Visceral obesity, metabolic syndrome, insulin resistance and cancer

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This paper presents emerging evidence linking visceral adiposity and the metabolic syndrome (MetSyn) with carcinogenesis. The link between obesity and cancer has been clearly identified in a multitude of robust epidemiological studies. Research is now focusing on the role of visceral adipose tissue in carcinogenesis; as it is recognised as an important metabolic tissue that secretes factors that systemically alter the immunological, metabolic and endocrine milieu. Excess visceral adipose tissue gives rise to a state of chronic systemic inflammation with associated insulin resistance and dysmetabolism, collectively known as the MetSyn. Prospective cohort studies have shown associations between visceral adiposity, the MetSyn and increased risk of breast cancer, colorectal cancer and oesophageal adenocarcinoma. Furthermore, visceral adiposity and the MetSyn have been associated with increased tumour progression and reduced survival. The mechanisms by which visceral adiposity and the MetSyn are thought to promote tumorigenesis are manifold. These include alterations in adipokine secretion and cell signalling pathways. In addition, hyperinsulinaemia, subsequent insulin resistance and stimulation of the insulin-like growth factor-1 axis have all been linked with visceral adiposity and promote tumour progression. Furthermore, the abundance of inflammatory cells in visceral adipose tissue, including macrophages and T-cells, create systemic inflammation and a pro-tumorigenic environment. It is clear from current research that excess visceral adiposity and associated dysmetabolism play a central role in the pathogenesis of certain cancer types. Further research is required to elucidate the exact mechanisms at play and identify potential targets for intervention.

Visceral adiposity: Metabolic syndrome: Insulin resistance: Inflammation: Tumorigenesis

The prevalence of obesity has increased rapidly in recent years(1). Being overweight or obese is now the most prevalent body composition in some countries, accounting for 71% of males and 62% of females in the United States(2). Similar trends exist in Western Europe with greater than 66% of men and 49–57% of women being overweight or obese in the UK and Ireland(3,4). This pattern shows no signs of abating as obesity rates are increasing among children(5) and overweight children tend to become overweight adults(6). In countries where sedentary lifestyles and high-energy foods are abundant it is easy to see how energy intake exceeds that expended. It has been estimated that ingestion of 5% more energy than expended may result in an accumulation of 5 kg adipose tissue in a single year(7).

Epidemiological studies have demonstrated a robust link between obesity and cancer development at numerous sites, in particular the oesophagus, pancreas, colorectum, breast (postmenopausal), endometrium and kidney(8,9). This association carries relative risk (RR) estimates of 1.1–1.6 per 5 kg/m² incremental increase in BMI(8). Obesity also increases cancer-related mortality with studies reporting that obesity could account for 14% of all deaths from cancer in men and 20% in women(10). The causative link between obesity and cancer is further strengthened by research in animal models which demonstrates that energy
restriction decreases spontaneous tumour occurrence\(^{(11,12)}\). Furthermore, emerging clinical research suggests weight loss following bariatric surgery leads to a reduction in cancer incidence\(^{(13)}\). Thus, the potential mechanisms by which obesity increases both the incidence of certain malignancies, and cancer deaths, have become the focus of considerable research interest in recent years.

