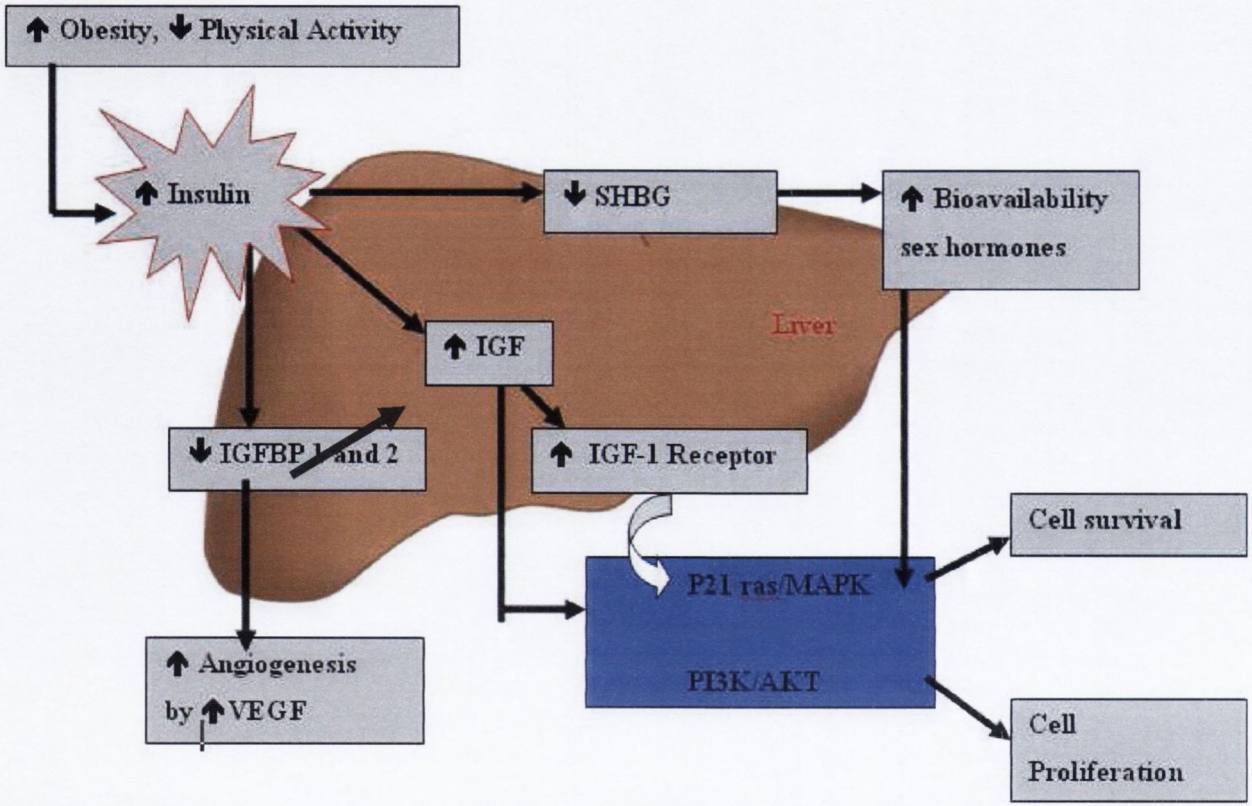
In a second longitudinal study on 4,888 postmenopausal women, 165 incident cases of breast cancer occurred over an 8 year period (Kabat *et al*, 2009). The presence of the metabolic syndrome at baseline was not associated with altered risk. Of the individual components measured at baseline, diastolic blood pressure was positively associated with breast cancer. In a time-dependent covariate analyses, the presence of the syndrome 3-5 years prior to diagnosis, indicated a positive association between the metabolic syndrome and breast cancer, due primarily to positive associations with serum glucose, serum triglycerides, and diastolic blood pressure (Kabat *et al*, 2009).

Sinagra et al. have reported a small case–control study from Italy which showed a higher prevalence of three components of the metabolic syndrome, type 2 diabetes, dyslipidemia and hypertension, in the 50 patients with malignant tumours compared with women with benign breast pathology or women with no breast pathology (Sinagra *et al*, 2002). Also, Pasanisi et al. found that the risk of breast cancer recurrence was increased in postmenopausal women (n=100) with metabolic syndrome (OR: 3.0 CI 1.2–7.1) (Pasanisi *et al*, 2006). These results suggest that metabolic syndrome may be an important prognostic factor for breast cancer.

Pathophysiological mechanisms wherby metabolic syndrome may promote the development of cancer

There are many potential pathophysiological mechanisms whereby components of the metabolic syndrome may promote the development of cancer, like alterations in endogenours hormone metabolism including insulin, bio available sex steroids, Insulin Like Growth Factor alpha (IGFα) and Insulin Like Growth Factor Binding Proteins (IGFBPs) (Figure 1.3). A metabolic consequence of obesity and specifically the acculmulation of intra abdominal fat is the development of insulin resistance, which leads to chronic hyperinsulinaemia. Epidemiological evidence to support this hypothesis comes from human observational studies where increased concentrations of fasting glucose, C peptide (a marker of insulin production), circulating insulin and insulin growth factor 1 (IGF-1) and Type 2 diabetes have been positively associated with increased cancer risk (Ma *et al*, 2004, Wei *et al*, 2005A, Larrsson *et al*, 2005, Schoen *et al*, 1999). Furthermore, insulin resistance is an adverse prognostic factor for breast cancer (Goodwin *et al*, 2002) and colorectal (Colangelo *et al*, 2002) cancer related mortality.

Figure 1.3: Hyperinsulinaemia and Tumourigensis



This Figure represents how insulin levels may promote cancer development. Firslty hyperinsulinaemia leads to increased IGF-1 levels and increased availability of IGF-1 to bind to receptors on normal and cancer cells. This receptor bound IGF-1 can modulate cell proliferation and survival. Secondly, insulin reduces IGFBP's which act as tumour suppressors by inhibiting cell growth by sequestering free IGF-1's and inhibiting the IGF-1 receptor. Thirdly both Insulin and IGF increase VEGF which is a critical angiogenic factor that influences endothelial cell survival and migration. Lastly insulin can reduce SHBG concentration which leads to increased availability of sex hormones like oestrogen. Legend: IGF: Insulin Like Growth Factor; IGFBP: Insulin Like Growth Factor Binding Proteins; SHBG: Sex hormone binding globulin; VEGF: Vascular endothelial growth factor; p21 RAS: Ras GTPase activating protein; MAPK: Mitogen-activated protein kinases; P13K: Phosphoinositide 3-kinase AKT serine/threonine protein kinase

1.3.4 Insulin resistance

Although insulin is widely known for it metabolic effects, it also has important mitogenic effects which maybe relevant in cancer. Figure 1.3 is a diagrammatic representation of how increased adiposity and increased insulin levels may promote cancer development, as well as leading to increased IGF levels and availability of sex hormones by reducing concentrations of sex-hormone-binding globulin (SHBG). The function of insulin is mediated through activation of the insulin receptor (IR). IR overexpression is a common phenomemon in human cancer (Frasca *et al*, 1999; Frittitta *et al*, 1999; Vella *et al*, 2001). Studies performed using specific ELISAs have indicated that approximately 80% of breast cancers showed an insulin receptor content higher than the mean value found in normal breast and approximately 20% of cancers showed IR values over 10 fold higher than mean value in normal breast (Papa *et al*, 1990). The IR may be expressed in two different isoforms A and B. In malignant cells, the A isoform (IR-A) expression is predominant (Frasca *et al*, 1999; Kalli *et al*, 2002) and its activation ellicts more mitogenic than metabolic effects (Frasca *et al*, 1999). Insulin binding to the overexpressed IR-A may favour cancer development and progression; through modification of growth and differentiation of tumours that would otherwise have likely remained irrelevent for an undetermined length of time. Insulin receptor content has been directly related to tumour size, grade (Papa *et al*, 1990), and multivariate analysis confirmed that IR content was the strongest independent predictive factor for disease free survival in breast cancer (Mathieu *et al*, 1997).

1.3.4.1 IGF and IGFBP

In recent years it has become evident that the IGF system plays a role in cancer development and progression (Khandwala *et al*, 2000; Yu & Rohan, 2000; Valentinis & Baserga 2001; LeRoith & Roberts, 2003; Pollak *et al*, 2004). IGFs also play an important role in mediating cell growth, differentiation, and transformation (Xue *et al*, 2007). The IGF system is a complex molecular network which includes two ligands (IGF-I and IGF-II), two receptors (IGF-IR and IGF-IIR), six high affinity binding proteins (IGFBP-1 to -6), and several binding protein proteases. Levels of IGF are influenced by circulating insulin levels which alter the level of IGFBP I and II increasing the bioavailability of IGF (Figure 1.3) (Jones & Clemmons 1995). IGFBP are inversely associated with body fat and insulin (Lukanova *et al*, 2002). Similar to insulin, IGF-I initiates its biological effects by binding to the cell surface receptor IGF-1R, which shares structural and functional

homology with IR (Siddle *et al*, 2001). At high concentrations IGF-1 and insulin can cross react with each others receptors (Jamali *et al*, 2001; Johansson *et al*, 2006). IGF-I activation induces a variety of biological actions that may favour tumour growth including mitogenic, anti-apototic, pro-angiogenic, induction of tumour-related lymphangiogenesis and motogenic (cell movement) effects (Samani *et al*, 2007). In terms of increased tumour invasion, biochemical and functional analyses show that activation of the IGF-IR triggers a loss of epithelial coherence and promotes cell migration which is very relevant for tumour metastases. Researchers from the University of British Columbia's Child and Family Research Institute examined tissue arrays representing 438 cases of invasive breast cancer linked poorer survival in breast cancer to phosphorylation of the IGF-1 and/or insulin receptors (Saxena *et al*, 2008).

1.3.4.2 Hyperglycaemia

Another consequence of insulin resistance is reduced glucose uptake and storage, both of which lead to an elevated blood glucose concentration or hyperglycaemia. Neoplastic cells use glucose for proliferation (Warburg *et al*, 1956), therefore higher circulating glucose concentration may encourage the development of cancer by providing a favourable environment for the growth of malignant cells (Xue *et al*, 2007). Fasting glucose has been associated with increased risk of breast cancer in 3 out of 5 studies reviewed by Xue *et al* with statistically significant effects in two of the studies, although cut-offs for hyperglycaemia were not consistent (Xue *et al*, 2007). Likewise fasting glucose has been associated with increased risk of colorectal cancer (Scheon *et al*, 1999).

1.3.4.3 Diabetes and Cancer Risk

The diabetic population represents an ideal patient group to examine the risk of cancer, due to the simultaneous presence of hyperglycaemia and hyperinsulinaemia that can promote cancer initiation or progression alone or in combination. Diabetes is a chronic disease, with Type 2 diabetes being the most widely studied, all with differing durations of disease, varying level of metabolic control and obesity, different drug treatments and of course possible complications associated with the disease. However, an increased frequency of malignancy has been reported in diabetic patients and has been ascribed to a wide variety of general and local mechanisms.

The risk is increased in both colorectal adenomas and carcinomas in most but not all studies (Elwing 2006, Limburg 2006). The risk is increased in both women and men in

colon and rectal cancer (Larsson *et al*, 2005). In addition to hyperinsulinaemia, hypothesized mechanisms of type 2 diabetes risk include slower bowel transit time and the elevated faecal bile acid concentration often observed in diabetes. A further dimension is that, at least in the case of colorectal cancer (Renehan & Shalet, 2005), there is one study in which the use of therapeutic insulin increased the cancer association with type 2 diabetes (Yang *et al*, 2004).

The risk of breast cancer is also increased in diabetic women, independent of obesity. Several biological mechanisms may be involved, but the effect of insulin on sex hormones abnormalities may be particular relevant to hormone dependent breast cancer. Insulin is an important regulator of Sex Hormone Binding Globulin (SHBG) in the liver. In the hyperinsulinaemic state SHBG is suppressed which increases the levels of bioactive oestrogens (Kaaks *et al*, 2005). IGF-1 stimultes androgen synthesis in the ovarian stroma and testosterone may competitively displace oestrogens from SHBG (Xue *et al*, 2007). Furthermore crosstalk between the IGF-1 signalling system and oestrogen activation has been reported, resulting in a synergistic effct of IGF-1 and oestrogen on the cell cycle signalling cascade and proliferation (Hamelers *et al*, 2003).

Four studies have examined diabetes and oesophageal adenocarcinoma, all report a significant increased risk but the magnitude of risk varied widely, due to a different incidence of diabetes in the controls compared to the general population in three of the studies (Cheng *et al*, 2000; Reavis *et al*, 2004; Rubenstein *et al*, 2005 Neale *et al*, 2009). However one study reported an attenuated increased risk after adjusting for BMI (OR 1.59 reduced to OR 1.32), indicating an effect of diabetes not just due to obesity and its related risk factors like gastro oesophageal reflux disease (GORD) (Neale *et al*, 2009). Also the association was greater for long-standing diabetes than for more recent diagnoses (Neale *et al*, 2009).

1.3.5 Inflammation

Excess adipose tissue has been associated with a chronic state of low grade inflammation (Das 2001; Wajchenberg 2000), which is recognised by elevated CRP levels, commonly present in otherwise healthy centrally-obese people (Visser *et al*, 1999). The level of adipocytokine production from adipose tissue is strongly influenced by immune cell populations present in adipose tissue, the number of which correlate with adiposity

(Donohue *et al*, 2010). The immune cells contributing to chronic inflammation (e.g. macrophages, neutrophils and eosinophils) are involved by producing inflammatory cytokines that may influence the carcinogenesis process (Seruga *et al*, 2008). For example elevated CRP concentrations can be ascribed to the increased expression of interleukin-6 (IL-6) in adipose tissue (Crichton *et al*, 1996) and its release into the circulation (Fried *et al*, 1998). IL-6 is a proinflammatory cytokine that stimulates the production of CRP in the liver (Banks *et al*, 1995). Higher adipose tissue content of IL-6 has been associated with higher serum CRP levels in obese subjects (Bastard *et al*, 1999).

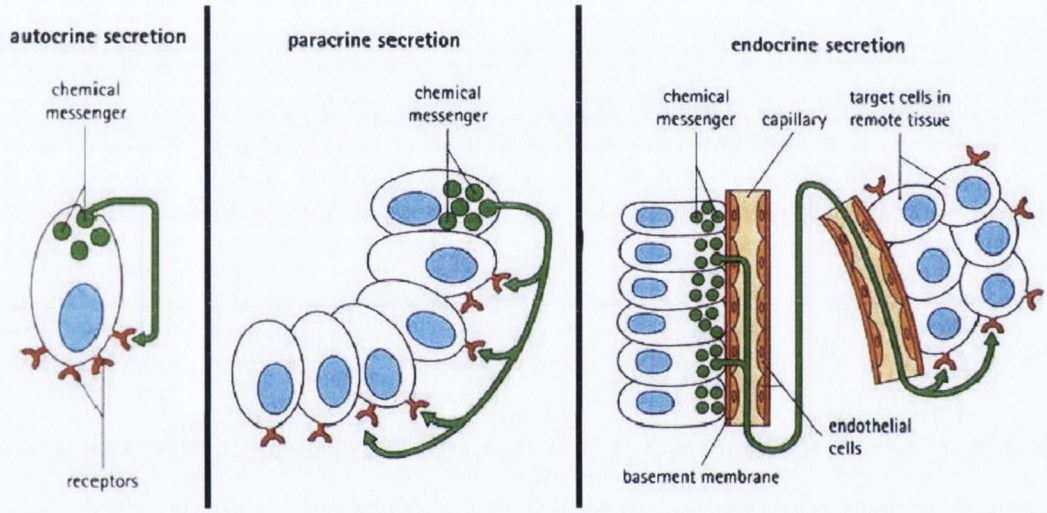
CRP has been recently highlighted as an important prognostic marker in a wide variety of cancers including cancers of the breast (O'Hanlon *et al*, 2002), and colon (Cahlin *et al*, 2008). This may be explained by chronic inflammation promoting carcinogenesis by inducing gene mutations, inhibiting apoptosis, or stimulating angiogenesis and cell proliferation (Kundu *et al*, 2008). Inflammation also induces epigenetic alterations that are associated with cancer development. Two key genes in the inflammatory process, cyclooxygenase-2 (COX-2) and nuclear factor kappaB (NF-kB), may provide a mechanistic link between inflammation and cancer and are potential targets for chemoprevention (Kraus & Arber 2009). NF-kB represents a family of closely related transcription factors and regulates the expression of genes, many of which play important roles in the regulation of inflammation and apoptosis. Its activation has been associated with promoting tumour growth (Karin 2008). COX-2 is key enzyme involved in eicosanoid biosynthesis, with many human cancers exhibiting an elevated prostaglandin (PG) levels owing to upregulation of COX-2 which is overexpressed in a variety of tmours. PGE(2) promotes cellular proliferation and angiogenesis, inhibits apoptosis, enhances invasiveness, and modulates immunosuppression (Arber 2008).

1.3.6 Adipokines

Obesity is, by definition an excess of body fat. Adipose tissue previously thought of as a simple storage sites for triglycerides, is now recognised as a complex endocrine organ that can directly influence tumour growth. Adipocyte conditioned media up-regulate genes involved in invasion, proliferation, angiogenesis and metastasis while simultaneously down regulating tumour suppressors in cancer cells (Iyengar *et al*, 2003). Breast cancer cells treated with adipocyte conditioned media found that adipocyte secreted factors stimulated breast cancer cell (MCF-7) migration and proliferation in vitro when compared

to controls. In vivo, tumours grew to three times the size of controls when co-injected with adipocytes (Iyengar *et al*, 2003). The aggressive growth in tumours is thought to be mediated by production of hormones, cytokines and other proteins with signalling properties collectively termed 'adipokines' that can act by endocrine, paracrine and autocrine mechanisms (Figure 1.4) (Tilg *et al*, 2006).

Figure 1.4: Autocrine, Paracrine and Endocrine Mechanisms of influencing target cells



Adipocytes produce adipokines that can influence tumour growth by its autocrine, paracrine or endocrinesignalling properties. Autocrine signalling is a form of signalling in which a cell secretes a hormone or chemical messenger that binds to autocrine receptors on the same cell, leading to changes in the cell. Paracrine signalling is a form of cell signalling in which the target cell is near ("para" = near) the signal-releasing cell. Endocrine signalling is when the endocrine organ (gland) secretes a type of hormone directly into the bloodstream where it travels to a target tissue and generates a response.

Two of these adipokines 'leptin and adiponectin' are of particular interest in relation to obesity, insulin resistance and the metabolic syndrome, and as participants in the biological mechanisms of carcinogenesis, and the development of invasive and metastatic disease. The metabolic effects and biological activities of leptin and adiponectin at the cellular level are largely in opposition to each other (Table 1.4). Leptin enhances the risk of cancer and its subsequent progression while adiponectin levels demonstrate an inverse association with cancer risk (Vona Davis & Rose 2007).

Table 1.4: Comparison of leptin and adiponectin pathophysiological relationships and effects on cancer biology (Reproduced from: Vona Davis & Rose 2007)

	Leptin	Adiponectin
Obesity	Increased	Decreased
Insulin activity	Reduced insulin sensitivity	Reduced insulin resistance
Type 2 diabetes	Increases risk	Reduces risk
Metabolic syndrome	Hyperleptinaemia	Hypoadiponectinaemia
Tumour Cell growth	Mitogenic	Anti-mitogenic
Tumpour Apoptosis	Reduced	Enhanced
Tumour Angiogenesis	Stimulated	Inhibited
Inflammatory effect	Pro-inflammatory	Anti-inflammatory

This table details the different metabolic effects and biological activities of leptin and adiponectin which are largely in opposition to each other. Leptin enhances the risk of cancer while adiponectin levels are inversely associated with cancer risk.

1.3.7 Leptin

Leptin is secreted by adipocytes in proportion to adipocyte tissue mass (Considine *et al*, 1996). Leptin acts to regulate food intake and increase thermogenesis to promote the use of stored energy (fat). The importance of leptin in regulation of body weight is demonstrated by the observation that a lack of functional leptin, while very rare, results in extreme obesity in humans (Montague *et al*, 1997). Obese patients become resistant to the effects of leptin and consequently become hyperleptinaemic (Cowey & Hardy 2007), with circulating leptin levels ranging from 5 to 10 ng mL^{-1} in normal healthy individuals and up to 40–100 ng mL^{-1} in obesity (Considine *et al*, 1996). High levels of leptin have been associated with glucose intolerance, degree of insulin resistance, type 2 diabetes and increasing number of features of the metabolic syndrome (Fischer *et al*, 2002; Wauters *et al*, 2003; Franks *et al*, 2005). Also leptin or leptin receptor overexpression can be induced by high levels of insulin, oestrogen or IGF-I, the factors that are increased in obese individuals (Lorincz & Sukumar 2006). Therefore leptin could be a mediator of the increased risk of cancer with obesity and metabolic syndrome.

1.3.7.1 Leptin In vitro Studies

At a cellular level, leptin has been found to act as a mitogen, metabolic regulator, with anti apoptotic and pro-angiogenic factors. In vitro studies have shown that leptin can promote cancer cell proliferation in oesophageal adenocarcinoma (OE-33, OE-19) and colonic (HT-29, LoVo) cancer cell lines (Beales & Ogunwobi 2007; Ogunwobi 2006; Hardwick *et al*, 2001; Hoda *et al*, 2007; Somasunder *et al*, 2003). Data on leptin-induced cell proliferation in breast cancer cell lines remains controversial. Some studies fail to demonstrate any effect on cell proliferation in response to leptin treatment (Somasunder *et al*, 2003), while others demonstrate that leptin has a direct effect on the growth stimulation of breast cancer cell lines (MCF-7, T47-D) (Dieudonne *et al*, 2002; Laud *et al*, 2002; Okumura *et al*, 2002; Hu *et al*, 2002; Somasunder *et al*, 2003). Different concentrations of leptin, measurement of cell proliferation, and expression levels of leptin receptor isoforms may contribute to different findings.

1.3.7.2 Serum leptin and cancer risk human studies

Increased plasma leptin levels are associated with colon and breast cancer risk. Serum leptin levels have been shown to be significantly elevated in breast cancer patients

compared to benign breast disease (Han *et al*, 2005) or compared to controls (Tessitore *et al*, 2000, Han *et al*, 2005, Chen *et al*, 2006A), although results are not consistent with no association reported in other studies (Ozet *et al*, 2001, Stattin *et al*, 2004, Sauter *et al*, 2004, Woo *et al*, 2006). Variation in findings may be due to the individual limitations of the studies, mostly with small sizes sample, different timing of screening with respect to fasting, inclusion of pre and post menopausal women which may introduce the additional effect of sex hormones or interact with leptin. In colorectal cancer, two case control studies showed an increased risk of colon cancer in men and women (OR = 2.72) with no association between serum leptin in rectal cancer (Stattin *et al*, 2003; Tamakoshi *et al*, 2005). No studies have examined the association between serum leptin and oesophageal adenocarcinoma risk in vivo to date. In BO, Kendall *et al*. describes a threefold increased risk of BO among men in the highest quartile of serum leptin (OR: 3.3), while one study found no association (Kendall *et al*, 2008).

However, although circulating leptin may exert significant biological effects, the measurement of serum levels alone is one dimensional and the effect of leptin produced locally by adipose cells and infiltrating macrophages, in close proximity to the proliferating tumour cells, may effect cancer progression for example by stimulating angiogenesis (Vona Davis & Rose 2007).

1.3.7.3 Expression of leptin receptor

Leptin exerts its effect through binding to the leptin receptor (Ob-R), six isoforms have been identified (ObRa–ObRf), although studies suggest that only ObRb, which has a long intracellular domain, has full signalling potential (Fong *et al*, 1998). Receptor binding induces activation of different signalling pathways including JAK/STAT (janus kinase signal transducer and activator of transcription), MAPK (mitogen-activated protein kinase, IRS1 and SOC3 (a suppressor of cytokine signaling). Ultimately, Ob-R induction can activate several genes involved in cell proliferation and up-regulate the expression of angiogenic factors, including vascular endothelial growth factor (VEGF) (Sweeney 2002). In breast cancer, significantly higher leptin and leptin receptors expression was found in breast cancer cells compared to benign breast lesions or normal adjacent tissue (Xiang-hou *et al*, 2009), so carcinogenesis could be induced by an overabundance of locally produced leptin. In fact one study reported leptin overexpression in 92% of breast cancers examined and overexpression was significantly associated with increased incidence of distant

metastasis (Ishikawa *et al*, 2004). Leptin overexpression was significantly associated with tumour size and lymph node involvement and pathological stage (Xiang-hou *et al*, 2009). One study assessed the effect of leptin and simultaneous treatment with estrogen and IGF-1 on cell proliferation. It showed that treatment with leptin alone had anti-proliferative effects, which has been shown in other studies but leptin combined with oestrogen or IGF-I had stimulatory effects on tumour cell growth (Lautenback *et al*, 2009).

In colon cancer, a progressive increase in leptin expression through the progression from normal colon (4.5% positive), to adenoma (29.5%) to carcinoma (73.5%) has been reported (Paik *et al*, 2009; Koda *et al*, 2007), suggesting that leptin may have a role in driving this malignant transformation. Leptin receptor (ObR) is associated with earlier-stage tumours, better pathological differentiation and improved patient survival in colon cancer (Uddin *et al*, 2009 Aloulou *et al*, 2008). While data on leptin in oesophageal carcinoma is limited, a small study (n = 4), reported a trend towards increased ObR expression in Barrett's epithelium the precursor to oesophageal carcinoma (Francois *et al*, 2008).

Clearly with the significant in vitro data, leptin appears to favour cancer cell growth locally, and facilitate the invasive potential of cancer cells. More prospective well designed studies are required to assess the clinical significance of elevated levels of leptin in relation to the link between obesity and cancer including crosstalk between leptin and altered metabolic profiles common in obese and metabolic syndrome patients.

1.3.8 Adiponectin

Adiponectin is the most abundant adipocytokine and is synthesized and secreted almost exclusively by adipocytes. Plasma adiponectin levels are inversely associated with various components of the metabolic syndrome including waist circumference, WHR, VAT, BMI (Cnop *et al*, 2003; Park *et al*, 2004; Steffes *et al*, 2004), and degree of insulin resistance (Haluzik *et al*, 2004), with plasma levels decreasing as the number of metabolic syndrome components increases (Ryo *et al*, 2004; Patel *et al*, 2006; Mojiminiyi *et al*, 2007; Santaniemi *et al*, 2006). The degree of reduction in adiponectin is thought to be more closely related to the severity of insulin resistance and hyperinsulinaemia than to the degree of adiposity (Weyer *et al*, 2001; Kern *et al*, 2003) A large prospective study (n=10,275) found a 40% lower risk of type 2 diabetes comparing highest to lowest quartiles of plasma adiponectin levels (Duncan *et al*, 2004). After adjustment for BMI,

serum concentrations are higher in women than in men; they are also are higher in post-menopausal compared with pre-menopausal women (Cnop *et al*, 2003).

Adiponectin can affect many mechanisms relevant to tumour biology; it has an insulin sensitising effect (Yamauchi *et al*, 2003), anti-proliferative, pro-apoptotic (Renehan *et al*, 2008A), and anti-angiogenic effects (Brakenhielm *et al*, 2004) as well as anti-inflammatory effects (Wang et al, 2007). The exact mechanism of tumour inhibition with adiponectin treatment is not clear but probably involves inactivation of MAP kinase 1 and 3, and extracellular signal-regulated kinase (ERK 1 and 2) and concomitant reduced glucose uptake (Dieudonne et al., 2006). Stimulation of apoptosis appears to occur through upregulation of proapoptotic genes (p53 and Bax) and downregulation of antiapoptotic genes (Bcl-2) (Dieudonne *et al*, 2006), while anti-angiogenic actions may occur through the induction of apoptosis in vascular endothelial cells and inhibition of cell migration (Brakenhielm *et al*, 2004).

Adiponectin can act by binding directly to its receptors or indirectly through insulin related mechanisms (Renehan *et al*, 2008A). Its action is more complex than leptin, as there are three major forms of adiponectin: low molecular weight, predominantly found in the circulation, a middle molecular, and a high molecular weight adiponectin making up the majority of intracellular adiponectin (Tilg & Kaser 2009). There are two receptors for adiponectin; AdipoR1 expressed abundantly in muscle and AdipoR2 which is almost selectively expressed in liver (Kelesidis *et al*, 2006). Thus, the biological effects of adiponectin not only depend on relative circulating concentrations but also its form and the tissue-specific expression of its receptor subtypes. The expression of both AdipoR1 and AdipoR2 have been reported in human breast cancer (Pfeiler *et al*,2010) and colorectal cancer cells (Byeon *et al*, 2010; Williams *et al*, 2008; Yoneda *et al*, 2008). In vitro studies have shown that adiponectin may control cell numbers, by inhibition of cell proliferation and enhanced apoptotic activity in breast and colorectal cancer cells (Kang *et al*, 2005; Dieudonne *et al*, 2006; Korner *et al*, 2005; Sugiyama *et al*, 2009). Adiponectin has similar growth suppressing activity on vascular endothelial cells together, which together with inhibition of cell migration results in inhibition of angiogenesis in in vivo models (Brakenhielm *et al*, 2004). Adipokine receptor expression was inversely associated with T-stage progression (characterized by number I – IV), tumour stage, high histological grade and well differentiation of colorectal cancer cells all indicative of how much the cancer has spread or a more advanced tumour (Byeon *et al*, 2010; Baressi *et al*, 2009;

Gonullu *et al*, 2010). Abundant expression of adiponectin receptors in colorectal cancer tissue may facilitate the anticarcinogenic effect of adiponectin; by contrast, low expression levels of adiponectin receptors may promote progression of colorectal cancer by protecting against the effects of adiponectin.

1.3.8.1 Serum levels adiponectin and cancer risk

In contrast to leptin, the epidemiological studies show more consistent (inverse) associations between circulating concentrations and the presence of cancer. In breast cancer, epidemiological studies found a positive association with low adiponectin levels and increased risk of breast cancer, stronger relationship reported in postmenopausal women with no influence of oestrogen receptor (ER) status (Tworoger *et al*, 2007; Chen *et al*, 2006B ; Miyoshi *et al*, 2003; Mantzoros *et al*, 2004). Adiponectin was associated with prognosis in breast cancers, low levels associated with larger tumours of high histological grade consistent with an aggressive phenotype (Miyoshi *et al*, 2003) while Chen et al reported no association with pathological features (Chen *et al*, 2006B). In colorectal cancer, nested data from the Health Professionals Follow-up Study demonstrated that men with low plasma adiponectin levels had a higher risk of colorectal cancer than men with higher levels (Wei *et al*, 2005B), but this was not replicated in a Swedish study (Lukanova *et al*,2006). Activation of AdipoR1 by adiponectin is able to inhibit leptin-stimulated cell proliferation of oesophageal carcinoma cells (Ogunwobi *et al*, 2008), inhibit apoptosis of a Barrett's adenocarcinoma cell line (Konturek *et al*, 2008).

1.3.9 Altered sex hormones in obesity and Cancers

1.3.9.1 Oestrogen and Breast Cancer

Breast cancer is a hormone dependent cancer and one of the most commonly sited mechanisms in the association of obesity with breast cancer is the increased synthesis and bioavailability of oestrogen associated with obesity (Thomas *et al*, 1997). Studies confirm that increased oestrogen levels are linearly related to increasing obesity in postmenopausal women (Key *et al*, 2003, McTiernan *et al*, 2006; Lukanova *et al*, 2004; Madigan *et al*, 1998; Boyapati *et al*, 2004). After the menopause, when the ovarian production of oestrogens has ceased, the circulating oestrogens are synthesized in the stromal cells of the adipose tissue by enzymatic aromatization of the steroid androstenedione to yield oestrone, and subsequent conversion to the more potent oestradiol at various sites (Rose

1993; Bulun *et al*, 1994). This mechanism of oestrogen production can lead to local oestrogen levels in breast tumours that are as much as 10-fold higher compared with the circulation (van Landeghem *et al*, 1985), although this is something that cannot routinely be measured. In addition, tumour necrosis factor alpha (TNF-α) and IL-6 are both secreted by adipocytes and can increase production of aromatase, which is directly related to increased synthesis of oestrogen (Purohit *et al*, 2002). Therfore in postmenopausal obese women both the production of androstenedione and its conversion to oestrone are increased, and there is an elevation in oestrogen concentrations.

Most studies show positive associations between sex hormones and postmenopausal breast cancer risk. One meta-analysis of six prospective studies indicated that women that developed postmenopausal breast cancer had a significant approximate 15% increase of oestrogens compared with those that did not develop the disease (Thomas *et al*, 1997). In a second pooled analysis of nine studies, postmenopausal women whose serum oestrogens and androgens were in the highest quintile were approximately twice as likely to develop breast cancer compared with those in the lowest quintile (Key *et al*, 2002). The same author examined the relationship of body mass index (BMI) with serum sex hormone in respect to breast cancer risk. It reported that adjusting for free oestradiol resulted in the greatest reduction in RR for breast cancer associated with a 5 kg/m^2 increase in BMI from 1.19 (95% CI's: 1.05 to 1.34) to 1.02 (95% CI's: 0.89 to 1.17), and concluded that the increase in breast cancer risk with increasing BMI among postmenopausal women is largely the result of the associated increase in oestrogens, particularly bioavailable oestradiol (Key *et al*, 2003). In the EPIC study postmenopausal women who developed breast cancer had significantly higher total and free oestradiol levels than did controls in blood samples collected 3 years before diagnosis (Kaaks *et al*, 2005). Further analysis by quintiles also showed increased risk of cancer in relationship to increasing serum oestradiol levels (Kaaks *et al*, 2005). Results from the Nurses Health Study indicated that postmenopausal breast cancer risk was increased in women with higher oestrogen levels, particularly with respect to tumours that were classified as both ER and progesterone receptor (PR) positive (Missmer *et al*, 2004).

1.3.9.2 Altered Androgen and SHBG

Obesity is associated with alterations in androgen secretion, transport, metabolism, and action, but behaves differently depending on sex (Pasquali *et al*, 2006). Obese women,

particularly those with the abdominal phenotype, tend to develop a condition of functional hyperandrogenism. Serum testosterone levels have been found associated with breast cancer risk in many case-control and cohort studies (Secreto & Zumoff 1994). In the EPIC study the relative risk of breast cancer among postmenopausal women between the top and bottom quintiles of androgens were almost double (OR 1.69 (1.23–2.33), androstenedione 1.94 (1.40–2.69), testosterone 1.85 (1.33–2.57) and free testosterone 2.50 (1.76–3.55) (Kaaks *et al*, 2005). Adjusting for androgens levels had a neglible effect on increased risk of breast cancer with increasing BMI (Key *et al*, 2003). These results suggest that the contribution of androgens to breast cancer risk is largely through their role as substrates for oestrogen production.

Body fat distribution has been demonstrated to substantially affect SHBG concentrations in obese women. SHBG binds testosterone and oestrogens so changes in SHBG concentrations lead to an alteration of androgen and oestrogen delivery to target tissues (Pasquali *et al*, 2006). In fact, female subjects with central obesity usually have lower SHBG concentrations in comparison with their age- and weight matched counterparts with peripheral obesity (Tchernof & Despres 2000; Pasquali *et al*, 1990). This seems to be partly dependent on higher circulating insulin in abdominally obese women and on the inhibiting capacity of insulin on SHBG liver synthesis (Pasquali *et al*, 2006). SHBG levels were inversely related to risk of breast cancer when comparing upper to lower quintiles of SHBG production (Kaaks *et al*, 2005). Adjustment for SHBG reduced the RR associated with increasing BMI and postmenopausal breast cancer but by much less than adjustment for the oestrogens (Key *et al*, 2003). Therefore, heavier postmenopausal women's increased risk of breast cancer may be related to their having higher oestrogen and possibly testosterone levels and lower SHBG levels compared with leaner women.

1.3.9.3 Tumour Receptor Status in Breast Cancer

Expression of ER, PR, human epidermal growth factor receptor 2 (HER2) alone or together has implications for anti-oestrogen therapy and breast cancer outcomes (Conzen 2008). The Iowa Women's Health Study has shown that postmenopausal obesity was associated with increased risk of hormone receptor - positive breast cancer, whether defined by ER, PR, or joint ER/PR status (Althuis *et al*, 2004). A consistent association between obesity or adult weight gain has primarily being associated with ER-positive tumours (Rose 2004) thus supporting the connection of obesity with elevated oestrogens

promoting tumour development. Overall, ER positivity in breast cancers is related to a good prognosis (Mauri *et al*, 1999), but obesity may negate this biological advantage. A large epidemiological study in Norway found that women with ER positive tumours who were obese prior to their breast cancer diagnosis were significantly more likely to die than lean women with ER-positive breast cancer (Maehle & Tretli 1996).

Further support for the role of oestrogen is the use of pharmacological suppression of oestrogen activity in breast cancer treatment. More recent clinical trials have demonstrated the efficacy of the same approach for breast cancer prevention (Miller 2004; Serrano *et al*, 2004). Weight loss through either caloric restriction or gastric bypass surgery has been shown to lead to a reduction in circulating oestrogens, although the relationship of the amount of weight lost to reductions in serum oestrogens was not always proportional (Berrino *et al*, 2001; Christou *et al*, 2008; Bastounis *et al*, 1998).

The mechanisms through which oestrogen stimulates cell proliferation are believed to be through the activation of ER transcriptional activity and possibly through the direct activation of intracellular signaling pathways such as the MAPK pathway (Lorincz & Sukamar 2006). Another carcinogenic effect of oestrogen includes direct genotoxic effects by increasing mutation rates through a cytochrome P450-mediated metabolic activation and induction of aneuploidy (Kulendran *et al*, 2009).

