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Obesity, adipokines and cancer: An update

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Title:

Obesity, adipokines and cancer: An update

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Abstract

Obesity causes dysfunction of adipose tissue, with resultant chronic inflammation and adverse interplay of various adipokines, sex steroids and endocrine hormones. All these drive tumourigenesis and explain the epidemiological link between obesity and cancer. Over the past decade, the associations among obesity, adipokines and cancer have been increasingly recognized. Adipokines and their respective signaling pathways have drawn much research attention in the field of oncology and cancer therapeutics. This review will discuss the recent advances in the understanding of the association of several adipokines with common obesity-related cancers, and the clinical therapeutic implications.

Introduction

Tackling obesity is a growing challenge. The increasing prevalence of obesity worldwide does not just propel the upsurge of incident diabetes, metabolic syndrome and cardiovascular diseases, but also of incident cancers. A meta-analysis, involving 282137 incident cases from prospective observational studies, had shown that increased body mass index (BMI) was associated with a higher risk of both common and less common cancers. (1) Increased risks of incident cancers by 6 to 59%, involving oesophageal adenocarcinoma, leukaemia, non-Hodgkin lymphoma, colon, thyroid and renal cancers, were associated with every increment of 5 kg/m^2 in BMI above normal in both sexes. In men, significant positive associations were also noted with rectal cancer and malignant melanoma. In women, positive associations were found with endometrial, gallbladder, pancreatic and post-menopausal breast cancers as well. (1) In fact, Calle et al had estimated that in the United States, obesity contributed to 14% of all cancer mortality in men and 20% of those in women. (2) In UK, a recent population-based cohort study involving 166955 subjects with cancer, suggested that BMI was associated with 17 out of 22 cancers studied. Furthermore, it also estimated that every unit of population-wide increment in BMI would lead to an addition of 3790 UK subjects developing one of the ten common obesity-related cancers annually. (3) In Asian-Pacific populations, a meta-analysis also showed that every increment of 5 units in BMI above 18.5 kg/m^2 was associated with an increase in cancer mortality by 1.09 for all cancers. (4) In Chinese, although the overall prevalence of obesity is lower than the west, even when Asian-Pacific BMI cut-offs are used (5), obesity has also been demonstrated as an independent predictor of incident cancers. In a community-based cohort of 2895 Hong Kong Chinese subjects

aged 25 to 74 recruited from the general population, over a median follow-up of 16 years, 209 (7.2%) of them developed cancers. Baseline waist circumference, an indicator of central adiposity, independently predicted incident cancers with a standardized odds ratio of 1.19 (95% CI 1.02 – 1.40; p = 0.031) even after adjustment for age of subjects. (6) All these suggested that the association between obesity and cancer was consistent across populations worldwide. In fact, in Asian-Pacific populations, the association between increased BMI and breast cancer was even stronger, in both pre- and post-menopausal women, than in populations of North America, Europe and Australia. (1) Recent meta-analyses also suggested that both pre- and post-menopausal breast cancer patients who were obese had poorer overall survival regardless of when BMI was ascertained. (7) Furthermore, in men, obesity increased the risk of prostate cancer specific mortality as well as biochemical recurrence. (8) Taken together, cumulative epidemiological evidence would suggest that overweight or obese subjects are not just at increased risk of cancer development: in those who have developed cancers, obese patients also tend to have worse prognosis.

Preclinical studies have provided insights into the pathogenic mechanisms linking obesity and cancer. While several molecular pathways have been proposed, all of them actually stem from a dysfunctional adipose tissue, with ultimate creation of a microenvironment that favours tumour development. (9, 10) In obesity, coupled with the expansion in adipose tissue mass are increases in tissue hypoxia, inflammation and insulin resistance. Furthermore, the delicate interplay among obesity-associated sex hormones, insulin growth factor 1 (IGF1) and the various adipokines further contributes to enhanced inflammatory signaling, angiogenesis, cellular proliferation

and ultimately, carcinogenesis. In this review, we will focus on the role of adipokines in the development of various cancers in the context of obesity.

