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Associations between adipokines and obesity-related cancer

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1. ABSTRACT

There is increasing evidence that obesity may have pathophysiological effects that extend beyond its well-known co-morbidities; in particular its role in cancer has received considerable epidemiological support. As adipose tissue becomes strongly established as an endocrine organ, two of its most abundant and most investigated adipokines, leptin and adiponectin, are also taken beyond their traditional roles in energy homeostasis, and are implicated as mediators of the effects of obesity on cancer development. This review examines these adipokines in relation to the prostate, breast, colorectal, thyroid, renal, pancreatic, endometrial and oesophageal cancers, and how they may orchestrate the influence of obesity on the development of these malignancies.

2. INTRODUCTION

Obesity has reached epidemic proportions worldwide. Recent data from different countries show that only one third of the population is normal weight, and approximately one third is obese. Obesity leads to several co-morbidities, such as diabetes, dyslipidaemia, hypertension, sleep apnoea, osteoarthritis, menstrual disorders, infertility, gout, stroke, ischaemic heart disease, congestive heart failure, deep vein thrombosis and pulmonary embolism (1).

Increased risk of cancer is another co-morbidity that is related to obesity. Since 1979, several epidemiological studies and meta-analyses have consistently demonstrated that an increased BMI (body

Table 1. Cancers strongly (relative risk greater than 1.2) associated with an increase in BMI of 5 kg/m^2

Cancer	RR (95% CI) for Men	RR (95% CI) for Women
Oesophageal adenocarcinoma	1.52 (1.33-1.74)	1.51 (1.31–1.74)
Thyroid	1.33 (1.04–1.70)	1.14 (1.06–1.23)
Colon	1.24 (1.20–1.28)	1.09 (1.05–1.13)[1]
Renal	1.24 (1.15–1.34)	1.34 (1.25–1.43)
Endometrium	NA	1.59 (1.50–1.68)
Gallbladder	1.09 (0.99–1.21)[1]	1.59 (1.02–2.47)

[1] Cancer with RR less than 1.2. All P less than 0.05, except for gallbladder cancer in men. NA: not applicable. Adapted from (3)

mass index) is associated with several types of cancer, such as prostate cancer in men, breast cancer in women, and oesophageal adenocarcinoma in both sexes.

Given the strong epidemiological evidence linking obesity and cancer, the identification of its pathophysiological basis is made necessary, to allow the development of preventive and even therapeutic strategies. Obesity presents with several hormonal changes, such as increased oestrogens, insulin and insulin-like growth factors. In addition, alterations in the immune response, in the nuclear factor kappa B (NF-kappa B) system, in oxidative stress, and in peroxidation are common in obesity. Finally, hypertension, acid reflux and increased iodine uptake are also considered other alterations that may predispose obese individuals to specific types of cancer (2). It is out of the scope of this manuscript to review all the pathophysiological bases of obesity and cancer. Here, based on the literature identified through searches on the PubMed database, we will address the roles of adipokines – polypeptides produced mainly by the adipose tissue – in the development of cancer types associated with obesity that were listed in a recent meta-analysis (3), plus prostate (the most common cancer in men), breast (the most common cancer in women) and pancreatic (the cancer with the lowest 5-year survival rate) cancers. Since no evidence between adipokines and gallbladder cancer has been described in the literature, this type of cancer will not be discussed in this review.

3. OBESITY AND CANCER: EPIDEMIOLOGICAL EVIDENCE

The first and largest epidemiological study investigating the associations between weight and cancer was published in 1979. This was a long-term prospective study involving 750,000 men and women evaluated between 1959 and 1972, showing that mortality was approximately 90% higher in men and women who were more than 40% heavier than the average. In that group, cancer mortality was also increased by a third among men, due to colon and rectum cancers, and by 55% among women, due to cancers of the gallbladder, biliary passages, breast, cervix, endometrial, and ovary (4).

In 2008, the World Cancer Research Fund issued an Expert Report acknowledging the association of excess body fat with increased risk of oesophageal adenocarcinoma and cancers of the pancreas, colon, rectum, post-menopausal breast, endometrium and kidney (5). Subsequently, a very large epidemiological study, the Million Women Study, identified associations between high body mass index (BMI) and increased risk of endometrial cancer (2.39), oesophageal adenocarcinoma (2.38), pre-menopausal colorectal cancer (1.61), kidney cancer (1.53), leukaemia (1.50), post-menopausal breast cancer (1.40), multiple myeloma (1.31), pancreatic cancer (1.24), non-Hodgkin's lymphoma (1.17), and ovarian cancer (1.14). The risk for all cancers combined was 1.12 (6).

The first meta-analysis published in 2001 demonstrated that nearly 35,000 and 37,000 new cases of cancer in Europe were related to obesity and to overweight, respectively. The cancers that were most strongly associated with overweight and obesity were endometrium, kidney, gallbladder, colon and breast (7). Several other meta-analyses have been published, associating obesity or high BMI with increased risk for several types of cancer: colon (both sexes) and rectal (men) (8-11), gallbladder (12), liver (13, 14), kidney (15, 16), pancreatic (17, 18), ovarian (19, 20), breast (21) and prostate cancers (22); leukaemia, non-Hodgkin's lymphoma and multiple myeloma (23, 24).