1.3.9.4 Exogenous Hormones and Breast Cancer

HRT is associated with an increase in breast cancer risk. A meta-analysis of >150,000 women, confirmed that women who had received HRT for >5 years had a relative risk of 1.35 for the development of breast cancer, accruing a 2.3% increase in breast cancer risk for each year of HRT use (Collaborative Group on Hormonal Factors in Breast Cancer 1997; Ewertz *et al*, 2005). The increased risk appeared to be confined to the time during which HRT was used. In the United States, results from the Womens Health Initiative (WHI) randomised trial of oestrogen plus progestin versus placebo demonstrated an increased risk (RR: 1.26) of developing breast cancer 5 years after initiating HRT (Women's Health Initiative 2002). As discussed earlier, reduced incidence of breast cancer has been observed in some countries where HRT use has declined.

Ironically, HRT use has been associated with favourable histology (smaller, lower grade, node negative) and had higher overall survival and disease free survival compared to nonusers regardless of the tumour's ER status (Sener *et al*, 2009; Kumar *et al*, 2007; Reeves *et al*, 2007). Although a clear pathophysiological mechanism cannot be explained, it maybe that HRT users are being followed-up more closely, with more regular mammograms, have an increased awareness of the risk associated with HRT and maybe more vigilant regarding physical examinations.

1.3.9.5 Exogenous Hormones and Oesophageal Cancer

The use of exogenous sex hormones appears to have a different effect of the risks of oesophageal and gastric cancer which was studied in a nested-case control study on 299 women with oesophageal cancer, 313 with gastric cancer, and 3191 randomly selected control women, frequency matched by age and calendar year in the General Practitioners Research Database in the United Kingdom (Lindblad *et al*, 2006). This study concluded that HRT leads to a 50% reduction in womens risk of gastric adenocarcinoma but there was no relationship between HRT and oesophageal adenocarcinoma. However, the lack of such an association does not exclude more complex cellular and molecular interactions that are not detectable in this sort of clinical study.

1.3.9.6 Exogenous Hormones and CRC Cancer

Similar to gastric carcinoma, the use of exogenous sex hormones might be protective for the development of colon cancer; most studies have found a decreased risk of colon or colorectal cancer in relation to ever versus never use of menopausal hormones (Johnson *et al*, 2009). Troisi et al. reported a suggestive, although not statistically significant, inverse association between use of any menopausal hormone therapy and colorectal cancer risk in the Breast Cancer Detection Demonstration Project (BCDDP) (Troisi *et al*, 1997). Results from three meta-analyses suggest a decreased risk of 11% to 20% of colorectal cancer with ever use compared to never use of menopausal hormones, with a stronger association for current use and long duration use (Grodstein *et al*, 1999; Hebert Croteau 1998; Nanda *et al*, 1999).

More recently the different hormone therapy regimens have been examined in relation to risk of colorectal cancer. Randomised clinical trial data from the WHI indicated a

decreased risk of colorectal cancer among estrogen plus progestin users, and no difference in the rates of colorectal cancer among oestrogen alone users (Chelbowski *et al*, 2004; Anderson *et al*, 2004). In contrast a follow up study on the BCDDP, found a statistically significant 17% decreased risk of colorectal cancer among ever users of unopposed oestrogen compared with never users, with the largest risk reduction among current users and among users of ≥10 years duration (Johnson *et al*, 2009). Perhaps a major difference between WHI and BCDDP that could help explain this discrepancy is the shorter follow up period in the WHI (5.6 yrs compared to 15 yrs) and the relatively short duration of hormone therapy in WHI, making it impossible to observe the effects of long-term use of hormone therapy. Similarly a non-significant 22% reduction in colorectal cancer risk among users of oestrogen plus progestin, with sequential regimen users having a larger reduction in risk at 36% compared with continuous users at 25% (Johnson *et al*, 2009).

Several biological mechanisms, via secondary bile acids, insulin-like growth factors, and oestrogen and progesterone receptors, have been postulated for the protective effect of menopausal hormone therapy on risk of colorectal cancer. A comprehensive overview of the biological aspects of hormones on colorectal cancer was recently published by Newcomb and colleagues (Newcomb *et al*, 2008). In brief, the original biological mechanism was proposed in 1980 when McMichael and Potter suggested that increased concentrations of bile acids within the colon may enhance colon carcinogenesis and that exogenous oestrogens and progestins may reduce bile acid production (McMichael & Potter 1980). More recently, epidemiologic research, although inconsistent, suggests a relation between serum IGF-1 and IGFBP-3 levels and colorectal cancer risk. Studies suggest that use of menopausal hormone therapy decreases both IGF-1 and IGFBP-3 levels (Heald *et al*, 2000; Morimoto *et al*, 2005). In addition oestrogen receptors, including ER α and ER β, and progesterone receptors have been identified in colon epithelial cells (Hendrickse *et al*, 1993; Thomas *et al*, 1993). Research indicates that decreasing levels of ER β coincide with the loss of differentiation of malignant colon cells, supporting a protective mechanism of ER β (Bardin *et al*, 2004; Konstantinopoulos *et al*, 2003).

1.3.9.7 Oesophageal cancer and oestrogen

As discussed, adenocarcinoma of the oesophagus is predominantly a male disease with a male to female ratio of 6-8:1 (Vizcaino *et al*, 2002). BO, identified as a potential risk

factor for adenocarcinoma also occurs predominantly in males with a male: female ratio ranging from 2:1 to 4:1 (Sarr *et al*, 1985; Winters *et al*, 1987). Lofdhal *et al* have suggested that the sex difference in oesophageal adenocarcinoma does not seem to be explained by differences in risk factor profile of known aetiological agents such as reflux, obesity *Helicobacter Pylori (H. Pylori)* and tobacco consumption (Lofdahl *et al*, 2008), with a possible protective role of hormones. Lagerghren postulated that either higher oestrogen and/or progesterone levels, lower testosterone or a combination of these may be the reason why women are apparently protected from developing oesophageal cancer (Lagerghren *et al*, 1998). In vivo and in vitro studies suggests that oestrogen may have an inhibitory effect on carcinogenesis in oesophageal cancer, however most studies focused on effects on squamous cell carcinomas and not adenocarcinoma (Chandanos & Lagergren 2009). Some research suggests that ERs might mediate the protective effect on oestrogen in the development of oesophageal cancer. Although the presence of ERs has been shown in oesophageal adenocarcinoma cell lines and in Barrett's oesophagus (Tiffin *et al*, 2003; Liu *et al*, 2004; Kalayarasan *et al*, 2008), data is not consistent with one study reporting oetrogen receptor β status is a potentially useful marker of worsening disease progression (Kalayarasan *et al*, 2008).

A dose-dependent decreased risk of oesophageal adenocarcinoma among those who breastfed compared to those who did not was observed implying a protective role of oestrogen (OR 0.41, 95% CI's: 0.20–0.82), but data was inconsistent for effect of parity. If the hypothesis of oestrogen protection is true, exposure oestrogen and anti-oestrogen therapy might instead effect the risk. One study on the oral contraceptive pill and HRT use reported a decrease in risk while another large study showed no decreased risk (reference). The use of anti oestrogen therapy (Tamoxifen) has been assessed in a large population-based cohort study of 138,885 women with breast cancer, a statistically non-significant 60% increased risk of oesophageal adenocarcinoma was found among women who were exposed to tamoxifen compared to unexposed women (OR 1.60, 95% CI's: 0.83–3.08) (Chandanos *et al*, 2006), with no association with squamous cell carcinoma (SCC). However five other studies with relatively small sample sizes (n<4000) showed exposure to tamoxifen did not have any increased risk of oesophageal cancer (Andersson *et al*, 1991; Fisher *et al*, 1994; Rutqvist *et al*, 1995; Curtis *et al*, 1996; Matsuyama *et al*, 2000).

From the available data, the importance of examining sex steroid hormone levels, their interaction with their receptors, the effect of gender and menopausal state (pre- and post

menopausal) in the different cancer sites may help further elucidate the role of these hormones.

1.4 Obesity and Oesophaeal Cancer - A Unique mechsnism

When considering the impact of obesity and cancer risk, we must also recognise a unique mechanism in oesophageal cancer, wherby increasing obesity may play a mechanical role through increased GORD; secondly pathways through BO may be important, and finally the metabolic alternations involving pro-inflammatory and pro-tumourigenic pathways in obesity, in particular male obesity, may play a key role.

1.4.1 Obesity and GORD

Many studies report a positive association between obesity and GORD (Wilson *et al*, 1999; Jacobson *et al*, 2006; Locke *et al*, 1999; Murray *et al*, 2003; Nilsson *et al*, 2003; Ruhl *et al*, 1999), which remains significant even after adjustment and controlling for the presence of hiatus hernia, smoking, race, gender, family history of GORD, and dietary fat intake (Hampel *et al*, 2005; Jacobson *et al*, 2006; Wilson *et al*, 1999). A recent meta-analysis of obesity and GORD showed that six of nine studies found significant positive associations between BMI and GORD symptoms (Hampel *et al*, 2005). There was a trend towards a dose-response relationship, with an increase in the pooled adjusted OR for GORD symptoms of 1.43 (95% CI's: 1.158-1.774) for BMI between 25-30, and 1.94 (95% CI's: 1.468-2.566) for BMI >30. Six of seven studies found significant associations with erosive oesophagitis (a condition in which areas of the oesophageal lining are inflamed and ulcerated). The pooled adjusted OR for erosive oesophagitis for BMI ≥25 was 1.76 (95% CI's: 1.16-2.68; $p<0.001$). Lagergren and colleagues reported that adenocarcinoma risk was multiplicative with increasing BMI and reflux severity. Among obese people (BMI >30) with reflux symptoms, the OR was 8.8 (95% CI's: 3.2 – 24.2) compared with lean people (BMI <22) without reflux (Lagergren *et al*, 1999).

1.4.2 GORD and Barrett's Oesopagus

The strongest risk factor for adenocarcinoma is BO (Lagergren 2005). Its pathological phenotype is specialised intestinal metaplasia (SIM), the only known precursor lesion for

adenocarcinoma. It is now well established that BO is a complication of severe and long-standing GORD (Winters *et al*, 1987). Subsequent studies confirmed the development of BO following induction of gastro-oesophageal reflux in an animal model (Bremener *et al*, 1970). Pathophysiological studies have shown that patients with Barrett's show a higher proportion of lower oesophageal sphincter failure, and peristaltic dysfunction than patients with erosive oesophagitis and over 90% have an associated hiatal hernia (Stein et al, 1992). However not all GORD patients (approx 20%) develop BO and it's important to look at factors that may influence the development of BO in GORD populations.

It is not known whether adenocarcinoma can develop without passing through the Barrett's stage. The rate at which BO progresses through increasingly severe dysplasia to adenocarcinoma is 30 – 125 times the rate of adenocarcinoma development in the general population (Reed 1988, Van der Veen *et al*, 1989; Drewitz *et al*, 1997; Cameron & Lamboy 1992; Nilsson *et al*, 2003). The low rate of progression presents a significant problem in selecting which patients to include in surveillance programs, and also suggests that other factors may have played a role above increasing reflux in the increasing incidence of distal adenocarcinoma reported over the last 30 years (Sikkema *et al*, 2009). Recently the relationship between obesity, metabolic syndrome and BO has been examined to identigy if they have a role in progression of BO to adenocarcinoma.

1.4.3 Obesity and Barrett's

Research on the association between obesity (as well as body fat distribution) and the presence and length of BO has emerged over the past 5-10 years and points to its role as a strong modifiable risk factor as evidenced by a positive correlation in 7 of 9 recent studies (Edelstein 2007; Veugelers *et al*, 2006; Anderson *et al*, 2007; El-Serag *et al*, 2005; Corley *et al*, 2007A; Smith *et al*, 2005; Stein *et al*, 2005; Vaughan *et al*, 2002). In a retrospective cross-sectional study of 65 cases of BO cases and 385 controls, obesity was shown to be associated with a 2.5 fold increase in the risk of BO – for each ten pound increase in weight, or five-point increase in BMI, there was a 10% and 35% increase in the risk of BO, respectively (Stein *et al*, 2005). In a population-based study of 167 cases of BO and 261 matched controls Smith et al reported that obese people with self-reported symptoms of acid reflux had markedly higher risks of BO (OR 34.4, 95%CI: 6.3-188) than people with reflux alone (OR 9.3, 95%CI: 1.4-62.2) or obesity alone (OR 0.7 95%CI: 0.2–2.4)

(Smith *et al*, 2005). This finding suggests that obesity plays a further role in the development of BO, over and above its role in promoting acid reflux.

1.4.4 Metabolic syndrome and Barrets Oesophagus

No studies have examined metabolic syndrome in oesophageal cancer, but we may gain some insights from the association of metabolic syndrome and BO, the strongest risk factor and only known pre cursor lesion for oesophageal adenocarcinoma. One report in the literature, describes metabolic syndrome and the association with BO (Ryan *et al*, 2008). Nearly half (46%) of Barrett's patients screened (n=102) had MetS and 78% were centrally obese. The presence of the metabolic syndrome was associated with elevated CRP, leptin, and a trend towards decreased adiponectin levels. Central obesity, integral to the metabolic syndrome may be more important than BMI, in the diagnosis and length of BO. El-Serag found that VAT was an even stronger independent risk factor for BO compared to BMI (El Serag *et al*, 2005). The length of Barrett's oesophagus increases the risk for both high-grade dysplasia and oesophageal adenocarcinoma (Hirota *et al*, 1999, Avidan *et al*, 2002). Long segment compared to short segment Barrett's oesophagus was significantly associated with metabolic syndrome (60% V's 24%) and central obesity (92% V 62%), hyperinsulinaemia and increased levels of IL-6. This data suggests that metabolic syndrome and the associated immune-inflammatory state may potentially fuel increased progression of BO, manifested here through length of Barrett's but not dysplasia but this hypothesis requires further study.

1.5 Bariatric surgery, weight loss

The world cancer research fund states that modifiable environmental factors are most important for cancer prevention including obesity. It recommends achieving a normal weight range for the prevention of cancer (WCRF/AICR 2007). Cancer incidence is clearly increased in obese individuals (Renehan *et al*, 2008B) but there is limited research on the effect of voluntary weight loss on cancer incidence, mainly because of the difficulty of achieving long term weight loss and maintenance.

Indirect evidence from cohort studies suggests that intentional weight loss is associated with reduced cancer risk. The Iowa womens health study on 21,707 postmenopausal women found intentional weight loss (>20lbs or 9 kg) was associated with an 11% reduction in all cancer incidence and 14% reduction in obesity related cancer (19% for breast cancer and 9% for colorectal cancer) (Parker *et al*, 2003). To examine the relationship between weight loss and cancer risk, the bariatric surgery patients represent an ideal group, that have demonstrated sustained long term weight loss as well as improvements in other co-morbidities like diabetes and hyperlipidaemia (Sjostrom *et al*, 2004; Buchwald *et al*, 2004).

The Swedish Obesity Subjects was the first prospective intervention trial, measuring anthropometry, biochemical and cardiovascular indicies in both the surgery group (n=2,010) and matched untreated severely obese controls (n=2,037) (Sjostrom *et al*, 2007). It found a 31% decreased overall mortality in the bariatric surgery group (p=0.0102) with cancer the commonest non-cardiac cause of mortality. Adams reports similar reductions of 40% in all cause mortality comparing 9,949 patients who had undergone gastric bypass surgery and 9628 severely obese persons in a retrospective cohort study, with a 60% reduction in cancer-specific mortality (Adams *et al*, 2007).

Recently cancer incidence was examined in an attempt to better understand why mortality was significantly reduced. Sjorstrom found bariatric surgery was associated with reduced cancer incidence in obese women but not in obese men (Sjorstrom *et al*, 2009). Adams found a similar reduction in the incidence of cancer in women only, and a decreased incidence of cancer diagnosed at regional or distant stages, with the apparent protective effect of surgery on risk of developing cancer was limited to cancers likely known to be obesity related (Adams *et al*, 2009). Both of these studies strengthen the case for causality between adiposity and cancer and emphasis the importance of studying the effect of gender. The observation of reduced incidence in women only may simply be due to the small sample size of men (15%) or a more noticeably effect on female hormone sensitive malignancies like breast cancer in the follow-up period, compared to other obesity related cancers such as colon, and oesophageal cancer more common in men as suggested by (Renehan *et al*, 2009). Reduced cancer risk may be attributed to the physiological and biochemical changes directly related to the change in the anatomy of the GI tract which may affect intestinal function. The intestinal microbiota have been proposed as a potential overlooked environmental factor that increase energy yield from diet, regulate peripheral

metabolism, increase body weight and cause obesity, with interesting results in animal studies but not in humans (Vrieze *et al*, 2010).

1.6 Obesity as a risk factor for postoperative complications

Surgery is the most effective treatment in eliminating most types of cancer before it metastasis to lymph nodes or distant sites. As obesity is associated with increased risk of cancer, it is inevitable that an increasing percentage of surgical oncology patients will be obese. Obesity has long been considered a risk factor for adverse post-surgical outcomes (Flancbaum & Choban 1998). A combination of factors, including the association of obesity with existing co-morbidities and medical complications, the complexity and duration of anesthesia and surgery, as well as metabolic disturbances like insulin resistance, hormonal and adipokine alterations, and chronic inflammation (Balkwill & Mantouras 2001), all permit the speculative thesis that obesity may increase the incidence of complications. There is some evidence that obese patients cannot effectively use their abundant fat stores as a fuel source for the acute phase response to surgery, a small study (n=17) showed obese patients preferentially oxidized proteins and carbohydrates in response to trauma or injury and had significantly lower rates of lipolysis compared to non obese patients (Jeevanandam *et al*, 1991). The consequence of excessive loss of protein and lean body mass may be associated with reduced muscle, immune and pulmonary function and increased mortality as seen in undernourished patients (Arora *et al*, 1982; Tellado *et al*, 1989).

1.6.1 Obesity and Mortality

Obesity has been associated with increased risk of mortality in critically ill trauma patients in some (Byrnes *et al*, 2005; Choban *et al*, 1991; Neville *et al*, 2004) but not all studies. Two large studies (n ~1150), on critically ill trauma patients found obesity was an independent risk factor for mortality (OR 1.6; 95% CI's: 1.0-2.3; P=0.003) (Brown *et al*, 2005), and obese patients were 7.1 times more likely to die in hospital after adjusting for other factors including diabetes, gender and age (Bochicchio *et al*, 2006). Other studies examining the influence of obesity on post-surgical mortality have failed to show any association (Kuduvalli *et al*, 2003; Mullen *et al*, 2008; Reeves *et al*, 2003). A large prospective cohort multi centre study carried out on 2258 patients undergoing major intra-

abdominal cancer surgery, including oesophagogastric, hepatic, pancreatic and rectal resections revealed that, after adjusting for other risk factors, obesity (BMI >30 kg m-2) was not a risk factor for mortality (Mullen *et al*, 2008). Similar results have been reported in patients undergoing coronary artery bypass graft (CABG) (Kuduvalli *et al*, 2003; Moulton *et al*, 1996), and a large meta analysis (n=85,048) on bariatric surgery patients report <1% 30-day to 2-year mortality rate (Buckwald *et al*, 2007).

1.6.2 Obesity and Post operative morbidity

The risk of surgical morbidity is multifactorial dependiung on type and severity of operation, the experience of surgeon, pre operative nutritional status and albumin to name a few. In the developed world, major morbidity complicates between 3% and 21.9% of surgical procedures (Gawande *et al,* 1999; Kable *et al*, 2002). For example the morbidity for colorectal cancer surgery is reported att 18-38%, generally higher in rectal cancer (Flancbaum & Choban 1998; Brooks-Brunn *et al,* 1997), but lower than morbidity for oesophageal cancer surgery reported at levels as high as 50% with further evidence suggesting that these risks may be further increased by neoadjuvant therapy, in particular combination chemotherapy and radiation therapy (Bailey *et al,* 2003; Fiorica *et al,* 2004; Reynolds *et al,* 2006B). Mortality is estimated to be 10 times higher for oesophageal cancer compared to colorectal cancer (10% and 1% respectively) due to the complexity of the surgery and perhaps increased complication rate. As large studies in these two cancers are lacking, other surgical populations will be reviewed to assess the effect of obesity on morbidity and mortality. However, it's important to recognise the limitations of these studies, most commonly the problem of small sample sizes, especially considering the small number of patients at the highest BMI categories and the limited number of events (complications and deaths) to be analysed. Studies are also limited by their single-institution, retrospective designs with limited patient follow-up. Some studies include large numbers of patients undergoing low-risk surgery in which the impact of BMI on outcome is least likely to be demonstrated. Some of the more specific complications associated with obesity like respiratory, wound and infectious complications are reviewed below and summarised in Table 1.6.

1.6.3 Respiratory Complications

Obesity causes or exacerbates many health problems, both independently and in association with other diseases. In addition to the obesity-related pulmonary disorders of sleep apnoea and hypoventilation syndrome, obesity is also associated with decreased vital capacity, decreased functional residual capacity and decreased forced expiratory volume (FEV1) (Harik-Khan *et al*, 2001; Jenkins *et al*, 1991; Canoy *et al*, 2004). While some studies have identified overweight and obesity as a risk factor for post-operative pneumonia, atelectasis and pulmonary embolism (Eichenberger *et al*, 2002; Merkow *et al*, 2009; Brooks-Brunn 1997; Hall *et al*, 1991), other studies have found no association between overweight and obesity and post-operative respiratory complications (Moulton *et al*, 1996; Mullen *et al*, 2008, Benoist *et al*, 2000).

1.6.4 Wound Complications

Wound dehiscence (opening of a wound along surgical suture) and wound infection are serious complications following surgery and are associated with increased morbidity, mortality and increased hospital stay (Pavlidis *et al*, 2001; Choban *et al*, 1997; Mangram *et al*, 1999; Graham *et al*, 1999, Doyle *et al*, 2009). A number of different explanations for why obesity is a risk factor for wound infection have been postulated, the avascularity of adipose tissue leads to hypoperfusion and decreased oxygen tension which may result in suboptimal neutrophil oxidative killing at the site of surgery in obese and increase the risk of infection (Anaya & Dellinger 2006). Unadjusted dosing of antibiotics in obese may leads to inadequate tissue drug levels, may predispose obese patients to surgical site infections (Milano *et al*, 1995). Insulin resistance (Reaven *et al*, 1988) and deranged glucose metabolism is associated with an increased risk of wound infection and impaired wound healing, recent data indicate that tight glucose control can reduce the incidence of postoperative mortality and morbidity, including wound infection (Patel *et al*, 2008). Obesity can increase the risk of wound dehiscence directly by increasing tension on the fascial edges at the time of wound closure, and indirectly by increasing the risk of wound infection which is also a risk factor for dehiscence (Derzie *et al*, 2000; Webster *et al*, 2003). Studies investigating risk factors for wound dehiscence have both supported (Merkow *et al*, 2009, Pavlidis *et al*, 2001; Riou *et al*, 1992) and opposed (Mäkelä *et al*, 1995) the hypothesis that obesity increases the risk of wound dehiscence (Doyle *et al*, 2009). The evidence that obesity is a risk factor for wound infections is more consistent, with a higher incidence of infection commonly reported post orthapedic surgery

(Karunakar *et al.* 2005, Namba *et al.* 2005) and higher rate of sternal wound infections and mediastinitis post CABG (Loop *et al*, 1990; Ridderstolpe *et al*, 2001; Lu *et al*, 2003) and wound infections post pancreaticoduodenectomy (House *et al*, 2008). In a recent study carried out by Merkow *et al*, the impact of BMI on short-term outcomes after colectomy was assessed in 3202 patients using prospectively collected data. Morbidly obese patients (BMI >35 kg m-2) were 2.6 times more likely to incur a surgical site infection, superficial or deep, and 3.5 times more likely to experience wound dehiscence (Merkow *et al*, 2009).

1.6.5 Infectious Complications

There is a large body of evidence to suggest that obesity increases the risk of post-operative infection. In a study of 849 patietns, Choban et al. found a lower incidence of nosocomial infections (wound infections, C diff, pneumonia, bactraemias) in the normal weight group compared to the obese group (0.5 V's 2.8%) and the severely obese group (4.3%) (Choban *et al*, 1995). Similar findings were reported in a study of 395 surgical patients by Canturk *et al.*, with significantly more infections occurring in obese patients compared with normal-weight patients (P <0.05) (Canturk *et al*, 2003). Severe obesity (>40kg/m2) was an independent risk factor for catheter-related (OR 2.2; CI: 1.5-3.4) and other blood stream infections (OR 3.2; CI: 1.9- 5.3) in an ICU setting (Dossett *et al*, 2009).

1.6.6 Visceral obesity and risk of post operative complications

Studies assessing the extent to which obesity (BMI) affects surgical risk have not produced consistent results, an emerging thesis is that central (visceral) adiposity is more strongly related to obesity related metabolic abnormalities, and may reflect a more sensitive measure of the adverse consequences compared to BMI which does not distinguish lean and fat mass (Schoen *et al*, 1999; Pischon *et al*, 2006). In a study of 133 patients classified as obese using BMI >25 kg m^2 and visceral fat area, obesity was associated with a significantly higher incidence of wound infection, overall complication rate and hospital stay post laparoscopic colectomy for sigmoid colon cancer, but no relationship was observed with BMI alone (Tsjinaka *et al*, 2008). Systemic complications were significantly more frequent in visceral obese patients defined using BMI >25kg/m2 and WC (>85cm male; >90cm female) compared to non visceral obese patients (19.0% vs. 3.9%, P=0.036), and visceral obesity was the only significant independent risk factor (odds ratio 8.1, P=0.018) (Nitori *et al*, 2009). In another study CT assessment of intra-

abdominal and subcutaneous fat levels in 139 gastric and colorectal cancer patients found a 10 fold increased risk of surgery-related complications in patients with excess intra-abdominal and subcutaneous fat (Tsukada *et al,* 2004).

Table 1.5: Summary of studies examining the impact of obesity on adverse post-operative outcomes

Author, Year	Study Design	Subjects	Results
General surgical procedures			
Kuduvalli *et al*, 2003	Retrospective	n = 4713 coronary artery bypass surgery patients	BMI >30 kg/m^2 associated with atrial arrhythmia and sternal wound infections BMI >35 kg/m^2 associated with atrial arhythmia and sternal wound infections, harvest site infections, prolonged mechanical ventilation and longer hospital stay
Zacharias *et al*, 2005	Retrospective	n = 8051 cardiac surgery patients	BMI >30 kg/m^2 and BMI >35 kg/m^2 associated with atrial fibrillation BMI >30 kg/m^2 associated with atrial fibrillation
Dossett *et al*, 2009	Prospective	n = 2,037 ICU Ward	BMI >30 kg/m^2 was an independent risk factor for catheter-related and other blood stream infections
Brown *et al*, 2005	Retrospective	n = 1,153 Critical injured blunt trauma patients.	Obese patients suffered more complications ($p = 0.002$). longer stays in the hospital mechanical ventilation increased mechanical ventilation
Choban *et al*, 1995	Retrospective	n = 849 General surgery	BMI 27-31 kg/m^2 and BMI > 31 kg/m^2 was associated increases in the number of nosocomial infections
Brooks Braun 1997	Retrospective	n = 400 Abdominal surgery	BMI>27 kg/m^2 was associated postoperative pulmonary complication
Cantürk *et al*, 2003	Retrospective	n = 395 Surgical patients	Increase in the total number of nosocomial infections ($p < 0.05$
House *et al*, 2008	Retrospective	n = 356 Pancreatico duodenectomy	BMI >30 kg/m^2 was associated with wound infections. $p = 0.01$ Visceral fat area was associated with complications $p = 0.01$and postoperatively, pancreatic fistula $p = 0.01$

Author, Year	Study Design	Subjects	Results
Cancer specific surgery			
Merkow *et al*, 2009	Retrospective	n = 3202 colectomy patients	BMI >30 kg/m^2 associated with pulmonary embolism BMI >35 kg/m^2 associated with pulmonary embolism, surgical site infection, wound dehiscence and renal failure
Mullen *et al*, 2008	Prospective	n = 2258 abdominal cancer surgery patients	BMI >30 kg/m^2 and >35 kg/m^2 associated with increased morbidity but not mortality or major complications
Benoist *et al*, 2000	Retrospective	n = 584 colorectal resection	BMI>27 kg/m^2 associated with postoperative intra-abdominal collections requiring treatment and anastomotic leakage
Tsukada *et al*, 2004	Prospective	n = 139 gastric or colorectal cancer	Intra-abdominal and subcutaneous fat was associated with medical complications (pneumonitis or arrhythmia) and surgery-related complications (anastomotic leakage, intra-abdominal collections, or abdominal wound infection)

BMI: Body Mass Index

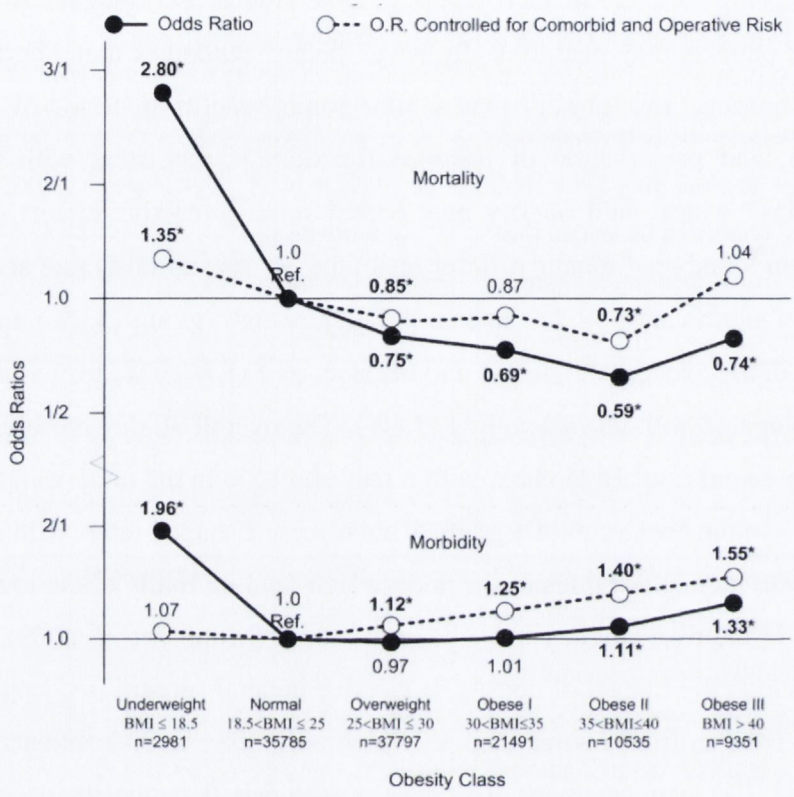
This table presents a summary of the different studies assessing impact of obesity on adverse post-operative outcomes. It describes the study design, the number of subjects and the type of surgery performed and any relevant results focusing on complications associated with obesity like respiratory, wound and infectious complications. The studies are divided according to general surgical procedures and cancer specific surgeries.

1.6.7 Obesity Paradox

Other than an increased risk of wound complications, several studies have failed to demonstrate an increased risk of death or severe complications in obese patients undergoing surgery. In fact, recently some studies have suggested that overweight and obese patients may paradoxically have "better" outcomes than "normal" weight patients. This concept, that obesity may confer some benefits in terms of adaptive response to stress, and preservation of immune function, is consistent with a described "obesity paradox" where mild obesity may confer some protective effects (Mullen *et al*, 2009). Mullen found no dramatic differences in the 30-day mortality rate according to BMI class, with a significantly higher rate in the underweight group (5.0%) and significantly lower rates in the overweight (1.3%) and obese class I (1.2%), II (1.0%) and III (1.2%) patients, as compared with normal weight (1.8%). The overall 30-day morbidity rates were highest at the extremes of BMI class, with a rate of 19.5% in the underweight group and a rate of 13.8% in the obese class III group. This reverse J shaped relationship is depicted in Figure 1.5 with the highest rates in the underweight and morbidly obese extremes and the lowest rates in the overweight and moderately obese (Mullen *et al*, 2009). Another large study examining the impact of obesity in elective general surgery is a single institution study of 6336 patients from Switzerland, in which only 808 (12.8%) patients were obese and only 110 (1.7%) patients morbidly obese, concluded that obesity of any degree is neither protective of, nor a risk factor for, death or complications in patients undergoing elective general surgery.

Figure 1.5: Morbidity and Mortality for general surgery patients

(Reproduced from Mullen et al, 2009 – Data from 121 medical centres)



* $p < 0.05$ for Odds ratio different than 1.0.

This graph represents a comparison across BMI Categories of 30 day mortality and morbidity in 118,707 patients undergoing non-bariatric general surgery. Normal BMI class patients are used as reference. The graph shows the unadjusted odds ratios and the odds ratios adjusted for over 30 significant co-morbid and operative risk factors. It demonstrates a reverse J shaped relationship between BMI and surgical outcomes with the highest rate of morbidity and mortality observed in the underweight and extremes of obesity (Class III Morbid Obesity, Mullen et al, 2009).

1.6.8 Undernutrtion and morbidity and mortality

There is no doubt that protein energy under-nutrition has serious implications for health. Underweight patients undergoing major intra abdominal cancer surgery have a nearly 2-fold increased risk of morbidity and a 3 fold increased risk of mortality compared with normal weight patients (Mullen *et al*, 2009). In addition, associations have been reported between degree of pre operative weight loss and increased post operative complications (Heys *et al*, 2005) and post operative mortality and reduced survival (Zacharakis *et al*, 2010). In the elderly, stable body weight is a predictor of lower subsequent mortality while weight loss is associated with increased mortality, particularly short-term weight loss, possibly reflecting underlying disease effects (Sullivan *et al*, 2002). Mortality has been shown to be up to 8 times higher and dependency at discharge up to 3 times more frequent (Sullivan *et al*, 1999).

There are several techniques used to detect malnutrition; Malnutrition Universal Screening Tool (MUST) (Elia 2003), Subjective Global Assessment (SGA) (Detsky *et al*, 1987A), Nutritional Risk Index (NRI) (Buzby *et al*, 1988), Mini Nutritional Assessment (MNA) (Guigoz & Vellas 1997), anthropometric measurements, serum albumin, prealbumin, lymphocyte count to name a few. It's estimated that approximately one third to half of patients are undernourished on admission to hospital, and that nutritional status worsens during the course of hospitalisation. In a recent study by the British Association of Parenteral and Enteral Nutrition (BAPEN), 28% of patients (5089 patients) screened on admission to hospital in the UK were found to be at risk of malnutrition (Russell & Elia 2008). In Europe, data collected on Nutrition Day 2006 which included 21,007 patients from 325 hospitals in 25 countries showed that on average 27% of patients were considered to be at nutritional risk, with 42% in the UK at risk (Schindler *et al*, 2010). Cancer patients, depending on the tumour type, are of course most likely to have suffered a recent weight loss, weight loss occurs in 30–80% cancer patients and is severe (with loss of >10% of the initial body weight) in 15% of patients (Dewys *et al*, 1980; Chute 1985; Wigmore *et al*, 1997; Russell & Elia 2008). Weight loss is usually the combined result of reduced dietary intake due to cancer anorexia, the direct and indirect tumour effects, surgery, chemotherapy and physiological factors (Naber *et al*, 1997; Barrera *et al*, 2002). In the French Comprehensive Cancer Centres, one in three cancer patients were malnourished (Pressoir *et al*, 2010). Interestingly pre-existing obesity was identified as a risk factor for malnutrition in the cancer patient population, perhaps because of a

misidentification, reduced awareness or a delay in nutrition support in this category of patients (Pressoir, *et al*, 2010).

Although the pathogenesis of under-nutrition and cancer cachexia is a complex multi-factorial process, the consequences of under-nutrition are widely acknowledged (Tucker & Miguel, 1996). Nutritional depletion is associated with changes in body composition, tissue wasting and impaired organ function, poor wound healing, increased risk of infection, depressed immune system, prolonged length of hospital stay and an increase in morbidity and mortality (McAtear 1999; Davies & Bristow 1999). The importance of nutritional depletion as a major determinant of the development of postoperative complications has subsequently been confirmed in many studies (Table 1.7), summaries some of the studies that link poor nutritional status with outcomes.

The adverse effects of post operative complications can result in longer post operative recovery times and longer length of hospital stay which has implications for healthcare costs and of course reduce patient's quality of life (Marín Caro et al 2007). In view of this, ensuring adequate nutritional intake has been a major focus of perioperative care recently. Research has focused on the methods of delivering nutritional support, their comparative clinical benefits, and modulation of patients' perioperative immune function to minimize the metabolic changes associated with surgical trauma and reduce post operative infectious complications.

Table 1.6: Summary of studies examining the impact of undernutrition on adverse post-operative outcomes

Author	Subjects	Method of Assessment	Clinical Outcome
Busby *et al*, 1980	Elective GI Surgery N=100	Prognostic Nutritional Index	Increased post-op complications, sepsis Increased mortality
Haydock & Hill 1986	General Surgery N=66	% WT loss, BMI, MAC, TSF, Alb, Transferrin	Impaired wound healing
Detsky *et al*, 1987B	GI Surgery N=202	SGA	Increased risk major post-op complications
Sagar & MacFie 1994	Cardiac surgery N=936	BMI	Increased risk of major and septic complications
Giner *et al*, 1996	Intensive Care	Alb, weight:height ratio	Increased complications, Increased length of stay Reduced discharge
Van Nes *et al*, 2001	Geriatric Patients N=1145	MNA	3-fold Increase in-hospital mortality Increased length of stay.
Middleton *et al*, 2001	N=819	SGA	Increased length of stay Decreased one yr survival
D'Alegría 2008	Hospitalised Pts N= 350 (n=134 cancer diagnosis)	SGA MAC, TSF, BMI	Increased post operative complication and mortality
Pressoir *et al*, 2010	French Comprehensive Cancer Centres N=1545	BMI , WT loss	Increased mortality Increased antibiotics use
Garth *et al*, 2010	elective upper GI or CRC surgery N=95	Pre-op WT loss, Alb, time to achieve adequate nutrition post surgery	Increased length of stay Increased risk of complications

Legend WT, weight ; BMI Body Mass Index; MAC Mid Arm Circumference; TSF Triceps Skinfold Thickness; Alb Albumin; SGA Subjective Global Assessment; MNA mini nutritional Assessment; Pre-op Pre operative; GI Gastro intestinal ; CRC colorectal cancer; post-op Post operatively.