**Adipose tissue and the metabolic syndrome**

WHO defines obesity as an abnormal or excessive fat accumulation in adipose tissue, to the extent that health is impaired\(^{(1)}\). Fat is principally deposited in two compartments; subcutaneously and viscerally. Attention was first drawn to the different patterns of fat distribution over 60 years ago by Jean Vague. He described two distinct types of fat deposition: upper-body, male-type fat (visceral) and lower-body, female-type fat (subcutaneous), and the association of visceral fat with type 2 diabetes, atherosclerosis and gout\(^{(14,15)}\). Visceral adipose tissue largely comprises omental adipose tissue and also includes other intra-abdominal fat sources such as mesenteric fat (mesenteric) and pericolic fat (periocolic), and is more metabolically active than subcutaneous adipose tissue\(^{(16)}\). Visceral adipose tissue has multiple endocrine, metabolic and immunological functions and has been shown to be central to the pathogenesis of the metabolic syndrome (MetSyn), a pro-inflammatory, pro-coagulant state associated with insulin resistance\(^{(17)}\). The multiple risk factors that commonly appear together as the MetSyn include abdominal obesity, atherogenic dyslipidaemia (raised TAG and reduced HDL cholesterol), elevated fasting plasma glucose and hypertension\(^{(18)}\). The importance of adipose tissue location in terms of dysmetabolism risk is evident as an increased ratio of visceral fat area to subcutaneous fat area has been shown to be strongly related to disorders of glucose and lipid metabolism in obese subjects\(^{(19)}\). Furthermore, visceral obesity is more strongly associated with increased risk of insulin resistance, the MetSyn and CVD than BMI alone\(^{(20)}\).

Visceral fat has been identified as an independent risk factor for breast cancer\(^{(21)}\), oesophageal adenocarcinoma\(^{(22)}\), colorectal adenocarcinoma\(^{(23)}\) and colorectal adenomas\(^{(24,25)}\). The other elements of the MetSyn, i.e. dyslipidaemia, hypertension and insulin resistance have also been independently linked with increased cancer risk\(^{(26–29)}\). The synergistic impact of these factors on cancer risk is the focus of the Me-Can Study, a prospective international population-based study of 580 000 people\(^{(30)}\). Initial findings suggest that a combination of components of the MetSyn is associated with increased RR of colorectal cancer development (men: RR 1.25, 95% CI 1.18, 1.32; women: RR 1.14, 95% CI 1.02, 1.08)\(^{(31)}\), endometrial cancer (RR 1.37, 95% CI 1.28, 1.46)\(^{(32)}\), bladder cancer in men (RR: 1.1, 95% CI 1.01, 1.18)\(^{(33)}\) and pancreatic cancer in women (RR 1.58, 95% CI 1.34, 1.87)\(^{(34)}\). Similarly, in studies of pancreatic and colorectal cancer a high prevalence of MetSyn, central obesity and systemic inflammation has been identified\(^{(35–37)}\) and has been shown to be associated with advanced tumour stage and reduced survival\(^{(38–41)}\).

**Oesophageal adenocarcinoma: a model of visceral obesity, metabolic syndrome and cancer**

The link between visceral adiposity, the MetSyn and cancer is probably best illustrated in the oesophageal adenocarcinoma model. Oesophageal adenocarcinoma develops along a predefined sequence of events. It begins with the development of Barrett’s oesophagus in response to chronic reflux of acid and bile, where the normal squamous lining of the oesophagus is replaced with specialised intestinal metaplasia, which then progresses through dysplasia and ultimately adenocarcinoma\(^{(42)}\). The incidence of oesophageal adenocarcinoma in Ireland has increased by nearly 50% in recent years\(^{(43)}\), a trend mirrored across developed countries\(^{(44)}\) and coincides with the sharp increase in the prevalence of obesity\(^{(4)}\). Epidemiological studies highlight a marked association between oesophageal adenocarcinoma and obesity, and a recent meta-analysis reported that a BMI ≥ 30 kg/m\(^2\) is associated with a RR of 3-0 for developing oesophageal adenocarcinoma, a higher association than for any other cancer\(^{(45)}\).