A more recent meta-analysis of 141 articles confirmed strong associations between higher BMI and increased risk for oesophageal adenocarcinoma, and for thyroid, colon, and renal cancers in men; and for endometrial, gallbladder, oesophageal adenocarcinoma and renal cancers in women (Table 1). That meta-analysis found additional weaker, but still positive, associations (relative risk less than 1.20) between increased BMI and rectal cancer and malignant melanoma (men); postmenopausal breast, pancreatic, thyroid, and colon cancers (women); and leukaemia, multiple myeloma, and non-Hodgkin lymphoma (both sexes) (3). Of particular interest, the same meta-analysis found that increased BMI was negatively associated with lung cancer and with oesophageal squamous cancer, both in men and in women. However, most of the lung cancer patientsqe are smokers and tend to have lower BMIs than non-smokers. When non-smokers are analysed separately, that negative association ceases to exist (3, 25). Another meta-analysis found associations between high BMI and all 20 cancer types that were analysed, except oesophageal and prostate cancer (26).

4. ADIPOKINES – AN OVERVIEW

Over the last decade, there has been a paradigm shift from the concept that adipose tissue is a mere storage site for energy (27). It is now known that adipose tissue is a metabolically active organ that plays active roles in energy homeostasis, immunity, endocrine balance and bone remodelling (28). Adipose tissue is responsible for the synthesis and secretion of several polypeptide growth factors and cytokines, known as adipokines or adipocytokines. They are produced exclusively, or substantially, by white adipose tissue preadipocytes and mature adipocytes. The list of adipokines grows by the day,

with more than 50 molecules being listed to date (29). The most abundant and well-known ones are leptin – the first described adipokine, produced mainly by the adipose tissue, and adiponectin – produced exclusively by it.

Adipokines play an important role in the pathophysiology of cancer in obesity. The list of adipocytokines is extensive, and we will discuss the roles of the two most abundant adipokines in cancer: leptin and adiponectin.

5. LEPTIN

Leptin is a 16-kDa adipokine that is produced mainly, but not exclusively, by white adipose tissue. Others sites of production include the placenta, intestine, stomach, ovaries, bone marrow, brain, pituitary, liver, mammary epithelial cells and skeletal muscle. Leptin levels are positively correlated with white adipose tissue mass, and are therefore increased in obesity. Its synthesis is influenced by insulin, tumour necrosis factor alpha (TNF-alpha), glucocorticoids, sex hormones and prostaglandins. Its expression is also stimulated by hypoxia (commonly found in solid tumours), through the hypoxia-induced factor-1 (HIF-1) (30).

The main role of leptin is to regulate energy homeostasis by controlling energy intake and energy expenditure, through its action on the arcuate nucleus of the hypothalamus. It has additional effects in the endocrine and immune systems, including reproduction, glucose homeostasis, bone formation, tissue remodelling, and inflammation (31, 32). Leptin binds to its receptor and activates different signalling pathways, such as the JAK/STAT (Janus Kinase/Signal Transducer and Activator of Transcription), MAPK (mitogen-activated protein kinase), PI3K/Akt (phosphatidylinositol 3-kinase/protein-kinase B), AMPK (5' AMP-activated protein kinase) and IRS (insulin receptor substrate) pathways, which affect cell proliferation and survival. For a review on the intracellular signalling pathways activated by leptin, see Fruhbeck (33).

Congenital leptin deficiency, which is observed in rare cases of mutations in the leptin gene, is associated with hyperphagia, impaired thermogenesis, immune defects, insulin resistance, dyslipidaemia, lipotoxicity, hypogonadotropic hypogonadism, functional and structural alterations in the brain, and impairment of cognitive development, all reversible by leptin treatment (34-40). Low levels of leptin are also observed in patients with lipodystrophic syndromes and in anorexia nervosa. Leptin is a pleiotropic hormone, being mitogenic, anti-apoptotic, pro-angiogenic, and pro-inflammatory in various cellular systems. Being the most abundant adipokine and increased in obesity, its role in the pathogenesis of cancer has been extensively investigated.

Leptin stimulates growth, migration and invasion in tumour cell models, which are relevant in the pathogenesis of cancer (30, 41). Leptin also increases the production of cytokines by macrophages (such as IL-6, IL-12, and TNF-alpha), stimulating cancer cells (42). By reducing tissue sensitivity to insulin, leptin is responsible for hyperinsulinaemia, which also stimulates cell growth. Leptin appears to be involved in angiogenesis as well (43). Leptin also plays a role in hormone-dependent neoplasms, such as in the cancer of the endometrium and in breast cancer, by activating aromatase (44), an enzyme catalysing the transformation of androstenedione to oestrone.

5.1. Prostate cancer

Epidemiological studies found contradictory results associating leptin with prostate cancer. A recent review summarises those studies, with 3 out 9 studies showing positive associations between blood leptin levels and prostate cancer (45). In the Physicians' Health Study, a 25-year prospective study, no associations were found between leptin and prostate cancer risk and mortality (46). A genetic study demonstrated that the leptin polymorphism (-2548 G/A), leading to higher leptin levels, is associated with susceptibility to prostate cancer and risk of advanced disease (47). It is suggested that, regardless of these contradictory data, leptin may be associated with more advanced, hormone-refractory prostate cancer (48).