Adipokines in obesity-related cancer development

The adipose tissue is a complex, highly active endocrine organ. It is integrally involved in carcinogenesis via dysregulated secretion of various adipokines, which are polypeptide cytokines produced by white adipose tissue, either exclusively or substantially, and can act both locally and systemically. (11, 12) These adipokines have been implicated in cancer development and progression through their effects on insulin resistance, lipolysis and various inflammatory pathways. (9) In the context of obesity, the hypertrophic expansion of adipose tissue induces local hypoxia, inflammatory activation and reactive angiogenesis, changes which favour tumourigenesis. Some of the proinflammatory adipokines, such as interleukin-6 (IL-6) and leptin, have been shown to stimulate cancer stem cells, which are stromal cells with tumourigenic potential, leading to increased tumour growth and survival. (10) On the other hand, cancer cells are known to stimulate lipolysis in the cancer-associated adipocytes, the delipidation of which is followed by their differentiation to a fibroblast-like phenotype with increased secretion of proinflammatory cytokines such as IL-6 and plasminogen activator inhibitor-1 (PAI-1). (10) Thus the interaction of the cancer-associated adipocytes with their neighbouring cancer cells creates a tumour permissive microenvironment which would support cancer growth, progression and metastases. (10)

To date, more than 15 adipokines have been reported in the literature to be associated with cancers and this list is still growing. (11, 13) While the circulating levels of majority of pro-inflammatory adipokine levels, like leptin (Table 1), IL-6 and tumour necrosis factor alpha (TNF-α), are increased in cancers, some adipokines like adiponectin are protective against tumourigenesis and its serum levels are usually decreased in the cancer patients. (11) (Table 1) We previously demonstrated that, in a Chinese community cohort in Hong Kong, subjects who developed cancers also had higher baseline levels of C-reactive protein, IL-6, soluble tumour necrosis factor receptor 2 (a surrogate marker of TNF-α activity) and lipocalin 2. (6)

New insights into the role of specific adipokine in various obesity-related cancers

Adiponectin

Adiponectin is one of the most abundant adipokines secreted by adipocytes. It is secreted into the circulation as three oligomeric complexes, including trimer, hexamer, and high molecular weight (HMW) multimer. Among them, HMW adiponectin is the major active form mediating the insulin sensitizing effect of this adipokine. (14) Adiponectin has been shown to modulate the biological actions of several growth factors, including platelet-derived growth factor BB, basic fibroblast growth factor, and heparin-binding epidermal growth factor-like growth factor, through specific binding of these growth factors in an oligomerization dependent manner, with HMW adiponectin being able to bind all three growth factors. (15) These in vitro findings suggest that adiponectin, especially HMW adiponectin, can exert its anti-proliferative action by reducing the bioavailability of these growth factors at a pre-receptor level. The biosynthesis and secretion of these oligomers by

adipocytes are tightly controlled by molecular chaperones in the endoplasmic reticulum. (14) In the context of obesity, both the intracellular assembly and the secretion of the HMW adiponectin are impaired. (14) The resultant hypoadiponectinaemia in obesity both directly and indirectly promotes carcinogenesis. Adiponectin acts through two main receptors AdipoR1 and AdipoR2, both of which were reported to be expressed in several cancer cells in vitro and in vivo. (9, 16) Binding of adiponectin to these receptors impact on downstream signaling pathways (Figure 1) including the activation of AMP-activated protein kinase (AMPK) and ceramidase activities, and the inhibition of phosphatidylinositol 3-kinase, wingless type protein (Wnt) / β-catenin, extracellular regulated kinase 1 or 2 (ERK1/2), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, signal transducer and activator of transcription (STAT3), and nuclear factor κB (NF-κB). (16) Furthermore, there are emerging data on the role of T-cadherin, an adiponectin-binding protein, which docks adiponectin to responsive tissues, as demonstrated in the heart, muscle and vasculature(17). While both in vivo and in vitro studies had shown that T-cadherin inhibited tumour cell proliferation and invasiveness(18), there have also been a few studies suggesting that it may promote tumour angiogenesis. (17) Nevertheless, hypoadiponectinaemia in general increases fatty acid and protein synthesis (and hence promotes cell growth), proliferation, and DNA-mutagenesis, and inhibits cell cycle arrest and apoptosis. (16) Furthermore, hypoadiponectinaemia also indirectly affects tumorigenesis via several mechanisms. Firstly, insulin resistance is increased, with resultant elevation in insulin and bioavailable IGF1 levels, which enhance tumour cellular proliferation. Secondly, as adipocytes constitute one of the predominant stromal cell types in the tumour microenvironment, adiponectin could act as a stromal factor that helps balance the local redox and metabolism. (19) Finally,

hypoadiponectinaemia exerts pro-inflammatory effects via enhancing the production of various proinflammatory cytokines including TNF-α and IL-6, further contributing to the tumour permissive microenvironment that facilitates tumourigenesis. (9, 10)

Adiponectin and breast cancer

The association between adiponectin and breast cancer risk depends on menopausal status. Conflicting data have been reported regarding the association in pre-menopausal women. Macis et al. reported that low serum adiponectin levels predicted incident breast neoplastic events independently of age and BMI in pre-menopausal women (20). However, in a recent meta-analysis involving 4249 breast cancer cases and including those studied by Macis et al (20), the inverse association between serum adiponectin level and breast cancer risk did not reach statistical significance in premenopausal women (relative risk 0.72; 95% CI 0.30 – 1.72) (21). On the other hand, two large meta-analyses demonstrated clearly a consistent inverse association in post-menopausal women (21-23), with every increment of 3ug/ml in adiponectin level corresponding to a 5% risk reduction in post-menopausal breast cancer. (21)