Visceral obesity itself may promote gastrointestinal reflux disease and predispose to Barrett’s oesophagus, and this may be one contributory factor to the association with oesophageal adenocarcinoma\(^{(46)}\). However, the observation that obesity is a risk factor independent of reflux\(^{(47,48)}\) suggests other mechanisms are at play. A study at this centre in 2008 reported that the prevalence of the MetSyn in Barrett’s oesophagus patients far exceeded population norms with the MetSyn present in 46% of patients and central obesity in 78%. The syndrome was also significantly associated with the length of specialised intestinal metaplasia; 60% of patients with long-segment Barrett’s oesophagus had MetSyn and 92% were centrally obese compared with 23% and 62% (P = 0.007 and P = 0.005) respectively in short-segment Barrett’s oesophagus. Long-segment Barrett’s oesophagus was also associated with systemic inflammation, with significantly higher serum levels of IL-6 observed in patients (P = 0.03)\(^{(49)}\). The obesity, inflammation, malignancy association is further strengthened by studies which have identified increased visceral adiposity and altered secretion of adipose-derived hormones in oesophageal adenocarcinoma\(^{(50)}\).

**Mechanisms underlying obesity and tumorigenesis**

The mechanisms by which visceral adiposity and the MetSyn are thought to promote tumorigenesis are manifold. Adipose tissue may promote tumour development in a paracrine manner (Fig. 1). This is supported by the observation that epithelial tumour cell growth is enhanced by injection into fat pads rather than subcutaneously\(^{(51)}\). We have suggested that chemokine production within the adipose tissue provides conditions which enhance tumour cell growth. Furthermore, a proteomic study of mammary fat tissue provides conditions which enhance tumour cell growth. Growth, immune response, apoptosis and numerous signalling molecules including hormones, cytokines and growth factors\(^{(52)}\). The paracrine influence of adipose
tissue on tumorigenesis is less fully investigated, whereas much research has focused on the systemic effects of visceral adiposity that are putatively involved in cancer biology. These include alterations in adipokine production, insulin and insulin-like growth factor (IGF) pathways, cancer cell signalling and inflammatory pathways (Fig. 1) and are discussed in further detail below.

**Altered adipokine production**

The existence of adipose tissue-derived factors that may influence metabolism has been suggested since the 1980s(53,54); however, it was the discovery of the adipokines leptin(55) and adiponectin(56) which led to the concept of adipose tissue as an endocrine organ. The altered secretion of these and other adipokines in obesity has been implicated in the pathogenesis of obesity-associated pathologies, including cancer(57). Excess adiposity, in particular visceral obesity, results in a state of chronic systemic low-grade inflammation, attributed to production of these inflammatory cytokines by both adipocytes and infiltrating immune cells creating a pro-tumorigenic environment(58).

Adiponectin is the most abundant adipokine and is secreted mainly from adipocytes in visceral fat; however, circulating levels are inversely correlated with obesity(59). It has been shown to be both anti-angiogenic and anti-inflammatory, can inhibit tumour growth in animal models and circulating levels are lower in cancer patients(60). Leptin may be considered the antithesis of adiponectin. It is an adipokine that acts centrally to regulate appetite and bodyweight(61) and circulating levels are positively associated with adiposity(62).

**Hyperinsulinaemia, insulin resistance and the insulin-like growth factor axis**

A core component of the MetSyn is insulin resistance. Nutritionally induced insulin resistance develops as a metabolic adaptation to increased circulating levels of NEFA, which are constantly released from adipose tissue. Increased NEFA levels force liver, muscle and other tissues to shift towards increased storage and oxidation of fats for their energy production. Consequently, insulin secretion rises to compensate for the decreased capacity to handle glucose(10,66,67). Furthermore, there is a decreased
expression of insulin-receptor levels and reduced intracellular insulin signalling in response to insulin receptor binding(68) resulting in hyperinsulinaemia and insulin resistance. The ratio of visceral to subcutaneous fat is a proxy measure of insulin resistance. The rate of lipolysis is higher in visceral adipose tissue than subcutaneous adipose tissue, leading to increased circulation of NEFA(69). Therefore, the risk of developing insulin resistance and hyperinsulinaemia increases with increasing visceral adipose tissue accumulation. Adipokines are believed to be central to the pathogenesis of insulin resistance(70), with high concentrations of TNF-α, IL-6, IL-1β, and low concentrations of adiponectin, having deleterious effects on glucose homeostasis leading to chronic hyperinsulinaemia and insulin resistance(71). A number of epidemiological studies have reported that insulin resistance status, characterised by hyperinsulinaemia, is associated with an increased risk of malignancy, including carcinomas of the breast, prostate and colon(27,60,72,73). Data from the Me-Can study reported that every 1 mmol/l increment in glucose increased risk of incident cancer in men (RR 1.05, 95% CI 1.01, 1.1) and women (RR 1.11, 95% CI 1.05, 1.16) and further increased RR for fatal cancer (men: RR 1.15, 95% CI 1.07, 1.22; women: RR 1.21, 95% CI 1.11, 1.33)(72). Interestingly, studies of type 2 diabetics have found that the risk of colorectal cancer is higher in those treated with insulin(74).