Leptin stimulates prostate growth and angiogenesis (43, 49, 50), and receptors for leptin are present in the prostate (51). *In vitro*, leptin stimulates growth of the androgen-insensitive, DU145 and PC3, prostate cancer cell lines but not androgen-sensitive cell lines, LNCaP (52, 53). Leptin has been reported to promote the proliferation and survival of DU145 and PC3 cell lines through the activation of the PI3K and the classical MAPK pathways; additionally, leptin mediates the growth effect through the JNK (c-Jun N-terminal kinase) MAP kinase pathway (52). Both the full-length and short forms of the leptin receptor have been implicated in these responses, and downstream targets of these pathways include c-jun, c-fos and other genes involved in cell proliferation.

Leptin can also promote neoangiogenesis in prostate cancer: the leptin gene can be induced under conditions of hypoxia, which often prevail inside solid tumours; it may have a role in vascular remodelling both on its own and through the induction and activation of a number of other pro-angiogenic factors, including vascular endothelial growth factor (VEGF), fibroblast growth factor 2 (FGF 2) and the matrix metalloproteinases 2 and 9 (54).

5.2. Breast cancer

The majority of breast cancers require action of oestrogens for their growth and progression. In addition, leptin in excess may also contribute to the pathogenesis of breast cancer. Vona-Davies and Rose summarises the contradictory results found in case-control studies (one of which was nested within a prospective study), with 3/10 showing positive correlations (55). More recently, another prospective observational study demonstrated that BMI and leptin were significantly correlated with pathological tumour classification and TNM stage in postmenopausal breast cancer patients (56). It seems that leptin may increase breast cancer risk in postmenopausal women specifically (56, 57), in which the only source of oestrogens is adipose tissue.

Leptin's effects on breast cancer can be explained by several mechanisms: 1) leptin is able to induce the growth of breast cancer cells through activation of the JAK/STAT3, MAPK-ERK1/2 (extracellular signal-regulated kinases 1/2), and/or PI3K (phosphoinositide 3-kinase) pathways; 2) leptin can mediate angiogenesis by inducing the expression of vascular endothelial growth factor (VEGF) (43); 3) leptin induces transactivation of human epidermal growth factor receptor 2 (ErbB-2), and interacts with insulin-like growth factor 1 (IGF-1) in triple negative breast cancer cells, transactivating the epidermal growth factor receptor (EGFR) and promoting invasion and migration; 4) leptin stimulates aromatase expression, increasing oestrogen levels and affecting the growth of oestrogen receptor (ER)-positive breast cancer cells; 5) leptin induces MAPK-dependent activation of ER (53, 58, 59); 6) leptin stimulates proteolytic cleavage of intercellular matrix, promoting cancer cell invasion (60).

In addition, leptin and its receptor are significantly overexpressed in human primary and metastatic breast cancer, being most abundant in less differentiated tumours (61). In breast cancer cells, the overexpression of leptin is associated with the leptin promoter polymorphism Lep-2548G/A (62). The subtype of leptin receptor seems to make a difference in the prognosis, since patients with elevated Ob-Ra expression have longer relapse-free survival, as compared to patients with high Ob-Rb/Ob-Ra ratio (63). The implication of leptin as a growth factor to breast cancer is further strengthened by the fact that leptin-deficient *ob/ob* (64) and leptin-resistant *db/db* mice (65) do not develop transgene-induced mammary tumours.

5.3. Colorectal cancer

Leptin levels were positively correlated with colorectal cancer in some prospective studies (66-68), but not in others (69, 70). It is questionable whether leptin is a cause or a mere bystander, since leptin is not as strongly associated with colorectal cancer in women, who have much higher leptin than men. Paradoxically, some studies observed significantly lower serum leptin concentration in patients with colorectal cancer, independent of BMI and weight loss (71, 72). In less differentiated colorectal cancers, the leptin expression is decreased (73), and the expression level may be positively correlated with a better prognosis (74).

Leptin receptors are expressed in human colon cancer cell lines and in human colon tumours, polyps and adjacent mucosa (75). In addition, leptin is overexpressed in primary colorectal cancers, which is significantly correlated with tumour grade and the presence of adenocarcinoma (76). Leptin stimulates growth of colon cancer cells via MAPK pathway (ERK 1/2 and JNK), JAK/STAT3 and PI3K/Akt, and reduces cell apoptosis (77-79). The pro-angiogenic effect of leptin plays an additional role on the pathogenesis of colorectal cancers (43). Moreover, leptin induces IL-6 production by $Apc^{Min/+}$ colon epithelial cells which leads to the growth and proliferation of preneoplastic cells (80). However, *in vivo* studies are contradictory. In $Apc^{Min/+}$, *ob/ob* and *db/db* mice, leptin supplementation did not affect tumorigenesis (81, 82). In a high-fat 1,2-dimethylhydrazine (a potent carcinogen)-treated rat model, growth of colonic cancer cells was enhanced by leptin (83), showing that leptin's effects may be synergistic to other environmental factors.