Breast cancer is one of the most common hormone-dependent cancers, and its positive correlation with obesity, especially in post-menopausal women, is explained, at least in part, by the increase in aromatase activity in the expanded adipocyte tissue. On the other hand, in vitro studies from our group had demonstrated that, adiponectin inhibited cell proliferation and induced apoptosis of human breast cancer cell-lines, independent of the presence of the estrogen receptor. (19, 24) Furthermore, in MMTV-polyomavirus middle T antigen (MMTV-PyVT) transgenic mice with reduced adiponectin expressions, hypoadiponectinaemia promoted mammary

tumourigenesis by down-regulation of phosphatase and tensin homolog (PTEN) activity. (25) In addition, treatment with recombinant adiponectin reduced mammary tumourigenesis in nude mice through suppressing the Wnt / glycogen synthase kinase (GSK)-3β / β-catenin pathway. Increased β-catenin activity correlated significantly with worse prognosis. (24) These preclinical data have provided mechanistic insight on the association between hypoadiponectinaemia and biologically aggressive tumour phenotype observed in patients with breast cancer. (26)

Adiponectin and prostate cancer

In vitro studies demonstrated that adiponectin down-regulated STAT3 signaling and inhibited cell growth and proliferation of both androgen independent and androgen dependent metastatic prostatic cancer cells. (27) However, the association between adiponectin and prostate cancer remains inconclusive, partly due to the scarcity of data. (28) While some evidence suggested that adiponectin was not related to overall prostate cancer risk, there were also data showing that patients with hypoadiponectinaemia suffer from more aggressive, metastatic and fatal prostate cancer. (16, 27) However, a recent nested case-control cohort did not find such an association in 272 cases with aggressive prostate cancer. (29)

Adiponectin and gastrointestinal cancers

Adiponectin has also been implicated in tumourigenesis of various gastrointestinal cancers. (30)

Hypoadiponectaemia increased the risk of Barrett's esophagus, which is more prevalent in obese individuals and is closely associated with the development of

esophageal adenocarcinoma. Recently, in vitro studies found that adiponectin could decrease the invasion and migration of esophageal cancer cell lines OE33 via the activation of protein tyrosine phosphatase 1B and, consequently, the inhibition of leptin-induced janus kinase (JAK) signaling. (31) In gastric cancer, adiponectin receptor AdipoR1 expression was associated with a better disease prognosis. Firstly, negative immunostaining for adipoR1 in tumour cells was significantly higher in patients with lymphatic metastases. Secondly, survival analysis revealed a longer survival in those with positive adipoR1 expression. (32) In hepatocellular carcinoma, hypoadiponectinaemia increased the risk of hepatic adenoma formation in animal studies. When adiponectin-knockout mice were fed a choline-deficient L-amino-acid-defined diet for 24 weeks, they developed more severe non-alcoholic steatohepatitis and also more liver tumours compared to the wild type mice. (33) Liver cancer microarray studies also demonstrated an inverse relationship between adiponectin expression and tumour size, suggesting a role of adiponectin in suppressing the proliferation and de-differentiation of liver cancer. (34) In pancreatic cancer, in-vitro studies also suggested the role of adiponectin in suppressing the proliferation of pancreatic cell lines via its impact on the NF-κB pathway. (30)

In the context of colorectal cancer, animal studies had shown that mice lacking adiponectin gene and its receptor, AdipoR1 or AdipoR2 were predisposed to colorectal polyp formation on high fat diet. (35) Furthermore, it was postulated that hypoadiponectinaemia led to increased activity of c-Jun N-terminal kinase (JNK), an oncogene that was abnormally elevated in colorectal cancer. (36) Through signaling pathways involving AMPK and mammalian target of rapamycin (mTOR), hypoadiponectinaemia also promoted colorectal cancer cell growth and inhibited

G1/S cell cycle arrest. (30) A recent meta-analysis demonstrated that an inverse association between adiponectin and colorectal cancer, among studies with prospective design (OR 0.716; 95% CI 0.606 – 0.847). (37)