The tumorigenic effects of insulin could be directly mediated by insulin receptors in the pre-neoplastic target cells, or may relate to changes in endogenous hormone metabolism, secondary to hyperinsulinaemia(23). In vitro studies demonstrate that insulin increases the neoplastic proliferation of cell lines at both physiological and pharmacological doses, and the insulin receptor is commonly expressed in human neoplasms(75). Whether there are differential downstream signalling effects in normal or transformed epithelial cells compared to insulin-responsive tissues (such as fat, liver and muscle) is the subject of current research, addressing in particular whether receptor activation results in cell survival and proliferation rather than altered energy metabolism(76).

The IGF system may also be relevant to the effects of hyperinsulinaemia in pro-tumour pathways. In the IGF-axis, binding of IGF-1 or IGF-2 to the IGF-1 receptor leads to cell proliferation, differentiation and protection from apoptosis and a dysregulation in this pathway can give rise to malignancy(77,78). Levels of IGF are influenced by circulating insulin levels, with increasing insulin leading to decreased levels of IGF-binding proteins 1 and 2, thus increasing the bioavailability of IGF(79). The IGF-1 axis has been implicated in the progression of breast, pancreatic, colorectal and oesophageal cancer(80–83). Obesity increases levels of bioactive-free IGF-1(84,85), high levels of which are associated with increased risk of malignancy.

In experimental murine models, diet-induced obesity increased both local tumour growth and metastases in wild-type mice compared with lean controls, an effect not seen in liver-specific IGF-1-deficient (LID) mice. In addition, chronic IGF-1 deficiency negates the enhanced expression of inflammatory cytokines and cell adhesion molecules normally up-regulated in obese compared with lean mice(86–88). Hence, it is possible that in obesity IGF-1 can affect tumour development both directly, by stimulating tumour growth and indirectly, by creating a micro-environment that is permissive for tumour growth.

### Cancer cell signalling

Eukaryotic cells coordinate cell growth in line with the availability of nutrients in their environment(89). Obesity as a condition of both systemic insulin resistance and nutrient excess may lead to the activation of intracellular pathways that promote tumour growth and progression. The systemic alterations associated with obesity include a change in inflammatory, sex hormone, insulin and adipokine secretion which may directly influence the tumour micro-environment. Cancers that arise in this environment may go on to develop progressive mutations and epigenetic alterations which are influenced by this obese milieu. The concept of oncogene addiction describes the apparent dependency of some tumours on one or a few genes to maintain the malignant phenotype(90). Clinical evidence of this is cited as the ability of therapies targeting specific genes or pathways to inhibit cancer cell growth or improve survival rates(91). Whole genome arrays have demonstrated that breast cancer may be subdivided into a number of types based on the genes over-expressed in certain subtypes and that targeting these predominant pathways provides avenues for chemotherapy treatment for each subtype(92–94). Molecular characterisation of tumours has been exploited to develop assays to predict subgroups of patients with poorer prognosis who may benefit from adjuvant therapy(95).