5.4. Thyroid cancer

There is evidence suggesting that obesity and increased BMI as positively correlated with thyroid cancer (84-86), but there are very few studies evaluating the association between leptin and thyroid cancer. In a small Turkish study, patients with papillary thyroid carcinoma had higher leptin levels as compared to controls (87).

Leptin receptors are expressed in the normal thyroid, and leptin treatment increases growth and secretion in the gland (88). In addition, leptin and leptin receptor are expressed in papillary thyroid cancer, and this expression is associated with aggressiveness (89, 90). All thyroid cancer cell lines – anaplastic (ARO), follicular (WRO) and papillary (CGTH-W3) – express long-form leptin receptors, but leptin stimulation does not alter the expression of the sodium-iodide symporter, cell growth or cell cycle. Leptin, however, promotes cell migration of papillary thyroid cancer cells and inhibits migration of anaplastic and follicular cancer cells (91). In a contradictory *in vitro* study, leptin stimulated cell proliferation and inhibited apoptosis of papillary carcinoma cells, via activation of PI3K/Akt (90).

5.5. Renal cancer

Studies associating leptin and renal cancer are scarce. In a case-control study that included 70 patients with renal cell carcinoma, leptin was inversely associated with cancer risk (OR: 0.53, CI: 0.28-0.99, p=0.05), which the authors attribute to leptin's pro-immunogenic effects (92). Similarly, higher serum leptin was an independent predictor of progression-free survival, but was also associated with tumour specimen venous invasion (93).

Leptin receptor is present in Caki-1, ACHN, 769P, A498, SKRC44 and SKRC49, and in the murine renal cancer cell line Renca. In the murine cell, leptin induces invasiveness (94). In another *in vitro* study, leptin increased the proliferation and mobility capabilities of Caki renal carcinoma cells by up-regulating the expression of the JAK/STAT3 and ERK1/2 signalling pathways (95). Leptin also induces collagen gel invasion of non-tumorigenic kidney MDCK epithelial cells through PI3K-, Rho-, and Rac-dependent signalling pathways (75). Leptin's effects on lymphangiogenesis, mediated by Akt and ERK1/2, and on lipid and protein biosynthesis, mediated by acyl-coenzyme A:cholesterol acyl transferase (ACAT), may explain the roles of leptin in the pathogenesis and in the phenotype of renal cancer (96). However, there is contradiction between the epidemiological and the molecular findings regarding leptin's role on kidney cancer.

5.6. Endometrial cancer

A few studies showed that leptin levels were correlated with the presence of endometrial cancer, but correlation disappeared when adjusted by BMI, suggesting

that leptin may be a bystander and not the cause of endometrial cancer (97-99).

Leptin receptors are present in the normal and malignant human endometrium (more intensely at early secretory phases), and are inhibited by treatment with progesterone (100). Specifically in malignant tissues, the expression of leptin receptors is increased through the stimulatory effect of hypoxia-inducible factor 1 alpha (which is in turn induced by solid tumour-associated hypoxia) (101). In malignant tissues, lower expression levels of leptin receptor short form (Ob-Ra, which activates JAK2, IRS-1, and MAPK) is observed, suggesting that aberrant leptin receptor isoforms may be involved in the pathogenesis of endometrial cancer (98). In addition, higher-grade and less differentiated tumours have lower expression levels of leptin receptor (102). In ECC1 and Ishikawa endometrial adenocarcinoma cells, leptin promotes endometrial cancer growth and invasiveness through MAPK and Akt pathways, and also induces the expression of cyclooxygenase-2 (COX-2), which increases tumorigenesis, increases metastasis potential and promotes angiogenesis (103). Leptin also enhances cyclin D1 expression (a cell cycle regulator required for completion of the G1/S transition) through JAK/STAT, MAPK and PKA (protein kinase A) activation, leading to human endometrial cancer proliferation (104). Additionally, leptin's effects on the pathogenesis of endometrial adenocarcinoma are attributed to the increase of several angiogenic factors (105).

5.7. Pancreatic cancer

One study showed that leptin levels were lower in patients with pancreatic cancer, compared to the normal population. In the same study, patients with chronic pancreatitis also had lower leptin, and patients with autoimmune pancreatitis had high leptin levels (106). Similarly, another case-control study showed that pancreatic adenocarcinoma was associated with low leptin levels, but the causality remained unclear (107). Hypoleptinaemia may be just a consequence of weight loss, observed in many pancreatic cancer patients (108). If in fact hypoleptinaemia increases the risk of pancreatic cancer, it could be explained by the increase in insulin resistance, which is another risk factor for the disease (109).

Leptin inhibits growth of two human pancreatic cancer cell lines (PANC-1, Mia-PaCa), possibly through its proimmunogenic effects (53). Both in *ob/ob* and *db/db* mice, larger tumours, increased mortality and high of mice developing metastases were observed. This suggests that obesity, but not leptin, may not play a role in the pathogenesis of pancreatic cancer (110).

5.8. Oesophageal adenocarcinoma

There are no data showing an association between serum leptin levels and oesophageal cancer risk. In a case-control study, leptin was not associated with squamous cell carcinoma of the oesophagus (111). However, hyperleptinaemia has been shown to increase the risk of Barrett's oesophagus (BE), a precancerous lesion (112). As in pancreatic cancer, hypoleptinaemia is observed in patients with weight loss and cachexia, independently of the presence of cancer (113).