Adiponectin and other cancers

Previous epidemiological studies showed discrepant results on the association between adiponectin and endometrial cancer. (27) Some suggested hypoadiponectaemia increased the risk of endometrial cancer independent of other conventional risk factors including BMI, especially in those younger than 65 years old. (16) A recent prospective cohort involving 167 incident endometrial cancer cases had shown, however, that the association between hypoadiponectaemia and endometrial cancer risk depended upon the use of menopausal hormonal therapy. Inverse association between adiponectin and endometrial cancer, which remained significant even after adjustment for estradiol levels and BMI, was only observed in women not on menopausal hormonal therapy, suggesting that adiponectin might influence cancer risk through mechanisms other than estrogen-mediated endometrial proliferation. (38) In fact, adiponectin might exert its anti-cancer effect via the NF-κB signaling pathway to suppress vascular endothelial growth factor (VEGF) expression. (27) Furthermore, in vitro studies also showed its suppression of endometrial cancer cell proliferation via enhancing the expression of the adaptor molecule LKB1, which is required for adiponectin-involved activation of AMPK. (39)

The association between adiponectin and renal cancer remains inconclusive. A recent case-control study involving 187 cases of renal cell carcinoma has even shown higher adiponectin levels in renal cell cancer cases. (40) Previous studies suggested that

AdipoR2 was downregulated in renal cancer tumour tissue, and hence the protective effect of adiponectin might have also been attenuated. (16, 27) Contrary to the above findings, it has also been suggested that adiponectin might be employed as a biomarker for renal cell cancer progression, as both total and high molecular weight oligomers were demonstrated to be higher in patients with localized disease than those with metastatic clear cell carcinoma, the commonest subtype of renal cell carcinoma. (16, 41)

Differentiated thyroid carcinoma, which included papillary thyroid carcinoma, was inversely associated with serum adiponectin levels. (42) In addition to the development of incident thyroid cancer, serum adiponectin levels also had implication in its prognosis. Patients with papillary thyroid carcinoma were more likely to have multicentric tumours, or tumours with extrathyroidal invasion and higher TNM stage if their tumour tissues were negative for both AdipoR1 and AdipoR2 expressions. (43)

With regard to haematological malignancies, the associations with adiponectin are heterogeneous. Inverse associations had been reported between serum adiponectin levels and risks of incident myelodysplastic syndrome, myeloproliferative disease, childhood myeloblastic leukaemia, monoclonal gammopathy of undetermined significance, multiple myeloma and chronic lymphocytic leukaemia. (16) This is in keeping with the notion that adiponectin inhibited proliferation of cells of myeloid lineage. Furthermore, adiponectin might prevent myeloma risk by suppressing the secretion and action of pro-inflammatory cytokines and their activation of the NF-κB signaling pathway. (44) On the contrary, there had been reports showing that higher

levels of serum adiponectin were associated with both adult and childhood non-Hodgkin's lymphoma. (16) It has been postulated such an association may be explained by the action of adiponectin in enhancing the secretion of interleukin-10 (IL-10), a known growth factor produced by non-Hodgkin's lymphoma cells. (45)

Leptin

Leptin, the product of the *Obese (OB)* gene, is an adipokine primarily secreted by white adipose tissue. In addition to its key role in energy homeostasis as a satiety hormone, leptin also exerts other effects in an endocrine fashion. In the context of obesity, leptin level increases with the expansion of the adipose tissue mass. In humans, obesity is associated with leptin resistance, further increasing the circulating leptin level. By binding to its receptors (Ob-R), which are expressed in almost every tissue, leptin modulates various downstream signaling pathways (Figure 1) including JAK / STAT3, mitogen-activated protein kinase (MAPK), phosphatidylinositol 3-kinase / protein kinase B (PI3K/Akt), ERK1/2, AMPK and insulin receptor substrate (IRS) pathways. (9, 11) In contrast to the anti-inflammatory actions of adiponectin, leptin activates inflammatory cell response and induces pro-inflammatory cytokine production. (46) Furthermore, in vitro studies demonstrated that leptin could induce endothelial cell proliferation and activate vascular endothelial growth factor (VEGF), and other proangiogenic factors. (47) These resultant effects make leptin an adipokine with mitogenic, anti-apoptotic and pro-inflammatory properties, all being implicated in carcinogenesis.