Cancers that develop within an obese environment may become selectively altered to signal via specific pathways. For examples, in patients with non-small cell lung cancer, only a subset (approximately 10–20%) respond to the epidermal growth factor receptor targeted therapy gefitinib, and these patients often have an activating mutation of epidermal growth factor receptor(96). Patients with activating mutations are more likely to have adenocarcinomas, and to be female, non-smokers and Japanese(97). Similarly, obesity-related cancers may have a specific set of targets (malignfunctioning molecules or pathways), which may be exploitable in clinical practice. Certainly, a number of the putatively dysregulated adipokines and growth factors in obesity may signal via the same intracellular signalling pathways. Candidate pathways include the phosphoinositide 3-kinase (PI3K), mitogen-activated protein kinase and signal transducer and activator of transcription 3 pathways. Activation of these pathways leads to multiple downstream effects that underpin cancer progression and metastasis(98–100). Importantly, inhibitors of these pathways are under development at present in order to provide new therapeutic avenues(101–103).

Is there any evidence that cancers which develop within the obese milieu are ‘addicted to’ or preferentially signal via these pathways? Whole genome analysis of breast cancer tumours divided according to BMI demonstrate that an obesity-associated gene signature pattern is associated
with a shorter time to metastasis and is associated with an IGF signalling signature in multiple publically available breast cancer genome arrays\(^{104}\). Most data come from murine models. PI3K activity (measured by phosphorylated protein kinase B and mammalian target of rapamycin protein levels) is increased in diet-induced obesity in mice and is associated with an increased level of circulating IGF-1 compared with controls\(^{105}\). Mice fed a high-energy diet have twice the volume of tumours 17 d after colon cancer cell injection versus controls. PI3K pathway activity was demonstrated by increased phosphorylated protein kinase B levels\(^{106}\). In a mouse model of obesity-related skin cancer, obese mice had higher PI3K activity after UV exposure than lean mice\(^{117}\). Activity of mitogen-activated protein kinase phosphorylation and NF-κB signalling were also higher following UVB irradiation in the obese mice\(^{108}\). In breast and colorectal cancer, over-expression of the leptin receptor has been identified. As leptin has mitogenic and anti-apoptotic effects on cancer cells lines it is postulated that it acts through mitogen-activated protein kinase and PI3K pathways. This hypothesis is strengthened by the observation that inhibition of these pathways attenuates the growth-promoting effects of leptin\(^{109}\). In an obesity-associated hepatoma model, IL-6 and TNF-α induce the development of cancer via activation of signal transducer and activator of transcription 3 pathways\(^{110}\). Excess energy balance associated with the obese state may also influence tumour growth. Mouse tumour xenografts have decreased incidence and slower growth in mice that are fed an energy-restricted diet. Tumours that are resistant to dietary restriction have constitutive activation of the PI3K pathway\(^{111}\). The proposed cell signalling pathways that are altered in the obese state and associated with tumorigenesis are illustrated in Fig. 2.