Leptin receptors are overexpressed in oesophageal carcinoma cells (114, 115), and this overexpression indicates poorer prognosis. Leptin administration causes proliferation of human oesophageal squamous cancer cell line (KYSE410) with a mutant p53 gene, but not in a cell line without the mutant p53 (53). This effect seems to be mediated by the transactivation of the epidermal growth factor receptor, mediated by HB-EGF and transforming growth factor alpha (TGF-alpha) (115). Other studies confirmed leptin's anti-apoptotic and growth-promoting effects on oesophageal carcinoma cells (116), which are mediated by the activation of MAPK (through p38 and ERK), PI3K/Akt, JAK2 and EGFR (117, 118). In SEG-1 and BIC-1 cells lines, leptin has stimulatory actions on cell proliferation, but does not have anti-apoptotic effects (119).

6. ADIPONECTIN

Adiponectin is a 30-kDa peptide, present physiologically as trimers, hexamers or high-molecular-weight multimeric complexes (28). Adiponectin is expressed exclusively and in large quantities by adipocytes, making up approximately 0.01% of total human plasma protein content (120); it is negatively regulated by several other products of adipose tissue that become elevated during obesity, such as TNF-alpha, IL-6 and IL-18 (121). Adiponectin levels are negatively correlated with body fat and BMI. The two isoforms of the adiponectin receptor, AdipoR1 and R2, are most abundantly found in striated muscle and the liver, respectively, but are widely expressed in many types of normal and cancerous cells (122).

The main functions of adiponectin include anti-inflammation, anti-atherogenesis and insulin sensitisation. Circulating levels of adiponectin correlate inversely with inflammation states and insulin resistance (28), and a study by Ouchi *et al.* demonstrated that adiponectin modulates the inflammatory response in endothelial cells that is associated with coronary artery disease (123). Additionally, adiponectin has been identified as a likely angiogenic inhibitor that maintains the balance of quiescent vasculature present in adult adipose tissue (124).

However, as opposed to what is observed in the case of leptin, the role of adiponectin under physiological conditions appears to be redundant – neither its deletion nor its overexpression leads to any significant body weight differences in mice. Nonetheless, adiponectin has been shown to play an active role in regulating neovascularisation in tumours, suggesting that its effects may be more pronounced under pathological conditions, where there is more aggressive angiogenic activity than in slowly expanding adipose tissue (124).

6.1. Prostate cancer

Although the correlation between adiponectin levels and prostate cancer has not been consistently proven,

there is evidence to suggest that adiponectin is inversely related not only to the risk and incidence of prostate cancer, but also to the histological grade and disease stage (125, 126).

In vitro, adiponectin is a potent inhibitor of cell growth and proliferation in the metastatic prostate cancer cell lines, DU145, PC3 and LNCaP, through the downregulation of STAT3 signalling, which is constitutively active in androgen-independent DU145 cells. STAT3 increases the activity of the androgen receptors, leading to an amplification of the mitogenic signal; this forms the basis of hormone-refractory prostate cancer, and is crucial for the survival of DU145 cells (127).

Adiponectin also exerts an inhibitory effect on cell proliferation, regardless of androgen-dependence, through an AMPK-mediated pathway. Binding of adiponectin to its receptors activates AMPK, which regulates a diverse array of metabolic functions within the cell; notably, it phosphorylates and activates TSC2, which is an inhibitor of mTOR (mammalian target of rapamycin). mTOR and its downstream effectors, for example the PI3K/Akt pathway, have been implicated in several cancers, including prostate cancer, in which the phosphatase and tensin homolog (PTEN) gene is frequently inactivated (125).

6.2. Breast cancer

The association between adiponectin levels and breast cancer risk appears to be dependent on menopausal state. In postmenopausal women, there is evidence for a significant correlation between reduced adiponectin, as seen in obesity, and breast cancer incidence; however no such correlation was found in premenopausal women, in the same study (128).

Adiponectin inhibits breast cancer cell proliferation *in vitro*, in part by inhibiting the TNF-alpha-mediated NF-kappa B signalling pathway. TNF-alpha is a pro-inflammatory cytokine which promotes oestrogen biosynthesis; especially in obese, post-menopausal women, where adipose tissue is the main source of oestrogens (129), elevated oestrogen production stimulated by TNF-alpha supports the survival and growth of breast cancer cells. In the same way, adiponectin suppresses the induction of VEGF expression by TNF-alpha, disabling an important pro-angiogenic response (125). The lack of angiogenic support in a growing tumour can lead to considerable tumour cell apoptosis and reduction in tumour weights and volumes, as demonstrated in adiponectin-treated mice by Brakenhielm *et al.* (124).

Adiponectin inhibits the invasiveness of breast cancer cells by activating the AMPK pathway (130). In addition, adiponectin also stimulates the peroxisome proliferator-activated receptor (PPAR)-alpha pathway in breast cancer cells, inhibiting proliferation and promoting differentiation. Adiponectin-dependent activation of PPAR-gamma has also been shown to increase nuclear levels of BRCA1, a tumour suppressor protein involved in DNA repair, and therefore in reducing cancer risk (131).