Table 1.6 summarizes some of the studies that link poor nutritional status and adverse post-operative outcomes. It describes the number and type of subjects, how undernutrition was assessed or defined, and the impact on clinical outsome specifically postoperative morbidity and mortality.

1.7 Specific Aims and Objectives of this PhD

This thesis describes several studies of the impact of obesity on different cancers – oesophageal, breast and colorectal cancer - from its' aetiology, factors linked to progression of cancer and treatment outcomes. Despite epidemiological evidence, the precise biological mechanism by which obesity increases the risk of cancer remains unknown, there is an intriguing potential link relating to altered metabolic, endocrine and immuno-inflammatory effects of obesity and the alterations they induce. The hypothesis of this thesis is that patients with excess total body fat (obesity), and specifically the subgroup of individuals with an excess of intra abdominal or visceral adipose tissue is at substantially higher risk of being characterised by insulin resistance and by the features of metabolic syndrome and this has an adverse impact on cancer incidence, clinico – pathological tumour features, morbidity, mortality and survival.

The aims and objectives of individual chapters are summarised below:

Chapter 3

To retrospectively examine obesity as a risk factor for postmenopausal breast cancer in Irish patients diagnosed and treated at a major teaching hospital since 2001

- Calculate the odds ratio for postmenopausal breast cancer if above the normal BMI range;
- Correlate pathological features/aggressiveness of tumour with overweight/obesity at time of surgery;
- Study the effect of obesity (at the time of diagnosis) on survival.

Chapter 4 and 5

To further examine the role of obesity in cancer aetiology by determining the incidence of metabolic syndrome, hormonal abnormalities and adipocytokine levels in prospective study on breast and colorectal cancer patients.

- To assess if the clustering of these altered risk profiles (central obesity, hypertension, and raised plasma glucose, triglycerides and HDL cholesterol) in the diagnosis of the 'metabolic syndrome' establishes a cumulative risk for cancer and fuels cancer progression;

- The relevance of metabolic syndrome to the biology and adverse clinico-pathological features (tumour stage, tumour size, lymph node involvement, metastasis, lymphovascualur invasion) of breast and colorectal cancer will be assessed in an Irish population;
- To directly measure visceral, subcutaneous and total fat using computed tomography;
- Provide Irish data on the incidence of hormonal abnormalities, adipocytokine levels and add to our understanding of adipose tissue as a regulatory organ which may help to identify future treatment targets.

Chapter 6 and 7

To examine if obesity impacts on operative risk especially morbidity or mortality associated with the management of localised adenocarcinoma and colorectal cancer.

- To compare the incidence of minor, major, respiratory, wound complications across the BMI categories;
- To correlate pathological features/aggressiveness of tumours with overweight/obesity at time of surgery;
- Study the effect of obesity (at the time of diagnosis) on overall survival in different genders and different anatomical cancer sites in a cohort of Irish cancer patients treated with curative intent.

Chapter 8

To identify if obesity and the metabolic syndrome represents a modifiable (environmental) risk factor that is associated with the development of specialized intestinal metaplasia (SIM) or Barrett's Oesophagus in patients who have GORD.

- To compare the incidence of central obesity, metabolic syndrome, inflammation and insulin resistance in BO patients compared to those patients who have GORD.

CHAPTER 2

METHODOLOGY.

2.1 Introduction

The study and method of patient selection and other details for each study is described in the relevant chapter (i.e. **Chapter 3:** Obesity increases the risk of postmenopausal breast cancer and is associated with more advanced stage at presentation but no impact on survival; **Chapter 4:** Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer; **Chapter 5:** Metabolic syndrome and leptin are associated with adverse pathological features in male colorectal cancer patients; **Chapter 6:** Pathological features in male colorectal cancer patients impact of obesity on outcomes in the management of localised adenocarcinoma of the oesophagus and oesophagogastric junction; **Chapter 7:** Impact of obesity on surgical and oncological outcomes in the management of colorectal cancer; **Chapter 8:** Lack of differential pattern in central adiposity and metabolic syndrome in Barrett's oesophagus and gastro-oesophageal reflux disease.

The methods common to most studies are described in this chapter.

2.2 Ethical Approval

Ethical approval was obtained form the Joint research ethics committee of St James's and the Federated Dublin Voluntary Hospitals for the prospective studies presented in chapter 4, chapter 5 and chapter 8. The study was explained to patients in detail and any questions were answered. Each volunteer willing to participate signed the consent form or a relative if the patient was unable to give informed consent, before the measurements were made. Copies of the approval and consent forms for each study can be found in Appendices.

2.3 Recruitment Procedure

This is explained in more detail in the individual chapters. For the prospective studies, potential patients for recruitment were obtained from the Cancer Co-ordinators (Nurse Specialists), by attending the multidisciplinary meeting where new cases and treatment plans are discussed by contacting admissions department and the patient theatre lists for scheduled surgeries. Medical charts were screened for inclusion /exclusion criteria, as well as details about medication use, past medical history, alcohol and tobacco use (Case Report Form Appendix IV).

2.3.1 Patient Analysis and Tracking System

The medical and histopathology records of the cancer cases are routinely recorded on a computerised Cancer Database (Patient Analysis and Tracking System [PATS] ™, Dendrite Clinical Systems, UK). This system is used to record all patient details, presenting symptoms, results of diagnostic tests, cancer treatment, tumour pathologies and postoperative complications for patients. The information available on PATS was mainly used for the retrospective studies presented in chapter 3, chapter 6 and chapter 7. Anthropoemtric information on PATS (weight and height) is sourced from the patients medical chart recorded on admission to hospital, or as standard while undergoing pulmonary function tests, or on initiation of chemotherapy and some was entered as part of a previous audit of from dietetic records.

2.4 Anthropometry

2.4.1 Weight and Segmental Body Composition Analysis

To minimize variability, all anthropometric measurements were taken by the same investigator throughout the study, as was practically feasible. Weight was measured using a high specification digital scale (Tanita BC-418 MA) with a maximum weighing capacity of 200kg (Tanita UK Ltd, Middlesex, UK). The scale uses a single-point load cell weighing system in the scale platform to guarantee absolute precision and up to 300, 000 uses before calibration. No Calibration was required during the study period.

The weighing scales was placed on a level fixed surface in a room with adequate space and lighting, plugged into the power using the AC adaptor and powered on. The subject's height and age were entered into the Tanita scales using the computer interface (Bi-Directional RS-232C) (Figure 2.1). All subjects were asked remove their shoes and socks, any heavy clothing and remove any items from their pockets. The scales has a choice of adult and athlete mode, for the purpose of these studies the adult mode was always chosen. Subjects were asked to stand facing forward in their bare feet placing their ball of the foot on the silver foot panels, while taking both hand grips in their right and left hands, holding them with their hands hanging loosely by their sides.

The Tanita scales provides a weight and a complete body composition analysis in less than 30 seconds using the platform-based 8 polar electrode system to calculate regional body composition with separate body mass readings for the right arm, left arm, trunk, right leg

and left leg. It also has an in built thermal printer to print out a complete body composition profile in seconds (Appendix): including Weight (kg to the nearest 0.1kg), Body Fat Percentage (Range 1-75% to the nearest 0.1%), Body Mass Index (BMI), Body Fat Mass, Fat Free Mass, Total Body Water (to the nearest 0.1kg) and Basal Metabolic Rate (1kJ unit or 1kcalL unit). Basal Metabolic Rate is calculated using Tanita's proprietary formula and takes into account Fat Free Mass, as well as weight and age. All subjects were weighed once on each weighing occasion.

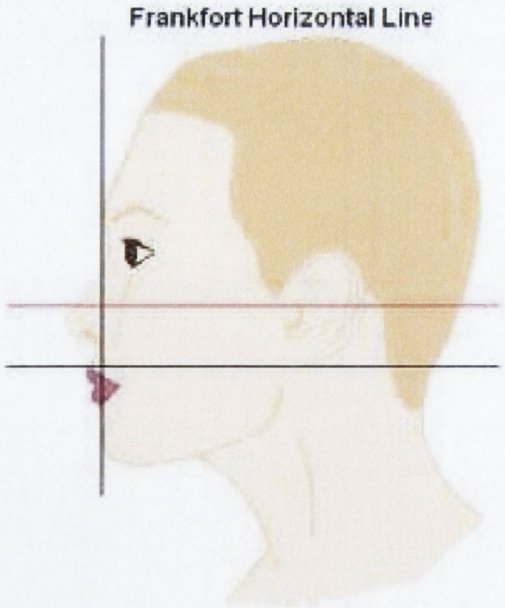
Figure 2.1: Tanita BC 418 Segmental Body Composition Analyser

The Tanita scales as seen above provides a weight and a complete body composition analysis using the platform-based 8 polar electrode system (two sensors for each hand and foot respectively), to calculate regional body composition (Body Fat Percentage, Body Fat Mass, Fat Free Mass, Total Body Water) with separate body composition readings for the right arm, left arm, trunk, right leg and left leg.

2.4.2 Height

In the prospective studies height was measured to the nearest mm with a Seca portable stadiometer (SECA Ltd, London, UK). All subjects removed their shoes and socks and stood facing forward with feet flat on the base plate, with heels against the back the plate, back as straight as possible and arms hanging freely at the sides. The head plate was lowered to just above the subject's head, which was then carefully positioned with no additional extra pressure so that the Frankfort plane was horizontal, in order to extend the participant to maximum height. This is a standard plane used for the correct orientation of the head. It is established by a line passing through the tragion (front of the ear) and the lowest point of the eye socket (Figure 2.2). A reading was taken to the nearest mm. Although there is a well-recognised diurnal variation in height (Werther, 1998); a person is tallest on rising in the morning and shrinks during the day as the spine becomes compressed. As it was impossible to measure all subjects at the same time of the day, it is unlikely that it affected the classification of BMI.

Figure 2.2: Frankfort Plane for measuring Height

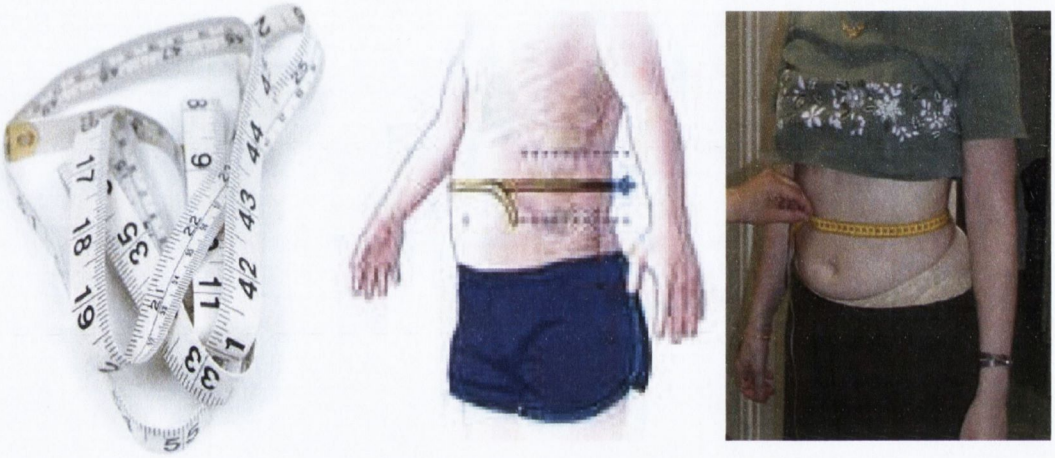


To determine the Frankfort Horizontal Line (red horizontal line), an imaginary line is drawn horizontally from right at the supratip to above the auricular canal, right above the tragus.

2.3.3 Waist Circumference

Waist circumference was measured directly on the skin, at the midpoint between the supra iliac crest and lower ribs margin (Figure 2.3) at the end of a normal expiration. Measurements of body circumferences were made with a plastic insertion tape measure (Lasso, Child Growth Foundation, London, UK). All waist circumference measurements were made to within 0.1cm.

Figure 2.3: Measurement of Waist Circumference



2.3.4 Body Mass index

BMI was computed as weight in kilograms divided by height in meters squared (kg/m2). BMI was defined using the World Health Organisation definitions, with a BMI of 20–24.9 kg/m^2 normal, overweight 25–29.9 kg/m^2, and obese >30 kg/m^2.

2.5 Blood Biochemistry

Blood samples were taken by a trained phlebotomist (Laura Healy) after a 12-hour overnight fast. Blood samples were obtained by venupuncture after minimal compression with a tourniquet. Blood collected for determination of plasma concentration of glucose (fasting) were collected in tubes containnig fluoruide oxalate; HbA1c, total-, HDL- and LDL- cholesterol, triglycerides collected in lithium coated tubes, fasting insulin levels, inflammatory markers (C reactive protein (CRP) and serum amyloid A (SAA)) and hormone samples (Oestrogen, Progesterone, Testosterone SHBG, Adipokines) in red

serum tubes. Tubes were inverted 8-10 times to ensure that the coagulant was mixed throughout. Samples taken for future determination were centrifuged at 3000rpm for 10 min at 4 degrees. Serum and Plasma was immediately harvested and frozen at -20C to -80C. Determination of concentrations of total- HDL- LDL- cholesterol, TAG, insulin, glucose and sex hormones were performed by the central laboratory at St James's Hospital according to the standard operating procedures.

2.5.1 Adipokine Analysis

Concentrations of Leptin and Adiponectin were assessed in serum by enzyme linked immunosorbant assay (ELISA) using R&D systems DuoSet ELISA development system. Cytokine specific capture antibodies (50µl/well at 4µg/ml and 50 µl/well 2µg/ml for leptin and adiponectin respectively in PBS) were added to 96-well microtitre plates (Nunc) and incubated overnight at 4°C. The plates were then washed 4 times with wash solution (PBS/0.05% Tween 20) and then incubated with 200µl/well of blocking solution (PBS supplemented with 1% Bovine Serum albumin BSA) at room temperature for 2hr to block non-specific binding sites. Following washing, plates were incubated overnight at 4°C with 50µl/well of test supernatant or the corresponding cytokine standard. The plates were then washed and incubated with with 50µl/well of a biotinylated anti-cytokine antibody at 12.5ng/ml and 2µg/ml for leptin and adiponectin respectively in assay diluent (PBS supplemented with 1% BSA) at room temperature for 1hr. After washing the plates they were incubated for 30 mins at RT (room temperature) with 100µl/well of extravidin horse radish peroxidase (HRP) at 1/200 dilution in assay diluent. Finally, after washing thoroughly, the plates were incubated with 100µl/well of substrate (one 10mg OPD tablet (o-Phenylenediamine dihydrochloride) dissolved in 0.05M phosphate citrate buffer pH 5 and immediately prior to use 40 µl of fresh 30% hydrogen peroxide was added) and left for approximately 20 mins and then stopped with 50µl/well of 1.5M H_2SO_4. The O.D. value of test samples and cytokine standards were measured at 492nm using a microtitre plate reader and cytokine concentrations for test samples determined after reference to a standard curve prepared from recombinant cytokines of known concentration and potency.

2.5.2 Insulin Resistance

While there are many ways to measure insulin sensitivity/resistance, the euglycaemic hyperinsulinaemic clamp, insulin suppression test, intravenous glucose tolerance test to name a few. For the purpose of these studies, considering the experimental limitations the degree of insulin resistance was estimated by Homeostatic model assessment (HOMA) according to the method described by Matthews et al (Matthews *et al*, 1985). The insulin resistance score (HOMA-IR) was computed with the formula: *Fasting plasma glucose (mmol/l) X fasting serum insulin (mU/I) divided by 22.5.* Low HOMA-IR values indicate high insulin sensitivity, whereas high HOMA-IR values indicate low insulin sensitivity (insulin resistance).

2.6 Metabolic Syndrome Classification

Metabolic syndrome was diagnosed according to the criteria set out by the International Diabetes Federation (Alberti *et al*, 2006): central obesity (waist circumference ≥ 94cm European males, ≥ 80 cm European females) plus any two of the following: raised Triglycerides ≥ 1.7mmol/l or specific treatment for this lipid abnormality; reduced HDL <1.03 mmol/l in males or <1.29mmol/l in females; raised blood pressure: systolic: ≥ 130mmHg or Diastolic ≥85 mmHg, or treatment of previously diagnosed hypertension; fasting plasma glucose ≥ 5.6 mmol/l or previously diagnosed Type II Diabetes.

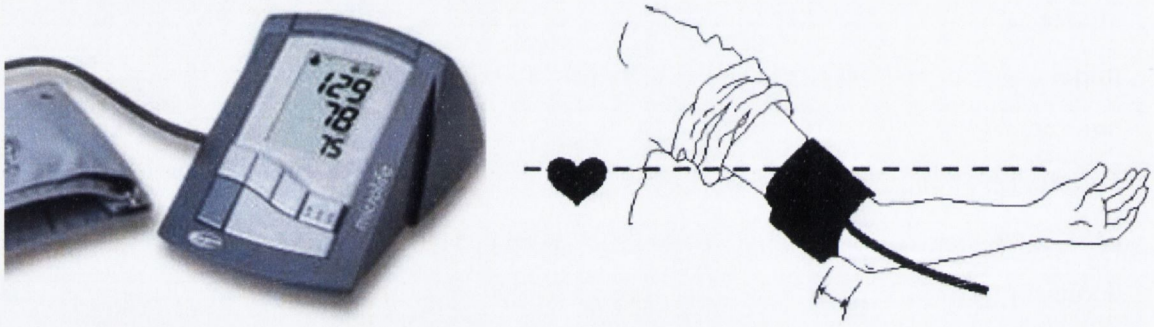
The NCEP ATP III definition for metabolic syndrome was also used in chapter 8 concurrently with the IDF definition. At the time of analysis, published studies as well as a study from our own unit reported metabolic syndrome incidecne using the NCEP ATP III definition, so to facilitate comparison we classified metabolic syndrome according to both definitions aw well as highlighting the higher incidence of MetS observed seen with the IDF definition.

2.6.2 Blood Pressure

Blood pressure was measured using an automatic digital sphygmomanometer (microlife BP 3AC1-1), providing fast reliable measurement of systolic and diastolic blood measurements to the nearest 1mm/hg with accuracy reported at ± 3mm/Hg. This device has been used in other clinical studies. Measurements were taken by placing the cuff on the upper arm (usually left) and tightening the cuff to achieve a snug fit on the upper arm. The patients' arm was supported so that the cuff is at the same height as the heart. The

pump begins to inflate the cuff, after reaching the inflation pressure, the pump stops and the inflation pressure begins to fall, in case the inflation pressure is not sufficient, the monitor automatically re-inflates to a higher level. The systolic and diastolic blood pressures now appear in the LCD display. The mean blood pressure result was determined from two independent measurements.

Figure 2.4: Blood pressure monitor and placement of cuff on upper arm at level of heart



2.7 Data Handling

All data collected and results of tests were entered into an excel database for Windows Version (Microsoft Corporation, 2003). The databases were then imported into a Statistical Package for the Social Sciences for Windows Version 14.0 and 16.0 (SPSS Inc., Chicago). Details of the statistical methods used are described in each chapter. P values of less than 0.05 were considered to indicate statistical significance. Survival graphs were plotted using SPSS. The issue of patient confidentialty was dealt with by assigning a code number to each patient. Hospital medical charts were read and the information recorded either on the hospital

2.8 Power Calculations

The statistical power of each study was assessed and appropriate sample size calculations were carried out in the design stage of the study presented in this thesis. Put simply this is the probability of correctly identifying a difference between the two groups in the study sample when one genuinely exists in the populations from which the samples were drawn. It depends on several factors but as a general rule higher power is achieved by increasing the sample size.

For a study comparing two means, the equation for sample size is where n is the total sample size:

$$N = \frac{Z\alpha + Z\beta)^2 \, X \, (\sigma_1^2 + \sigma_2^2)}{\delta^2}$$

The letter 'Z' represents a standard normal distribution, where alpha (α) represents the the value for the desired significance (usually 0.5), and Beta (β) represents the value for statistical power. See Table 2.X for the Zα and Zβ values used for the different levels of significance and power.

Table 2.1 Values for different Significance and Power

Significance (α)	Power (β)
α =0.10; 90% probability; Z=1.645	β= 0.05; 95% Power; Z=1.645
α =0.05; 95% probability; Z=1.960	β= 0.10; 90% Power; Z=1.282
α =0.02; 98% probability; Z=2.326	β= 0.15; 85% Power; Z=1.036
α =0.01; 99% probability; Z=2.576	β= 0.20; 80% Power; Z=0.842

Sigma (σ) represents the magnitude of the chance variation affecting the system under study, as measured by the standard deviation. In principle, delta (δ) is the minimum expected difference and ideally would detect any differene between the two process variants. However it is clear that it would require a very large sample size to detect a very small yield difference, therefore we specified what difference (δ) we consider is important to detect or clincaly relevant.

Sample size calculation for a difference in proportions (equal sized groups)

A similar approach can be used to calculate the sample size required to compare proportions in two equally sized groups.

$$N = \frac{[p1\,(1 - p1) + p2\,(1 - p2)] \times \text{Power}}{(p1 - p2)^2}$$

Unequal sized groups

The methods described above assume that comparison is to be made across two equal sized groups. However, this may not always be the case in practice, for example in an observational study. It is possible to adjust the numbers to reflect this inequality. The first step is to calculate the total sample size (across both groups) assuming that the groups are equal sized. This total sample size (N) can then be adjusted according to the actual ratio of the two groups (k) using the formulas below for the revised total sample size (N′) and the individual sample sizes in each of the two groups.

Total Sample Size:

$$N' = \frac{N\,(1 + k)^2}{4k}$$

Individual Sample Size

$$N'/(1 + k) \quad \text{and} \quad kN'/(1 + k)$$

The coefficient of variation which is the typical error expressed as a percent of the subject's mean score was not assessed and this is an oversight of the studies. Although all measurements were performed by the same person, reducing inter-observer variation but intra-observer variation cannot be ruled out.

CHAPTER 3

OBESITY INCREASES THE RISK OF POSTMENOPAUSAL BREAST CANCER AND IS ASSOCIATED WITH MORE ADVANCED STAGE AT PRESENTATION BUT NO IMPACT ON SURVIVAL.

Published in *Breast J.* 2010;16(1):95-7.

"Obesity increases the risk of postmenopausal breast cancer and is associated with more advanced stage at presentation but no impact on survival."

Laura A Healy, Aoife M Ryan, Suzanne Rowley, Terence Boyle, Elizabeth Connolly, Michael J Kennedy, John V Reynolds

3.1 Summary

Background: Obesity adversely affects women's health, and in addition to the well-established cardiovascular and metabolic risks the association between obesity and cancer is increasingly recognised. Postmenopausal breast cancer is associated with obesity, but the impact of obesity on clinico-pathological features and outcome is unclear.

Objective: To define the association of obesity with post-menopausal breast cancer in an Irish population, and to compare obese with non-obese cohorts with symptomatic breast cancer for tumour size, pathological stage, axillary nodal involvement and survival in an Irish population.

Design & Setting: A retrospective case control study was undertaken in 200 patients presenting to a tertiary centre. Data was compared to 519 healthy female controls. Multivariate logistic regression models were used to calculate the odds ratio (OR) of developing postmenopausal cancer according to body mass index (BMI), as well as the impact BMI has on tumour size, nodal involvement, pathological stage and survival. Actuarial survival was calculated from date of diagnosis by the Kaplein-Meier method and log rank test.

Results: Postmenopausal breast cancer patients were significantly heavier than age matched controls with 65% being overweight or obese versus 54% of controls (p=0.030). A dose dependent relationship existed between BMI and postmenopausal breast cancer. The adjusted odds ratio was 2.2 (95% CI's: 1.3-3.7) for individuals in the highest BMI quartile compared with the lowest BMI quartile ($p < 0.05$). Obesity was associated with larger tumours (P= 0.002) and a later stage of disease at presentation (P=0.026) but not with axillary node involvement (P=0.332). Median and overall survivals were equivalent (P=0.913) when comparing obese to non obese.

Conclusion: Obese women are twice as likely to get postmenopausal breast cancer compared to normal weight women. Obesity was associated with larger tumours and later presentation but no difference in survival. Obesity is a preventable risk factor for breast cancer and given the high and increasing prevalence of obesity in Ireland, obesity needs to be addressed on a national level with targeted lifestyle treatment programs.

3.2 Introduction

Obesity is a recognised risk factor for Type II diabetes, metabolic syndrome and cardiovascular disease. There is emerging evidence that obesity is associated with many cancer sites, and obesity is associated with increased cancer mortality (Calle *et al*, 2003; Flegal *et al*, 2005). The World Cancer Report of 2003, the most comprehensive global assessment of cancer statistics to date, predicts a 50% worldwide increase in cancer incidence by 2020 (Stewert & Kleihues, 2003), and the rising incidence of overweight and obesity may be fuelling cancer rates. A recent study on 1.2 million middle aged women from the UK, followed up for an average 5.4 years showed an increase risk in endometrial cancer, adenocarcinoma of the oesophagus, kidney cancer, leukaemia, multiple myeloma, pancreatic cancer, non-Hodgkin's lymphoma, ovarian cancer, all cancers combined, colorectal cancer in premenopausal women, and breast cancer in postmenopausal women and (Reeves *et al*, 2007).

The relationship between BMI and breast cancer is unique in that the increased risk appears exclusive to postmenopausal women (Food Nutrition, Physical Activity, and the prevention of Caner 2007). All measures of obesity including waist hip ratio (WHR) (Lahmann *et al*, 2004; Connolly *et al*, 2002) weight gain, and percentage body fat have been associated with increased risk of postmenopausal breast cancer (Lahmann *et al*, 2003). BMI may also be negatively associated with breast cancer prognosis, even in early stage disease (Chlebowski *et al*, 2002; Enger *et al*, 2004). Obese patients have double the death rate from breast cancer compared to non obese individuals (Calle *et al*, 2003). Obesity is thought to be associated with lower rates of self-detection, delayed diagnosis, larger tumours, lymph node involvement and increased likelihood that the cancer has spread beyond the primary site at the time of diagnosis (Cui *et al*, 2002; Berclaz *et al*, 2004).

There has been no systematic assessment of obesity and postmenopausal breast cancer in an Irish population. The purpose of this study was to establish data for risk of postmenopausal breast cancer and the impact of obesity on incidence, tumour size, stage, nodal involvement and survival.

3.3 Patients and methods

A retrospective analysis of a prospectively compiled database of patients with histologically confirmed postmenopausal breast cancer, diagnosed or treated at the Breast Care Unit of St James's Hospital, Dublin between 1998 and 2006 was performed. Patients were excluded if BMI was not recorded or if they had a previous malignancy. Thirty percent (n=200) of the patients on the database met our inclusion criteria. The medical and histopathology records of the cancer cases were recorded on a computerised Breast Cancer Database (Patient Analysis and Tracking System ^{TM}, Dendrite Clinical Systems, UK). Data recorded included age, sex, tumour site, pathology, smoking and alcohol intakes, co-morbid disease, no of pregnancies, age of menarche, and use of exogenous hormones. Adiposity was estimated by BMI, computed as weight in kilograms divided by height in meters squared (kg/m^2), with a BMI of 20-24.9 kg/m^2 defined as normal, overweight 25-29.9 kg/m^2, and obese >30 kg/m^2. Subjects were also divided into 4 equal categories using the 25th, 50th, and 75th centiles of BMI among healthy controls. (<23.05 kg/m^2 quartile I, 23.06-25.30 kg/m^2 quartile II, 25.31 - 28.62 kg/m^2 quartile III, and >28.63 kg/m^2 quartile IV).

Anthropometric data on 519 age matched healthy female controls were used for comparison, controls under the age of 65 years were obtained from nationwide data as part of the North/South Ireland Food Consumption Survey (McCarthy *et al*, 2002), and over 65 year-old controls were interviewed and nutritionally assessed by a registered Dietitian at several day centres for the elderly in Dublin. Weight, height and BMI were calculated, and data regarding cigarette and alcohol consumption, and socio-economic status was gathered. Information on hormone use and age of first pregnancy, parity, adult weight gain was not available in the control group, and therefore could not be considered in this study.

3.3 Statistical Analysis

BMI was grouped into quartiles for analysis based on BMI distributions amongst the controls subjects. Relative risks were expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models. Analysis was also performed using the common cut-off points for BMI and we also tested for linear trend by including BMI as a

continuous risk factor in the logistic regression. All analyses were adjusted for the effects of age, cigarette consumption (current smoker, ex-smoker, never smoker), and heavy alcohol intake. Mann Whitney U tests, Chi squares and Anova were employed to identify significant differences between categorical and continuous variables in the obese and non-obese categories, with significance defined as $P<0.05$. Data was analysed in SPSS Version 14.0. Actuarial survival was calculated from the date of diagnosis by the Kaplein Meier method and comparisons between the groups were made by the log rank test.

This study was adequately powered to detect a clinically relevant difference of 3kg/m2 (+/- 5.3 kg/m2) in BMI and a 1.5cm (+/-2.5cm) difference in mean tumour size with 95% power using a cut-off for statistical significance of 0.05. In respect to difference in tumour pathology, this study was adequately powered to detect a 15% difference in the proportion of patients diagnosed with late stage and node positive disease among obese and non obese with 80% power using a cut-off for statistical significance of 0.05 As the median survival was not reached in the obese or non-obese groups, sufficient time had not passed to examine the influence of obesity on median survival.

3.5 Results

3.5.1 Nutritional Status Pre Illness

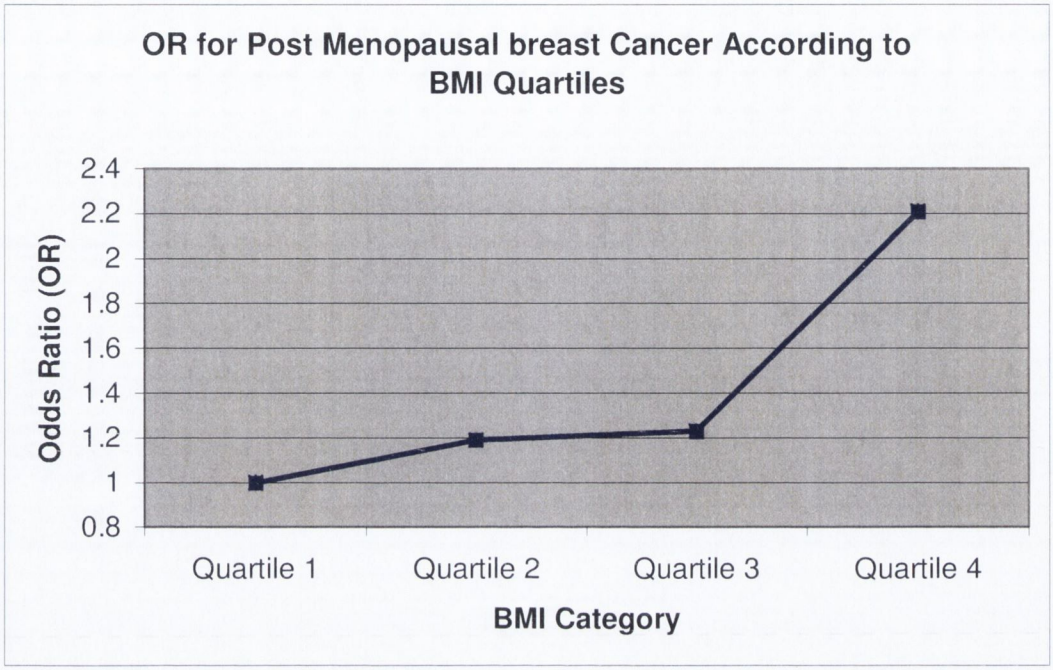
The average body weight was 70kg. Sixty-five percent of postmenopausal breast cancer patients were overweight or obese versus 54% of controls (p=0.030). Females who developed postmenopausal breast cancer were significantly heavier than healthy controls with a median BMI of 27.75 kg/m^2 (+/-5.3kg/m^2) compared to controls median BMI of 26.3 kg/m^2 (+/- 4.8 kg/m^2), p=0.001.

3.5.2 BMI and Risk of Postmenopausal Breast Cancer

BMI was positively associated with breast cancer risk. Thirty seven percent of patients with postmenopausal breast cancer had a pre illness BMI in the top quartile. When compared to the lowest quartile, the OR rose significantly with increasing BMI. When compared to the first quartile the OR of postmenopausal breast cancer in ascending order of BMI quartiles was 1.2 (95% CI's: 0.7 to 2.0) (p=0.523), 1.2 (95% CI's: 0.7-2.1) to 2.2 (95% CI's: 1.3 to 3.7) (p =0.002). This association between pre-illness BMI and the risk of cancer is illustrated in figure 3.1. When the heaviest quartile was divided in two (28.6-

31.6kg/m^2 and > 31.6 kg/m^2) the pattern became more striking. The OR for patients with BMI >31.6kg/m2 postmenopausal breast cancer was 2.6 (95%CI, 1.4 to 4.7) compared to the lowest quartile (p=0.001). Analysed by common cut off points for BMI, the risk of postmenopausal breast cancer doubled for obese women OR 2.0 (95% CI's: 1.3 to 3.3) versus individuals with a normal BMI 20-25 kg/m^2 (p=0.004). When analysed as a continuous factor BMI was also linearly related to risk of postmenopausal breast cancer (OR 1.06; p=0.001) (Table 3.1).

Figure 3.1: Odds ratio for Postmenopausal Breast Cancer (■), according to BMI quartiles



This graph demonstrates that BMI was positively associated with breast cancer risk when comparing 4 equal quartiles defined as BMI <23.05 kg/m^2 quartile I, BMI: 23.06-25.30 kg/m^2 quartile II, BMI 25.31 - 28.62 kg/m^2 quartile III, and BMI >28.63 kg/m^2 quartile IV. The lowest BMI quartile were used as reference, the OR of postmenopausal breast rose significantly with increasing BMI, comparing highest quartile to loweset quartile the OR was 2.2 (95% CI's: 1.3 to 3.7) (p =0.002).

Table 3.1: Odds Ratios (OR) and 95% confidence intervals (CI s) associated with body mass index (BMI) for Post menopausal Breast Cancer

Factor	Case/ controls	OR (95% CI's)	P Value
*Pre Illness BMI**			
Quartile 1	*37/129*	*Reference*	
Quartile 2	42/130	1.19 (0.7-2.0)	0.523
Quartile 3	48/131	1.23 (0.7-2.1)	0.438
Quartile 4	73/129	2.21 (1.3-3.7)	0.002*
*Common cut-off Points for BMI***			
Underweight	7/21	1.18 (0.5-3.0)	0.719
Normal	65/221	1.00 (referent)	
Overweight	75/183	1.41 (0.9-2.1)	0.100
Obese	53/94	2.04 (1.3-3.3	0.004*
Continous Model			
BMI	200/519	1.06 (1.03-1.1)	0.001*

*Cut off points for pre illness BMI: I – first Quartile (<23.05), II (23.06-25.3), III (25.31 –28.62), IV (>28.63).

** Standard cut off Points for Underweight (<20), Normal (20-24.9), Overweight (25-29.9), Obese (>30)

The anthropometric data on 200 postmenopausal cancer patients were compared to 519 age matched healthy female controls. BMI was grouped into quartiles for analysis based on BMI distributions amongst the controls subjects. Analysis was also performed using the common cut-off points for BMI and we also tested for linear trend by including BMI as a continuous risk factor in the logistic regression. All analyses were adjusted for the effects of age, cigarette consumption (current smoker, ex-smoker, never smoker), and heavy alcohol intake. Relative risks are expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models.

3.5.3 Obese vs Non-obese patients

The mean age was 58.6 years (age range 39-80 years). Performance status, smoking and alcohol intakes were similar in obese and non-obese with a third of patients current smokers and 4% with a history of heavy alcohol intake (Table 3.2). The majority of patients (98%) were assessed in triple assessment clinics in the Breast Care Unit, involving clinical examination, imaging (usually mammography and/or ultrasonography), and fine needle aspiration cytology (De Blacam et al, 2008). Ductal tumours represented more than 76% cases, while 58% of cancers were diagnosed Stage II. Surgery was the most common primary treatment (n=176) with adjuvant radiotherapy (n=142) or chemotherapy (n=153). Twenty-one patients had chemotherapy as a first line treatment and two thirds progressed to surgery (n=14) or had adjuvant radiotherapy (n=14).

3.5.4 Tumour Size

The average tumour size was 3.5 +/- 2.4 cm. High BMI was also positively associated with tumour size in univariate analysis (p=0.050). When comparing the highest quartiles to the lowest BMI quartile, women had a 4.6-fold increased risk of a larger tumour (>2cm) (p=0.002). When analysed according to common cut-offs for BMI, overweight and obese patients had nearly 3-fold and 2-fold higher risk compared to normal weight patient. BMI analysed as a continuous risk factor was found to be significantly associated with tumour size (p=0.028) (Table 3.3).