Leptin and breast cancer

As in adiponectin, the association between leptin and breast cancer also seems to depend on menopausal status. While there is consistent evidence showing that serum leptin level correlates positively with breast cancer risk in postmenopausal women, an inverse relationship has been reported in premenopausal subjects. (27, 48, 49) Nonetheless, previous in vitro studies had already demonstrated that leptin promoted mammary tumourigenesis via activation of JAK/STAT3 and PI3K signaling pathways. (50) Leptin has also been shown to affect the prognosis of breast cancer. Leptin-receptor-positive tumours had higher metastatic potential than those that were negative for leptin-receptor. (51) A recent study confirmed that leptin stimulated proliferation of breast cancer cells but not of normal breast cells. In particular, leptin induced proliferation of estrogen-dependent breast cancer cell lines such as MCF7 and T47D but not of the estrogen-independent breast cancer cell lines MDA-MB-231. (52) In fact, functional bidirectional crosstalk had been demonstrated between leptin and estrogen receptors. Leptin could amplify estrogen signaling by activation of estrogen receptor-α and aromatase gene *(CYP192A)* expression. Estradiol, on the other hand, could modulate leptin receptor expression in animal studies and also induced expression of leptin and its receptor in MCF7 breast cancer cells. (50) The effect of leptin on estrogen-independent breast cancers, however, has remained controversial. A study by Colbert et al. in 67 Chinese patients with breast cancer demonstrated that more than 61% of breast cancer tissues, which included estrogen receptor positive, estrogen receptor negative and triple (estrogen, progesterone and HER2 receptors) negative tumours, were stained positive for leptin and its receptor. Furthermore, leptin and its receptor were positively associated with proangiogenic factors like Notch and vascular endothelial growth factor (VEGF), and hence implicated in tumour aggressiveness and poorer prognosis. (53)

Leptin and prostate cancer

Data on the association between leptin and prostate cancer has also been conflicting. Some studies suggested that higher leptin levels were linked to more advanced and hormone-refractory prostate cancer. (27) In vitro studies demonstrated that leptin exerted its pro-carcinogenic effects via the activation of PI3K, MAPK and JNK-MAP kinase pathways. (27) Leptin could induce proliferation, inhibit apoptosis and promote the migration of androgen-insensitive prostate cell lines DU145 and PC3 but did not have an effect on the androgen-sensitive cell line LNCaP. (28)

Leptin and gastrointestinal cancers

Although leptin was linked with colorectal cancer risks in multiple epidemiological studies, a recent meta-analysis did not observe any significant association between leptin and colorectal carcinoma. (37) Nonetheless, animal studies had shown that leptin-deficient mice were less prone to colonic polyp formation upon induction by azoxymethane or when fed with a high fat diet, when compared to control mice. (54) Furthermore, leptin could stimulate the proliferation of the human colorectal cancer cell line HCT-116 via the PI3K-AKT signaling pathway. (10) Recently, leptin was shown to induce the proliferation of gastric cancer cells through activation of STAT3 and ERK1/2. (55)

On the contrary, although studies on the association between leptin and pancreatic cancer are scarce, most of them showed that leptin levels were lower in patients with pancreatic cancer than in controls. While some had attributed the hypoleptinaemia to the weight loss that was commonly observed in pancreatic cancer patients (27), a

recent study suggested that patients with newly diagnosed pancreatic cancer had significantly lower serum leptin levels and these differences were independent of age and BMI. (56) In vitro studies also showed that leptin could inhibit human pancreatic cancer cell lines PANC-1 and Mia-PaCa. (27)

Leptin and other cancers

A recent prospective cohort study involving 167 incident endometrial cancer cases demonstrated that, as in the case of adiponectin, the association between leptin and endometrial cancer risk also depended upon the use of menopausal hormonal therapy. Leptin was significantly associated with increased risk of endometrial cancer, even after adjustment for estradiol level and BMI. However, this was only observed in women not on menopausal hormonal therapy, suggesting that leptin might also influence cancer risk through mechanisms other than estrogen-mediated endometrial proliferation. (38)

The association between leptin and renal cell carcinoma has remained inconclusive over the years. (27) A recent report observed that higher leptin levels were found in patients with renal cell carcinoma, which, though attenuated, remained significant after adjustment for BMI. However, this association was shown to differ by race, as it was significant in Caucasians but not among African Americans. (40)

In differentiated thyroid cancers, the expression of leptin and its receptor was associated with a higher risk of lymph node metastases. (42) Moreover, leptin could affect the migration of thyroid cells, conferring higher metastatic potential and worse prognosis. (57) In the context of haematological malignancies, however, no positive

associations were reported between leptin levels and multiple myeloma or non-Hodgkin lymphoma. (44, 58)

Recently, there have been more studies looking into the association between leptin and malignant melanoma. (59, 60) Leptin was found not only to correlate positively with the risk of developing malignant melanoma, but also accelerate tumour growth. Interestingly, it has been proposed that serum leptin receptor levels might possibly be employed as a new tumour marker of malignant melenoma as its levels are inversely associated with the stage of the disease, with highest levels found at the *in situ* stage and lowest at stage IV. (59)