The increased insulin resistance and hyperinsulinaemia due to a fall in adiponectin in obesity also has an impact on breast cancer. A number of studies support the role of insulin in stimulating proliferation in breast cancer cells, both through the insulin receptor signalling pathway and through interaction with oestrogens. Insulin may also serve to bolster the expression of VEGF. Therefore, the modulation of insulin levels is another indirect route through which adiponectin may protect against breast cancer.

6.3. Colorectal cancer

The association between colorectal cancer and adiponectin levels is still controversial (69, 132), but many studies have shown that low circulating adiponectin is correlated with an increased incidence of colorectal cancer (133-135), even after correction for BMI and insulin resistance.

Expression of the adiponectin receptors, AdipoR1 and R2, is elevated in colorectal cancer cells as compared to non-tumour colorectal tissue (136), giving support to the hypotheses that adiponectin causes colorectal cancer. On the other hand, adiponectin may indeed inhibit colorectal cancer cells, through the activation of the AMPK pathway, which inhibits mTOR, leading to anti-proliferative and pro-apoptotic effects of adiponectin (137). Furthermore, adiponectin can reduce lipogenic activity – which is essential to maintain membrane integrity in the rapidly dividing tumour cells – in colorectal cancer cells, by suppressing SREBP-1c activity. This in turn leads to a decrease in the expression of key lipogenic enzymes such as FAS (138).

Other roles of adiponectin, especially its interference with the proliferative and pro-inflammatory effects of leptin, TNF-alpha and IL-6, seem to operate independently of AMPK. As previously mentioned, adiponectin inhibits the activation of STAT3 by IL-6 and of the NF-kappa B pathway by TNF-alpha (134, 139). The study by Fenton *et al.* highlights the suppression by adiponectin of two separate leptin-mediated pathways. Adiponectin signals through the MAPK pathway to phosphorylate and activate I-kappa-K, an inhibitor of NF-kappa B. Additionally, adiponectin is able to suppress the pro-inflammatory IL-6 trans-signalling induced by leptin, by decreasing the availability of the soluble IL-6 receptor (sIL-6R) and increasing sgp130, the natural inhibitor of the IL6-sIL-6R complex (139).

6.4. Thyroid cancer

There are no studies evaluating the relationship between adiponectin and thyroid cancer. A follow-up study of patients with end-stage renal disease, who have a higher risk for developing cancer, showed that the most common site of cancer was the kidney (26.7%), followed by thyroid (13.3%) and stomach (13.3%). Lower adiponectin was an independent predictor of malignancy, but the associations between hypoadiponectinaemia and each type of cancer were not analysed (140). Further studies are necessary to evaluate whether hypoadiponectinaemia is associated with thyroid cancer.

6.5. Renal cancer

In general, renal cancer has a strong inverse association with serum adiponectin levels, as reported by a number of studies (141-143). Where the details of the disease are concerned, the correlation with adiponectin is less conclusive: while it is agreed that decreased adiponectin is related to the presence of metastasis in renal cell cancer, its association with tumour grade appears to be inconsistent. Evidence supports a role for adiponectin in renal cancer that is independent of BMI – in fact, Horiguchi *et al.* report a slight tendency for higher BMI to be associated with better clinicopathological features of the cancer, an observation may be due to cancer-induced cachexia, characterised by a preferential loss of skeletal muscle rather than adipose tissue (143). Spyridopoulos *et al.* suggest that an indicator of visceral adiposity, such as waist-to-hip ratio, may be a better parameter than BMI in gauging adiponectin's effects in renal cancer (142).

Both adiponectin receptors, especially AdipoR1, are known to be expressed in normal renal tissue as well as renal cancer tumour cells, and there are indications that the receptors may be downregulated in cancer tissue as compared to healthy tissue, reducing the protective potential of adiponectin in tumour cells (141). Few studies have investigated the specific molecular actions of adiponectin in renal cancer. Clear-cell renal cell carcinoma, the most common form of renal cancer, is well-known to be highly angiogenic, which suggests that adiponectin may have an important anti-angiogenic role in the development of the cancer (141). Low adiponectin levels are also implicated in the activation of several cancer-promoting factors, including STAT3, ERK 1/2 and Akt, whereas higher levels of adiponectin act to suppress them.

6.6. Endometrial cancer

The correlation between low adiponectin levels and endometrial cancer has been established independently of BMI (144, 145), although a combined decrease of adiponectin and obesity, as it often occurs, constitutes a greater risk (146). Significantly, this relationship is especially strong in premenopausal women, contrary to that of breast cancer risk (128, 145, 146). Possibly related to this is the finding that AdipoR1 and R2 are expressed in the human endometrium, and that their expression is increased during the midluteal period of the menstrual cycle.

The role that adiponectin plays in endometrial cancer is fairly similar to that which it plays in breast cancer. Both tissues respond to oestrogens, which promote cell proliferation; both tissues also express the pro-angiogenic factor VEGF. Adiponectin suppresses the biosynthesis of oestrogens and the expression of VEGF through its effects on the NF-kappa B signalling pathway (145). Excess insulin, such as in the case of insulin resistance, may augment the mitogenic effects of oestrogen, whereas adiponectin is an insulin sensitiser. The activation of AMPK is also an inhibiting effect of adiponectin on endometrial cancer (147).