3.5.5 Tumour Pathology

BMI was significantly associated with pathological stage in univariate analysis, where 43% of obese patients were diagnosed at stage III/IV compared with 27% of non-obese patients (p=0.020). In logistic regression models accounting for differences in smoking and alcohol intake, the OR rose significantly with increasing BMI, with 3.5-fold increased risk of advanced pathological stage for the highest quartile of BMI compared to the lowest quartile (p=0.026) (Table 3.4). Obesity (BMI>30kg/m2) was associated with a 2.5-fold increase in the likelihood of a more advanced pathological stage when compared to patients with a normal BMI (p=0.044). Forty-three per cent obese women and 32% overweight women had tumours diagnosed at Stage III or IV, compared to 24% normal weight, and 0% of underweight women. When analysed as a continuous factor BMI was also linearly related to advanced pathological stage (OR 1.08; p=0.015), and there was no difference in incidence of ER+ tumours between obese and non obese (68% vs 67% p=0.513).

Table 3.2: Treatment Characteristics of Study Population

Characteristic	Non Obese	Obese	P value
Age (Mean ±SD)	58.6 ± 8.6	58.6 ± 8.0	0.842
Body Weight	63.8 ± 8.3	87.2 ± 11	0.000
Current Smokers	50 (35)	15 (28)	0.601
Heavy Alcohol Intake	5 (4)	2 (5)	0.380
Performance Scores			
Karnofskys >90%	135 (92)	47 (89)	0.688
ECOG Score	111 (76)	35 (66)	0.235
Family Hx Breast Cancer	49 (33)	16 (33)	0.710
HRT Use (n=130)	49 (50)	14 (44)	0.341
Same Day Diagnosis	82 (77)	28 (78)	0.579
Tumour Site (>1)	11 (65)	6 (35)	0.320
Tumour Size (cm)	3.4 ± 2.3	4.1 ± 2.7	0.050
Treatment Approach			
Curative	141 (96)	50 (94)	0.442
Palliative	6 (4)	3 (6)	
Primary Treatment			
Surgery	132 (90)	44 (83)	0.159
Chemotherapy	15 (10)	6 (11)	
Hormone Therapy	0	1 (2)	
Palliative Care	0	2 (4)	
Pathological Stage			
Stage I or II	107 (73)	30 (57)	0.020
Stage III or IV	39 (27)	23 (43)	
ER Positive	97 (68)	35 (67)	0.513
Residual Tumour			
No Residual tumour	130 (92)b	48 (92)	0.508
Micro / Macro	3 (2) / 8 (6)	0 / 4 (8)	
Lymph Node			
Negative	48 (33)	14 (27)	0.260
Positive	97 (67)	38 (73)	

Mann Whitney U tests, Chi squares and Anova were employed to identify significant differences between categorical and continuous variables in the obese and non-obese categories, with significance defined as P<0.05. The above table shows a comparison of demographic characteristics, performance status, treatment approaches as well as clinico-pathological tumour features were compared stage.

Table 3.3: Association between BMI and Tumour Size > 2cm Odds Ratios (OR) and 95% confidence intervals (CI s)

Factor	Tumour Size		OR (95% CI's)	P Value
	No (%)	No (%)		
*Pre-illness BMI**	*<2cm*	*>2cm*		
Quartile 1	*18 (49)*	*19 (51)*	*Referent*	
Quartile 2	10 (24)	31 (76)	2.82 (1.0-7.9)	0.047*
Quartile 3	7 (15)	39 (85)	5.27 (1.8-15.5)	0.003*
Quartile 4	12 (18)	56 (83)	4.57 (1.8- 11.8)	0.002*
*Common Cut-off Points for BMI **				
Underweight	*4 (57)*	*3 (43)*	*0.51 (0.9-2.7)*	*0.433*
Normal weight	22 (34)	43 (66)	Referent	
Overweight	11(16)	60 (84)	2.91 (1.2-6.8)	0.014*
Obese	10 (20)	39 (80)	2.01 (0.8-5.0)	0.135
Continuous Model				
BMI	47 (25)	145 (75)	1.08 (1.0 – 1.17)	0.028*

*Cut off points for pre illness BMI: I – first Quartile (<23.05), II (23.06-25.3), III (25.31 –28.62), IV (>28.63).

** Standard cut off Points for Underweight (<20), Normal (20-24.9), Overweight (25-29.9), Obese (>30)

Ψ Data adjusted for age, smoking, and alcohol intake.

Logistic Regresssion Analysis was performed to further examine the association between BMI and Tumour size. Analysis was performed using BMI quartiles, common cut offs for BMI as defined above and we also tested for linear trend by including BMI as a continuous risk factor in the logistic regression All analyses were adjusted for the effects of age, cigarette consumption (current smoker, ex-smoker, never smoker), and heavy alcohol intake. Relative risks are expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models.

Table 3.4: Association between BMI and Pathological Stage Odds Ratios (OR) and 95% confidence intervals (CI 's)

Factor	Pathological Stage		OR (95% CI's)	P Value
	No (%)	No (%)		
*Preillness BMI**	*Stage I/II*	*Stage III/IV*		
Quartile 1	*30 (81)*	*7 (19)*	*Referent*	
Quartile 2	32 (76)	10 (24)	1.85 (0.5-6.3)	0.329
Quartile 3	32 (68)	15 (32)	2.50 (0.7-8.1)	0.127
Quartile 4	44 (60)	29 (40)	3.51 (1.2-10.6)	0.026*
*Common Cut-off Points for BMI **				
Underweight	*7 (100)*	*0*	*0.0*	*0.999*
Normal weight	50 (76)	16 (24)	Referent	
Overweight	50 (68)	23 (32)	1.60 (0.7-3.6)	0.251
Obese	30 (57)	23 (43)	2.46 (1.0-5.9)	0.044*
Continuous Model				
BMI	137 (10)	60 (90)	1.08 (1.0 – 1.2)	0.015*

*Cut off points for pre illness BMI: I – first Quartile (<23.05), II (23.06-25.3), III (25.31 –28.62), IV (>28.63).

** Standard cut off Points for Underweight (<20), Normal (20-24.9), Overweight (25-29.9), Obese (>30)

Ψ Data adjusted for age, smoking, and alcohol intake.

Logistic Regresssion Analysis was performed to further examine the association between BMI and Pathological Stage. Analysis was performed using BMI quartiles, common cut offs for BMI as defined above and we also tested for linear trend by including BMI as a continuous risk factor in the logistic regression All analyses were adjusted for the effects of age, cigarette consumption (current smoker, ex-smoker, never smoker), and heavy alcohol intake. Relative risks are expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models.

3.5.6 Nodal Status

BMI was not associated with axillary node involvement; 67% of non-obese women were lymph node positive compared with 71% of obese patients (p=0.351) (Table 3.5). When divided into quartiles, the percentage of women with positive nodes increased with increasing obesity, from 62% in the lowest quartile to 73% in the highest quartile with an OR of 1.5, although this was not significant (p=0.612). When analysed according to common cut-offs, BMI seemed to be inversely related to nodal status, with the risk of nodal involvement being 1.25 fold for obese (p=0.655) and 1.5 fold increase for underweight patients (p=0.655).

3.5.7 Survival

At a median follow-up of 44.5 months, the median survival was not reached in the obese or non-obese groups (Figure 3.2). The 1, 3, and 5-year survival in the obese group was 94 months, 89 months and 82 months, compared with 95 months, 89 months and 78 months respectively in the non-obese group. Median survival for ER+ tumours was 108 months compared with 95 months for ER- tumours (p=0.026). We also examined BMI and survival, stratified by ER status. The 1, 3 and 5 year survival of the obese ER+ was 100, 93 and 82 months respectively compared with 97, 94 and 84 months in the non obese ER+ group (p=0.172). In the ER- cohort the 1, 3 and 5 year survival of the obese ER- was 87, 80 and 80 months respectively compared with 93, 77 and 77 months in the non obese ER- group (p=0.172).

Table 3.5: Association between BMI and Nodal Status Odds Ratios (OR) and 95% confidence intervals (CI s)

Factor	Nodal Status		OR (95% CI's)	P Value
	No (%)	No (%)		
*Preillness BMI**	*Negative*	*Positive*		
Quartile 1	*14 (38)*	*23 (62)*	*Referent*	
Quartile 2	14 (34)	27 (66)	1.36 (0.5-3.7)	0.553
Quartile 3	15 (31)	33 (69)	1.43 (0.5-3.8)	0.475
Quartile 4	19 (27)	52 (73)	1.57 (0.6-3.8)	0.332
*Common Cut-off Points for BMI **				
Underweight	*2 (29)*	*5 (71)*	*1.51 (0.3-9.1)*	*0.655*
Normal weight	24 (37)	41 (63)	Referent	
Overweight	22 (30)	51 (70)	1.44 (0.7-3.1)	0.343
Obese	14 (27)	38 (73)	1.25 (0.5-2.9)	0.612
Continuous Model				
BMI	62 (31)	135 (69)	1.01 (0.9–1.1)	0.616

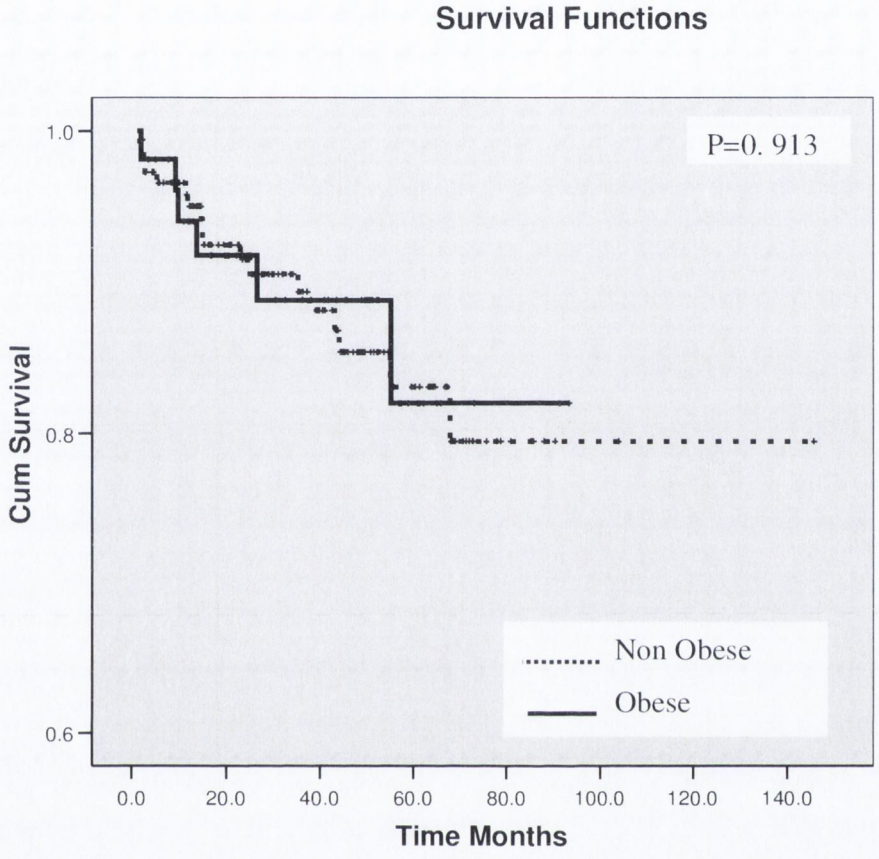
*Cut off points for pre illness BMI: I – first Quartile (<23.05), II (23.06-25.3), III (25.31 –28.62), IV (>28.63).

** Standard cut off Points for Underweight (<20), Normal (20-24.9), Overweight (25-29.9), Obese (>30)

Ψ Data adjusted for age, smoking, and alcohol intake.

Logistic Regresssion Analysis was performed to further examine the association between BMI and Nodal Status. Analysis was performed using BMI quartiles, common cut offs for BMI as defined above and we also tested for linear trend by including BMI as a continuous risk factor in the logistic regression All analyses were adjusted for the effects of age, cigarette consumption (current smoker, ex-smoker, never smoker), and heavy alcohol intake. Relative risks are expressed as odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression models.

Figure 3.2: BMI and Survival in Postmenopausal Breast Cancer Patients



This graph represents a comparison of survival in obese and non obese cohorts with postmenopausal breast cancer (n=200). As you can see from the graph median and overall survivals were equivalent in both categories. The 1, 3, and 5-year survival in the obese group was 94 months, 89 months and 82 months, compared with 95 months, 89 months and 78 months respectively in the non-obese group.

3.6 Discussion

This study of an Irish population supports the association between obesity and increased incidence of postmenopausal breast cancer. In this study obesity was associated with double the risk of postmenopausal breast cancer compared with normal weight patients. Previous studies have reported a risk from 1.4 (95% CI's: 0.95-2.06) (Lahmann *et al*, 2003) to 2.52 (95% CI's1.62-3.93) (Chlebowski *et al*, 2002). A pooled analysis of data from seven prospective cohort studies involving 337 819 women and 4385 invasive breast cancers showed a 8% increased risk per added 5kg/m2 in postmenopausal women, while another pooled analysis based on 53 case control studies with more than 58 000 cases and 95 000 controls, showed a 19% increased risk per 5kg/m2 for postmenopausal breast cancer (Key *et al*, 2003; van der Brandt *et al*, 2000). There is evidence to suggest that obesity can further increase the risk of women developing postmenopausal breast cancer who are genetically susceptible (Carpenter *et al*, 2003). The definition of obesity varies between studies, some studies use quartiles of BMI while other use common cut-off points or pick an arbitrary value of <22 kg/m2 or >31. In this study we used both quartiles of BMI, common cutoffs and assessed BMI as a continuous variable, and we found a significant relationship for all definitions of obesity. We recognise the limitations of the retrospective nature of the study and that other potential risk factors like family history, parity, age at first childbirth, reproductive history, hormone use, early adult BMI and lifetime weight gain were unable to be adjusted for in regression models. We also recognise that not all patients had BMI assessment at presentation, this is now a routine in the Unit since 2006.

It has been hypothesized that the underlying explanation for an increase in breast cancer risk among obese women is through increased conversion of androgens to estrogens by the enzyme aromatase. In addition obesity is associated with low levels of sex hormone binding globulin (SHBG), which in turn increases the availability of free ostradiol to target tissues (Borugian *et al*, 2003). Obesity's effect on pathways involving insulin resistance, insulin like growth factors and adipocytokines like leptin may influence tumour growth (Cowet & Hardy 2006). For example leptin has been shown *in vitro* to have direct growth stimulating effects on various malignant cells including breast cancer (Laud *et al*, 2002). It has also been reported that both high serum levels and high leptin receptor expression are associated with a poor prognosis in breast cancer (Ishikawa *et al*,

2004; Miyoshi *et al*, 2006). Daling et al compared large tumours (>2cm) from highest body weight quartile to similar size tumours from the lowest body weight quartile and found that the tumours from the obese women had a higher Ki-67 expression ratio, a higher mitotic count, and a higher S phase fraction when compared to the non obese women (Daling *et al*, 2001). This indicates a possibly more rapid growth rate in obese women tumours. Hormone replacement therapy (HRT) is associated with increased risk of breast cancer (Rossouw *et al*, 2002), combined (oestrogen progesterone). As information was unavailable on HRT use in our control population we were unable to adjust our analysis to control for HRT use. However we know that approximately one third of patients with breast cancer (31%) had used HRT at some stage, 15% between 5-10 years and 9% over 10 years; while 34% had never used HRT and use was unknown in 35% patients. It is estimated that as HRT use declines the relative impact of obesity on breast cancer may grow (Li *et al*, 2006).

Obesity was associated with larger tumours at presentation, which is concordant with some previous studies (Berclaz *et al*, 2004). Many theories have been put forward to explain this association; obese women may delay seeking treatment (Wee *et al*, 2000) and obese women may have larger breasts, so palpation for lumps may be more difficult, resulting in delay in detection and diagnosis of breast cancer. Women with larger breasts may be diagnosed with a later stage cancer (Hall *et al*, 1999; Hoe *et al*, 1993). However we found no difference between obese and non-obese in detection or palpability of breast lump as reported symptom. A more advanced pathological stage has been associated with obesity, but the impact of obesity on axillary nodal status is less clear. In this study, no association between obesity and nodal involvement was evident.

Obesity has been associated with a poorer survival in breast cancer, but no significant difference was observed in this study between the obese and non-obese cohort. A significant association between obesity and survival was seen in 26 reports incorporating 29,460 women whereas eight reports on 3,727 women did not see any association (Chlebowski *et al*, 2002). In a large European study on 14,709 patients who were followed up for a maximum of 20 years obesity was associated with risk of recurrence, reduced disease free and overall survival, and the development of second cancers (Majed *et al*, 2008), but when subgroup analysis was performed according to menopausal status only second primary cancers remained significant. The majority of studies have examined prognosis in pre and post menopausal grouped together, we know that pre and post

menopause women do not incur the same risk of breast cancer from obesity, its therefore possible that obesity has a different effect on survival in pre and post menopausal women. In a recent report, the effect of BMI on mortality was shown to be dependent on age. An elevated BMI may be detrimental to survival of women at younger ages (Fowable *et al*, 1994; Elkum *et al*, 2007), but as women approach mid seventies those with a high BMI were observed to have a lower risk of death (Reeves *et al*, 2007). Survival was further stratified according to obesity, we found that survival was equivalent among obese and non obese ER- and ER+ tumours (p=0.172).

In conclusion, this study in an Irish population has shown that obesity is independently associated with increased risk of postmenopausal breast cancer. There is no difference in the detection, assessment, or treatment of obese women compared to non-obese women. Obesity is associated with larger tumours at presentation and more advanced pathological stage but not with nodal involvement. Accordingly, survival was not significantly different, irrespective of ER status. Obesity is one of the few modifiable risk factors for postmenopausal breast cancer and thus an important measure for breast cancer prevention. Further research is needed to fully understand the underlying biological mechanisms and to determine molecular and pharmacological targets to improve the treatment of obese breast cancer patients.

CHAPTER 4

METABOLIC SYNDROME, CENTRAL OBESITY AND INSULIN RESISTANCE ARE ASSOCIATED WITH ADVERSE PATHOLOGICAL FEATURES IN POSTMENOPAUSAL BREAST CANCER

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"Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer."

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4.1 Summary

Background: Obesity is associated with both an increased risk of postmenopausal breast cancer and increased mortality rates. The mechanism is unclear, and central (visceral) obesity, insulin resistance, altered sex steroids, and altered adipokines, are mooted as possible factors. These features may cluster in the so-called Metabolic Syndrome (MetS). The relevance of Met S to the biology of breast cancer is unknown, and this was the focus of this study.

Methods: All postmenopausal women with newly diagnosed breast cancer (n=105) were recruited. A detailed clinical history was performed, as well as body composition analysis, metabolic screen, and measurement of adipokines and inflammatory markers.

Results: The median age was 68 years (40-94) and the mean BMI was 28.3 ± 5.2 kg/m^2, with 87% of patients centrally obese. MetS was diagnosed in 39% of patients, and was significantly associated with central obesity ($p<0.005$) and increased inflammation with CRP levels doubling in MetS patients compared to Non-MetS (10.3 Vs 5.8mg/L; $p=0.084$). Patients with later pathological stage (II- IV) were significantly more likely to be obese ($p=0.007$), centrally obese ($p=0.009$), hyperglycaemic ($p=0.047$), hyperinsulinaemia ($p=0.026$) and 51% had MetS compared with 12% for early stage disease. Patients with node positive disease were significantly more likely to be hyperinsulaemic ($p=0.030$) and have MetS ($p=0.028$) than node negative disease.

Conclusion: The data suggests that MetS and central obesity are common in postmenopausal breast cancer patients, and that MetS may be associated with more aggressive tumour biology.

4.2 Introduction

There is an emerging interest in the relationship between obesity and cancer incidence and mortality, although precise mechanisms remain unclear. For breast cancer, epidemiological data reveal an increased incidence associated with obesity exclusively in post-menopausal women (Lahmann *et al*, 2004). Obesity may be associated with lower rates of self-detection, delayed diagnosis, larger tumours, and a greater likelihood of metastatic involvement of lymph nodes and other sites at diagnosis (Cui *et al*, 2002). Following curative treatment, obesity may also be associated with increased recurrence (Berclaz *et al*, 2004; Ziegler *et al*, 1997). Obese patients have approximately double the death rate from breast cancer compared to non obese individuals (Calle *et al*, 2003).

Although delayed detection and diagnosis may be factors in the worse outcomes associated with obesity, there is an intriguing potential link relating to altered metabolic, endocrine and immuno-inflammatory responses that are commonly to obesity and better described in association with type 2 diabetes and cardiovascular disease. Metabolic syndrome defines features that may be associated with central obesity, including high blood glucose levels, impaired glucose tolerance, dyslipidemia, and high blood pressure (Alberti *et al*, 2006). An emerging hypothesis is that the endocrine, metabolic, and immune cell changes associated with central obesity and the metabolic syndrome may fuel cancer risk, cancer progression, and outcomes.

This association has not heretofore been systematically studied in women with postmenopausal breast cancer. We report herein from this prospective study a high prevalence of metabolic syndrome in postmenopausal breast cancer, and an association between central obesity, metabolic syndrome and adverse features and outcomes.

4.3 Patients and methods

This was a study of patients presenting to a specialist Breast Cancer Unit, in St James's Hospital, Dublin, with newly diagnosed postmenopausal breast cancer. Patients were excluded from the study if they had a previous history of cancer. The study was approved by the hospital ethics committee for research involving human subjects according to the Helsinki agreement. 105 patients consented to participate in the study equivalent to 92%

participation rate (105/115) and 72% of eligible patients (105/145) that presented to the hospital.

Patients underwent a nutritional assessment (weight, height, BMI, Body composition analysis) at time of diagnosis before cancer treatment was initiated, with a research dietitian. Blood pressure measurements and venous blood sample for metabolic syndrome screening as detailed in the methods section. Details about medication use, past medical history, alcohol and tobacco use were also examined. Breast cancer is graded using a modification by Elston of the Scarff-Bloom-Richardson grading scheme (Elston, 1987) and Nottingham Prognostic Indicator (NPI) was calculated to predict outcomes (Galea *et al*, 1992).

4.4 Statistical analysis

Statistical analysis was conducted using SPSS® Version 14.0 for Windows™ (SPSS® Inc., Chicago, IL). Means (± standard error of mean) were compared with each other using one way analysis of variance. Cross-tabulation was used to compare differences between groups for categorical variables. Significant differences were tested using Pearson Chi-square analysis. For 2X2 table Fischer's exact test was used. For complex analysis of more than 2 groups, ANOVA analysis was used and where statistically significant effects were encountered ($p<0.05$), comparisons of means were made using Scheffe *post-hoc* multiple comparisons test. For values that did not comply with Levene's test for homogeneity of variance, the Tamhane *post-hoc* multiple comparisons test was used.

A fifteen percent difference in metabolic syndrome incidence was considered clinically relevant and this study was adequately powered to detect this. When comparing metabolic syndrome and non metabolic syndrome groups clinically relevant differences in variables with a known standard deviation were used to determine sample size. This study was adequately powered to detect a clinically relevant difference of 3kg/m2 (+/- 5.3 kg/m2) in BMI, a 3cm (+/-2.1cm) in waist circumference, a 1.5cm (+/-2.5cm) difference in tumour size; 5mg/dl difference (+/-4.2mg/dl) in CRP, and 2.0 point increase in insulin resistance (+/- 2.0) between groups with 95% power using a cut-off for statistical significance of 0.05. In respect to difference in tumour pathology, this study was adequately powered to detect a 15% difference in the proportion of patients diagnosed

with late stage and node positive disease among obese and non obese with 80% power using a cut-off for statistical significance of 0.05

4.5 Results

One hundred and five female post-menopausal breast cancer patients were recruited. Patient Demographics are shown in Table 4.1. The median age was 67 years (Range 40-94). There was no difference in method of detection, duration of symptoms, diagnosis or treatment between metabolic syndrome and non metabolic syndrome patients. The majority of patients were treated with curative intent (97%), with surgical resection (92%) the most common primary treatment, with 3% having primary chemotherapy and a further 5% having primary hormone treatment.

4.5.1 Anthropometry and Metabolic Profile

The mean BMI was 28.2 ± 5.3 kg/m2, with 72% of patients either overweight or obese, with 87% centrally obese (>80 cm) (Table 4.2). Metabolic Syndrome was present in 39% of patients, and was more common in obese patients (61% obese Vs 21% non-obese; p=0.000). Metabolic Syndrome patients were significantly heavier, with a mean 11Kg increase compared with patients without metabolic syndrome, and a 13cm mean greater waistline. The MetS cohort also had significantly greater BMI as well as increased total fat, trunk fat, as well as being more frequently hypertensive (93% v 61%) and on anti-hypertensive medications (66% v 35%). The mean CRP level of MetS patients was 10.3mg/L compared with 5.8mg/L in non MetS (p=0.084). Significantly more MetS patients were hyperglycaemic (p=0.000), hyperinsulinaemic (p=0.000), and had insulin resistance (p=0.003), with 37% of metabolic syndrome patients hyperinsulinaemic compared with 7% in patients without MetS (p=0.001) (Table 4.3).

Table 4.1: Demographic and Treatment Details

Characteristic	No Met Syn (n=63)	Met Syn (n=42)	P value
Age (mean ± SE)	65.3 ± 1.4	67.8 ± 1.8	0.286
Current smokers	10(17)	9 (22)	0.350
Heavy alcohol intake (>14IU)	19 (34)	12 (30)	0.822
Duration of symptoms (weeks)	5.6 ± 0.7	8.8 ± 3.4	0.313
Family Hx Cancer	26 (45)	16 (40)	0.396
HRT Use (n=80)	13(27)	6 (18)	0.280
Assessment			
Symptomatic Detection	55(90)	41 (98)	0.140
Screening Detection	6 (10)	1 (2)	
Triple Assessment	51 (81)	32 (76)	0.326
Same Day Diagnosis	45 (71)	28 (67)	0.373
Treatment Approach			
Curative	62 (98)	40 (95)	0.351
Palliative	1 (2)	2 (5)	
Primary Treatment			
Surgery	60 (95)	37 (88)	0.394
Hormone Therapy	2 (3)	3 (7)	
Chemotherapy	1 (2)	2 (5)	
Type of Surgery			
Breast Conserving	30 (49)	18 (46)	0.856
Mastectomy	30 (51)	21 (54)	

BMI: Body Mass Index; HRT: Hormone Replacement Therapy

Demographic details as well as method of detection, diagnosis, assessment and treatment details were compared among metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 4.2: Anthropometric Details of Postmenopausal breast cancer patients

Characteristic	No Met Syn (n=63)	Met Syn (n=42)	P value
Anthropometry			
Body weight (Kg)	67.1± 1.6	78.4 ± 2.0	**<0.001**
Mean BMI (kg/m^2)	26.3 + 0.6	31.1 + 0.8	**<0.001**
Waist Circumference (cm)	92.3 ± 1.8	105.6 ± 1.7	**<0.001**
Central Obesity (>80cm>94cm)	49 (79)	42 (100)	**0.001**
BMI Categories			
Underweight (<20 kg/m^2)	3 (5)	-	**<0.001**
Normal Weight (20-25kg/m^2)	21 (34)	4 (10)	
Overweight (25-30 kg/m^2)	25 (40)	12 (30)	
Obese (>30 kg/m^2)	13 (21)	25(61)	
Body Composition			
Total Fat %	34.9 ± 0.9	39.5 ± 1.0	**0.001**
Total Fat Mass (kg)	24.2 ± 1.2	39.5 ± 1.0	**0.001**
Trunk Fat Mass %	31.2 ± 1.1	35.8 ± 1.1	**0.005**
Trunk Fat Mass (kg)	11.8 ± 0.6	14.9 ± 0.8	**0.003**

BMI: Body Mass Index

This table compares the nutritional assessment (weight, height, BMI, Body composition analysis) at time of diagnosis before cancer treatment was initiated, among metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 4.3: Metabolic Profile of Postmenopausal breast cancer patients

	No Met Syn (n=63)	Met Syn (n=42)	P Value
Hypertensive (BP >130/85) (mmHg)	30 (61)	36 (93)	**0.001**
Systolic BP (mmHg)	130 ± 2	140 ± 3	**0.008**
Diastolic BP (mmHg)	76 ± 2	80 ± 2	0.156
Anti HTN Medications	22 (35)	27 (66)	**0.002**
Lipid Profile			
Total Cholesterol (mmol/L)	4.8 ± 0.1	4.8 ± 0.2	0.795
Dyslipidaemia (>5.2mmol/L)	26 (42)	18 (44)	0.502
LDL Cholesterol (mmol/L)	2.7 ± 0.09	2.8 ± 0.1	0.630
HDL Cholesterol (mmol/L)	1.6 ± 0.04	1.3 ± 0.05	**<0.001**
Triglyceride (mmol/L)	1.1 ± 0.05	1.8 ± 0.1	**<0.001**
Serum Hormone Levels			
Progesterone (nmol/L)	1.44 ± 0.3	2.3 ± 0.8	0.291
Oetradiol (pmol/L)	99.2 ± 14.0	82.6 ± 6	0.355
Testosterone (nmol/L)	1.07 ± .07	1.14 ± 0.08	0.530
SHBG (nmol/L)	57.0 ±3.3	49.4 ±3.8	0.137
Inflammatary Markers			
SAA (mg/L)	10.2 ±3.1	13.0 ± 4.2	0.584
CRP (mg/L)	5.8 ± 1.0	10.3± 2.7	0.084
High CRP (>10 mg/L)	6(10)	8 (20)	0.140
Adipocytokine Levels (n=62)			
Leptin	1,387.8 ± 154.8	1,696.2 ± 137.6	0.324
Adiponectin	8,000.2 ± 59.3	8,090.0 ± 85.8	0.381
Glucose Metabolism			
Fasting Glucose	5.1 ± 0.05	6.0 ± 0.02	**<0.001**
HbA1c (n=86)	0	3 (9)	0.058
Insulin	8.2 ± 1.6	13.7± 1.9	**0.015**
Hyperinsulinaemia (>12mU/L)	4 (7)	13 (37)	**0.001**
HOMA-IR	1.8 ± 0.3	4.8 ± 1.1	**0.003**

SHBG: Sex hormone binding globulin; CRP: C-reactive protein; HbA1c: Glycosylated haemoglobin; SAA: Serum Amyloid A; HDL: High density lipoprotein; LDL: Low density haemoglobin; HTN Hypertension, BP: Blood Pressure

This table compares the incidence of Hypertension, and pre treatment fasting glucose, lipid profile, serum hormone and adipocytokine levels as well as markers of inflammation among *metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).*

4.5.2 Metabolic Syndrome, Obesity and Tumour Pathology

The average tumour size was 2.8 +/- 0.15 cm. Obesity (BMI>30kg/m2) was positively associated with large tumour size (>2cm) (p=0.021) a later clinical (p=0.022) and pathological stage (p=0.007) but obesity was not associated with positive nodal status (p=0.196) (Table 4.4).

The presence of MetS was significantly associated with a later stage of disease at presentation (P=0.022) with 78% diagnosed at clinical Stage II, III and Stage IV compared with 55% in non metabolic syndrome patients. Patients with MetS had a more advanced pathological stage with 93% Stage II, III and Stage IV compared with 63% in the non-Met S cohort (p<0.001). Node positive patients were significantly more likely to by hyperinsulinemic (22% Vs 5%, p=0.028) and have MetS (50% vs 39%, p=0.028). The individual features that contribute to the metabolic syndrome were associated with tumour size, tumour stage and nodal status (See table 4.5).

Metabolic syndrome was not associated with hormone receptor status or serum levels of oestrogen, progesterone or testosterone, or SHBG levels (Table 4.6). However, when obese and non-obese cohorts were compared (Table 4.6), low SHBG (p=0.002) and high insulin levels (p=0.006) were associated with obesity. Also SHBG levels decreased as the number of features of metabolic syndrome increased (0 features: 87 $\pm$ 15.8 compared to 5 features: 32 $\pm$2.7; p=0.003). Increasing insulin levels were significantly (p=0.001) associated with increasing number of features of metabolic syndrome

Table 4.4: Tumour Pathology of Postmenopausal breast cancer patients

Characteristic	No Met Syn (n=63)	Met Syn (n=42)	P value
Tumour Site (>1)	4 (7)	6 (15)	0.178
Tumour Size (cm)	2.7 ± 0.2	3.0 ± 0.2	0.310
Tumour Size >2cm (n=91)	37 (69)	30 (79)	0.233
Clinical Stage			
Stage 0,I	24 (45)	8 (22)	0.156
Stage II	26 (49)	24 (67)	
Stage III	2 (4)	3 (8)	
Stage IV	1 (2)	1 (3)	
Clinical Stage			
Stage 0 or I	24 (45)	8 (22)	**0.022**
Stage II, III or IV	29 (55)	28 (78)	
Pathological Stage			
Stage 0,I	22 (37)	3 (7)	0.007
Stage II	22 (37)	24 (59)	
Stage III	14 (24)	12 (29)	
Stage IV	1 (2)	1 (5)	
Pathological Stage			
Stage 0 or I	22 (37)	3 (7)	**<0.001**
Stage II, III or IV	37 (63)	38 (93)	
Lymph Node			
Negative	32 (55)	13 (33)	**0.028**
Positive	26 (45)	26 (67)	

LVI: lymphovascular invasion; NPI: Nottingham Prognostic Index

This table compares the clinico pathological features of tumours among metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).
LVI: lymphovascular invasion; NPI: Nottingham Prognostic Index

Table 4.5: Obesity, Hyperglycaemia, Hyperinsulinaemia Met Syndrome and Tumour Pathology

	Tumour Size < 2cm (n=25)	Tumour Size > 2cm (n=68)	P Value	Path Stage (Stage 0,1) (n=25)	Path Stage (Stage 2-4) (n=77)	P Value	Node Negative (n=46)	Node Positive (n=53)	P Value
Obesity (BMI >30kg/m^2)	5 (20)	30 (46)	**0.021**	4 (16)	34 (45)	**0.007**	15 (33)	22 (43)	0.196
Central Obesity (>80cm)	20 (80)	61 (91)	0.138	18 (72)	71 (94)	**0.009**	38 (83)	49 (94)	0.067
Hyperglycaemia (Glucose >5.6mmol/l)	4 (16)	20 (29)	0.148	3 (12)	24 (31)	**0.047**	10 (22)	16 (30)	0.235
Hyperinsulinaemia (Insulin >20mg/l)	2 (9)	10 (18)	0.288	0	12 (19)	**0.026**	2 (5)	10 (22)	**0.030**
Metabolic Syndrome	8 (33)	30 (45)	0.233	3 (12)	38 (51)	**<0.001**	13 (30)	26 (50)	**0.028**

This table summarizes the effect of Obesity (BMI), Central Obesity (Waist Circumference) Hyperglycaemia, Hyperinsulinaemia and the clustering together of these abnomalies as dignosed using the IDF definiton for Metabolic Syndrome on three important prognostic factors for outcome tumour size, advanced pathological stage and positive nodal status. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 4.6: Obesity and Serum Hormone Levels

	Non Obese (n=65)	Obese (n=40)	P value
Progesterone	1.20 ± 0.1	1.17 ± 0.3	0.916
Ostradiol	96.21 ± 13.5	86.32 ± 6.4	0.594
Testosterone	1.10 ± 0.1	1.13 ± 0.1	0.778
SHBG	59.24 ±3.4	43.52 ± 2.8	**0.002**
Insulin	7.02 ± 0.8	11.69 ± 1.6	**0.006**
CRP	6.19 ±1.1	10.25 ± 2.8	0.127
SAA	8.29 ± 1.6	16.81 ± 6.2	0.108

SHBG: sex hormone binding globulin, CRP: C reactive protein, SAA: Serum amyloid A

A further analysis of serum hormone levels was performed dividing the patients into two groups according to BMI, and comparing patients with a BMI >30kg/m2 (n=40) to those whose BMI<30kg/m2 (n=65). Anova analysis was used to compare continuous variables and values are shown as mean ± standard error.

4.6 Discussion

This study of an Irish population supports the association between obesity, the metabolic syndrome and postmenopausal breast cancer. Metabolic Syndrome was present in 39% of postmenopausal breast cancer patients, approximately double the rate reported in a recent population study (Waterhouse *et al*, 2009). The fact that menopause induces redistribution of fat mass leading to increased abdominal obesity, and affects lipid metabolism (Carr *et al*, 2003), possibly beginning in the years proceeding the actual time of menopause, may explain the increased risk of metabolic syndrome in postmenopausal women (Park *et al*, 2003; Lobo *et al*, 2009). Sixty six percent of obese patients had metabolic syndrome compared with 32% of overweight patients and 16% of normal weight patients, this is similar to rates of metabolic syndrome reported in a study of postmenopausal obese women (Simoncig-Netjasov *et al*, 2008).

Obesity is associated with an increased risk of many cancers, including oesophageal and colorectal adenocarcinoma, uterine, renal, and pancreatic, as well as a markedly increased risk of mortality from cancer, hence a unifying hypothesis that may impact on cancer biology is an intriguing concept. For breast cancer, worse outcomes have been previously ascribed to delay in diagnosis (Wee *et al*, 2000) and reduced detection of masses in often larger breasts (Hall *et al*, 1999; Hoe *et al*, 1993). The majority of patients in this study had symptomatic cancer at presentation; however a clear association of the altered metabolic and hormonal profile with pathological features and outcomes emerged. Metabolic syndrome, strongly associated with but not exclusive to obese patients, was associated with larger tumours at presentation, as well as nodal disease, and to our knowledge this is the first report to establish such an association in a prospective study. A previous study reported an increased prevalence of type 2 diabetes mellitus, hypertension, and dyslipidemia among breast cancer cases compared with women with benign breast pathology or women with no breast pathology (Sinagra *et al*, 2002). Another retrospective study found that metabolic syndrome adversely effects breast cancer recurrence; the relative risk of recurrence being 6.7 times greater in those with metabolic syndrome and high testosterone levels (>40) (Pasanisi *et al*, 2006).