IL-6, TNF-α and various cancers

Both IL-6 and TNF-α are key cytokines involved in inflammation and immunity. They are produced and secreted by several cells, including macrophages and adipocytes. Both M1 and M2 macrophages are present in adipose tissue, but they differ in the profile of cytokines they produced. In the context of obesity, local tissue hypoxia around adipocytes promotes the switch of macrophages from M2 to the M1 phenotype. This changes the production profile from anti-inflammatory cytokines like interleukin-10 of the M2 macrophages to pro-inflammatory cytokines like IL-6 and TNF-α of the M1 macrophages. (9) Consequently, both the production and secretion of these two adipokines are increased, and together they enhance tumourigenesis via their pro-inflammatory effects. IL-6 promotes carcinogenesis mainly through the JAK/STAT3 signaling pathway, which is involved in tumour proliferation, survival and angiogenesis. TNF-α, on the other hand, activates the NF-κB and JNK signaling

pathways. (11) Furthermore, both adipokines can promote carcinogenesis through enhancing the conversion of non-cancer cells to tumour stem cells. (10)

Large amount of epidemiological evidence supported the role of IL-6 and TNF-α in carcinogenesis and its progression. Serum IL-6 was shown to correlate positively with advanced staging in colorectal, breast and cervical cancers, hepatocellular and renal cell carcinoma. (61) The IL-6 receptor/STAT3 pathway also contributed to the pathogenesis of multiple myeloma by protecting the myeloma cells from apoptosis. (62) Furthermore, it had been reported to be associated with poor prognosis in esophageal, gastric, colorectal, pancreatic, bladder, breast, ovarian and prostate cancers, hepatocellular and renal cell carcinoma. (61) Similarly, high levels of circulating TNF-α were found in patients with lung, pancreatic, breast and prostate cancers. (63) In differentiated thyroid cancer, however, the exact role of IL-6 remains to be elucidated. (42) In a Chinese community cohort in Hong Kong with a relatively low prevalence of obesity, we previously demonstrated central obesity predicted cancer development, and baseline IL-6 and soluble TNF receptor 2 levels were independent predictors of incident cancer development after a median interval of 9.5 years, even after adjusting for conventional cancer risk factors. (6)

Interplay of adipokines in cancers

Although adipokine may individually be involved in the development of various obesity-related cancers and impact on their progression, there are diverse and complex interplay via crosstalk with each other through their respective downstream signaling pathways. (Figure 1) In fact, the associations between leptin and some cancers are often related to adiponectin as well. In esophageal cancer, for example, leptin-induced

proliferation of esophageal adenocarcinoma cell lines could be inhibited by adiponectin via AdipoR1. (30, 31) Similarly, leptin-induced proliferation of hepatocellular tumour cells was also inhibited by adiponectin via the STAT3 signaling pathway. (10)

Other adipokines and cancers

Increasing epidemiological evidence has shown that a number of other adipokines are also involved in obesity-related cancers. Neutrophil gelatinase-associated lipocalin (NGAL) or lipocalin-2, for example, was over-expressed in breast, gastric, esophagus and brain cancers. (11) Recently, lipocalin-2 was also noted to be associated with tumour invasiveness, possibly attributed to its ability to scavenge iron into cancer cells. (64) Resistin, another pro-inflammatory adipokine, was found to be present at higher levels in advanced non-small cell lung, colon, breast and prostate cancers. (11) A recent meta-analysis also suggested a consistent positive association between resistin and colorectal cancers, although the number of studies was limited. (37)

Clinical and therapeutic implications

Owing to the fast growing prevalence of both obesity and cancer worldwide, together with their associated morbidity and mortality, they have become major global healthcare concerns.

Tackling obesity and cancer are equally challenging. It was not until recently that there was evidence showing that weight reduction could reduce incident cancer rates. A recent meta-analysis, involving six observational studies on 51740 subjects including the largest prospective Swedish Obese Subjects (SOS) study cohort,

reported a 45% relative risk reduction of cancer in obese subjects after bariatric surgery (95% CI 0.41 – 0.73; p <0.0001). If stratified by gender, the protective effect of bariatric surgery was found to be protective in women but not in men. (65) This might reflect a reduction of sex steroid-related cancer. Nonetheless, several mechanisms had been postulated to link bariatric surgery with cancer risk reduction, and one of them was reported to act via modulation of the adipokines. (66) While adiponectin level was shown to increase for up to 1 year post-operatively, leptin and resistin levels were shown to decrease significantly up to 2 and 6 years after surgery, respectively. (66)