A study by Cong *et al.* has expanded considerably the known mechanism of adiponectin through the AMPK pathway, by observing that while adiponectin similarly induced cell cycle arrest and apoptosis in both investigated endometrial carcinoma cell lines, HEC-1-A and RL95-2, these effects occurred via different pathways: the protein kinase Akt is inactivated and cyclin D1 is downregulated in HEC-1-A cells, whereas in RL95-2 cells there was a reduction in cyclin E2 expression, as well as an inhibition of the p42/44 MAPK. These two cell lines differ genetically in that the RL95-2 line is deficient in the tumour suppressor PTEN, which regulates the PI3K signalling pathway; how this difference might explain the observations remains to be elucidated (148).

6.7 Pancreatic cancer

Evidence for the correlation between pancreatic cancer and serum adiponectin levels is conflicting. Adiponectin in pancreatic cancer patients has separately been observed to be elevated (149, 150), decreased (110, 151), and unchanged (106). An important caveat to consider in interpretation is that the results quoted above are not necessarily comparable in terms of study design and epidemiological relevance. Notably, case-control studies (149, 150) were liable to obtain evidence in support of increased adiponectin associated with pancreatic cancer, whereas the study on male Finnish smokers, which reported an inverse correlation, was of a prospective design (151).

This raises a host of possible explanations for the discrepancy, which tend to attribute the elevated adiponectin levels to reverse causation. Adiponectin has been tied to cancer cachexia, such that its increase may be due to weight-loss brought about by cancer progression (152); this is in agreement with the observation that adiponectin levels are increased in cases of anorexia nervosa or prolonged voluntary weight-loss (153). Elevated adiponectin in compensation for insulin resistance is also a suggested factor, as is resistance to adiponectin itself, as a consequence of a downregulation of either the adiponectin receptors or their downstream signalling pathways.

Regardless of the speculations, the direct action of adiponectin on pancreatic cancer cells has not yet been investigated. It has been observed that NF-kappa B activation occurs in cell cultures, animal models and human tissue of pancreatic cancer (154). Similarly, the activation of carcinogenic pathways involving STAT3, mTOR, PI3K and ERK, mediated by IL-6, have also been found to contribute to the survival and proliferation of pancreatic cancer cells (155). Although adiponectin is able to specifically counteract these pathways in other cancers, further studies are needed to conclusively establish adiponectin's role in pancreatic cancer.

6.8. Oesophageal adenocarcinoma

The association between oesophageal adenocarcinoma and adiponectin remains inconclusive, despite there being some evidence for an inverse correlation between adiponectin levels and oesophageal cancer, and between adiponectin and BE (156, 157). There has, however, been some doubt thrown on those associations (158).

Table 2. Possible physiopathological bases for the development of cancer in obese individuals

Hormonal changes	Increased oestrogens
	Increased insulin
	Increased insulin-like growth factors
Immune alterations	Disrupted immune response
	Increased activation of NF-kappa B
	Increased oxidative stress
	Increased peroxidation
Adipocytokines	Increased leptin
	Decreased adiponectin
	Other adipocytokines e.g. TNF-alpha, IL-6, PAI-1
Miscellaneous	Hypertension
	Chronic systemic inflammation
	Increased acid reflux
	Increased iodine uptake
	Decreased vitamin D bioavailability

Table 3. Effects of leptin on different types of cancer

Effects	**Signalling pathway or molecular mechanism**	**Cancers involved**
Growth	MAPK/ERK/JNK	Prostate Breast Colorectal Renal Endometrial Oesophageal
	JAK/STAT	Breast Colorectal Renal Endometrial Oesophageal
	PI3K/Akt	Prostate Breast Colorectal Thyroid Endometrial Oesophageal
	IL-6 induction	Colorectal
	PKA	Endometrial
	EGFR transactivation	Oesophageal
	Aromatase induction	Breast
Apoptosis inhibition	MAPK/ERK/JNK, JAK/STAT or PI3K/Akt	Colorectal Thyroid Oesophageal
Invasion/metastasis	MAPK/ERK/JNK, JAK/STAT or PI3K/Akt	Endometrial Renal
	EGFR transactivation	Breast
	Intercellular matrix proteolysis	Breast
Angiogenesis	MAPK/ERK	Renal Endometrial[1]
	PI3K/Akt	Renal Endometrial[1]
	VEGF induction	Prostate Breast Colorectal
	FGF 2 induction	Prostate
	Matrix metalloproteinases	Prostate
Lipid/protein biosynthesis	ACAT	Renal

[1] These pathways lead to the induction of COX-2 in endometrial cancer cells.

In contrast, while the question of whether serum adiponectin levels are related to the incidence of oesophageal adenocarcinoma remains unresolved, its receptors AdipoR1 and R2 have been identified in many oesophageal adenocarcinoma cell lines and BE tissue (114, 116, 159). Konturek *et al.* showed that the neoplastic tissue had decreased expression of the adiponectin receptors, raising the possibility that adiponectin had reduced biological function, and thus less protective capacity, in tumour cells (159).