Insulin, insulin resistance, and related growth factors are possible factors linking obesity, metabolic syndrome and cancer (Cowet & Hardy 2006). Other epidemiological studies

confirm that increased circulating levels of insulin and markers associated with insulin resistance including C peptide, Insulin Growth Factor (IGFs) and type 2 diabetes are associated with increased risk of postmenopaual breast cancer (Bruning *et al*, 1992; Muti *et al*, 2002; Schairer *et al*, 2004; Michels *et al*, 2003; Irwin *et al*, 2005). Insulin has diverse metabolic functions and can act as a growth factor influencing cell proliferation and cell death. It is a powerful mitogenic agent in normal mammary tissue as well as breast cancer cell (Cullen *et al*, 1990; Belfiore *et al*, 1996). Insulin acts via binding to the Insulin receptor (IR) and IR concentrations are higher in breast cancer tissue than in normal breast tissue. IR has also been directly related to tumour size, grade (Papa *et al*, 1990), and mortality (Mathieu *et al*, 1997). Hyperinsulinaemia was significantly associated with a more advanced stage of disease stage of disease and positive nodal status ($p=0.030$) but not with tumour size or grade of disease. Hyperglycaemia (>5.6mmol) was also more common in metabolic syndrome and was significantly associated with tumour size >2cm. Cancer cells use glucose for proliferation (Warburg *et al*, 1956), and one of the central characteristics of malignant tissues is increased metabolism of glucose (Dang *et al*, 1999). Therefore, a higher circulating glucose levels may encourage cancer development by providing an environment that promotes tumour growth (Xue *et al*, 2007).

The pathways of sex hormones and receptors on cancer tissue were studied, as the increased breast cancer risk seen in obese postmenopausal women could relate to altered sex hormone levels or receptor expression. The Endogenous Hormones and Breast Cancer Collaborative Group analysed individual data from eight prospective studies and reported a substantially reduced risk for BMI after adjusting for serum oestrogen concentrations (Key *et al*, 2002; Key *et al*, 2003). During the menopausal transition total oestrogen decreases markedly, and most oestrogen is derived by the aromatase conversion of plasma androstenedione to oestrone in adipose tissue. Oestrone is metabolized to oestradiol, and its free oestradiol, unbound to sex hormone-binding globulin (SHBG) that is the most biologically active in the breast. Earlier published studies report higher concentrations of estrogens and lower concentrations of SHBG in obese menopausal women when compared to normal weight women (Nelson *et al*, 1988; Kaye *et al*, 1991; Newcomb *et al*, 1995). In this study, there was no association between obesity and serum oestrogen, or progesterone levels when comparing all categories, and no patterns emerged for metabolic syndrome. However, low levels of SHBG were significantly associated with increasing obesity, suggesting increased bioavailable oestrogen. In other studies, plasma SHBG levels are consistently associated with abdominal obesity, showing negative correlations

with waist-to-hip ratio and CT-measured visceral fat area (Ivandic *et al*, 2002; Tchernof *et al*, 1999).

Obesity is associated with low grade inflammation, and is another factor which promotes cancer. Obesity induces macrophage accumulation in adipose tissue, which produce many of the pro inflammatory molecules released by adipose tissue and have been implicated in the development of obesity-induced inflammation (Bastarrachea *et al*, 2007). CRP and SAA are acute phase proteins released in response to inflammation, while mean levels were higher in metabolic syndrome group, significant differences were not found.

A combination of growth factors and receptor changes may underlie the association between obesity, metabolic syndrome and postmenopausal breast cancer. Insulin and oestrogen enhance proliferative activity in normal and malignant human mammary epithelial cells in culture; moreover insulin can reduce SHBG and increase bioavailable oestrogen (Borugian *et al*, 2003). Cells have a variety of receptors including ER, Insulin Growth Factor-1 receptor (IGF-1R), peroxisome proliferator-activated receptors (PPARγ) and leptin receptors; therefore it seems reasonable to look for cross-talks between the involved metabolic pathways. The ER can bind to and directly activate the IGF-1R and the IGF-I signalling enhances ER activation; IGF-1 and oestrogen have synergistic effects on cell cycling signalling and proliferation in human mammary cancer cell lines (Stoll *et al*, 2002; Hamelers *et al*, 2003). It may be that targeted studies of linked insulin and oestrogen pathways in breast cancer may uncover important targets, and that the absence of altered ER expression in this study may be of no biological significance.

In conclusion, this prospective study established a high prevalence of MetS and central obesity in an unselected prospective cohort of postmenopausal breast cancer patients. The presence of the MetS is associated with a more aggressive tumour phenotype. The prevalence of these altered metabolic profiles may be a key factor in determining the metastatic potential and prognosis of postmenopausal breast cancer, this need to be confirmed in larger prospective studies. Moreover, insights into mechanisms may also be uncovered through case-controlled studies with pre-menopausal breast cancer patients. Obesity and its adverse consequences is one of the few modifiable risk factors for postmenopausal breast cancer and thus an important measure for breast cancer prevention, and therapeutic strategies that target these abnormalities represent a novel approach to the prevention and management of breast cancer.

CHAPTER 5

METABOLIC SYNDROME AND LEPTIN ARE ASSOCIATED WITH ADVERSE PATHOLOGICAL FEATURES IN MALE COLORECTAL CANCER PATIENTS

Metabolic syndrome and Leptin are Associated with Adverse Pathological Features in Male Colorectal Cancer Patients

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5.1 Summary

Introduction: Metabolic syndrome (MetS) defines a clustering of factors including central obesity, hypertension, and raised plasma glucose, triglycerides and HDL cholesterol. Central obesity is associated with the risk of colorectal cancer, but the impact of MetS on colorectal cancer biology and outcomes is unclear.

Methods: A prospective observational study of colorectal cancer patients in an Irish population. Patients underwent a metabolic and nutritional assessment prior to treatment, including measurement of serum hormones and adipokines, including leptin and adiponectin, as well as CT measurement of visceral fat. MetS was defined according to the International Diabetes Federation definition[2].

Results: 130 consecutive colorectal cancer patients (66 male: 64 female) were recruited. MetS was diagnosed in 38% patients, exceed the population norms reported at 21%[3]. Males had significantly ($p < 0.05$) greater visceral fat area compared with females. MetS was associated with node positive disease ($p=0.026$), percent nodal involvement ($p=0.033$) as well as extramural vascular invasion ($p= 0.049$) in males, no significant association was observed in females. HDL-cholesterol was also significantly associated with a more advanced path stage ($p=0.014$) and node positive disease ($p=0.028$). Leptin was associated with nodal status ($p=0.036$), microvascular invasion ($p=0.054$), advanced pathological stage ($p= 0.046$) and later Dukes stage ($p=0.042$).

Conclusion: We report a high prevalence of MetS and visceral obesity in a colorectal cancer population. MetS and plasma leptin are associated with a more aggressive tumour phenotype in males only, and the implications of this with respect to prevention and treatment require further study.

5.2 Introduction

The increasing incidence of colorectal adenocarcinoma parallels the increased prevalence of obesity in the Western world. Epidemiological studies indicate that obesity is a risk factor for colorectal cancer and adenomas (Dignam *et al*, 2006). The underlying mechanisms linking obesity and colorectal cancer are unclear, but central (visceral) compared with subcutaneous fat, and the altered metabolic, endocrine and immunoinflammatory consequent on central obesity are mooted as factors that may fuel tumourigenesis (Cowey S & Hardy, 2006).

MetS defines features that link with central obesity, including high blood glucose levels, impaired glucose tolerance, dyslipidemia, and hypertension (Alberti *et al*, 2006). MetS has been associated with colorectal adenomas and adenocarcinoma, with a dose- response relationship between increasing numbers of features and the incidence of colorectal cancer (Kang *et al*, 2010; Stocks *et al*, 2008; Ahmed *et al*, 2006). One study reported a stronger association between MetS and risk of colorectal cancer in men, and the presence of MetS was associated with a higher morbidity, higher rate of liver metastasis, increased recurrence and reduced survival (Colangelo *et al*, 2002; Shen *et al*, 2008; Trevisan *et al*, 2001).

The association between MetS, visceral obesity and adipokines with colorectal cancer clinico-pathological variables has not been systematically studied. We report herein that MetS, in particular visceral adiposity, as well as plasma leptin was associated with adverse features, including node positivity and vascular invasion.

5.3 Patients and methods

This was a prospective study of newly diagnosed colorectal cancer patients presenting to the Colorectal Cancer Centre at St James's Hospital, Dublin. Patients were excluded from the study if they had a previous history of cancer. The study was approved by the hospital ethics committee for research involving human subjects according to the Helsinki agreement. Informed consent was obtained prior to involvement. Patients underwent a nutritional assessment at time of diagnosis before cancer treatment was initiated, with a

research dietitian who also carried out other measurements as detailed below. Details about medication use, past medical history, alcohol and tobacco use were also examined.

Colon cancer is defined as a tumour anywhere from the caecum/terminal ileum to the rectosigmoid junction or above 15cm from the anal verge. Rectal cancer is defined as a tumour where the distal margin is 15cm or less from the anal verge. For the purpose of this research colon and rectal cancers were grouped together. Routine preoperative assessment involves a colonoscopy and CT scan in all patients, and a transrectal ultrasound and MRI for rectal patients. The tumour is staged according to the TNM staging system (and the American Joint Committee on Cancer classification and Duke's staging system) (Greene *et al*, 2002; Turnbull *et al*, 1967). Treatment of colon cancer is primarily surgical resection of tumour with adjuvant chemotherapy if there remains a high probability of recurrence for example, positive margins, extramural or lymphovascular invasion, node positive disease. Rectal cancer patients with Stage T3 or T4 cancer would be considered for neoadjuvant therapy involving a regimen of chemotherapy (5 Fluorouracil(FU)) and radiation therapy (40 – 45 Gy in 20-25 fractions) and adjuvant chemotherapy would be considered in patients with lymph node involvement if not contraindicated due to patients age, co-morbidities, or poor performance indices.

5.3.1 CT-measurement of visceral fat

The cross-sectional surface areas of the different abdominal fat compartments were calculated at the disc space between the L3 and L4 vertebral body by Dr Julia Howard and Peter Beddy. All patients were scanned on a Siemens Emotion single-slice or a multislice Somatom Sensation scanner (Siemens, Erlangen, Germany). Individual scans were analysed on a Siemens Leonardo workstation (Siemens). The appropriate scan slice at the L3–L4 disc space was selected. The total fat area (TFA) was then measured by drawing a line around the skin surface with a cursor. The software calculated the area within the highlighted line. The cross-sectional fat content of this area was obtained by using a Hounsfield threshold value of −50 to −150. The visceral fat area (VFA) was then calculated by repeating the technique with an area delineated by a line drawn around the inner layer of the abdominal wall musculature. The subcutaneous fat area (SFA) was calculated by subtracting VFA from TFA. All areas were measured in square centimetres. One investigator completed all the measurements and was blinded to the clinical details of the subjects.

5.4 Statistical analysis

Statistical analysis was performed using the SPSS® Statistical Package for the Social Sciences Version 14.0 for Windows™ (SPSS® Inc., Chicago, IL). All P values are two-sided. Primary outcomes were to assess if obesity, MetS and features of MetS were associated with clinicopathological features. Further analysis was undertaken comparing male to female. Differences were assessed using Pearson Chi squares for categorical variables. For 2X2 table Fischer's exact test was used. Mann Whitney U test and ANOVA were used to compare continuous variables

A fifteen percent difference in metabolic syndrome incidence was considered clinically relevant and this study was adequately powered to detect this. When comparing metabolic syndrome and non metabolic syndrome groups clinically relevant differences in variables with a known standard deviation were used to determine sample size. This study was adequately powered to detect a clinically relevant difference of 3kg/m2 (+/- 5.3 kg/m2) in BMI, a 3cm (+/-2.1cm) in waist circumference, a 1.5cm (+/-2.5cm) difference in tumour size; 5mg/dl difference (+/-4.2mg/dl) in CRP, 2.0 point increase in insulin resistance (+/- 2.0), and a 20cm2 difference in subcutaneous (+/- 12cm2) visceral (+/- 10cm2) and total fat (+/-20cm2) between groups with 95% power using a cut-off for statistical significance of 0.05. In respect to difference in tumour pathology, this study was adequately powered to detect a 15% difference in the proportion of patients diagnosed with late stage and node positive disease among obese and non obese with 80% power using a cut-off for statistical significance of 0.05

5.5 Results

One hundred and thirty colorectal cancer patients were recruited (Table 5.1). The majority of patients were treated with curative intent (87%), and surgical resection (90%) the most common primary treatment. Twenty one (16%) patients had neoadjuvant chemotherapy therapy prior to surgery, all of whom had rectal cancer and a further 32 (24%) of colon cancer patients had adjuvant chemotherapy.

52 patients (38%) had MetS. There was no significant difference in median age, gender, alcohol intake, smoking status or performance status with similar ECOG, Karnofskys and ASA grades (ASA, 1963) between patients with and without MetS. MetS was associated with an increased prevalence of cardiovascular disease (P=0.001) and diabetes mellitus (P< 0.001).

5.5.1 Anthropometry & Metabolic Profile

The mean BMI was 26.3 ± 0.5 kg/m2, with 57% of patients either overweight or obese, and 71% centrally obese (>80 cm female; >90cm Male). MetS was more common in obese patients (63% obese Vs 33% non-obese; p< 0.001). MetS patients were significantly heavier (mean 10Kg increase) compared with patients without MetS, and had an 11cm greater waistline. BMI, total fat mass and trunk fat mass measured by bioelectrical impedence analysis were significantly higher in MetS patients (Table 5.2). Using CT measurements, total fat, visceral and subcutaneous fat area were significantly (p<0.05) compared with patients without MetS.

The metabolic profile of patients in both groups is shown in Table 5.3. MetS patients were more frequently hypertensive (87% v 48%) and perscribed anti-hypertensive medications (35% v 56%). Significantly more MetS patients were hyperglycaemic (p=0.000), hyperinsulinaemic (p=0.014), with 25% of MetS patients hyperinsulinaemic compared with 6% in patients without MetS (p=0.014). Inflammatory markers (CRP, SAA) were similar in MetS and non-metabolic syndrome. Insulin resistance measured by HOMA-IR was increased (p=0.071) in the MetS group compared with the non-MetS group. Leptin levels were non-significantly (p=0.099) increased in the MetS cohort.

Table 5.1: Demographic & Treatment Details

Characteristic	No Met Syn (n=78)	Met Syn (n=52)	P value
Age (mean ± SE)	66.5 ± 1.4	68.2 ± 1.5	0.430
Male:Female	39:39	27:25	0.486
Colon/Rectal	48/30	27/25	0.441
Current smokers	21(28)	7 (14)	0.068
Heavy Alcohol Intake (>14IU >21IU)	12 (16)	13 (27)	0.204
Duration of symptoms (weeks)	15.9± 2.4	17.9 ± 4.7	0.680
Performance Status			
Karnofskys score (>90%)	57 (80)	40 (89)	0.168
ECOG score (2+)	67 (94)	45 (94)	0.607
ASA Grade	56 (78)	29 (64)	0.245
Co-morbid Disease			
Cardiovascular Disease	29 (38)	35 (67)	**0.001**
Respiratory Disease	5 (7)	4 (8)	0.527
Diabetes	0	10 (19)	**0.000**
Treatment Approach			
Curative	63 (84)	45 (90)	0.247
Palliative	12 (16)	5 (10)	
Primary Treatment			
Surgery	69 (90)	47 (90)	0.567
Neoadjuvant Treatrment	12 (16)	8 (16)	0.587

BMI: Body Mass Index; HRT: Hormone Replacement Therapy

Demographic details as well as Performance Status, Co-morbid Disease and treatment details were compared among metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 5.2: Anthropometric Comparison of MetS vs non-MetS Patients

Characteristic	No Met Syn (n=78)	Met Syn (n=52)	P value
Anthropometry			
Body weight (Kg)	68.3± 1.5	77.9 ± 2.1	**< 0.001**
Mean BMI (kg/m^2)	24.5 + 0.5	29.1 + 0.4	**< 0.001**
Waist Circumference (cm)	91.5 ± 1.4	102.7 ± 1.5	**< 0.001**
Central Obesity (>80cm>94cm)	45 (59)	51 (100)	**< 0.001**
BMI Categories			
Underweight (<20 kg/m^2)	11(15)	-	**< 0.001**
Normal Weight (20-25kg/m^2)	33 (43)	10 (20)	
Overweight (25-30 kg/m^2)	22 (29)	23 (46)	
Obese (>30 kg/m^2)	10 (13)	17 (34)	
Body Composition			
Total Fat %	26.9 ± 1.3	32.7 ± 1.2	**0.003**
Total Fat Mass (kg)	19.3 ± 1.2	26.1 ± 1.5	**<0.001**
Trunk Fat Mass %	26.6 ± 1.3	32.1 ± 1.2	0.200
Trunk Fat Mass (kg)	12.6 ± 2.1	16.9 ± 2.5	**0.004**
CT Measurements			
Total Fat (cm^2)	260.6 ± 16.7	409.5 ± 19.2	**<0.001**
Visceral Fat (cm^2)	111.57 ± 8.6	188.5 ± 12.3	**<0.001**
Subcutaneous Fat (cm^2)	169.1 ± 10.8	221.7 ± 13.4	**0.003**

This table compares the nutritional assessment (weight, height, BMI, Body composition analysis) at time of diagnosis before cancer treatment was initiated, among metabolic syndrome and non metabolic syndrome patients. It also quantifies total, visceral and subcutaneous fat area as determined by assessment of CT scans (See Methods for more detail). Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 5.3: Metabolic Profile

Characteristic	No Met Syn (n=78)	Met Syn (n=52)	P value
CEA	48.1 ± 24.3	59.9 ± 45.6	0.802
Hypertensive (BP >130/85 mmHg)	37 (48)	45 (87)	**<0.001**
Systolic BP (mmHg)	126 ± 1.7	139 ± 2.5	**<0.001**
Diastolic BP (mmHg)	73 ± 1.3	78 ± 2	0.070
Anti HTN Medications	27 (35)	29 (56)	**0.045**
Lipid Profile			
Total Cholesterol (mmol/L)	4.4 ± 0.1	4.4 ± 0.2	0.876
Dyslipidaemia (>5.2mmol/L)	14 (24)	10 (23)	0.555
LDL Cholesterol (mmol/L)	2.7 ± 0.09	2.8 ± 0.1	0.630
HDL Cholesterol (mmol/L)	1.35 ± 0.04	1.17± 0.05	**0.008**
Triglyceride (mmol/L)	1.1 ± 0.05	1.8 ± 0.2	**<0.001**
Serum Hormone Levels			
Progesterone (nmol/L)	2.0 ± 0.5	1.4 ± 0.2	0.374
Oetradiol (pmol/L)	110.7± 9.7	91.3 ± 6.8	0.133
Testosterone (nmol/L)	8.13 ± 1.1	8.36 ±1.2	0.891
SHBG (nmol/L)	50.8 ±2.5	47.8 ±4.5	0.551
Inflammatary Markers			
SAA (mg/L)	60.1 ±16	68.1 ± 22	0.770
CRP (mg/L)	23.8 ± 4.1	20.7± 4.3	0.617
High CRP (>10 mg/L)	31 (41)	21 (42)	0.519
Adipokine Levels			
Adiponectin units	8.55 ± 1.3	8.55 ± 1.3	0.989
Leptin units	7.95 ± 1.4	11.36 ± 1.3	0.099
Glucose Metabolism			
Fasting Glucose (mmol/L)	5.2 ± 0.09	6.1 ± 0.1	**<0.001**
Hyperglycaemic (>5.6mmol/L)	12 (16)	39 (75)	**<0.001**
HbA1c (n=86)	0	2 (5)	0.174
Insulin(mU/L	5.5 ± 0.5	13.1± 4.8	**0.041**
Hyperinsulinaemia (>12mU/L)	3 (6)	9 (25)	**0.014**
Hyperinsulinaemia (>20mU/L)	0	5 (14)	**0.011**
HOMA-IR	1.3 ± 0.1	5.0 ± 2.3	**0.071**

SHBG: Sex hormone binding globulin; CRP: C-reactive protein; HbA1c: Glycosylated haemoglobin; SAA: Serum Amyloid A; HDL: High density lipoprotein; LDL: Low density haemoglobin; HTN Hypertension, BP: Blood Pressure

This table compares the incidence of Hypertension, and pre treatment fasting glucose, lipid profile, serum hormone and adipocytokine levels as well as markers of inflammation among metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

5.5.2 Metabolic Syndrome and Tumour Pathology

In the entire cohort MetS was not associated with size of tumour (p=0.250), Dukes stage (0.090), clinical or pathological stage (p=0.110) (Table 5.4). Lymph node involvement approached significance (44% vs 28%; p=0.050). There was no difference in the incidence of synchronous tumour, nodal yield, structures involved, residual or metastatic disease. No significant relationship was seen with other features of MetS (central obesity, hyperinsulinaemia, hyperglycaemia)

In males (Table 5.5), however, a distinct relationship between MetS and clinico-pathological features was evident, being associated with lymph node status (p=0.026) and degree of nodal involvement (p=0.033) and extramural invasion (p=0.049). No significant association was observed in females.

5.5.3 Adipokines

Leptin (p<0.001) increased with increasing BMI and adiponectin (p=0.001) and SHBG (p=0.031) significantly decreased with increasing levels of BMI (Figure 5.1). Adiponectin showed no association with central obesity, MetS, insulin resistance or tumour pathology (Table 5.6). Leptin was also associated significantly associated with central obesity (p< 0.000) and visceral fat area, insulin >12 (p=0.020) but not hyperglycaemia (p=0.238) or MetS (0.099). It was also associated with positive nodal status (p=0.036), vascular invasion (p=0.054), advanced pathological stage (p= 0.046) and Dukes stage (p=0.042)

Table 5.4: Tumour Pathology

Characteristic	No Met Syn (n=78)	Met Syn (n=52)	P value
Tumour Site (>1)	3 (4)	2 (4)	0.685
Tumour Size (cm)	3.7 ± 0.3	3.8 ± 0.3	0.770
Size >30mm	46 (70)	34 (76)	0.325
Dukes' Stage			
A or B	43 (73)	25 (58)	0.089
C or D	16 (27)	18 (42)	
Clinical Stage			
Stage I	6 (11)	6 (14)	0.340
Stage II	16 (29)	18 (43)	
Stage III	25 (45)	3 (8)	
Stage IV	9 (16)	6 (14)	
Clinical Stage			
Stage 0 or I	22 (39)	24(57)	0.061
Stage II, III or IV	34 (61)	18 (43)	
Pathological Stage			
Stage I	17 (26)	9 (21)	0.287
Stage II	28 (43)	15 (34)	
Stage III	14 (22)	17 (39)	
Stage IV	6 (9)	3 (7)	
Pathological stage			
Stage 0 or I	45 (69)	24 (54)	0.087
Stage II, III or IV	20 (31)	20 (45)	
Residual disease			
R0: No residual tumour	63 (82)	42 (81)	0.832
R1: Microscopic residual tumour	4 (5)	4 (8)	
R2: Macroscopic residual tumour	10 (13)	6 (11)	
Nodal Involvement			
No of nodes removed	17.6 ± 1.1	15.3 ± 1.2	0.176
Lymph Node Positive	18 (28)	20 (44)	0.050
No. of poditive nodes			
0 nodes	47 (72)	25 (56)	0.186
1-3 nodes	11 (17)	13 (29)	
4+ nodes	7 (11)	7 (16)	
Differentiation			
Well (grade 1)	10 (14)	8 (16)	0.488
Moderate (grade 2)	57 (80)	40 (80)	
Poor (grade 3)	4 (6)	1 (2)	
Extramural Vascular invasion	19 (29)	19 (40)	0.151
Metastases present	3 (4)	2 (4)	0.994

LVI: lymphovascular invasion; NPI: Nottingham Prognostic Index

This table compares the clinico pathological features of tumours among metabolic syndrome and non metabolic syndrome patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 5.5: Metabolic Syndrome and Tumour Pathology (Male)

	MALE			FEMALE		
Characteristic	**No Met Syn (n=39)**	**Met Syn (n=27)**	**P value**	**No Met Syn % (n=39)**	**Met Syn % (n=27)**	**P value**
Tumour Size (>3cm)	69	68	0.597	71	83	0.238
Pathological stage						
Stage 0 or I	77	57	0.121	63	52	0.296
Stage II, III or IV	23	43		37	47	
Vascular Invasion	21	46	0.049	36	34	0.572
Lymph Node Positive	17	45	0.026	37	44	0.416
Nodal Involvement (No + nodes)						
0	83	54	0.033	63	56	0.519
1-3	10	41		23	17	
4+	7	5		14	26	

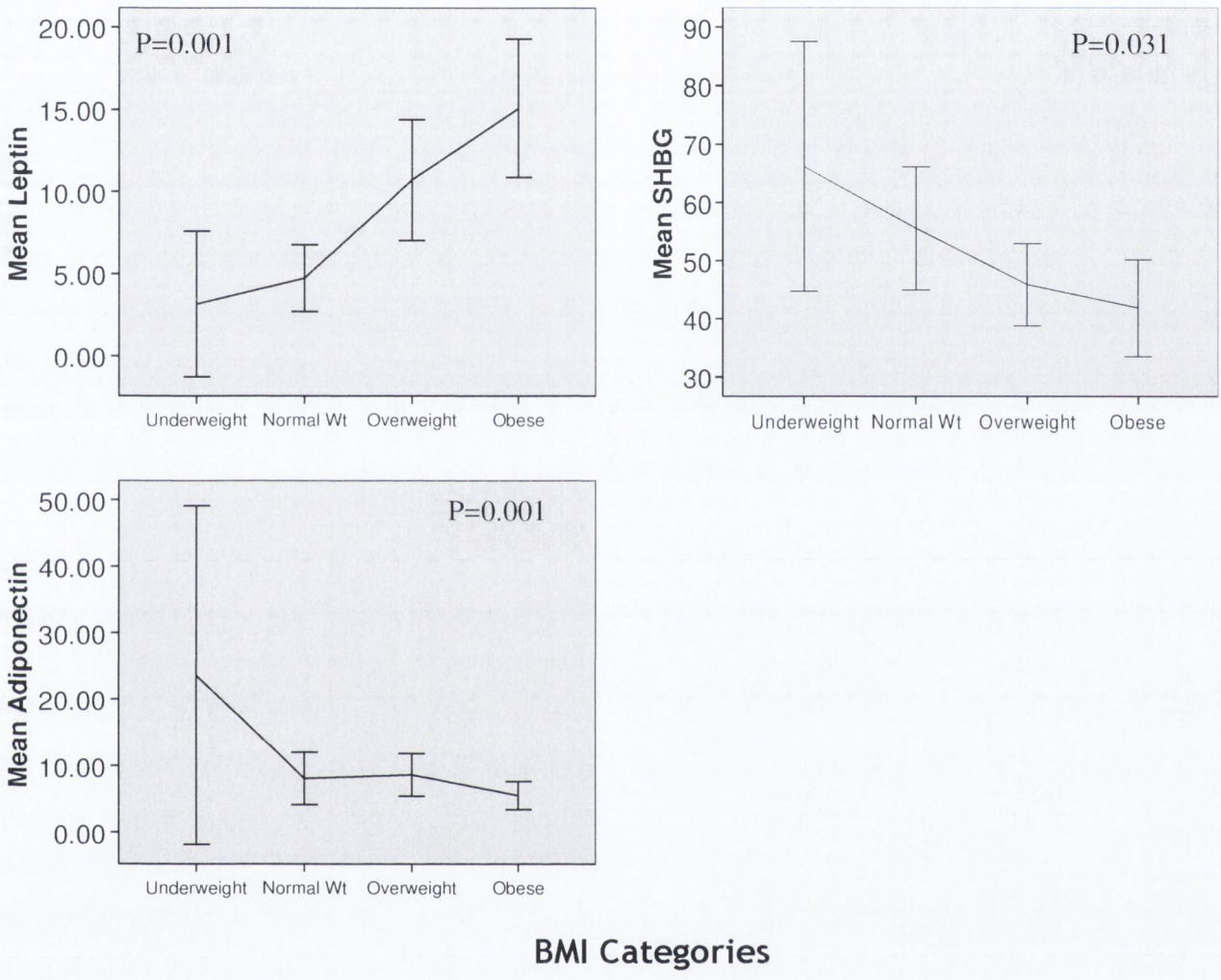
Gender analysis was performed to examine any difference in association between metabolic syndrome and significant clinico pathological features. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 5.6: Leptin and Tumour Pathology

Characteristic	Leptin (n=56)	P value	Adiponectin (n=56)	P value
Tumour Size				
<3cm	12.5 ± 2.8	0.092	6.4 ± 2.3	0.406
>3cm	8.3 ± 1.2		8.7 ± 1.2	
Dukes A/B	7.9 ± 1.3	0.042	8.0 ± 1.4	0.619
Dukes C/D	12.7 ± 2.1		9.2 ± 2.1	
Pathological stage				
Stage 0 or I	7.9 ± 1.0	**0.046**	8.0 ± 1.4	0.830
Stage II, III or IV	12.2 ± 2.1		8.4 ± 1.9	
Vascular Invasion		0.054		
Absent	8.2 ± 0.9		7.5 ± 1.3	0.576
Present	12.5 ± 2.3		9.2 ± 2.0	
Lymph Node Negative	7.8 ± 0.9	**0.036**	8.0 ± 1.4	0.854
Lymph Node Positive	12.7 ± 2.2		8.5 ± 2.0	
Waist Circumference (<80cm <94cm)	3.4 ± 0.5	**< 0.001**	10.9 ± 3.0	0.255
Waist Circumference (>80cm >94cm)	12 ± 1.1		8.0 ± 1.1	
Obesity				
BMI<30	7.4 ±1.0	**0.001**	9.5 ± 1.4	0.179
BMI>30	15.1 ± 1.9		5.7 ± 1.2	
Hyperglycaemia				
<5.6 mmol/L	8.4 ±1.3	0.238	8.9 ± 1.4	0.600
>5.6 mmol/L	11.1 ± 1.5		7.5 ± 1.7	
Insulin <12 mU/L	8.5 ± 1.3	**0.020**	8.0 ± 1.5	0.417
Insulin >12 mU/L	17.7 ± 4.9		3.5 ± 2.7	
Insulin <20 mU/L	9.4 ± 1.5	0.324	8.0 ± 1.5	0.409
Insulin >20 mU/L	14.9 ± 1.0		3.6 ± 1.9	

Leptin and Adiponectin ELISA levels were analysed for a small unselected group of colorectal cancer patients (n=56). Analysis was performed to assess if leptin or adiponectin was associated with measures of obesity, central obesity and hyperglycamia and hyperinsulinaemia and also significant clinico-pathological features. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error.

Figure 5.1: The change in serum leptin, SHBG and adiponectin levels across BMI categories.



Error Bars represent +/- 2X St Error of Mean

Mean Leptin, adiponectin and SHBG were compared across BMI categories. The above graphs shows mean leptin ($p<0.001$) increases with increasing BMI and adiponectin ($p=0.001$) and SHBG ($p=0.031$) significantly decreased with increasing levels of BMI.

5.6 Discussion

In Ireland colorectal cancer is the second commonest cancer diagnosed and the second leading cause of cancer-related death, with rates predicted to increase by approximately 50% by 2020 and 100% by 2035 (National Cancer Registry Ireland, 2006; National Cancer Registry Ireland, 2008). Modifiable risk factors for colon cancer are sought, and in this regard, studies of colon cancer risk have reported strong positive associations with obesity, particularly with central adiposity (Martinez 2005). Obesity is associated with the incidence and mortality of many cancers, notably oesophageal adenocarcinoma, post-menopausal breast cancer, endometrial, uterine, renal, and pancreatic cancer; hence a unifying hypothesis that may impact on cancer biology is an intriguing concept. In this regard, there is an increasing focus on central fat and the altered metabolic, immune, inflammatory and hormonal milieu consequent on obesity.

Epidemiological evidence in colorectal cancer have linked fasting glucose, C peptide, insulin and insulin growth factor 1 (IGF-1), HDL cholesterol, triglycerides, leptin, visceral fat and type 2 diabetes as increasing the risk (Cowey & Hardy 2006; Trevisan *et al*, 2001; Wei *et al*, 2005A; Schoen *et al*, 1999; Larsson *et al*, 2005; Howard *et al*, 2010). The clustering of these risk factors is the cornerstone of the MetS. To our knowledge the impact of MetS on tumour pathology has not been addressed. This study of an Irish population reveals that MetS was present in 38% of CRC patients, approximately double the rate reported in a recent population study (Waterhouse *et al*, 2009). MetS was not exclusive to the obese, and 23% of patients with a normal BMI had MetS, but the majority of MetS patients being overweight (51%) or obese (63%). Cardiovascular disease and diabetes clustered with MetS, and it would appear that visceral obesity and MetS is a more sensitive indicator of underlying co-morbid medical conditions compared with BMI-defined obesity, consistent with other reports (Schoen *et al*, 1999; Després *et al*, 2006; Frezza *et al*, 2006).

An intruiging thesis is that the male preponderance of colorectal cancer may be linked to visceral adiposity (Moore *et al*, 2004; Terry *et al*, 2002). Although the incidence of obesity (20% vs 22% p=0.463) was similar among males and females, respectively, visceral obesity was significantly more common in men, with a significantly greater waist circumference (98.5 $\pm$ 1.5cm vs 93,2 $\pm$1.7cm p=0.019) and visceral fat area in men (180

vs 106 p< 0.001) while subcutaneous fat area was significantly higher in females (159 V 214 p<0.001). Total and visceral fat area were associated with hyperglycaemia (p=0.020), insulin resistance (p < 0.001), with no relationship with subcutaneous fat (p=0.567). MetS was more common in males compared to females, albeit non-significant (49% vs39% p=0.486). This is the first study to report an association with a more aggressive tumour phenotype in males (node positive disease, extent of nodal involvement, and vascular invasion), previous studies have linked the presence of MetS with an increased risk of liver metastasis, recurrence and mortality rate (Shen *et al*, 2008; Trevisan *et al*, 2001).

The specific components of MetS were also assessed for impact on tumour pathology. Of the individual features of MetS, only HDL cholesterol was significantly associated with a more advanced path stage (p=0.014) and node positive disease (p=0.028). Reduced HDL cholesterol has been associated with increased cancer risk as well as the development of distant metastasis in colorectal cancer patients (Notarnicola *et al*, 2005). Whether it is an independent factor or a co-variate to obesity, reduced physical activity or insulin resistance is unclear. Also HDL and their protein and lipid constituents also influence oxidation and inflammation which maybe important in cancer progression.

Recent studies in colorectal cancer and MetS support the hypothesis of an additive effect of individual features of MetS. Stock et al found the risk of colorectal cancer doubled with the presence of 3 factors (obesity, hypertension and hyperglycaemia), compared to risk for isolated factors (Stocks *et al*, 2008). A dose-response association between an increased number of MetS components present at baseline and colorectal cancer incidence after multivariate adjustment (Ahmed *et al*, 2006). An increased relative risk of death from colorectal carcinoma in the cluster analysis of MetS compared with individual factors was reported by Trevisian. A large UK study demonstrated that insulin resistance-related biomarker clustering predicted cancer mortality, after 21.5 years of follow up (Loh *et al*, 2010). MetS has been associated with the presence of adenomas, and risk increased incrementally with the presence of 0, 1, 2 and >3 clinical features of MetS (Kim *et al*, 2007). This may support the hypothesis that clustering of the metabolic risk factors may have a role in promoting the development and progression of invasive cancer from a pre cancerous lesion, but this needs to be confirmed in further prospective studies.

Visceral obesity is associated with the production of adipokines, with raised plasma leptin and reduced plasma adiponectin. Leptin is secreted by adipocytes in proportion to

adipocyte tissue mass. Two case control studies showed increased risk of colon cancer in men and women (OR = 2.72) with no association between serum leptin in rectal cancer (Stattin *et al*, 2003; Tamakoshi *et al*, 2005). Leptin exerts its effect through binding to the leptin recptor (Ob-R), which can activate several genes involved in cell proliferation and up-regulate the expression of angiogenic factors. In colon cancer, a progressive increase in leptin expression through the progression from normal colon (4.5% positive), to adenoma (29.5%) to carcinoma (73.5%) has been reported, suggesting that leptin may have a role in driving this malignant transformation of invasive cancer from a pre cancerous lesion (Franks *et al*, 2005; Koda *et al*, 2007). Leptin was also associated with aggressive tumour features in this study: positive nodal status, vascular invasion, advanced pathological stage. Leptin expression in poorly differentiated cancer may be significantly reduced compared with well-differentiated cancer (Koda *et al*, 2007). Adiponectin is inversely associated with waist circumference, visceral fat, and insulin resistance and levels decrease as the number of MetS components increases (Park *et al*, 2004; Steffes *et al*, 2004; Santaniemi *et al*, 2006). In this study adiponectin was inversely associated with BMI (p=0.001), but not with MetS, central obesity, insulin resistance or tumour pathology, and it appeared to have less association with pathologic variables than leptin. The role of leptin and its receptor and the effect on clino-pathological features needs to be confirmed in further prospective studies.

In conclusion, this prospective study established a high prevalence of MetS and visceral obesity in an unselected prospective cohort of colorectal cancer patients. The presence of the MetS is associated with a more aggressive tumour phenotype in males only. This study supports the hypothesis of an additive effect of the individual features of MetS. The pathophysiological mechanisms whereby obesity promotes colorectal cancer development are likely to be multifactorial. The prevalence of visceral obesity and these altered metabolic profiles may be a key factor in determining the metastatic potential and prognosis but need to be confirmed in larger prospective studies as well as examining the potential pro-inflammatory and pro-tumourigenic pathways facilitated through the altered metabolic state. Obesity is one of the few modifiable risk factors for colorectal cancer and therapeutic strategies that target the associated abnormalities represent a novel approach to the prevention and management of this cancer.