Adipokines remain one of the major players in obesity related carcinogenesis. Both adipokines and their respective downstream signaling pathways have become novel targets in cancer therapeutics research. As adiponectin itself is difficult to synthesize, synthetic small peptides like ADP-355, which can mimic the action of adiponectin, are being tested in preclinical studies to restrict proliferation of several adiponectin receptor-positive cancer cell lines. (67) Furthermore, as HMW adiponectin constitutes the most active oligomeric form of adiponectin, a novel class of non-thiazolidinedione peroxisome proliferator-activated receptor (PPAR) ligand, AMG131, has been developed to increase the ratio of high molecular weight to total adiponectin concentrations in the circulation. (30) Pegylated leptin receptor antagonist 2 (PEG-LPrA2) are also being tested in preclinical studies to reduce the proliferation and angiogenesis of breast cancer cells. (67) Preclinical studies have shown that monoclonal antibodies against IL-6 and its receptors can significantly inhibit tumour growth either alone or in combination with conventional chemotherapy. Among them, siltuximab, a monoclonal antibody against IL-6, is being evaluated in phase 2 clinical

trials against transplant-refractory multiple myeloma, hormone-refractory prostate cancer and metastatic renal cell carcinoma. Besides, results have been promising in other solid tumours including ovarian and non-small cell lung cancers. Inhibitors against downstream signaling pathways like JAK or STAT3 inhibitors are also being studied in phase 1 or 2 clinical trials on advanced solid tumours and haematological malignancies. (61)

Although there are emerging data on the association between genetic polymorphisms of obesity-related genes and cancer susceptibility, there is currently insufficient evidence to recommend their use as predictors for incident cancer, or as prognostic biomarkers in those who have developed cancer. Nevertheless, a recent meta-analysis suggested that the *LEP* G2548A polymorphism, which had been reported to alter serum leptin levels, was associated with increased overall cancer risk (Odds ratio 1.27; 95% CI 1.05 – 1.54). (68) However, with regard to adiponectin, no consistent association has been found between cancer susceptibility and genetic polymorphisms of either the adiponectin gene (*ADIPOQ*) or adiponectin receptor genes (*ADIPOR1/R2*) in studies on non-Hodgkin's lymphoma, breast, colorectal and prostate cancers. Three *ADIPOQ* single nucleotide polymorphisms (SNPs) had been reported to be associated with a reduced risk of endometrial cancer in a Chinese study. However, serum adiponectin level was not measured in that study and whether these SNPs were biologically relevant remained to be elucidated. (16) Therefore, in this era of genetics and epigenetics, future research should be directed towards investigating whether these SNPs can be usefully employed as biomarkers in clinical oncology practice.

523 **Conclusions**

524 With advances in basic and translational research, and assay development, novel
525 adipokines are continually being found to be implicated in obesity-related
526 tumourigenesis. Improved understanding of the interplay of adipokines with various
527 malignancies has unraveled the pathogenic mechanisms underlying the associations
528 between obesity and cancer, and led to more targeted cancer therapeutics to counter
529 the increasing challenge posed by obesity-related cancers, consequent to the obesity
530 epidemic.
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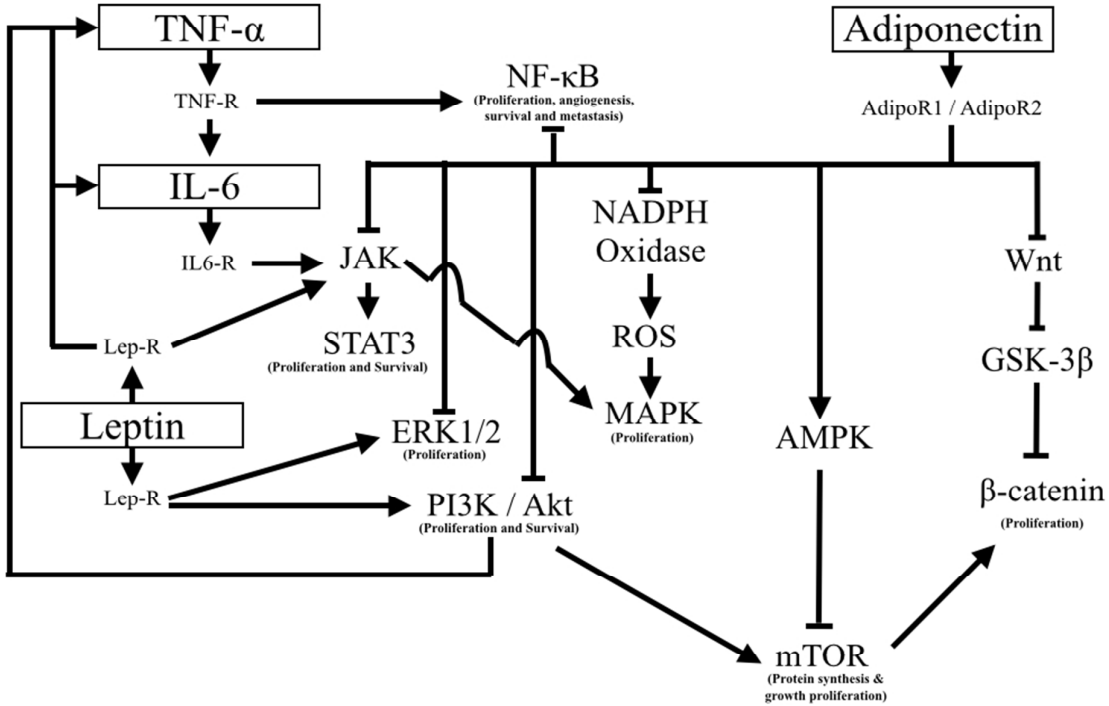
Table 1: Reported associations of adiponectin and leptin with various obesity-related cancers