The anti-proliferative and pro-apoptotic effects of adiponectin on oesophageal adenocarcinoma have been demonstrated *in vitro*. Adiponectin was shown to increase apoptosis in a dose-dependent manner, with the concomitant increased expression of Bax and decreased expression of Bcl2, in the OE-19 cell line (159). Bax is pro-apoptotic whereas Bcl-2 is anti-apoptotic, such that the reciprocal regulation of the two proteins propels the adenocarcinoma cells towards apoptosis. In a study using four oesophageal adenocarcinoma cell lines and an additional non-tumorigenic cell line, globular adiponectin suppressed the proliferative effect of leptin. That effect was specifically mediated by AdipoR1, through AMPK and serine/threonine phosphatases that have not as yet been clearly identified (116). It has also been proposed that the abnormal activation of ERK 1/2, which promotes survival and proliferation in BE tissue, may be due to a deficiency in serum adiponectin (157).

7. PERSPECTIVES

There is strong epidemiological and molecular evidence showing that obesity is a risk factor for the development of several types of cancer. The pathophysiological bases for that association between obesity and cancer are summarised in Table 2.

The adipokines leptin and adiponectin, which levels are respectively elevated and decreased in obesity, may play important roles in the pathogenesis of obesity-related cancer. Both have crucial effects of cell proliferation, apoptosis, cell invasiveness and angiogenesis, regulating tumour formation. Tables 3 and 4 summarise the effects of leptin and adiponectin on the reviewed cancer types.

Obesity is also associated with increased levels of several other adipocytokines, such as interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-alpha). These adipocytokines determine a proinflammatory state leading to DNA damage (160) and angiogesis (161), and subsequently to the promotion of carcinogenesis and metastasis (162-164). They also increase insulin resistance and cause hyperinsulinaemia, which increases the risk for cancer. Moreover, each adipocytokine has additional specific effects. For example, IL-6 can cause growth of androgen receptor-positive prostate tumours through activation of the androgen receptor (165). TNF-alpha up-regulates CXCR4 expression, which, along with its ligand CXCL12, is implicated in metastases and tumour cell survival in a wide range of cancers (166). In the future, targeted therapies, such as IL-6 antibodies (siltuximab), may be clinically available for the treatment of cancer (167).

Although there has been considerable development in elucidating the actions of adiponectin and

Table 4. Effects of adiponectin on different types of cancer

Effects	Signalling pathway or molecular mechanism	Cancers involved
Growth inhibition	MAPK/ERK inhibition	Renal Endometrial Oesophageal
	JAK/STAT inhibition	Prostate Colorectal Renal
	PI3K/Akt inhibition	Renal Endometrial
	NF-kappa B inhibition	Breast Colorectal
	PPAR activation	Breast
	AMPK activation	Endometrial Oesophageal Prostate Colorectal
	Oestrogen biosynthesis inhibition	Breast Endometrial
Apoptosis	PPAR activation	Breast
	AMPK activation	Oesophageal Colorectal Endometrial
Invasion/metastasis inhibition	AMPK	Breast
Anti-angiogenesis	VEGF downregulation	Breast Endometrial
	Caspase-mediated endothelial cell apoptosis	Renal
Anti-inflammation	IL-6 trans-signalling inhibition	Colorectal
Lipogenesis downregulation	AMPK-mediated SREBP-1c inhibition	Colorectal

leptin in several cancers, the precise pathways and downstream effectors that are called into play are still far from understood. There is also a need to reconcile the gap between *in vitro* and *in vivo* studies, to increase the relevance of experimental results to physiological systems; further studies using animal models, such as leptin *ob/ob* or adiponectin knockout mice, would be valuable in this respect. As many adipokines are thought to affect the process of cancer progression, a clearer understanding of the effects of leptin, adiponectin and other adipokines on cancer will allow the development of prophylactic or therapeutic therapies against cancer in obese individuals.

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Abbreviations: ACAT: acyl-coenzyme A:cholesterol acyl transferase; Akt: protein kinase B; AMPK: 5' AMP-activated protein kinase; BE: Barrett's Oesophagus; BMI: body mass index; COX: cyclooxygenase; EGF: epidermal growth factor; EGFR: epidermal growth factor receptor; ER: oestrogen receptor; ERK; extracellular signal-regulated kinase; FGF: fibroblast growth factor; HIF: hypoxia-induced factor; IGF: insulin-like growth factor; IRS: insulin receptor substrate; IL: interleukin; JAK: Janus kinase; JNK: c-Jun N-terminal kinase; MAPK: mitogen-activated protein kinase; mTOR: mammalian target of rapamycin; NF-kappa B: nuclear factor kappa B; PAI: plasminogen activator inhibitor; PI3K: phosphoinositide 3-kinase; PKA: protein kinase A; PPAR: peroxisome proliferator-activated receptor; PTEN: phosphatase and tensin homolog; SREBP: sterol regulatory element binding protein; STAT: signal transducer and activator of transcription; TGF: transforming growth factor; TNF: tumour necrosis factor; VEGF: vascular endothelial growth factor.

Key Words: Adipocytokine, Adipokine, Adiponectin, Cancer, Leptin, Obesity, Review

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