CHAPTER 6

IMPACT OF OBESITY ON OUTCOMES IN THE MANAGEMENT OF LOCALISED ADENOCARCINOMA OF THE OESOPHAGUS AND OESOPHAGOGASTRIC JUNCTION

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"Impact of obesity on outcomes in the management of localised adenocarcinoma of the oesophagus and esophagogastric junction."

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6.1 Summary

Background: Obesity trends in the western world parallel the increased incidence of adenocarcinoma of the oesophagus and oesophagogastric junction. The implications of obesity on standard outcomes in the management of localised adenocarcinoma, in particular operative risks, have not heretofore been systematically addressed.

Methods: This retrospective analysis of prospectively collected data included 150 consecutive patients, 36 (24%) were obese (BMI > 30), and 114 non-obese, of whom 43 were normal weight (BMI 20-25) and 71 were overweight (BMI 25-30). Eighty- one patients underwent multimodal therapy. The primary end-points were in-hospital mortality and morbidity, and median and overall survival.

Results: Thirty of 36 (84%) obese patients were in the BMI range 30-35. Compared with the non-obese cohort, obese patients had significantly increased respiratory complications (p=0.037), peri-operative blood transfusions (p=0.021), anastomotic leaks (p=0.009), and length of stay (p=0.001), but no difference in mortality (p=0.582) or major respiratory complications (p=0.171). Median and overall survival was equivalent (p=0.348) in both groups.

Conclusions: Obesity was associated with increased respiratory complications and anastomotic leak rates, but not with major respiratory complications, mortality, or survival. These outcomes suggest that the added risks of obesity on standard outcomes in oesophageal cancer surgery are modest and should not independently have a significant impact on risk assessment in oesophageal cancer management.

6.2 Introduction

The pattern of oesophageal cancer in Europe and North America has changed dramatically in recent decades, with a marked increase in the incidence of adenocarcinoma of the oesophagus and oesophagogastric junction (Enzinger & Mayer, 2003). The explanation for this increase is unclear, but several risk factors, including chronic gastro-oesophageal reflux disease (GORD), obesity/diet, and *H.pylori* eradication, are plausibly linked with this emerging trend (Enzinger & Mayer, 2003; Devesa *et al,* 1998). Increasing epidemiological evidence strongly links obesity and both the incidence of adenocarcinoma at these sites but also death from this cancer (Engel *et al*, 2003; Brown *et al*, 1995; Vaughan *et al*, 1995; Chow *et al*, 1998; Lagergren *et al*, 1999; Ryan *et al*, 2006; Calle *et al*, 2003).

Consequently, the oesophageal surgeon today is presented increasingly with the challenge of managing obese patients with adenocarcinoma of the oesophagus or junction. The risk of operative mortality is up to 10%, with an approximate 50% risk of morbidity, and some evidence suggests that these risks may be further increased by neoadjuvant therapy, in particular combination chemotherapy and radiation therapy (Bailey *et al*, 2003; Fiorica *et al*, 2004; Reynolds *et al*, 2006A). The management of localised disease moreover has major impact on quality of life over several months (Blazeby *et al*, 2005; Reynolds *et al*, 2006B). Studies of the implications of obesity, defined by World Health Organization (WHO) criteria (WHO 2000) as a body mass index (BMI) of greater than 30 Kg/m^2, are therefore important, particularly with regard to risk assessment for oesophageal surgery. A combination of factors, including the association of obesity with existing co-morbidities and medical complications, the complexity and duration of anesthesia and surgery, as well as insulin resistance, hormonal alterations, and chronic inflammation (Balkwill *et al*, 2001), all permit the speculative thesis that obesity may increase the incidence of complications.

The principal risks following oesophagectomy relate to respiratory complications. Intuitively, obese patients may be at higher risk, as pulmonary function in the obese is characterized by reductions in functional residual capacity, expiratory reserve volume, and PaO_2, and an increase in the alveolar-arterial oxygen difference [(A-a)DO2] (Adams *et al*, 2000; Flanchbaum *et al*, 1998). The obese patient may consequently be more vulnerable to

significant hypoxia from common postoperative problems such as atelectasis. Abnormalities in control of breathing are also common, and obstructive sleep apnoea may occur in up to 40% of males with morbid obesity, and obstructive hypoventilation syndrome may also occur (Brooks-Brumm *et al*, 1997). Intra-operative or postoperative ventilation may be impaired by reduced compliance of the lung and chest wall and an increase in airway resistance. Moreover, where ventilator support is required postoperatively, weaning may be delayed due to this reduced chest wall compliance, and obese patients compared with non obese patients have an up to a five-fold increase in oxygen uptake when changing from positive pressure ventilation to spontaneous breathing as a result of the increased work of breathing (Balkwill *et al*, 2001; Adams *et al*, 2000).

Notwithstanding theoretical concerns, there is currently no reported systematic assessment of the relationship between obesity and standard outcomes in the management of localised cancer of the oesophagus and oesophagogastric junction. We report herein the experience of this Unit, and highlight the largely equivalent outcomes at this time between obese and non-obese cohorts.

6.3 Patients and methods

A retrospective analysis of a prospectively compiled database of patients with histologically proven adenocarcinoma of the oesophagus or oesophagogastric junction who underwent surgery in St. James Hospital, Dublin between the period of January 1998 and December 2005 was performed. This study was approved by the hospital's ethics committee. Severely malnourished patients with a BMI <20kg/m2 (n=5) and patients who underwent an emergency oesophagectomy were excluded from the analysis. Pre-operative weight and height was used to calculate BMI. The pre-operative medical co-morbidities and presenting symptoms were noted, as well as the reported and actual weight loss at time of diagnosis. The patient's age, cigarette and alcohol consumption, performance status, initial routine blood results and pulmonary function test scores were also noted. Obesity was defined as per WHO and NIH Clinical Guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults as a BMI > 30Kg/m^2 (Expert Panel on the Identification, Evaluation, and Treatment of Overweight in Adults 1998).

All patients had localised disease based on clinical, endoscopic, and computed tomographic (CT) assessment. Endoscopic ultrasound was not routinely used, fluorodeoxyglucose (FDG)-positron emission tomography (PET) scanning has been routine since 2004. Using CT-criteria, the mediastinal, left gastric and celiac lymph nodes were classified as N1 (invaded) if the maximal transverse diameter of these nodes were larger than 1 cm. Localised disease was defined as T_{1-3}, N_{0-1}. All tumours of the oesophagogastric junction were assigned as Type I, II or III, (Siewert & Stein 1998); Type I was adenocarcinoma of the distal oesophagus, usually arising in specialised intestinal metaplasia; Type II is a true adenocarcinoma of the cardia arising immediately at the oesophagogastric junction; and Type III is a subcardial gastric carcinoma infiltrating the oesophagogastric junction and distal oesophagus from below.

Patients with Type I and II tumours were considered for multimodal therapy involving a regimen of chemotherapy (cisplatin and fluorouracil) and radiation therapy (40-44 Gy in 15 – 20 fractions) as previously described (Walsh *et al*, 1996). The majority (97%) of patients undergoing an oesophagectomy had a thoracotomy as a component of their surgical management, either combined with an abdominal and neck exploration (3-stage) for mid and upper-oesophageal cancers, or cancer arising in long-segment Barrett's oesophagus, or with an abdominal exploration (2-stage) for most lower third and junctional tumours, or combined with a total gastrectomy for junctional tumours with significant gastric extension (Type III). All intra-thoracic and cervical anastomoses were performed with interrupted single-layer 3.0 Polydioxanone (Ethicon, Dublin). A 2-field lymphadenectomy (abdominal and thoracic) was performed in all transthoracic cases. The length of operation, intra-operative blood loss and blood products given were all noted.

The Unit protocol is that all patients had epidural analgesia, and that patients are extubated immediately following surgery and managed in a high dependency unit (HDU). All patients are fed enterally from 12 hours postoperatively via a needle catheter jejunostomy and a Gastrografin contrast study is performed routinely in day 8 postoperatively before initiating oral fluids. A dietitian, throughout the hospitalization period and at 3 months follow-up, monitored nutritional intake, complications, and body weight changes.

All complications from surgery to discharge from hospital were prospectively documented. Respiratory failure was defined as the requirement for mechanical ventilation

beyond 24 hours after surgery. Adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF) were defined as per Bone et al (Bone *et al*, 1992), sepsis required evidence of systemic inflammatory response syndrome (SIRS) with microbiological evidence of infection, and the diagnosis of pneumonia required either positive sputum cultures of clear clinical and radiographic evidence of consolidation.

Major respiratory complications for the purpose of this analysis were defined as pneumonia, empyema, respiratory failure and ARDS, and any patient who experienced more than one major complication was only included in the analysis once.

The tumour stage was defined according to the TNM staging system and the American Joint Committee on Cancer Classification (Greene *et al*, 2002). Fat-clearing methods were not used to increase lymph node yield. The definition of a curative resection was that all visible tumour was removed and that proximal, distal and circumferential margins were free of tumour on histological examination. In patients undergoing neoadjuvant therapy, the extent of residual carcinoma in the oesophagectomy specimen was assigned to one of five tumour regression grades (TRG) categories as per Mandard et al (Mandard *et al*, 1994). TRG1 represents fibrosis within the oesophageal wall with no identifiable residual cancer cells, pathological complete response (pCR); TRG2 represents rare residual cancer cells scattered throughout the fibrosis; TRG3 represents an increase in the number of residual cancer cells, but fibrosis still predominated. TRG4 represents residual cancer cells outgrowing fibrosis; and TRG5 represents a complete absence of regression change. A TRG of 1 or 2 is deemed a good response, and a TRG of 3-5 is a poor response.

6.4 Statistical methods

Statistical Analysis was performed using statistical package for the social sciences (SPSS) Version 11.0 for windows. ANOVA was employed to identify significant differences between BMI Categories, with significance defined as $P<0.05$. Post-operative complications were compared using univariate Chi Square Tests. The primary comparison was between obese and non-obese cohorts, but some comparisons were also made between three cohorts i.e. obese, overweight and normal weight. Multinominal logistic regression models were used to account for potential confounding factors associated with

post operative complications. The model included age, sex, heavy alcohol intake and current smokers. From the models we obtained hazard ratios (HR) and 95% confidence intervals (CIs) levels for the obese group relative to non obese group. Actuarial survival was calculated from the date of first treatment by the Kaplein Meier method and comparisons between the groups were made by the log rank test.

This study is adequately powered to detect a 15% difference in morbidity and respiratory complications with 80% power using a cut-off for statistical significance of 0.05, unfortunately it was not adequately powered to detect differences in mortality.

6.5 Results

6.5.1 Patient Demographics

In this period resection for localised disease with curative intent (anticipated clear margins (R0)) was undertaken in 150 patients, of which 81 (54%) had neoadjuvant chemoradiation therapy prior to surgery according to the Unit protocol. Forty-three patients (29%) were normal weight (BMI 20-25 Kg/m^2, with a weight range between 50-85kg seventy patients (47%) were overweight (BMI 25-30 Kg/m^2), with a weight range of 80-130kg. and thirty six patients (24%) were obese with a BMI greater than $30Kg/m^2$with a weight range between 80-130kg. The median BMI was 27 kg/m^2. In the obese group, 30 (83%) were in the range 30-35 Kg/m^2 [80-115kg], 5 (14%) were between 35 and 40 Kg/m^2 [101-125kg] and 1 (3%) was over 40 Kg/m^2 [131kg].

The clinical pattern of presentation was similar in both groups (Table 6.1). There was no significant difference between obese and non-obese in known Type 2 Diabetes, respiratory disease or in performance status. The incidence of cardiovascular disease was influenced by BMI, as 7 of 43 (16%) of the 20-25 BMI had a history of cardiovascular disease, compared with 28 of 70 (40%) in the 25-30 range, and 17 of 36 (47%) in the over 30 range (p=0.003).

In obese patients, preoperative forced expiratory volume (FEV) 1 (p=0.046) and the FEV1/forced vital capacity (FVC) ratio (p=0.014) were significantly poorer compared with the non-obese group. This did not relate to tobacco consumption, where the highest percentage of current smokers (40%) was in the normal weight groups compared with overweight (14%) and obese (19%) groups (p =0.042).

Table 6.1: Demographics of Obese and Non-Obese Groups

Demographic details	Non-obese (n=114)	Obese (n=36)	P value
Sex: male/female	98/16	31/5	0.216
Age: median (range)	62 (37-79)	62 (29-79)	0.521
Symptoms			
Dysphagia	81 (71)	29 (81)	0.183
Heartburn	36 (32)	11 (31)	0.541
Regurgitation	39 (34)	12 (33)	0.546
Weight loss > 10%	34(33)	4 (13)	0.059
History of GORD > 1 year	31 (27)	10 (28)	0.562
Smoking and alcohol			
Never smoked	41 (36)	7 (20)	0.076
Ex smoker (>1 year)	46 (40)	22 (61)	
Current smoker	27 (24)	7 (19)	
Heavy alcohol	20 (18)	9 (25)	0.352
Co Morbid disease			
Cardiovascular	35 (31)	17 (47)	0.033
Respiratory disease	19 (17)	8 (22)	0.299
Type II Diabetes	9 (8)	2 (6)	0.258
Performance Status			
Karnovsky > 90%	108 (96)	34 (95)	0.367
ECOG – fully active	79 (70)	26 (73)	0.345
ASA Grade I or 2	95(87)	34(94)	0.322
Pulmonary Function Tests			
FEV 1	3.1 (1-5.5)	2.7 (1.1-4.1)	0.046
FVC	4.0 (2.0-6.4)	3.8 (1.7-5.9)	0.297
FEV1/FVC ratio	79 (42-94)	74 (53-89)	0.014

The clinical pattern of presentation including demographic details, symptoms, performance status, presence of co-morbid disease and specific pulmonary function tests were compared among obese and non obese patients. Chi square analysis was used to compare categorical variables and values shown as N (%).

6.5.2 Treatment Characteristics

There was no significant difference in EG junction classification among the BMI categories (Table 6.2). Sixty seven per cent of obese patients had multimodal therapy compared with 50% of non-obese patients (p=0.018). The majority of patients in both groups underwent a 2-stage oesophagectomy.

6.5.3 Tumour Pathology

The R0 resection rate was 83% and 84% respectively in obese and non-obese groups (p=0.198). In patients undergoing multimodal therapy, the complete pathological response rate was 12% in the obese group compared with 21% in the non-obese group (p=0.425), and there was no differences between groups in terms of achieving a major histomorphological response (TRG1 or 2) at the primary site, observed in 42% and 45% respectively in obese and non-obese groups (p=0.495) (Table 6.2). In this cohort, non-obese patients had more advanced cancer according to pathologic stage, with 46% patients presenting with Stage 3 disease vs 25% of obese patients (P=0.013). There was no significant difference in nodal status with the majority of patients being node-positive, 53% in the obese group compared with 61% in the non-obese group (p = 0.082). The median nodal yield was significantly (p=0.008) greater in the non-obese group at 15 (5-46) compared with 10 (4-28) in the obese patient. Non-obese patients had significantly greater number of positive nodes (3 (0-25) vs 1 (0-8) p=0.037). Barrett's epithelium was present in 56% of resected specimens in the obese group and 44% in the non-obese group (p=0.180).

Table 6.2: Tumour Type, Treatment Details and Pathology

	Non-obese (n=114)	Obese (n=36)	P value
Tumour location			
Lower: Type 1 OG Junction	53 (47)	11 (31)	0.290
Type 2 OG Junction	42 (38)	21 (60)	
Type 3 OG Junction	17 (15)	3 (9)	
Mid Oesophageal	2 (2)	0	
Associated Barrett's	50(44)	20 (56)	0.180
Type of surgery			
2-stage oesophagectomy	96 (84)	33 (92)	0.486
3-stage oesophagectomy	14 (12)	1 (3)	
Trans-hiatal	3 (3)	1 (3)	
Thoraco-abdominal	2 (2)	1 (3)	
Multimodal therapy	57 (50)	24 (67)	0.018
Pathology			
Stage 0 / 1	22 (19)	11 (31)	0.013
Stage 2	39 (34)	16 (44)	
Stage 3	52 (46)	9 (25)	0.082
Node positive	70 (61)	20 (53)	
Resection Margins Clear	93 (84)	29 (83)	0.257
Number of nodes analysed	15 (5-46)	10 (4 – 28)	0.008
Response to Neoadjuvant Therapy (n=81)			
Tumour regression grade 1 and 2	26 (45)	10 (42)	0. 495
Tumour regression grade 3, 4 and 5	31 (55)	14 (58)	
Pathological complete response	12 (21)	3 (12)	0.425

Clinical Stage, treatment, pathological staging, tumour regression with multimodality therapy were compared among obese and non obese patients. Chi square analysis was used to compare categorical variables and values shown as N (%).

6.5.4 Surgery and In-Hospital Complications

There was no significant difference (p = 0.150) between the mean duration of surgery in the obese (350 min) and non-obese groups (320 min) (Table 6.3). The use of blood products intra-operatively and in the first 48 hours after surgery in the obese group (p = 0.021), with 24% of patients requiring over 2 units of blood compared with 7% in the non-obese group.

In-hospital mortality was 6% in both groups. Twenty one of 36 (58%) obese patients had a respiratory complication, compared with 43 of 114 (38%) non-obese patients (p = 0.037). There was however no significant difference between obese and non-obese groups in major respiratory complications including pneumonia (p=0.502), ARDS (p=0.630) and respiratory failure (p=0.299). There were two cases of empyema, both in the obese group (p=0.057). Five patients in the obese group developed an anastomotic leak, 3 radiologically and 2 clinical, compared with 1 clinical and 1 radiological leak in the non-obese group (p=0.009). All were managed non-operatively, and one clinical leak in both groups was managed with endoprosthesis. There were no significant differences between groups with respect to venous thromboembolism (p=0.436), major wound problems (p = 0.760), arrhythmias (p=0.168), and renal dysfunction (p= 0.482). The median stay in the High Dependency Unit postoperatively was 4 days [0-14] in the obese group compared with 4 days [0-32} in the non-obese group (p=0.937). The median hospital stay was significantly (p=0.001) greater at 23 (13-94) days in the obese group compared with 18 (1-61) days in the non-obese group.

By multivariate analysis (Table 6.4), obese patients, compared with the non-obese cohort, were 2.6 times more likely to suffer any respiratory complication (p=0.014), 2.7 times more likely to have a pleural effusion (p=0.019) and 11 times more likely to have an anastomatic leak (p=0.006).

Table 6.3: In-Hospital Postoperative Morbidity and Mortality

	Non-obese (n=114)	Obese (n=36)	p value
Mortality	7 (6)	2 (6)	0.582
Sepsis	12 (11)	5 (14)	0.386
All respiratory complications	43 (38)	21 (58)	0.037
Major respiratory complication*	21 (19)	10 (28)	0.171
Respiratory failure	12 (11)	2 (6)	0.299
ARDS	7 (6)	2 (6)	0.630
Pneumonia	15 (13)	4 (11)	0.502
Empyema	0	2 (6)	0.057
Pleural effusion	27 (24)	15 (42)	0.032
Atelectasis	9 (8)	5 (14)	0.121
Thromboembolism	3 (3)	1 (3)	0.436
Major wound complications	3 (2)	0	0.760
Arrhythmia	13 (11)	7 (19)	0.168
Anastomotic leak	2 (2)	5 (14)	0.009
Renal dysfunction	9 (8)	2 (6)	0.482
Blood products**			
0	64 (58)	13 (39)	0.021
1-2 units	38 (34)	12 (36)	
> 2 units	8 (7)	8 (24)	

* denotes number of patients with a major respiratory complication i.e. pneumonia, respiratory failure, ARDS or empyema

** denotes blood products given intra-operatively or within 48 hours postoperatively

All complications from surgery to discharge from hospital were prospectively documented and compared according to BMI>30kg/m2 or <30kg/m2. Tale 6.3 shows the difference in incidence of morbidity and mortality in obese compared to non obese. Major respiratory complications for the purpose of this analysis were defined as pneumonia, empyema, respiratory failure and ARDS, and any patient who experienced more than one major complication were only included in the analysis once.

Table 6.4 – Relative Hazard ratios for Obesity and Postoperative Complication

	P Value	OR	95% CI's
All Respiratory Complications	0.014	2.6	1.2-5.9
Major Respiratory complications	0.283	2.7	1.1-6.4
Pleural Effusion	0.019	2.7	1.1-6.4
Anastomotic Leak	0.006	11	2.0-61.7

OR: Odds Ratio; CI's 95% Confidence Intervals.

Adjusted for Age, Sex, Heavy Alcohol Intake and Current Smokers

Following on from Univariate analysis, multinominal logistic regression models were used to account for potential confounding factors associated with post operative complications including age, sex, heavy alcohol intake and current smokers. From the models we obtained hazard ratios (HR) and 95% confidence intervals (CIs) levels for the obese group relative to non obese group which are presented in Table 6.4.

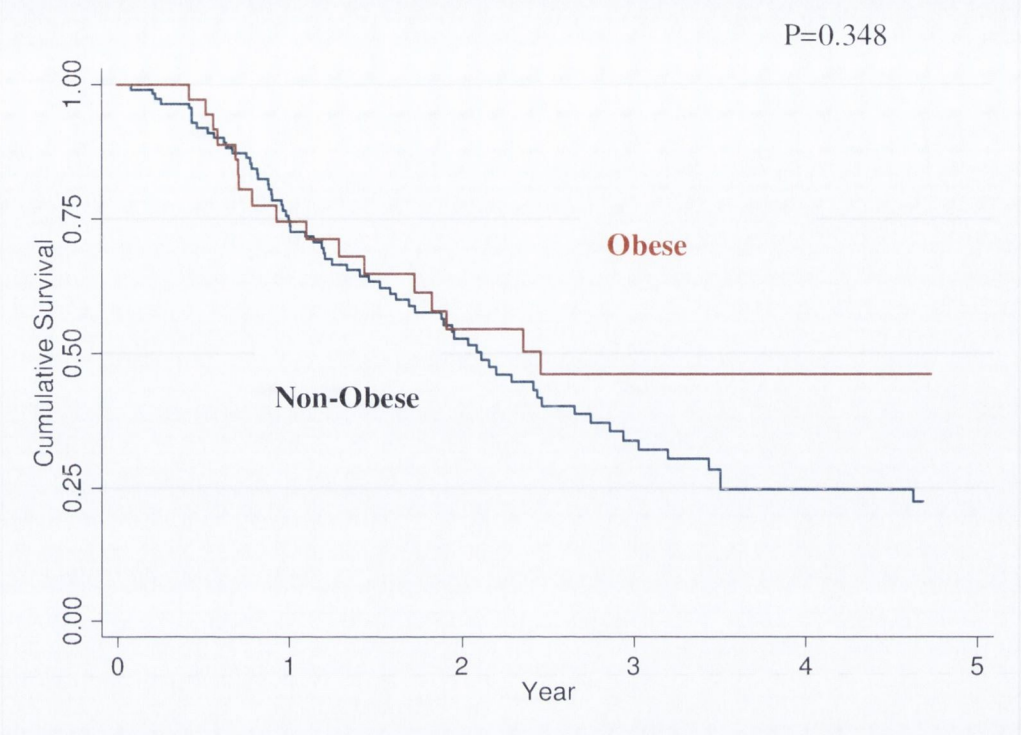
6.5.5 Postoperative Nutrition

All patients were nutritionally supported via a feeding jejunostomy in the postoperative period. The median duration of postoperative nutrition support (full feeding or overnight feeding) in the obese group was 16 days (10-80) and 15 (2-53) in the non-obese group (p=0.128). Obese patients lost more weight post operatively as in-patients compared to non-obese patients (4.7 (0-26) Kgs vs 2.8 (0-14) Kgs p=0.048).

6.5.6 Survival

At a median follow-up of 39 months, the median survival (Figure 6.1) in the obese group was 27 months, compared with 25 months in the non-obese group (p=0.348). The 1, 3, and 5-year survival in the obese group was 75%, 46% and 46%, compared with 75%, 34% and 22% respectively in the non-obese group.

Figure 6.1 – Survival in Obese and Non Obese in Oesophageal Cancer Patients



Non-Obese

Survival time	No at Risk	Deaths	% Survival
0 year	114	0	100%
1 year	81	23	75%
3 years	21	36	34%
5 years	10	7	22%

Obese

Survival time	No at Risk	Deaths	% Survival
0 year	36	0	100%
1 year	26	8	75%
3 years	11	9	46%
5 years	6	0	46%

This graph represents a comparison of survival in obese and non obese cohorts with oesophageal cancer (n=150). At a median follow-up of 39 months, the median survival in the obese group was 27 months, compared with 25 months in the non-obese group (p=0.348). The 1, 3, and 5-year survival in the obese group was 75%, 46% and 46%, compared with 75%, 34% and 22% respectively in the non-obese group.

6.6 Discussion

Obesity, defined as a BMI greater than 30 Kg/m^2, has increased in incidence in the developed world in the last decade. In the United States, for instance, approximately 34% of the population are obese, and in 2008 220,000 operations were performed for morbid obesity (Flegal *et al,* 2010; Taylor 2008). The increased incidence of adenocarcinoma of the oesophagus and oesophagogastric junction in recent decades parallels the increasing prevalence of obesity. In an Irish cohort we recently reported that 82% of patients developing adenocarcinoma of the oesophagus or oesophagogastric junction were overweight or obese, and that obesity in males was associated with a four-fold increase risk of adenocarcinoma (Ryan *et al*, 2006). The explanation for this association is unclear. One possible mechanism links the typical male central adiposity with chronic GORD, both of which are independently associated with adenocarinoma of the oesophagus and junction (Lagergren *et al*, 2006). In addition to a mechanical link, the pleiotropic properties of the adipocyte have come under scrutiny, as adipocytes from central fat may have endocrine, paracrine and immunological properties (Kershaw *et al*, 2004). This may be manifested in the metabolic syndrome which is a constellation of atherogenic dyslipidemia, elevated blood pressure, and elevated blood glucose associated with insulin resistance. The pro-inflammatory response associated with central adiposity and the metabolic syndrome may, at least theoretically, promote inflammation and tumourigenic pathways that are relevant to oesophageal adenocarcinoma and other tumour types (Balkwill *et al*, 2001).

Surgery for oesophageal cancer is associated with a significant risk of morbidity and mortality, and has a major impact on quality of life (Enzinger & Mayer, 2003). A recent review of 70,000 patients reported a mortality of 6.7% between 1990 and 2000 (Jamieson *et al*, 2004). The combined Veterans Administration experience for the same period reported an approximate 50% major morbidity rate and 10% mortality rate (Bailey *et al*, 2003). In the United Kingdom, McCulloch and colleagues reported a 12% in-hospital mortality rate from a multicentre series (McCulloch *et al*, 2003). The recent advent of multimodality regimens, in particular neoadjuvant combination chemotherapy and radiation therapy, may further increase operative risks (Fiorica *et al*, 2004; Reynolds *et al*, 2006B). It is unassailable that there is no common elective cancer surgery that carries the same risks. In an era of risk stratification and informed consent, data on the impact of obesity on outcomes after oesophagectomy is increasingly important, and to our

knowledge this is the first report specifically addressing the relationship of obesity to the standard outcome indicators of an oesophageal unit.

In this study, no increase in in-hospital mortality was observed in the obese cohort. Respiratory complications were rigorously recorded, and an increased incidence of complications was observed in the obese cohort. There was however no increase in the more major complications of postoperative pneumonia, respiratory failure or ARDS in the obese group. The incidence of anastomotic leaks was increased in the obese group, however the incidence of clinically evident leaks was not significantly different. The incidence of anastomatic leak was low (3%) compared to the reported incidence of up to 10% post oesophagectomy (Junemann-Ramirez *et al*, 2005; Briel *et al*, 2004). In univariate analysis obesity was the only factor associated with anastomotic leak, and there was no relationship with incidence and age, sex, ASA grade (ASA, 1963), smoking or alcohol use. In this regard, a recent study after resection and primary anastomosis for left sided colonic emergencies, obesity was associated with risk of anastomotic leak (Bionda *et al*, 2005). The factors involved in the increased leaks observed in the obese group in this study are unclear, but we would speculate that the dependence of touch and judgment rather than clear visibility of the right gastroepicloic vessels, as well as increased tension of the conduit in the high thorax or in the cervical site may compromise vascularity of the gastric anastomotic site. Other factors such as diabetes and cardiovascular disease may also be contributory, but this was not evident in this analysis.

The concern that obese patients would have a higher incidence of wound infections and dehiscence could not be verified, and the incidence of clinical venous thromboembolism was low in this study where all patients received prophylactic low molecular weight heparin. Blood transfusion requirements were significantly increased in the obese group, and obesity was associated with a significantly longer duration of post-operative hospital stay.

Oesophagectomy is associated with significant metabolic, endocrine, and immunoinflammatory changes. A similar spectrum of response is seen after major blunt trauma. In studies of blunt trauma patients, however, and in contrast to this study, Smith-Choban et al reported a 42% mortality in obese versus 7% for non-obese, and respiratory failure due to ARDS was the primary cause (Smith–Choban et al, 1991). In a study by Neville et al (Neville *et al*, 2004) of 242 patients admitted to intensive care unit (ICU)

after blunt trauma, 62 were obese, and the odds ratio of mortality was 5.7 compared with the non-obese cohort. In a study of patients undergoing liver transplantation, obesity was associated with an increased incidence of multiple organ failure (Sawyer *et al*, 1999). The lack of major added risks associated with obesity in this study is consistent with reports of equivalent complication rates in obese and non-obese patients undergoing cardiac surgery, where the increase risk of complications appears to be only evident in patients with extreme obesity, with a BMI of greater than 40 (Wigfiled *et al*, 2006). Only 2 patients in this study had a BMI > 40, both had sleep apnoea and one had obesity hypoventilation syndrome, both survived without major complications, but clearly risk assessment in the morbidly obese patient cannot be inferred from this study of predominantly patients in the BMI range of 30 to 35.

Frequent symptoms of reflux are associated with increased risks of Barrett's oesophagus, and these risks are substantially elevated by obesity and smoking (Smith *et al*, 2005). In one population based study in obese patients (BMI>30), the risk of Barrett's oesophagus was minimal with no reflux symptoms (OR: 0.7 95% CI's: 0.2-2.4), and increased dramatically with weekly reflux symptoms (OR: 34.4 95% CI's: 6.3-188). There was no difference in the reported incidence of GORD in this population which may explain why the lack of association between obesity and Barrett's oesophagus. This study addressed in addition the standard oncological indicators, and there was no difference in RO resection rate, tumour response rate, and survival. Nodal yield was less in the obese cohort, perhaps reflecting the lack of routine fat clearing mechanisms by pathologists.

The limitations of the study are acknowledged, in particular the retrospective nature of the analysis. Prospective study in this Unit now encompasses assessment of the metabolic syndrome, comprehensive respiratory physiology analysis pre-treatment as well as documentation on intra-operative and early postoperative dynamics in respiratory physiology, and studies of immune function and metabolism in the perioperative period. Underweight patients (BMI < 20) were also excluded because of the small number (n=5) of the cohort and the fact that they represent a high-risk group, but when all patients were included and the population was divided into either quintiles or tertiles, a significant association of the highest quintile or tertile with anastomotoic leak and respiratory complications remained evident (data not shown).

In conclusion, this study shows that obese patients undergoing surgical or multimodality management of localised adenocarcinoma of the oesophagus or oesophagogastric junction have an increased incidence of respiratory complications and radiological anastomotic leaks, a greater requirements for blood products compared with non-obese patients, and a longer hospital stay. There was no difference in mortality or major complications, and the cancer survival outcomes are equivalent. Risk stratification is the ultimate motivation for establishing complication rates in obese patients undergoing oesophageal surgery, and this study shows that surgery was undertaken in an obese population, predominantly patients with a BMI between 30 and 35, with no major increased risk of serious morbidity or mortality.

CHAPTER 7

IMPACT OF OBESITY ON SURGICAL AND ONCOLOGICAL OUTCOMES IN THE MANAGEMENT OF COLORECTAL CANCER

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"Impact of Obesity on Surgical and Oncological Outcomes in the Management of Colorectal Cancer"

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7.1 Summary

Introduction: Obesity is an established risk factor for colorectal cancer, particularly in males, and may negatively impact on oncologic outcomes. The aim of this study was to examine the impact of Body Mass Index (BMI) on mortality and morbidity, tumour pathology, mortality, and overall survival in a consecutive cohort of Irish colorectal cancer patients treated with curative intent.

Methods: A retrospective analysis of BMI data entered prospectively into a comprehensive electronic data-base of colorectal cancer patients was undertaken. Patients were excluded if they had emergency surgery, previous malignancy, or the BMI was not recorded. Analysis was performed comparing genders, obese with non obese and comparing BMI categories.

Results: Of the 414 patients, 10% were underweight (<20kg/m^2), 35% were normal weight (20-25kg/m^2), 37% were overweight (25-30kg/m^2) and 18% were obese (≥30.00kg/m^2). Obesity overall was not significantly associated with pathological stage (p=0.099) or positive lymph node status (p=0.109) or degree of nodal involvement (p=0.068). In colon cancer and in males only obesity was significantly (p<0.05) associated with more advanced pathological stage, node positivity, and degree of nodal involvement. There was no difference in the overall incidence of major (p=0.244) and minor complications (p=0.078) when comparing obese with non obese, but pelvic abscesses were more common in obese patients (p=0.037). The underweight cohort had a higher rate of major complications (p=0.041), sepsis (p=0.024) and post operative death (p=0.006). Survival was equivalent between BMI categories and obese and non obese groups (p=0.469).

Conclusion: Obesity was associated with more advanced tumours in males and in colon cancer patients only, and with a higher risk of postoperative pelvic abscesses, but no significant differences with non-obese cohorts in the main outcome measures of in-hospital mortality, major morbidity, and survival. Conversely, the adverse consequences of under-nutrition were highlighted in this study.

7.2 Introduction

Colorectal cancer incidence parallels the increasing prevalence of obesity in the Western world. It is well established that obesity is a risk factor for the development of colorectal cancer (Dignam 2006), and colorectal adenomas. In Ireland, colorectal cancer is the second commonest cancer diagnosed and the second leading cause of cancer-related death, and rates are predicted to increase by approximately 50% by 2020 (National Cancer Registry Ireland, 2006). Previous reports have shown that obesity may be associated with unfavourable surgical outcomes, including anastomotic leak, requirement for blood transfusion (Benoist 2000; Rullier *et al,* 1998), increased operative mortality, and reduced survival (Meyerhardt 2003; Murphy *et al*, 2000; Tsukada 2004). Visceral or central obesity has also been associated with increased post-operative complications and the presence of metabolic syndrome, a consequence of visceral obesity, is associated with reduced survival (Trevisan 2001; Cholangelo 2002).

In this Cancer Centre, a comprehensive data-base of all clinical, pathological and outcome data has been maintained prospectively since 2000. The goal of this report is to assess the impact of BMI-defined obesity on standard outcomes and performance measures in the management of localised colorectal cancer.

7.3 Methods and materials

An analysis of a prospectively compiled database was performed, on 414 patients with a histologically proven colorectal carcinoma, who were diagnosed in St James Hospital, Dublin, between 2000 and 2008. The Patients Analysis Tracking System (PATS, Dendrite, U.K.) records all patient details, treatment, tumour pathologies and postoperative complications for patients. Patients were excluded if BMI was not available (n=336) and emergency cases (n=53). This study was approved by the hospital's ethics committee.

Upon presentation a complete history, family history and physical examination were carried out. Pre-operative evaluation includes full blood count, liver, renal and bone profiles, carcinoembryonic antigen (CEA) measurement, urinalysis, electrocardiogram, chest X-ray and computed topography (CT) scan for staging as well measures of performance status. The Karnofsky scoring tool (0-100%) is used as a quantitative marker

to score cancer patients' general wellbeing (Karnofsky 1949). The ECOG (Eastern Cooperative Oncology Group) score measures physical activity and runs from 0 to 4; 0 meaning fully active, able to carry on all pre-disease performance without restriction and 4 meaning completely disabled (Oken 1982). The American Society of Anaesthesiologists (ASA) (ASA, 1963) grade patients according to physiological reserve and the attendant risk from anaesthesia and surgery (Grade I meaning normal healthy patient and grade IV meaning incapacitating systemic disease which is constantly life-threatening.

Colon cancer is defined as a tumour anywhere from the caecum to the rectosigmoid junction or above 15cm from the anal verge. Rectal cancer is defined as a tumour where the distal margin is 15cm or less from the anal verge. The distal colon includes only the rectum and sigmoid colon (Strul *et al,* 2006) Patients with synchronous tumours were included once and classified according to the largest tumour (n = 14). Preoperative weight and height were used to calculate BMI. Obesity was defined as a BMI greater than 30 kg/m2 as per World Health Organization (WHO 1998) and was also classified according to underweight (BMI<20kg/m2); normal weight (BMI 20-25kg/m2) and overweight (25-30kg/m2).

All treatment considerations are discussed at a weekly multidisciplinary team conference. Treatment of colon cancer was primarily by surgical resection with adjuvant chemotherapy for node-positive patients and for node-negative patients with adverse pathological features. Most rectal cancer patients with T3 or T4 tumours were offered neoadjuvant therapy involving a regimen of chemotherapy (5 Fluorouracil(FU)) and radiation therapy (40 – 45 Gy in 20-25 fractions). Pathologic staging is according to the TNM staging system (and the American Joint Committee on Cancer classification (Greene 2002) [16] and Duke's staging system revised by Turnbull *et a.* (Turnbull 1967).