**Visceral obesity, inflammation and cancer**

As early as the nineteenth century it was perceived that cancer is linked to inflammation and an inflammatory component is present in the microenvironment of most neoplastic tissues. Key features of cancer-related inflammation include the infiltration of immune cells, the presence of cytokines and chemokines, including TNF-α, IL-1β, IL-6 and chemokines such as monocyte chemotactic protein-1 and CXCL8\(^{112}\). Thus, cancer-related inflammation is a key component of the tumorigenic process and is increasingly referred to as the seventh hallmark of cancer. NF-κB, first described in 1986 by Ranjan Sen and David Baltimore, is a central coordinator for multiple inflammatory and anti-inflammatory signalling pathways and has become one of the most investigated transcription factors\(^{113}\). Activation of NF-κB has been shown to control a range of cellular processes in cancer including inflammation, proliferation, angiogenesis, metastasis, chemoresistance and radioresistance\(^{114,115}\). Obesity has been shown to increase the systemic activation of NF-κB\(^{116}\). It is constitutively active in a wide range of human tumour cells, and its suppression has been shown to inhibit their growth, leading to the ‘NF-κB addiction’ theory in tumour cells\(^{114}\).
The omentum is one of the largest components of the visceral adipose depot in human subjects and has been the subject of research for more than 3600 years (117). The word ‘omentum’ has its origins in the practice of Egyptian priests examining the abdominal viscera during embalming the body. They would tell fortunes by it and give good or bad ‘omens’ for the deceased (117). Adipose tissue, including the omentum, is thought to be a primitive immune organ, but unlike other adipose tissue depots the omentum has many unique functions (118). It migrates to and surrounds areas of inflammation and infection within the peritoneal cavity and is a rich source of pro-angiogenic and inflammatory mediators (119). Dense lymphoreticular structures within the human omentum, termed milky spots contain a range of innate and adaptive immune cells, namely macrophages, mast cells, T- and B-cells (120). More recent studies have also demonstrated the presence of natural killer and invariant natural killer T-cell populations within the human omentum, which are altered by obesity and cancer (121). These innate lymphocytes are capable of killing virally infected or tumour cells in a non-antigen-specific manner. In addition to an important role in immunosurveillance of the peritoneal cavity, another key function of the human omentum is to support B-cell function. The omentum collects antigens and cells from the peritoneal cavity and supports T-dependent B-cell responses, including isotype switching, somatic hypermutation and limited affinity maturation, despite the lack of identifiable follicular dendritic cells (122).

Macrophages are the most abundant leukocyte population in adipose tissue (123). Infiltration of inflammatory macrophages into adipose tissues correlates with increasing obesity levels and triggers insulin resistance and fuels inflammation. A significant number of macrophages are also present in lean, metabolically healthy human subjects suggesting that not all adipose tissue macrophages are programmed to be pro-inflammatory. Current evidence indicates that macrophages undergo a functional conversion to promote inflammation during obesity (124). In visceral fat, obesity alters the state of adipose tissue macrophages from an anti-inflammatory M2 phenotype to a pro-inflammatory M1 state (123) further potentiating metabolic dysfunction, insulin resistance and inflammation in obese individuals.

The majority of studies so far evaluating the immune cell properties of visceral adipose tissue have predominantly focused on macrophages. T-cells, however, may be key regulators of adipose tissue inflammation, and a recent study in a murine model revealed a significant increase in CD8+ T-cell infiltration into expanding visceral adipose tissue, which preceded macrophage infiltration (125). These T-cells were found to be responsible for both the establishment and maintenance of adipose tissue inflammation in obesity (125). We have recently shown that the human omentum is a particularly rich source of CD8+ T-cells in patients with obesity-associated oesophageal adenocarcinoma. A high percentage of CD4+ and CD8+ omental T-cells were activated with an inflammatory T-helper 1 phenotype (CD69+CD45RO+IFN-γ+) (126). Interestingly, we also demonstrated that significantly more interferon-γ+ T-cells were present in the omentum of cancer patients compared with non-cancer controls (126). The role of T-cells in adipose tissue inflammation and cancer has not received a lot of attention so far but offers potential immunotherapeutic targets for obesity-associated morbidity.

Conclusion

Adipose tissue is not simply an energy store but acts in a co-ordinated fashion to exert systemic hormonal and metabolic effects. There is sound epidemiological evidence relating excess adiposity and associated dysmetabolism to a broad range of cancer subtypes and emerging clinical research continues to bolster this observation. The recognition of visceral obesity as a major contributing factor to the development of cancer mandates further research into pathophysiological mechanisms. Much work remains to elucidate the independent and synergistic effects of inflammation, insulin resistance, the IGF-axis and adipokines on carcinogenesis in obesity. Clearly, the association between obesity and cancer is an important area to target in public health policy and one that will assume increasing importance over the coming years.

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