All complications from surgery to discharge from hospital were prospectively documented. Complications were divided into major and minor complications; major complications include pneumonia, ARDS, abdominal or pelvic abscesses, sepsis, organ failure, myocardial infarction, while minor complications include low hemoglobin, urinary retention, confusion, nausea, pyrexia, abdominal pain if not accompanied by any major complications. Pulmonary complications for the purpose of this analysis were grouped together and include pneumonia, pulmonary embolism, pulmonary effusion, pulmonary

oedema and ARDS. Wound complications include wound dehiscence, discharge and infection.

7.4 Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences Version 16.0 for Windows (SPSS Inc, Chicago, III). All P values are two-sided. Primary outcome measures were to assess if obesity was associated with post operative morbidity, tumour pathology, mortality and survival. After comparing obese to non obese, further analysis was undertaken comparing underweight, normal weight, overweight and obese. Any difference in incidence of complications was assessed using Chi squares for categorical variables and Mann Whitney U test and ANOVA for continuous variables. Survival was estimated from the date of first diagnosis using the methods of Kaplan and Meier and differences assessed using the log-rank test. Further analysis was performed comparing male and female cohorts to assess any significant differences.

Because of the low incidence of morbidity and mortality associated with colorectal surgery, this study was not sufficiently powered to detect differences. In respect to difference in tumour pathology, this study was adequately powered to detect a 15% difference in the proportion of patients diagnosed with late stage and node positive disease among obese and non obese, in the gender and cancer site specific analysis with 80% power using a cut-off for statistical significance of 0.05. A 6 month difference in survival was considered clinically significant and this study was powered to detect this.

7.5 Results

7.5.1 Baseline Characteristics

Of 414 eligible patients, 273 (66%) had cancer of the colon and 141 (34%) had cancer of the rectum. Forty one patients (10%) were underweight (<20 kg/m2), 145 patients (35%) were normal weight (20-24.99kg/m^2), 153 (37%) were overweight (25.00-29.99kg/m^2), and 75 (18%) were obese (≥30.00kg/m^2). In the obese group, 17 patients (4%) had a BMI greater than >35 kg/m^2. The incidence of obesity was similar for both colon and rectal

cancer, at 19% and 17% respectively. There was no significant difference in median age, gender, or alcohol intake between obese and non-obese cohorts (P=0.347) (See Table 7.1). Non obese patients had similar ECOG scores but had lower ranked Karnofskys score (p< 0.0001) and were more like to be current smokers (P=0.002). Weight loss, nausea and vomiting were more frequently reported in non obese patients, while obese patients more commonly reported rectal bleeding and dyspnoea as symptoms (p=0.043). The median duration of symptoms prior to presentation was 8 weeks (p=0.488). Obesity was associated with an increased prevalence of cardiovascular disease (P< 0.001) and diabetes mellitus (P=0.019).

Table 7.1: Demographics of Study Population according to Obesity

Characteristics	Non Obese (n = 337) (81%)	Obese (n = 77) (19%)	P value
Age (Mean) yrs	64.7 ± 12.8	65.7 ± 10.3	0.501
Sex: Male	194 (58)	43 (56)	0.440
Female	143 (42)	34 (44)	
Current smoker	86 (26)	7 (9)	**0.002**
Heavy drinker	50 (15)	13 (17)	0.908
Hx of Colorectal cancer	65 (20)	15 (20)	0.530
Performance Status			
Karnofskys score (>90%)	293 (88)	73 (95)	**0.043**
ECOG score (2+)	322 (96)	74 (96)	0.498
Presenting Symptoms			
Weight Loss	124 (37)	20 (26)	**0.046**
PR Bleed	170 (50)	56 (73)	**0.000**
Bowel Obstruction	6 (2)	1 (1)	0.615
Nausea & Vomiting	51 (15)	6 (8)	0.061
Dyspnoea	22 (7)	11 (15)	**0.027**
Co-morbid Disease			
Cardiovascular Disease	126 (37)	47 (61)	**0.000**
Respiratory Disease	43 (13)	8 (11)	0.363
Diabetes	22 (7)	12 (17)	**0.006**

The clinical pattern of presentation including demographic details, symptoms, performance status and presence of co-morbid were compared among obese and non obese patients. Chi square analysis was used to compare categorical variables and values shown as N (%).

7.5.2 Treatment

Three hundred and thirty seven patients underwent surgery alone, 77 patients had neoadjuvant chemotherapy and radiation therapy prior to surgery, and 179 received adjuvant chemotherapy and a further 35 had adjuvant radiotherapy. The most common procedure was an anterior resection (35%), followed by a hemicolectomy (34%), sigmoid colectomy (12%), and abdoperineal resection (10%). The median length of operation was approx 3 hours and similar in obese and non obese patients (p=0.801). 14% of non obese and the same percentage of obese patients had more than 2 units of blood transfused intra operatively (p=0.599).

7.5.3 Tumour Pathology

BMI was not associated with tumour size (p=0.169) or pathological stage, however more obese patients had stage III or IV disease at time of resection (63% v 54%; p=0.099). Two thirds of obese patients had positive lymph node status compared with 47% of non obese patients (p=0.109), and nearly double the amount of obese patients had 4 or more nodes involved compared with non-obese patients (28% v 14%; p=0.067). There was no difference in incidence of synchronous tumour, nodal yield, structures involved, residual or metastatic disease when comparing obese to non–obese (Table 7.2). Analysis of the male cohort revealed a distinct relationship between obesity and node positive disease and degree of nodal involvement (p=0.012) in males only (Table 7.3). Further analysis of colon cancer only showed a significant relationship between obesity and pathological stage and degree of nodal involvement (p=0.012) (Table 7.4), but this was not evident in the rectal cancer cohort (Table 7.5).

Table 7.2: Obesity and Tumour Pathology

Characteristics	Non Obese (n = 337) (81%)	Obese (n = 77) (19%)	P value
Type of tumour			
Colon	222 (66)	51 (66)	0.533
Rectal	115 (34)	26 (34)	
Proximal	136 (40)	28 (36)	0.304
Distal	201 (60)	49 (64)	
Multimodal Rx	67 (20)	10 (13)	0.095
Mean Tumour Size (mm)	45	41	0.169
Size >30mm	200 (69)	43 (65)	0.295
Pathological stage			
Stage 0-2	152 (46)	28 (37)	0.099
Stage 3-4	176 (54)	47 (63)	
Residual disease			
R0: No residual tumour	254 (77)	59 (78)	0.963
R1: Microscopic residual tumour	44 (13)	10 (13)	
R2: Macroscopic residual tumour	34 (10)	7 (9)	
No of nodes analysed	15.2 ± 0.5	13.3 2 ± 0.9	0.141
Lymph Node Positive	153 (47)	41 (65)	0.109
Nodal Involvement (No. + nodes)			
0	175 (53)	33 (45)	0.068
1-3	98 (30)	20 (27)	
4+	55 (17)	21 (28)	
Differentiation			
Well (grade 1)	28 (9)	7 (9)	0.868
Moderate (grade 2)	275 (85)	60 (82	
Poor (grade 3)	22 (7)	6 (8)	
Synchronous tumour	10 (3)	3 (4)	0.428

Clinical Stage, treatment, pathological staging, nodal involvement and degree of residual disease were compared among obese and non obese patients. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 7.3: Obesity and Tumour pathology in Males only

	Non Obese Males	Obese Males	P Value
Pathological stage			
Stage 0-2	93 (49)	15 (36)	0.078
Stage3- 4	96 (51)	27 (64)	
Nodes Positive 4+	32 (17)	13 (31)	**0.012**
Node Positive	82 (43)	25 (60)	**0.040**

Table 7.4: Obesity and Tumour Pathology in Colon Cancer only

Colon Cancer	Non Obese	Obese	P Value
Pathological stage			
Stage 0-2	100 (46)	16 (32)	**0.051**
Stage 3-4	118 (54)	34 (68)	
Lymph Node Positive	98 (46)	29 (58)	0.077
Nodal Involvement (No. + nodes)			
0	117 (52)	21 (42)	**0.017**
1-3	63 (29)	12 (24)	
4+	35 (16)	17 (34)	

Table 7.5: Obesity and Tumour Pathology in Rectal Cancer only

Rectal Cancer	Non Obese	Obese	P Value
Pathological stage			
Stage 0-2	52 (48)	12 (48)	0.577
Stage 3-4	57 (52)	13 (52)	
Lymph Node Positive	54 (48)	12 (50)	0.526
Nodal Involvement (No. + nodes)			
0	58 (52)	12 (50)	0.980
1-3	35 (31)	8 (33)	
4+	19 (17)	4 (17)	

The above 3 tables shows the subgroup analysis performed to examine effect of gender specifically male gender and different anatomical site of cancer on the association of obesity with more advanced pathological tumour features (Table 7.3-7.5). Chi square analysis was used to compare categorical variables and values shown as N (%).

7.5.4 Post Operative Complications

Thirty per cent of patients suffered any one post operative complication; however there was no difference in the incidence of major and minor complications in obese and non obese (Table 7.6). The incidence of pulmonary (p=0.521) or wound complications (p=0.164), anastomotic leak (p=0.550), infection (p=0.662) was similar in both groups. Further analysis was carried out comparing the four BMI categories and potential influence of multimodal treatment and laparoscopic or open surgery. Being underweight was associated with a higher incidence of major complications (p=0.041), sepsis (p=0.024) and post operative death (p=0.006). The incidence of pelvic abscesses was higher in obese patients (p=0.037) compared with non obese. An open or laparoscopic operation had no bearing on postoperative complications, or multimodality treatment approaches.

Table 7.6: BMI Categories and Post operative complications

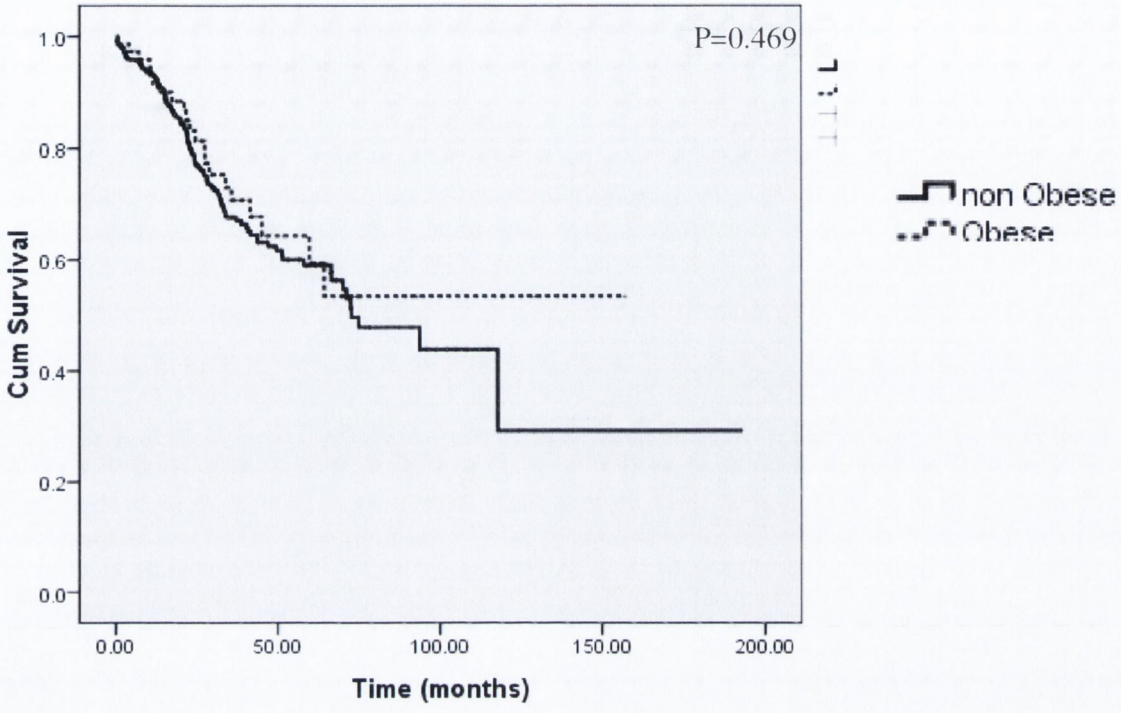
Characteristics	Underweight (n=41) 10%	Normal (n = 145) 35 %	Overweight (n = 153) 37%	Obese (n = 75) 18%	P value
Post operative	16 (40)	36 (29)	45 (30)	27 (37)	0.180
Major Complications	6 (15)	5 (4)	7 (5)	5 (7)	**0.041**
Minor Complications	2 (5)	3 (2)	3 (2)	6 (8)	0.076
Wound Complications	3 (8)	11 (8)	4 (3)	7 (10)	0.152
Pulmonary Complications	5 (13)	7 (5)	6 (4)	5 (7)	0.215
Sepsis	5 (13)	2 (1)	1 (1)	4 (5)	**0.024**
Anastomatic Leak	2 (5)	5 (4)	4 (3)	2 (3)	0.883
Pelvic Abscess	0	0	5 (3)	4 (5)	**0.037**
Infection	1 (3)	4 (3)	4 (3)	2 (3)	0.919
Post op Death (within 30 days)	4 (10)	2 (1)	2 (1)	1 (1)	**0.006**
Blood Products	8 (21)	15 (11)	22 (16)	10 (14)	0.108

All complications from surgery to discharge from hospital were prospectively documented and compared according to BMI categories; Underweight <20kg/m2, /normal Weight 20-25kg/m2 Overweight 25-30kg/m2 and Obesity>30kg/m2. Major respiratory complications for the purpose of this analysis were defined as pneumonia, ARDS, abdominal or pelvic abscesses, sepsis, organ failure, myocardial infarction. Minor complications included low hemoglobin, urinary retention, confusion, nausea, pyrexia, abdominal pain if not accompanied by any major complications. Pulmonary complications were grouped together and include pneumonia, pulmonary embolism, pulmonary effusion, pulmonary oedema and ARDS. Wound complications include wound dehiscence, discharge and infection.

7.5.5 Survival

The median follow-up was 73 months. The 1,3, and overall 5-year survival was similar in both groups, with 60% 5-year survival in both groups (Figure 7.1). In rectal cancer the difference approached significance (p=0.074) in the obese group compared with the non obese group, with 71% vs 59% 5-year survival in obese compared with non-obese cohorts. There was no difference in colon cancer survival (p=0.721).

Figure 7.1: Survival in Obese and Non Obese in Colorectal Cancer Patients



Obese

Survival time	No at Risk	Deaths	% Survival
0 years	75	0	100%
1 year	64	5	92%
3 years	31	11	71%
5 years	13	3	60%

Non obese

Survival time	No at Risk	Deaths	% Survival
0 years	338	0	100%
1 year	268	21	93%
3 years	120	58	68%
5 years	57	11	60%

This graph represents a comparison of survival in obese and non obese cohorts with colorectal cancer (n=414). At a median follow-up of 73 months, the 1, 3, and 5-year survival was similar in both groups, with 60% 5-year survival in both groups

7.6 Discussion

Surgery for colorectal cancer is associated with an approximate 18-38% morbidity risk and 1% risk of in-hospital mortality, with a higher incidence of complications in rectal cancer (Staib *et al,* 2002; Bokey 1995). In this study of an Irish cohort undergoing surgery for localised colorectal cancer, no major added risk of obesity was evident other than risk of pelvic abscesses, despite higher rates of cardiovascular co-morbidities and diabetes mellitus in the obese cohort. The lack of major added operative risks associated with obesity in this study is consistent with reports which suggest that only morbid obesity is associated with increased risks, and that a BMI between 30 and 35 kg/m^2, the range for the majority of obese subjects in this study, does not confer an added risk (Merkow 2009).

Obesity is a risk factor for the development of colorectal cancer (Huxley *et al,* 2009), with the greatest risk reported in men of all ages and in pre-menopausal women compared with postmenopausal women (Frezza 2006; Kim 2007). One explanation for this gender difference is the predominance of central obesity in males. Central adiposity is strongly related to metabolic abnormalities, and may reflect a more sensitive measure of the adverse consequences of obesity (Schoen *et al,* 1999; Pischon *et al,* 2006). In a study of 133 patients classified as obese by visceral fat area, obesity was associated with a significantly higher incidence of wound infection, overall complication rate and hospital stay post laparoscopic colectomy, but no relationship was observed with BMI (Tsujinaka 2008). Visceral obesity independently increases cardiovascular risk (Després & Lemieux 2006), diabetes and is associated with insulin resistance; therefore visceral defined obesity may be a more sensitive indicator of underlying co-morbid medical conditions compared with BMI-defined obesity. This measure of obesity, along with CT-measured visceral fat, and serum measurement of adipokines and cytokines is now standard in this Unit over the last year, and this may represent a more valid interpretation of obesity with colorectal cancer outcomes in future analyses, but was beyond the scope of this study.

Reports associating obesity and differential survival in males and females also are conflicting. Meyerhardt *et al,* reported overall increased mortality and disease recurrence to be restricted to women (Meyerhardt *et al,* 2003). Conversely, a large cohort study of over 700,000 adults, reported increasing BMI was positively associated with increased mortality with a more pronounced effect seen in males only (Murphy *et al,* 2000). More recently Dignam *et al.* (Dignam 2006) reported no significant difference in survival according to increasing BMI or sex. Increased visceral obesity has also been associated

with reduced survival (Haydon 2006), and the association of visceral adiposity with the metabolic abnormalities that define the metabolic syndrome has been reported to increase the risk of colon cancer mortality (Trevisan 2001; Cholangelo 2002). Obesity was not associated with tumour size, nodal status and pathological stage, but a significant relationship was seen with a more advanced pathological stage, positive lymph nodes and degree of nodal involvement in male patients and colon cancer only analysis. Lymph node yield and node positivity are important determinants of outcome. Sixteen of the 17 studies reviewed by Chang (Chang *et al,* 2007), found that an increased number of lymph nodes evaluated were associated with improved survival rates for patients with stage II colon cancer. Although nodal evaluation was similar in obese and non obese and among males and females, a higher nodal yield was found in colon cancer patients compared to rectal cancer and in non obese colon cancer patients compared to obese cancer patients. The overall survival however was equivalent across all BMI categories and, intriguingly, there was a trend towards improved oncological outcomes in the rectal cancer cohort. This concept, that obesity may confer some benefits in terms of adaptive response to stress, and preservation of immune function, is consistent with a described "obesity paradox" where mild obesity may confer some protective effects (Mullen 2009).

A limitation of the study is that BMI could only be obtained at diagnosis, and the overall incidence of obesity (18%) in this study was lower than the 31% recently reported in Irish adults (>45 years) (Morgan *et al,* 2008). The measurement of BMI at diagnosis does not reflect changes in BMI prior to diagnosis, which may be important in determining outcomes and survival. Weight loss is a common symptom of colorectal cancer and is observed in up to 80% of patients with advanced disease. Weight loss has been associated with longer hospital stay, reduced response and increased complications to anticancer therapy, increased overall cost of care, and reduced survival (Heys *et al,* 2002; Bauer 2002; Dewys *et al,* 1980; Heys *et al,* 1998; Gupta *et al,* 2004; Gupta *et al,* 2005; Dixon *et al,* 2003; Steinberg *et al,* 1992). In this study, underweight patients had significantly more major complications after surgery specifically increased sepsis and a significantly higher post operative mortality rate. Other limitations of the study include the retrospective design and the sole reliance on BMI as a marker of obesity and nutritional status. Information on anthropometric measures of body fatness (i.e. waist-to-hip ratio and waist circumference) was not available to examine the effect of abdominal obesity on complications after treatment for colorectal cancer outcomes or survival. Further studies are needed to examine the relationship between central obesity and colorectal cancer

outcomes and the potential pro-inflammatory and pro-tumourigenic pathways facilitated through the altered immunological, metabolic and endocrine milieu in obesity.

In conclusion, these data fail to identify any significant difference in the major operative and oncological outcomes in a large consecutive series of patients undergoing curative therapy for colorectal cancer. It appears that obesity in the range of 30-35 Kg/m^2 is not associated with detriment or benefit with respect to standard operative and oncological outcomes in the management of localised colorectal cancer.

CHAPTER 8

LACK OF DIFFERENTIAL PATTERN IN CENTRAL ADIPOSITY AND METABOLIC SYNDROME IN BARRETT'S OESOPHAGUS AND GASTRO-OESOPHAGEAL REFLUX DISEASE

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"Lack of differential pattern in central adiposity and metabolic syndrome in Barrett's oesophagus and gastro-oesophageal reflux disease."

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8.1 Summary

Background: Obesity is an established risk factor for oesophageal adenocarcinoma, although the mechanism is unclear. A pathway from reflux to inflammation through metaplasia is the dominant hypothesis, and an added role relating to visceral adiposity and the metabolic syndrome, has been mooted in Barrett's oesophagus (BO) patients. Whether BO differs from gastro-oesophageal reflux disease (GORD) in obesity and metabolic syndrome profiles is unclear, and this was the focus of this study.

Methods: Patients with proven BO or GORD were randomly selected from the unit data registry and invited to attend for metabolic syndrome screening, anthropometry studies including segmental body composition analysis, and laboratory tests including fasting lipids, insulin and C-reactive protein. Metabolic syndrome was defined using the National Cholesterol Education Program (NCEP) and the International Diabetes Federation (IDF) criteria.

Results: One hundred and eighteen BO patients and 113 age- and sex -matched GORD controls were studied. The incidence of obesity (BMI>30kg/m^2) was 36% and 38%, respectively, with the pattern of fat deposition predominantly central and an estimated trunk fat mass of 13 and 14 kg, respectively. Using the NCEP criteria, metabolic syndrome was significantly more common in the BO cohort (30% versus 20%, $p<0.05$), but there was no significant difference using IDF criteria (42% versus 37%, $p=0.340$).

Conclusions: Central obesity and the metabolic syndrome are common in both Barrett's and GORD cohorts, but not significantly different suggesting that central obesity and the metabolic syndrome does not per se impact on the development of BO in a reflux population. In BO, the importance of obesity and the metabolic syndrome in disease progression merits further study.

8.2 Introduction

There has been a marked recent increase in the incidence of oesophageal adenocarcinoma in the Western world, and this has been paralleled by an increased prevalence of obesity. Epidemiologic evidence strongly links obesity with oesophageal adenocarcinoma (Ryan *et al*, 2006; Lagergren *et al*, 1999; Chow *et al*, 1998; Vaughan *et al*, 1995; Brown *et al*, 1995). The exact mechanism is unclear, but pathways through GORD and the specialized intestinal metaplasia (SIM) of BO are most plausible. Severe or chronic GORD is a significant risk factor, and SIM is the sole recognized pathologic precursor of adenocarcinoma of the oesophagus.

Obesity may promote GORD and BO through mechanical factors, including a decrease in the lower oesophageal sphincter pressure, associated hiatus hernia, an altered refluxate, and increased gastro-oesophageal pressure gradients (Hampel *et al*, 2005; Pandolfino *et al*, 2006). Since obesity is positively associated with the prevalence and death rates of many other cancers, other mechanisms are likely to be important (Calle *et al*, 2003). There has consequently been an emerging focus on the systemic inflammatory state consequent on the altered metabolism in obese patients and the associated impact of adipokines, cytokines, and procoagulant factors released by adipocytes, particularly central or visceral fat. This may be manifest in the metabolic syndrome, described originally in association with cardiovascular disease and type 2 diabetes, where the usual screening variables are waist circumference, circulating levels of triacylglycerols and high-density lipoprotein cholesterol, fasting hyperglycemia, and hypertension. It is estimated that between 20 and 30% of adults have the metabolic syndrome (Ford *et al*, 2002; Qiao *et al*, 2009). The exact prevalence is unknown in Ireland, but one study recently reported a prevalence of 21% in an Irish population over 50 years of age (Waterhouse *et al*, 2009).

It is important to determine where obesity and metabolic syndrome fit into the paradigm of reflux-associated oesophageal adencoarcinoma, in particular whether there are factors in addition to the promotion of reflux that determine the development of SIM or the progression to adenocarcinoma. We have recently reported a high prevalence of metabolic syndrome and central obesity in a BO cohort (Ryan *et al*, 2008). Other studies have supported an association between visceral obesity and BO (Cook *et al*, 2008; Edelstein *et*

al, 2007; Corley *et al*, 2007A; Corley *et al*, 2007B), as well as a link with altered adipokines including reduced plasma adiponectin (Rubenstein *et al*, 2008) and increased leptin (Kendall *et al*, 2008). What is unclear to date is whether the relationship between obesity and the metabolic syndrome represent a continuum from GORD to BO, or distinct pathways. The primary aim of this study was to perform a detailed nutritional assessment, screen for metabolic syndrome in a patient population with GORD and compare them to BO cohort.

8.3 Patients and methods

The study was approved by the institutional review board. Informed consent was obtained from all patients prior to participation. For the BO cohort, patients diagnosed with endoscopically evident Barrett's oesophagus and confirmed by the presence of specialized intestinal metaplasia were eligible for inclusion. Long segment Barrett's (LSB) was defined as Barrett's of 3 cm or greater and short-segment Barrett's (SSB) was defined as less than 3 cm. Another population of patients with symptomatic GORD who had significant acid reflux and proven acid reflux (>14.92 De Meester score) identified by 24 hr pH study over the same time period were also identified from the gastric physiology laboratory data-base. All GORD patients routinely underwent endoscopy to exclude Barrett's oesophagus, 71% were performed in our unit and the remainder at referral source or privately.

Patients were invited by letter to attend an Oesophageal Clinic to participate in a nutritional and metabolic assessment. The existing Body Mass Index (BMI) or nutritional status of the patient was not available to the researcher inviting the patients. An interview was conducted relating to reflux symptoms, medication use, medical history, and alcohol and tobacco use. Patients were excluded from the study if they had cancer of the oesophagus or oesophagogastric junction, or had undergone anti reflux surgery. Patients underwent a nutritional assessment (weight, height, BMI, Body composition analysis), blood pressure measurements and venous blood sample for metabolic syndrome screening as described in detail in the methods section. Both NCEP and IDF metabolic syndrome definitions were used in thic chapter see Table 8.1 for comparison.

Table 8.1: Comparison of NCEP-ATPIII and IDF definitions for Metabolic Syndrome

Definitions	NCEP-ATP III 2001	IDF 2005
Criteria for Diagnosing Metabolic Syndrome	*≥3 out of 5 necessary*	*Central obesity + ≥ 2 other factors*
Fasting Glucose (mmol/l)	6.1-7.0	>5.6 or *NIDDM*
Abdominal Obesity	≥ 102 cm Male ≥ 88 cm Female	>94 cm Male >80 cm Female
Triglycerides (mmol/l)	≥ 1.7	≥ 1.7
HDLc (mmol/l)	<1.03 Male <1.29 Female	<1.03 Male <1.29 Female
Hypertension (mm/Hg)	Systolic ≥ 130 Diastolic ≥ 80	Systolic ≥130 Diastolic ≥ 85 or *on treatment*

NIDDM: Non-insulin dependent diabetes mellitus

The above table highlights the differences and similarities between the two most widely used definitions for metabolic syndrome; the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATPIII) and International Diabetes Federation (IDF).

8.4 Statistical analysis

Statistical analysis was conducted using SPSS® Version 14.0 for Windows™ (SPSS® Inc., Chicago, IL). Cross-tabulation was used to compare differences between GORD and BO cohorts for categorical variables. Significant differences were tested using Pearson Chi-square analysis. For a two by two variable analysis, the Yates Correction of Continuity was used to compensate for overestimation of the chi square analysis. The expected frequency in any cell should be 10 or more and if this assumption was violated, Fishers exact probability test was used. Differences in mean laboratory data and anthropometric data across categories were evaluated using one way analysis of variance with a significance level defined as <0.05. Further analysis also assessed any difference between males and females.

A fifteen percent difference in metabolic syndrome incidence was considered clinically relevant and this study was adequately powered to detect this. When comparing BO to GORD and long to short segment Barrett's, clinically relevant differences in variables with a known standard deviation were used to determine sample size. This study was adequately powered to detect a clinically relevant difference of 3kg/m2 (+/- 5.3 kg/m2) in BMI, a 3cm (+/-2.1cm) in waist circumference, 5mg/dl difference (+/-4.2mg/dl) in CRP, and 2.0 point increase in insulin resistance (+/- 2.0) between groups with 95% power using a cut-off for statistical significance of 0.05.

8.5 Results

Seventy two percent of BO patients and 62% from the GORD cohort agreed to be studied. Two hundred and thirty one patients were recruited, 118 with proven SIM in BO, and 113 with GORD confirmed by 24hr pH studies. The male: female breakdown was 79:39 and 67:46 for BO and GORD, respectively. The mean age was 56 and 54 for BO and GORD. The mean (±SEM) acid reflux score was 66± 6 and 46± 4 in BO and GORD, respectively (p=0.003). BO patients were less likely to be current smokers, 16% vs 24% (p=0.012).

8.5.1 Anthropometric Details

Seventy eight percent of BO patients and 73% of GORD patients were overweight or obese according to BMI (>25 kg/m^2) (p=ns). There was no significant difference in

central obesity with similar mean waist circumference in BO and GORD (Table 8.2). When classified according to the NCEP ATP III definition of central obesity cut-off points (>88cm for women and >102cm for males) a 7% difference was observed comparing BO to GORD (60% v 53% respectively; p=0.185). Using the IDF definition of > 80 cm in women and > 94 cm in men, the percentage was 78 and 77, respectively (p=0.566). There was no significant difference in body composition with a similar degree of total body fat and trunk fat in both groups, with 13 kg trunk fat mass in BO and 14 kg in the GORD cohort (p=0.229).

Table 8.2: Anthropometric Details of BO versus GORD

	BO (n=118)	GORD (n=113)	P Value
Weight (kg)	80.3 ± 1.4	80.3 ± 1.5	0.982
Mean BMI (kg/m2)	28.3 ± 0.4	28.5 ± 0.5	0.820
BMI Categories			
Underweight	2 (2)	-	0.318
Normal Weight	24 (21)	30 (27)	
Overweight (25-30)	49 (42)	40 (35)	
Obese (>30)	42 (36)	43 (38)	
Waist Circumference	100.4 ± 1.1	99.4 ± 1.2	0.566
Female Only	100.6 ± 1.4	100.2 ± 1.4	0.443
Male Only	99.9 ±1.8	98.3 ± 2.2	
Central Obesity (>80cm>94cm)	91 (78)	87 (77)	0.506
Central Obesity (>88cm>102cm)	70 (60)	60 (53)	0.185
Body Composition			
Total Fat %	28.9 ± 0.9	25.1 ± 0.9	0.054
Total Fat Mass (kg)	23.5 ± 0.9	25.2 ± 1.0	0.226
Trunk Fat Mass %	29.1 ± 0.8	31 ± 0.9	0.113
Trunk Fat Mass (kg)	13.2 ± 0.5	14 ± 0.5	0.229

Values shown as (Mean ± Standard error of mean) or N (%).
BMI: Body Mass Index; BO: Barrett's Oesophagus; GORD: Gastro oesophageal reflux disease

This table compares the nutritional assessment (weight, height, BMI, Body composition analysis), among patients with Barrett's Oesophagus and patiens with Gastro Oesophageal Reflux Disease.

8.5.2 Metabolic Profile

Using the NCEP ATP III criteria metabolic syndrome was diagnosed in 31% of BO cases and 20% of GORD cases (p=0.050) (Table 8.3). Thirty six BO patients (31%) had 4 or 5 features, compared with 23 (21%) in the GORD group (p=0.046). Using the IDF criteria the incidence was 41% and 37% for BO and GORD, respectively (p=0.340), with no difference in the number of features of metabolic syndrome.

BO and GORD cases were equally hypertensive according to the cut-offs for blood pressure measurement (>130/85mmHg) but BO had a higher mean diastolic pressure compared with the GORD cohort (p=0.002). Use of anti hypertensive medication was similar in both groups (p=ns). The mean ± SEM CRP level in BO patients was (6.1mg/L ± 1) compared with (5.9 mg/L ± 0.9) in the GORD cohort (p = 0.868). BO patients however were more likely to have a CRP above 10mg/L compared with GORD (13% versus 7% overall, p=0.122; 16% versus 4% for males, p = 0.027). There was no significant difference in prevalence of hyperinsulinemia (>20mU/L), insulin resistance (HOMA scores) or fasting lipid profiles.

8.5.3 Obesity, Metabolic syndrome and Length of Barrett's

Precise data concerning the length of Barrett's were available for 100/113 cases. There were 57 patients with LSB and 43 with SSB. There was no significant difference in median age between the 2 groups (Table 8.4). There were more obese patients (42%) with LSB compared with SSB (28%) (p=0.126) and LSB had significantly higher mean BMI compared to SSB (29kg/m^2 vs. 27kg/m^2; p=0.038). Eighty four percent of LSB patients were centrally obese compared with 70% of SSB patients (p=0.076), and LSB was significantly associated with a greater waistline (102 vs. 97 cm, $P = 0.026$). There was no difference in the body composition analysis, hypertension, lipid profile or incidence of hyperglycaemia or hyperinsulinaemia between short- and long-segment Barrett's. Fifty one percent of LSB patients had the metabolic syndrome compared with 35% in SSB (p=0.082).

Table 8.3: Metabolic Profile of Barrett's Vs GORD patient

	BO (n=118)	GORD (n=113)	P Value
Metabolic syndrome (NCEP)	36 (31)	23 (20)	0.050
Number features of Met Syndrome			
0	21 (18)	18 (16)	0.046
1	21 (18)	30 (26)	
2	40 (34)	42 (38)	
3	29 (25)	12 (11)	
4	7 (6)	11 (10)	
5	0	0	
Metabolic Syndrome (IDF)	49 (41)	42 (37)	0.340
Number features of Met Syndrome			
0	16 (14)	12 (11)	0.439
1	15 (13)	23 (20)	
2	38 (32)	36 (32)	
3	37 (32)	26 (23)	
4	11 (9)	14 (12)	
5	1 (1)	2 (2)	
Hypertensive (BP >130/85 mmHg)	77 (67)	66 (58)	0.115
Systolic BP (mmHg)	144 ± 1.9	141 ± 1.7	0.197
Diastolic BP (mmHg)	89 ±1.7	83 ± 0.9	0.002
Anti HTN Medications	29 (25)	19 (17)	0.098
Total Cholesterol (mmol/L)	5.1 ± 0.09	5.1 ±0.1	0.618
Dyslipidemia (>5.0 mmol/L)	71 (60)	61 (55)	0.229
LDL Cholesterol (mmol/L)	3.18 ± 0.08	3.05 ± 0.9	0.239
HDL Cholesterol (mmol/L)	1.3 ± 0.03	1.4 ± 0.03	0.317
Triglyceride (mmol/L)	1.4 ± 0.06	2.6 ± 1.1	0.262
CRP (mg/L)	6.1 ± 1.0	5.8 ± 0.9	0.868
High CRP (>10 mg/L)	15 (13)	7 (7)	0.122
Fasting Glucose (mg/L)	5.2 ±1.1	5.3 ±1.3	0.393
Insulin (mU/L)	7.5 ± 0.5	9.3 ± 0.6	0.025
Hyperinsulinemia (>20mU/L) n=185	3 (3)	4 (6)	0.287
HOMA-IR	1.8 ± 0.2	2.2 ± 0.1	0.161

Values shown as Mean ± Standard error of mean or N (%).

BO: Barrett's Oesophagus GORD: Gastro-Oesophageal Reflux Disease; BMI: Body Mass Index; NCEP: National Cholesterol Education Program; IDF: International Diabetes Federation; BP: Blood Pressure; HTN: Hypertension; CRP: C Reactive Protein; HOMA- IR: Homeostatic model assessment- insulin resistance

This table compares the incidence of metabolic syndrome and hypertension, as well as fasting glucose, lipid profile, serum hormone as well as markers of inflammation among patients with BO and GORD patients. Anova analysis was used to compare continuous variables and values are shown as mean ± standard error. Chi square analysis was used to compare categorical variables and values shown as N (%).

Table 8.4: Anthropometric and metabolic features of Long Segment Barrett's (>3cms) versus Short Segment Barrett's (<3cms)

	Short Segment (n=43)	Long Segment (n=57)	P Value
Age	57.8 ± 1.8	55.3 ± 1.6	0.303
Length of Barrett's Demeester Score	66.1 ± 10.2	76.5 ± 9.3	0.457
Waist Circumference (cm)	97 ± 1.9	102 ± 1.5	0.026
Central Obesity			
(>80cm>94cm)	70%	84%	0.076
(>88cm>102cm)	51%	64%	0.134
Mean BMI (kg/m2)	27.2 ± 0.6	29.2 ± 0.6	0.038
Overweight (25-30)	42%	43%	0.325
Obese (>30)	28%	42%	0.126
Body Composition			
Total Fat %	27.9 ± 1.3	29.2 ± 1.2	0.497
Fat Mass (kg)	22.1± 1.5	24.2± 1.2	0.281
Trunk Fat Mass %	27.8 ± 1.3	29.8 ± 1.	0.251
Trunk Fat Mass (kg)	12.3 ± 0.7	13.7± 0.6	0.143
Metabolic Syndrome			
IDF Definition	35%	51%	0.082
ATP III Definition	28%	35%	0.294
Hypertension	63%	70%	0.334
Fasting Glucose	5.1 ± 0.1	5.2 ± 0.1	0.499
HDL Cholesterol	1.4 ± 0.6	1.3 ± 0.3	0.155
Triglyceride	1.3 ± 0.1	1.4 ± 0.06	0.555
Insulin	6.6 ± 0.7	7.4 ± 0.7	0.429
Hyperinsulinaemia (>12)	10%	12%	0.515
HOMA-IR	1.5 ± 0.2	1.9 ± 0.3	0.318
CRP >5	23%	33%	0.191
GGT>40	25%	43%	0.038

Values shown as (Mean ± Standard deviation) or N (%).

Further analysis was performed to determine if there was any difference in the metabolic or anthropometric features in patients with differing lengths of BO.

8.6 Discussion

Obesity is a major independent risk factor for oesophageal adenocarcinoma (Ryan *et al*, 2006; Lagergren *et al*, 1999; Chow *et al*, 1998; Vaughan *et al*, 1995; Brown *et al*, 1995). Obesity is associated with GORD (Calle *et al*, 2003) and an increased risk of BO, and visceral obesity is a greater risk factor for BO than BM (El-Serag *et al*, 2005; Gerson *et al*, 2007; Jacobson *et al*, 2009). A previous report from this Unit of 102 patients with BO reported a prevalence of central obesity and metabolic syndrome of 78% and 46%, respectively, with raised IL-6, CRP, insulin, and reduced adiponectin in patients with metabolic syndrome (Ryan *et al*, 2008). In that study, we reported an intriguing association of these factors with long-segment compared with short-segment BO, suggesting a role in BO progression. Similar relationships with BMI and central obesity and length of Barrett's oesophagus were reported on in this study. The paradigm that obesity promotes GORD, and that chronic GORD predisposes to adenocarcinoma directly through BO metaplasia may be over-simplistic, and the impact of obesity and metabolic syndrome on inflammation and cancer pathways requires a greater understanding. One key question not previously addressed is whether differential patterns exist for BO and GORD.

In this analysis, there was a high incidence of obesity in both groups; 36% and 38% respectively, with the pattern of fat deposition predominantly central and an estimated trunk fat mass that was almost identical (13 vs 14 kg; BO vs GORD). The incidence of obesity and central obesity was similar in both groups, which is consistent with a recent report of 751 patients, where the mean BMI was 27.8 kg/m^2 overall but there was no difference between BO (n=165) and non-Barrett's groups (n=586) (Gerson *et al*, 2007). It would appear from both studies that where the control group contains mainly or exclusively subjects with GORD, then any specific association between BO and obesity is weakened. Cook et al published a meta-analysis concluding that increasing BMI does not present an increased risk of BO above what would be expected from GORD alone (Cook *et al*, 2008). A recent analysis of the Nurses Health Study found an increased risk of Barrett's oesophagus with obesity in women, results were similar in those who reported a history of GORD symptoms and also in the entire control population suggesting that the effects of obesity on the development of Barrett's oesophagus in women are mediated at least in part by mechanisms other than GORD (Jacobson *et al*, 2009).

With no change in anthropometric status between cohorts, the question whether metabolic syndrome was different was next addressed. The prevalence of metabolic syndrome varies according to the definition used; the geographic location and generally increases with age. Using the NCEP definition significantly more BO patients had metabolic syndrome compared with the GORD cohort (31% and 20% respectively p=0.050), but significance (p=0.340) was lost when the IDF definition was used (41% and 37% respectively). The differences reflect the lower fasting glucose threshold (5.6 vs 6.1mmol/l) and the 8cm lower waist circumference cut-offs in the IDF definition compared with the NCEP definition. Moreover, central obesity is uniquely a prerequisite for the IDF definition and consequently, together with lower cut-offs, may contribute to the higher prevalence reported with the IDF definition. The definitions have aroused some controversy, and there have been calls for consistency and new definitions based on insulin resistance and cardiovascular profile which may be overstated by the IDF definition (Sattar *et al*, 2008; Lund *et al*, 2006; Sandhofer *et al*, 2007). Although measurement of CRP was not significantly different between cohorts, there was a trend towards higher levels in the BO group, with 13% having levels above 10mg/L compared with 7% in the GORD group (p=0.122). Conversely, insulin levels were higher in the GORD group. Taken together, these data highlight some of the difficulties with the definition of metabolic syndrome, but establish an incidence of metabolic syndrome in BO and GORD cohorts that are similar but far exceed the most recent report on an Irish population, where the estimated prevalence is approximately 21% (NCEP) and 13% (IDF) (Ford *et al*, 2002; Qiao *et al*, 2009; Waterhouse *et al*, 2009). The association of metabolic syndrome with GORD is consistent with a recent study of 7078 patients undergoing endoscopy which reported that VAT was an independent risk factor for reflux oesophagitis, and that metabolic syndrome was significantly higher in oesophagitis patient compared with controls (Chung *et al*, 2008). In another study of 3669 patients undergoing repeat endoscopy, the presence of metabolic syndrome independently increased the likelihood of progression from non-erosive to erosive disease and reduced the likelihood of disease regression (Lee *et al*, 2009).

There are two limitations that need to be acknowledged and addressed regarding the present study, the small sample size and the retrospective nature of the study that is comparing the incidence of obesity among GORD and BO pts. A prospective study design

that watches the development of BO, during the study period and relates this to factors like obesity, may more precisely estimate the relative risk of BO in GORD.

In conclusion, obesity, in particular central obesity, is common in both BO and GORD. There is a modest trend for higher metabolic and inflammatory responses in the BO cohort, but no differential pattern emerged. Although metabolic syndrome is not exclusive to BO, the importance of obesity and the metabolic syndrome and the adiopocytokine profile in progression of disease merits further study. The high prevalence of obesity and metabolic syndrome in unselected cohorts of patients with GORD and BO, with three out of four were overweight or obese, over half with dyslipidemia, and a further one-fifth with hyperglycaemic and hyper-insulinemia, highlight the need health promotion and secondary prevention programs.

CHAPTER 9

GENERAL DISCUSSION & CONCLUSIONS

"Prevention offers the most cost-effective long-term strategy for the control of cancer."(WHO, 2010). The World Health Organization has predicted that cancer will overtake heart disease as the leading cause of death worldwide this year. In addition to this a recent study reported on the economic cost of all causes of death globally, including cancer, presented by the American Cancer Society Cancer earlier this month (Aug 2010). Cancer has emerged as the world's top "economic killer", costing the global economy nearly a trillion dollars a year. The economic cost was measured in terms of disability and years of life lost, not the cost of treating the disease, which wasn't addressed in the report and would double the total economic cost of cancer. This data provides compelling evidence to address the primary and secondary prevention of cancer that could not only save lives, but also millions of dollars.

Although several factors are contributory, the rising incidence of overweight and obesity globally is thought to be fuelling cancer rates and obesity is one of the strongest risk factors for many cancers in western worlds. Further support for the role of obesity in cancer is the increased incidence observed in developing and economically transitioning countries, likely due to an increase in environmental risk factors like detrimental lifestyle changes including obesity. In fact, it is estimated that 25% of all cancers and 50% of cancer deaths are preventable through good nutrition exercise and tackling obesity, and given the high and increasing prevalence of obesity in Ireland, obesity needs to be addressed on a national level, with targeted lifestyle treatment programs.

To date there is limited research on the effect of voluntary weight loss diet improvement and/or physical exercise on cancer incidence, but this is an area of promising prevention research and it's strongly recommended by the World Cancer Research Fund for primary and secondary prevention of caner. Indirect evidence from cohort studies suggests that intentional weight loss is associated with reduced cancer risk, as well the observed

reduction in cancer mortality with sustained and significant weight loss achieved by bariatric surgery, a surgical intervention for extreme obesity. For cancer survivors, individualised therapy is necessary considering all clinical aspects of treatment-related side effects and the potential for disease-related weight loss, to create an individualised nutritional care plan for appropriate weight management.

Prevention is the best treatment, and primary prevention of obesity needs to prioritised, although there are no easy solutions. Obesity is a complex problem that requires multiple prevention and control interventions over long periods, with full participation and commitment from various partners and stakeholders. In response to the growing challenge of obesity in Ireland, the National Taskforce of Obesity was established and it published 93 recommendations in 2005, focusing on the population as a whole, with specific actions taken in schools; primary care; community organisations; workplaces; in the area of food supply, and in media and marketing. Many of these recommendations have yet to be implemented, and the government have been criticised for the lack of funding to implement these recommendations.

While there is strong evidence relating obesity to increased risk of many cancers, data in this thesis provides the first Irish data supporting this observation in postmenopausal breast cancer, with double the risk reported for obese patients (BMI>30 kg/m^2) compared to normal weight patients (BMI:20-25 kg/m^2) (Chapter 3). We also assessed the impact of obesity on clinico-pathological tumour features and found that obesity was associated with larger tumours, lymph node involvement and a later presentation of disease, consistent with findings from other studies. Some reports have indicated that adiposity at time of diagnosis is associated with both reduced likelihood of survival and increased likelihood of recurrence, and obese patients have double the death rate from breast cancer compared to non obese individuals. Although we were unable to assess recurrence, we did not find any significant difference in survival. Although the precise mechanisms are not clear several hypotheses have been proposed, the most common that obesity influences breast cancer growth as a result of synergistic activity between the concomitants of hyperinsulinemia and the increased oestrogen concentrations. Further research is needed to fully understand the underlying biological mechanisms to explore the molecular and pharmacological targets that can be used to improve the treatment of obese breast cancer patients.

Measurement of obesity using BMI is simple, reproducible and easily attainable, but has certain limitations in its inability to distinguish muscle and fat mass and android or gyneoid body shape. Other anthropometric measures like waist circumference and waist hip ratio as well as body fat analysis have a stronger association with cancer risk, than with BMI alone. These measures of central obesity may more closely reflect an increased visceral adipose tissue which is associated with adverse alterations in metabolic risk profile, most of which are relevant to the diagnosis of metabolic syndrome. Furthermore, the metabolic syndrome itself represents multiple risk factors including central obesity and insulin resistance and may more closely reflect the adverse complications of obesity. The presence of the metabolic syndrome has been identified as a high risk state for cancer, but if its identification in individuals is superior to BMI alone is still a matter of debate, considering that the screening test for metabolic syndrome is simple and relatively low cost but more invasive as it requires a fasting blood sample. An interesting finding in the studies on metabolic syndrome presented in this thesis was that 10% of breast cancer and 20% of colorectal cancer with a normal BMI were identified as having metabolic syndrome; a concern is that these patients would not have been identified as at risk using BMI alone.

The underlying cause of the metabolic syndrome remains controversial. Several underlying factors appear to contribute to the development of metabolic syndrome, but central obesity and insulin resistance are mostly commonly cited as the driving forces behind the syndrome. In fact it has been referred to as the 'insulin resistance syndrome' and evidence of insulin resistance is required using the WHO definition as a pre-requisite for diagnosis. However not all patients who have metabolic syndrome are insulin resistant, and the fact that obesity is probably the major cause of insulin resistance further complicates this debate. The IDF definition published in 2006 abandoned insulin resistance and placed a greater emphasis on central obesity as the core feature of the syndrome making it an essential component for diagnosis, but in its most recent update in 2009 it demoted waist circumference from an obligatory component, to one of the five abnormal findings on which there is complete agreement on. The use of different definitions adds further complexity in estimating the prevalence of the syndrome and does not allow direct comparison of studies published. Our understanding of this complex set of risk factors is limited, and further research is needed.

This was the first prospective study to assess the relevance of metabolic syndrome to the biology and adverse clinico-pathological features of breast and colorectal cancer (Chapter 4 and Chapter 5). Metabolic syndrome was more common in cancer patients compared to population norms and was associated with an adverse metabolic profile, increased inflammation and a later pathological stage and node positive disease, but these findings needs to be confirmed in larger prospective studies and may also have implications for other solid tumours. Scientific research has shown a more rapid growth rate in obese women's tumours compared to similar size tumours from non obese, with a higher Ki-67 expression ratio, a higher mitotic count, and a higher S phase fraction in the obese cohort. The processes underling the metabolic syndrome may have a significant role in cancer progression; high insulin levels have metabolic and mitogenic effects that can promote growth and metastasis, the availability of glucose at high levels provides a favourable growth environment for malignant cells, as well as increased visceral adipose reflected by high waist circumference that secretes a variety of biologically active substances including leptin and pro-inflammatory cytokines which can promote carcinogenesis by inducing gene mutations inhibiting apoptosis or stimulating angiogenesis and cell proliferation. In the literature, studies on metabolic syndrome and cancer report a strong association with increased cancer incidence and increased cancer mortality with some studies describing a multiplicative (synergistic) effect of the presence of metabolic syndrome, greater than the sum of the individual risk factors.

Regardless of the underlying causes or driving forces, the metabolic syndrome is now both a public health and a clinical problem. From a public health perspective, more attention must be given to modification of lifestyles of the general public to reduce obesity and to increase physical activity, while at a clinical level, individual patients at risk need to be identified so that their multiple risk factors, including lifestyle risk factors, can be treated or reduced. To date a formal diagnosis of metabolic syndrome does not demand a specific treatment but pharmaceutical industries are working on the development of drugs that target several or all of the components of met syn. Critics of the metabolic syndrome have raised the issue of labelling low risk patients in an economically challenged health care system, when the identification of the syndrome may not influence decisions regarding treatment beyond the diagnosis of the individual components. Anecdotal evidence suggests that the metabolic syndrome as a concept provides an easily comprehensible public health message, increases awareness among health professionals on the importance

of risk factor clustering and the need for individual assessment, and the growing body of evidence on metabolic syndrome and other clinical conditions including liver disease, sleep apnoea and cancer also encourages health professionals not to focus simply on diabetes or CVD.

With the increasing prevalence of obesity in Ireland, the surgical oncologist today is presented increasingly with the challenge of managing obese patients with cancer. Traditionally obesity was thought to be a risk factor for increased post operative morbidity, with reports of increased infectious complications, wound complications and respiratory complications. We retrospectively examined the impact of obesity on post operative complications in oesophageal adenocarcinoma and colorectal cancer surgery (Chapter 6 and Chapter 7). Obesity was associated with an increase in minor complications but not major complications, and had no impact on survival, failing to identify any significant difference in the major operative outcomes in the surgical management of cancer. It may be interesting to further examine the impact of central obesity specifically which more accurately reflect the adverse metabolic consequences of obesity. Another limiting factor was the inability to take unintentional weight loss into account, especially common in the oesophageal cancer population. Weight loss correlates with advanced stage and the effect of severe or rapid weight loss may have further implications. The impact of under-nutrition in the larger colorectal cancer population and was significantly associated with mortality and major complications adding to the wealth of literature on the risks of under nutrition and the reverse J shaped relationship with BMI, morbidity and mortality with the highest risk in underweight patients. In fact, the lack of increased risk with obesity in some way supports the hypothesis described as the "obesity paradox" where mild obesity may confer some protective effects and improve outcomes in terms of adaptive response to stress, and preservation of immune function.

Obesity's role in promoting growth in precancerous lesions is an exciting area of research and its essential to determine the precise mechanisms linking obesity to cancer especially in the early stages and how we can intervene in these pathways by use of pharmacological inhibitors, behaviour modification or gene therapy. Leptin secreted by adipocytes in proportion to adipocyte tissue mass, represents an intriguing link. Leptin over expression is reported in breast cancers and was significantly associated with increased incidence of distant metastasis. In colon cancer, a progressive increase in leptin expression through the progression from normal colon (4.5% positive), to adenoma (29.5%) to carcinoma

(73.5%) has also been reported suggesting that leptin may have a role in driving this malignant transformation (Franks *et al*, 2005; Koda *et al*, 2007). Targeting leptin signaling may become a very appealing target to reduce carcinogenesis. Further studies are needed to clarify the role of leptin and identify new therapeutic options that act selectively on adipokine driven pathways.

The pathophysiological mechanisms whereby obesity promotes oesophageal cancer development are likely to be multifactorial. Barrett's Oesophagus is the only recognised pre cursor lesion for oesophageal cancer, and a long standing complication of GORD, with one fifth of GORD patients developing Barrett's. The development of BO is thought to be a culmination of both hereditary and environmental factors like increasing BMI. It is important to identify the modifiable environmental risk factors associated with such progression, the incidence of metabolic syndrome in BO compared to GORD patients was assessed in Chapter 8. While we found a modest trend for higher metabolic and inflammatory responses in the BO cohort, no differential pattern emerged with a similarly high incidence of central obesity and metabolic syndrome in age and sex matched GORD controls. This highlights the need for secondary prevention programmes to tackle obesity, as both BO and GORD patients risk for cardiovascular disease and diabetes appear to be higher than the risk of oesophageal cancer. However, the adiopocytokine profile in the progression of disease especially leptin, merits further study as well as the metabolic syndrome in the progression of Barrett's oesophagus and the dysplasia-metaplasia-carcinoma sequence with consideration to the effect of gender which needs to be addressed in all future studies.

In conclusion obesity and its complications like the metabolic syndrome are serious medical conditions which need urgent attention throughout the world. They create significant pressure on health care systems which are straining under the escalating costs of resulting chronic diseases like type 2 diabetes, cardiovascular diseases, and cancers. Turning the tide of obesity will be difficult, with many challenges; it will take a combination of government, community and individual actions to achieve significant and long lasting change.

CHAPTER 10

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APPENDIX

Ethical approval for the following studies were sought and approval given, subject to informed consent. Copies of the patient information leaflets and the consent forms for the two studies listed below are included in the Appendix. Also attached are copies of the letters sent to patients and care providers.

Metabolic syndrome, central obesity and insulin resistance are associated with adverse pathological features in postmenopausal breast cancer **(Chapter 4)**.

Metabolic syndrome and leptin are associated with adverse pathological features in male colorectal cancer patients **(Chapter 5)**.

Lack of differential pattern in central adiposity and metabolic syndrome in Barrett's Oesophagus and Gastro-oesophageal reflux disease **(Chapter 8).**

APPENDICES FOR CHAPTER 4 AND 5

ETHICAL APPROVAL

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March 15th 2007

REC reference: 2007/02/03

(Please quote REC reference on all correspondence)

Re: Central Obesity, Metabolic Syndrome and Cancer – impact on tumour stage treatment and disease free survival in breast, colorectal and Oesophageal malignancy.

List of documents (including version number and dates which have been reviewed by the Committee):

1. Confidential Protocol Form dated 28th January 2007.
2. Patient Information Leaflet and Consent Form
3. Study Protocol dated 10 November 2006, footnoted Metabolic Syndrome and Cancer Study version 1.0
4. Curriculum Vitae John Vincent Reynolds.
5. Curriculum Vitae Aoife Ryan
6. Curriculum Vitae Laura Healy

Dear Professor Reynolds,

The SJH/AMNCH Research Ethics Committee, at its meeting on March 7th 2007, agreed to give ethical approval to the above study.
The Committee expressed concern about the sample size and the effect of cancer cachexia but it was emphasized that this is not a condition attached to the ethical approval of the study.

Yours sincerely,

Daniel R. Lynch,
Secretary,
SJH / AMNCH Research Ethics Committee.

PATIENT CONSENT FORM

Title of research study:

CENTRAL OBESITY, METABOLIC SYNDROME, AND CANCER - IMPACT ON TUMOUR STAGE, TREATMENT, AND DISEASE FREE SURVIVAL IN BREAST AND COLORECTAL MALIGNANCY.

This study and this consent form have been explained to me. My doctor has answered all my questions to my satisfaction. I believe I understand what will happen if I agree to be part of this study.

I have read, or had read to me, this consent form. I have had the opportunity to ask questions and all my questions have been answered to my satisfaction. I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights. I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.

Name of sponsor:

PARTICIPANT'S NAME: _____

PARTICIPANT'S SIGNATURE: _____

Date: _____

Date on which the participant was first furnished with this form: _____

Where the participant is incapable of comprehending the nature, significance and scope of the consent required, the form must be signed by a person competent to give consent to his or her participation in the research study (other than a person who applied to undertake or conduct the study). If the subject is a minor (under 18 years old) the signature of parent or guardian must be obtained: -

NAME OF CONSENTOR, PARENT or GUARDIAN: _____
SIGNATURE: _____
RELATION TO PARTICIPANT: _____

Where the participant is capable of comprehending the nature, significance and scope of the consent required, but is physically unable to sign written consent, signatures of two witnesses present when consent was given by the participant to a registered medical practitioner treating him or her for the illness.

NAME OF FIRST WITNESS: _____SIGNATURE: _____
NAME OF SECOND WITNESS: _____SIGNATURE: _____

Statement of investigator's responsibility: I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature: _____
Date: _____

PATIENT INFORMATION LEAFLET AND CONSENT FORM

CENTRAL OBESITY, METABOLIC SYNDROME, AND CANCER - IMPACT ON TUMOUR STAGE, TREATMENT, AND DISEASE FREE SURVIVAL IN BREAST AND COLORECTAL MALIGNANCY.

Patient Information Sheet

Dear Patient,
You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives or your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

Please take time to decide whether or not you wish to take part in this study.
Thank you for reading this.

Why have I been chosen?
You have been chosen to take part in this study as you have been diagnosed with cancer. Before you begin your treatment we would like to screen you for diabetes, high cholesterol, and check the levels of some hormones produced by fat tissue in your blood. We would also like to check you body composition, height, weight and blood pressure, and ask you some questions about your normal activity levels. These tests will give us very helpful information about how body weight may be related to cancer.

What will happen to me if I take part?
If you agree to take part we will take some blood samples approximately 20mls (4 teaspoons) to check your cholesterol, blood sugar, insulin levels and hormone levels. We will check your blood pressure and measure your weight, height, waist circumference, hip circumference and using a special body composition analyser we will measure the fat and muscle composition of your body by asking you to stand on a special weighing scales. These tests should last no longer than 15-20 minutes.

What will happen if I chose not to take part?
If you choose not to take part there will be no adverse consequences to you as a patient.

What do I have to do?
If you agree to take part you will have blood tests taken after an overnight fast and then your body composition will be measured. This is a once off measurement and so you will not be called back to the hospital or have to take any additional medications as a result of this study.

What are the side effects/risks of taking part?
The various tests and measurements in this study are not harmful in any way. The blood samples will be taken using a needle and syringe and are expected to cause only minor discomfort such as bruising or a build up of blood under the skin.

What are the possible benefits of taking part?
There are many potential benefits to taking part – you will be able to have free screening for diabetes, high cholesterol, and high blood pressure as well as having your body composition checked. Should any of your blood tests reveal abnormal results we will inform your Consultant Surgeon/Oncologist or your GP.

What about confidentiality?

The researchers including your GP, the ethics committee and regulatory authorities will have access to your original medical records for the purpose of collecting data, verifying that the data is correct and checking that the study is conducted properly. By signing this form you are allowing your doctor, the researchers and the study staff to permit these people to see your medical records.

Confidentiality is promised in all cases and your identity will not be disclosed to the public. Any information that may leave the hospital, apart from that which we send to your GP will have your name and address removed and you will only be identified by your initials and study number. Under the Access to Health Records Act (1990), you may ask to see your study records.

What do you do with my information?
The information collected in this study will be processed to meet the purpose of the clinical study. It may also be used in reports of the study or for scientific presentations. You will not be identified in any such publication. The information obtained from this study, which relates to you may be used for future medical research, either in this field, or in a new area (but only with further ethics committee approval).

Compensation
Participation in this study is covered by an approved policy of insurance in the name of St. James's Hospital. In addition the medical practitioners involved in this study have current medical malpractice insurance cover. St. James's Hospital will comply with the ABPI guidelines and Irish Law (statutory and otherwise) in the unlikely event of your becoming ill or injured as a result of participation in this clinical study.

Payment for the study
There is no payment for participation in this study

Who do I call if I have questions or problems?
You can call the Research Dietitian who will be taking your measurements:
Laura Healy on 01 416 2180 or Professor John V Reynolds, Consultant Surgeon, 01 416 2500.

CASE REPORT FORM

Name:_____

MRN:_____

DOB:_____/_____/_____ **Age at diagnosis:** _____

DIAGNOSIS

Breast

Colon

Oesophageal

Informed Consent: Yes ☐ No ☐

Exclusion Criteria

If any of the criteria is checked yes, do not include the patient in the study.

Does the patient have a cardiac pacemaker in situ? Yes ☐ No ☐

Has the patient had a previous malignancy? Yes ☐ No ☐

Gender: Male ☐ Female ☐

Menopause State _____

If Premenopause, date start of last menstruation _____

Anthropometry :

Usual Body Weight _____ **Reported Weight Loss** _____

Weight: _____ **Waist Circum:** _____

Height: _____ **Hip Circum:** _____

Height 2: _____ **WHR:** _____

BMI: _____

Blood Pressure

Systolic: _____ **Heart Rate:** _____

Diastolic : _____

Smoking:_____ **Alcohol:**_____

MEDICATION:

Cholesterol Medication _____

Diabetes Medication _____

Blood Pressure Medication _____

Hormone Medication _____

Blood Collected

Fasting Yes ☐ No ☐ Fasting from (time)? _____

LETTER TO GP

GENERAL PRACTTIONER

ADDRESS

DATE:

CC: _____, Consultant Surgeon, St James Hospital.

RE: PATIENT NAME AND MRN

Dear Dr _____,

The above patient recently consented to take part in a research study entitled:

"Central obesity, metabolic syndrome, and cancer - impact on tumour stage, treatment, and disease free survival in breast, colorectal and oesophageal malignancy."

Below is a summary of the results found for your information:

Diabetes Screen:	5.0	(SJH Normal range is 3.0-6.0)
Total Cholesterol:	4.78	(SJH Normal range is 3.0 – 5.2)
LDL Cholesterol	3.23	(SJH Normal range is 2.0 – 3.36)
HDL Cholesterol	0.97	(SJH Normal range is 1.0 – 2.1)
Triglycerides	1.26	(SJH Normal range is 0.5 – 2.0)

I would be grateful if you could follow up on any abnormal results.

Yours Sincerely

_____

LAURA HEALY
Research Dietitian
(01) 4162180

APPENDICES FOR CHAPTER 8

ETHICAL APPROVAL

THIS NOTEPAPER MUST NOT BE USED FOR PRESCRIPTIONS OR INVOICING PURPOSES

THE ADELAIDE & MEATH HOSPITAL, DUBLIN
INCORPORATING
THE NATIONAL CHILDREN'S HOSPITAL

TALLAGHT, DUBLIN 24, IRELAND
TELEPHONE +353 1 4142000

Dan Lynch, Secretary, SJH / AMNCH Research Ethics Committee .
Telephone : 4142860. Fax : 4142371. Email: dan.lynch@amnch.ie

Professor John Reynolds
Professor of Surgery & Head of Department
Department of Clinical Surgery
Trinity Centre for Health Sciences
St. James's Hospital
Dublin 8

May 18th 2005

Re: Prospective Investigation of the Incidence of Central Adiposity, Metabolic Syndrome, Insulin Resistance and Adipokine Secretion Amongst Patients With Gastro-Oesophageal Reflux Disease/Barrett's Oesophagus Undergoing Upper GI PH Manometry Studies

Please quote this reference in all communications regarding this study 05/05/09 Chairman's Action.

Dear Professor Reynolds,

The proposal to conduct the study under the above title has been reviewed by the Vice-Chairman of the SJH / AMNCH Research Ethics Committee.
On behalf of the Committee, the Vice-Chairman has given ethical approval for this proposed study subject to the following condition:

- The Vice-Chairman has noted from your proposal that statistical advice has not been sought and that in answer to question 4(a) it has been indicated that this question is not applicable. Nevertheless in answer to question 20 it is indicated that 200 subjects and no controls are expected to participate in this project. The Vice-Chairman would welcome an explanation / justification for the belief that statistical significance is not applicable to this study.

Yours sincerely,

Daniel R. Lynch,
Secretary,
SJH / AMNCH Research Ethics Committee.

INVITATION LETTER TO CLINIC

ACID REFLUX CLINIC

PROFESSOR REYNOLDS & PROFESSOR KEELING

Department of Surgery, Medicine & Clinical Nutrition

Email: lhealy@stjames.ie

Direct: (01) 4284452; Secretary (01) 4162180

Dear,

I am writing to inform you that we have established a clinic at St James's Hospital for patients suffering with acid reflux/heartburn.

This study, which has approval from the Hospital's ethics committee, involves a 15minute **FREE** health check-up that screens for diabetes, high cholesterol, high blood pressure, and **FASTING BLOOD TEST**. We would also like to measure your height and weight. These tests give us very helpful information about acid reflux and may help in the treatment of your condition. You will be provided will a full report of your blood tests and nutritional assessment and should we notice any abnormal results we will inform your GP immediately.
Please read the information leaflet attached and decide if you would like to take part or not. Please contact one Laura Healy at the above number for an appointment time.

The next clinic will take place on the _____

With very best wishes,

Yours sincerely,

Prof John Reynolds, M.Ch., FRCSI,
Consultant Surgeon.

PATIENT INFORMATION LEAFLET

PROSPECTIVE INVESTIGATION OF THE INCIDENCE OF CENTRAL ADIPOSITY, METABOLIC SYNDROME, INSULIN RESISTANCE AND ADIPOKINE SECRETION AMONGST PATIENTS WITH BARRETTS OESOPHAGUS

Dear Patient

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives or your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

Why have I been chosen?
You have been chosen to take part in this study as you have or have a history of Barrett's Oesophagus. We would like to screen you for diabetes, high cholesterol, and check the levels of some hormones produced by fat tissue in your blood. We would also like to check your body composition, height, weight and blood pressure. These tests will give us very helpful information about how body weight is related to acid reflux.

What will happen to me if I take part?
If you agree to take part we will take some blood samples approximately 20mls (4 teaspoons) to check your cholesterol, blood sugar, insulin levels and we will measure your blood pressure. We will measure your weight, height, waist circumference and using a special body composition analyser we will measure the fat and muscle composition of your body by asking you to stand on a special weighing scales. These tests should last no longer than 20 minutes.

What do I have to do?
If you agree to take part you will have blood tests taken and your weight and height checked and then you are free to go home. This is a once off measurement and so you will not be called back to the hospital or have to take any additional medications as a result of this study.

What are the side effects/risks of taking part?
The various tests and measurements in this study are not harmful in any way. The blood samples will be taken using a needle and syringe and are expected to cause only minor discomfort such as bruising or a build up of blood under the skin.

What are the possible benefits of taking part?
There are many potential benefits to taking part – you will be able to have free screening for diabetes, high cholesterol, and high blood pressure as well as having your body composition checked. Should any of your blood tests reveal abnormal results we will inform your GP. This may mean that if you have any of these conditions you will be treated by your GP at an earlier stage.

What about confidentiality?

All of your study records will remain strictly confidential. The researchers including your GP, the ethics committee and regulatory authorities will have access to your original medical records for the purpose of collecting data, verifying that the data is correct and checking that the study is conducted properly. By signing this form you are allowing your doctor, the researchers and the study staff to permit these people to see your medical records.

Confidentiality is promised in all cases and your identity will not be disclosed to the public. Any information that may leave the hospital, apart from that which we send to your GP will have your name and address removed and you will only be identified by your initials and study number. Under the Access to Health Records Act (1990), you may ask to see your study records.

What do you do with my information?
The information collected in this study will be processed to meet the purpose of the clinical study. It may also be used in reports of the study or for scientific presentations. You will not be identified in any such publication. The information obtained from this study, which relates to you may be used for future medical research, either in this field, or in a new area (but only with further ethics committee approval).

Compensation
Participation in this study is covered by an approved policy of insurance in the name of St. James's Hospital. In addition the medical practitioners involved in this study have current medical malpractice insurance cover. St. James's Hospital will comply with the ABPI guidelines and Irish Law (statutory and otherwise) in the unlikely event of your becoming ill or injured as a result of participation in this clinical study.

Payment for the study
There is no payment for participation in this study

Please take time to decide whether or not you wish to take part in this study.
Thank you for reading this.

Who do I call if I have questions or problems?

Laura Healy,
Research Dietitian
St. James's Hospital
(01) 4284452 [Direct]
(01) 4162180 [Secretary]

PATIENT INFORMATION LEAFLET

PROSPECTIVE INVESTIGATION OF THE INCIDENCE OF CENTRAL ADIPOSITY, METABOLIC SYNDROME, INSULIN RESISTANCE AND ADIPOKINE SECRETION AMONGST PATIENTS WITH GASTRO-OESOPHAGEAL REFLUX DISEASE UNDERGOING UPPER GI PH & MANOMETRY STUDIES.

Dear Patient

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives or your doctor if you wish. Ask us if there is anything that is not clear or if you would like more information.

Why have I been chosen?
You have been chosen to take part in this study as you have undergone tests for acid reflux called pH & Manometry. We would like to screen you for diabetes, high cholesterol, and check the levels of some hormones produced by fat tissue in your blood. We would also like to check your body composition, height, weight and blood pressure. These tests will give us very helpful information about how body weight is related to acid reflux.

What will happen to me if I take part?
If you agree to take part we will take some blood samples approximately 20mls (4 teaspoons) to check your cholesterol, blood sugar, insulin levels and we will measure your blood pressure. We will measure your weight, height, waist circumference and using a special body composition analyser we will measure the fat and muscle composition of your body by asking you to stand on a special weighing scales. These tests should last no longer than 20 minutes.

What do I have to do?
If you agree to take part you will have blood tests taken and your weight and height checked and then you are free to go home. This is a once off measurement and so you will not be called back to the hospital or have to take any additional medications as a result of this study.

What are the side effects/risks of taking part?
The various tests and measurements in this study are not harmful in any way. The blood samples will be taken using a needle and syringe and are expected to cause only minor discomfort such as bruising or a build up of blood under the skin.

What are the possible benefits of taking part?
There are many potential benefits to taking part – you will be able to have free screening for diabetes, high cholesterol, and high blood pressure as well as having your body composition checked. Should any of your blood tests reveal abnormal results we will inform your GP. This may mean that if you have any of these conditions you will be treated by your GP at an earlier stage.

What about confidentiality?

All of your study records will remain strictly confidential. The researchers including your GP, the ethics committee and regulatory authorities will have access to your original medical records for the purpose of collecting data, verifying that the data is correct and checking that the study is conducted properly. By signing this form you are allowing your doctor, the researchers and the study staff to permit these people to see your medical records.

Confidentiality is promised in all cases and your identity will not be disclosed to the public. Any information that may leave the hospital, apart from that which we send to your GP will have your name and address removed and you will only be identified by your initials and study number. Under the Access to Health Records Act (1990), you may ask to see your study records.

What do you do with my information?
The information collected in this study will be processed to meet the purpose of the clinical study. It may also be used in reports of the study or for scientific presentations. You will not be identified in any such publication. The information obtained from this study, which relates to you may be used for future medical research, either in this field, or in a new area (but only with further ethics committee approval).

Compensation

Participation in this study is covered by an approved policy of insurance in the name of St. James's Hospital. In addition the medical practitioners involved in this study have current medical malpractice insurance cover. St. James's Hospital will comply with the ABPI guidelines and Irish Law (statutory and otherwise) in the unlikely event of your becoming ill or injured as a result of participation in this clinical study.

Payment for the study
There is no payment for participation in this study

Please take time to decide whether or not you wish to take part in this study.
Thank you for reading this.

Who do I call if I have questions or problems?

Laura Healy,
Research Dietitian
St. James's Hospital
(02) 4284452 [Direct]
(01) 4162180 [Secretary]

PATIENT RESULTS LETTER

ACID REFLUX CLINIC

PROFESSOR REYNOLDS & PROFESSOR KEELING

Department of Surgery, Medicine & Clinical Nutrition

Email: lhealy@stjames.ie

Direct: (01) 4284452; Secretary (01) 4162180

Dear ,

You recently attended an Acid Reflux Research Clinic where you consented to take part in a research study entitled: "**Prospective investigation of the incidence of central adiposity, metabolic syndrome, insulin resistance, adipokine and cytokine secretion amongst patients with Gastro-oesophageal reflux disease/Barrett's oesophagus.**"

Below is a summary of your results found:

Fasting Glucose:	1.0	(Normal Range 3.0 – 6.0)
Total Cholesterol:	**1.00**	(Normal range: 3.0 – 5.2)
LDL Cholesterol	1.00	(Normal range: 2.0 – 3.36)
HDL Cholesterol	1.00	(Normal range: 1.0 – 2.1)
Triglycerides	**1.00**	Normal range: 0.5 – 2.0)

Weight: 0.1 kg Height: 0.000 m

Body Mass Index (BMI) 00.0 kg/m^2 (Normal range is 20 – 25)➔ Overweight

Summary:

ABNORMAL RESULTS EXPLAINED

You may wish to discuss the above results with your GP.

If you would like an appointment to see a dietitian please call 01 4162180 and speak to Kathleen who will arrange the next available appointment for you.

Yours Sincerely,

LAURA HEALY

Research Dietitian

CC: Dr _____

SAMPLE TANITA BODY COMPOSITION PRINTOUT

WHOLE BODY ANALYSIS

TANITA
BODY COMPOSITION
ANALYZER
BC-[illegible]

12 JUN [illegible] 15:44

BODY TYPE	STANDARD
GENDER	FEMALE
AGE	40
HEIGHT	164 cm
WEIGHT	92.8kg
BMI	34.5
BMR	6766 kJ
	1617kcal
FAT%	43.8%
FAT MASS	40.7kg
FFM	52.1kg
TBW	38.2kg
DESIRABLE RANGE	
FAT%	23-34%
FAT MASS	15.6-26.9kg

IMPEDANCE

Whole Body	574 Ω
Right Leg	209 Ω
Left Leg	223 Ω
Right Arm	32[illegible] Ω
Left Arm	[illegible] Ω

SEGMENTAL ANALYSIS

Segmental Analysis

Right Leg	
Fat%	44.6%
Fat Mass	7.6kg
FFM	9.4kg
Predicted Muscle Mass	8.8kg
Left Leg	
Fat%	45.5%
Fat Mass	7.5kg
FFM	9.0kg
Predicted Muscle Mass	8.5kg
Right Arm	
Fat%	47.9%
Fat Mass	2.4kg
FFM	2.6kg
Predicted Muscle Mass	2.5kg
Left Arm	
Fat%	48.4%
Fat Mass	2.6kg
FFM	2.8kg
Predicted Muscle Mass	2.6kg
Trunk	
Fat%	42.1%
Fat Mass	20.6kg
FFM	28.4kg
Predicted Muscle Mass	27.1kg