Type of cancer	ADP level	Possible effects of ADP on cancer cells	LEP level	Possible effects of LEP on cancer cells	References
Esophagus	↓	Inhibit proliferation, decrease invasion and migration	↑	Increase proliferation	(31)
Stomach	↓	Inhibit proliferation and decrease migration	↑	Increase proliferation	(32, 55)
Colon	↓	Inhibit proliferation and decrease invasion	↑*	Increase proliferation	(10, 30, 36, 37)
Liver	↓	Inhibit proliferation, decrease invasion and migration	↑	Increase proliferation	(10, 33, 34)
Pancreas	↓	Inhibit proliferation	↓	Inhibit proliferation	(27, 30, 56)
Breast	↓#	Inhibit proliferation and decrease aggressiveness	↑ (Post-menopausal) ↓ (Pre-menopausal)	Increase proliferation and metastases	(19-21, 24, 26, 48-50, 52, 53)
Uterine	↓	Inhibit proliferation	↑	Increase cancer risk	(38, 39)
Prostate	↓*	Inhibit proliferation, decrease aggressiveness and migration	↑*	Increase proliferation and migration	(27-29)
Thyroid	↓	Inhibit proliferation, decrease invasion and migration	↑	Increase migration and metastases	(42, 43)
Lymphoma	↑	Increase proliferation	Inconclusive	-	(45, 58)
Myeloma	↓	Inhibit proliferation	Inconclusive	-	(44)
Kidney	↑	Increase metastases	Inconclusive	N/A	(40, 41, 57)
Melanoma	Inconclusive	N/A	↑	Increase cancer risk and invasion	(59, 61)

Significant association in postmenopausal women only; * Inconsistent associations reported

Figure 1: Schematic diagram showing the interaction of various major adipokines and their downstream signaling pathways



The arrows and blunt-arrows indicate stimulatory and inhibitory effects, respectively.

AMPK, AMP-activated protein kinase; ERK1/2, extracellular regulated kinase 1 or 2; GSK-3β, glycogen synthase kinase-3beta; JAK, janus kinase; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase; NF-κB, nuclear factor kappa B; P13K/Akt, phosphatidylinositol 3-kinase / protein kinase B; ROS, reactive oxygen species; STAT3, signal transducer and activator of transcription; TNFR, tumour necrosis factor alpha receptor; Wnt, wingless type protein

Table 1: Reported associations of adiponectin and leptin with various obesity-related cancers

Type of cancer	ADP level	Possible effects of ADP on cancer cells	LEP level	Possible effects of LEP on cancer cells	References
Esophagus	↓	Inhibit proliferation, decrease invasion and migration	↑	Increase proliferation	(1)
Stomach	↓	Inhibit proliferation and decrease migration	↑	Increase proliferation	(2, 3)
Colon	↓	Inhibit proliferation and decrease invasion	↑*	Increase proliferation	(4-7)
Liver	↓	Inhibit proliferation, decrease invasion and migration	↑	Increase proliferation	(4, 8, 9)
Pancreas	↓	Inhibit proliferation	↓	Inhibit proliferation	(7, 10, 11)
Breast	↓#	Inhibit proliferation and decrease aggressiveness	↑ (Post-menopausal) ↓ (Pre-menopausal)	Increase proliferation and metastases	(12-21)
Uterine	↓	Inhibit proliferation	↑	Increase cancer risk	(22, 23)
Prostate	↓*	Inhibit proliferation, decrease aggressiveness and migration	↑*	Increase proliferation and migration	(11, 24, 25)
Thyroid	↓	Inhibit proliferation, decrease invasion and migration	↑	Increase migration and metastases	(26, 27)
Lymphoma	↑	Increase proliferation	Inconclusive	-	(28, 29)
Myeloma	↓	Inhibit proliferation	Inconclusive	-	(30)
Kidney	↑	Increase metastases	Inconclusive	N/A	(31-33)
Melanoma	Inconclusive	N/A	↑	Increase cancer risk and invasion	(34, 35)

Significant association in postmenopausal women only; * Inconsistent associations reported

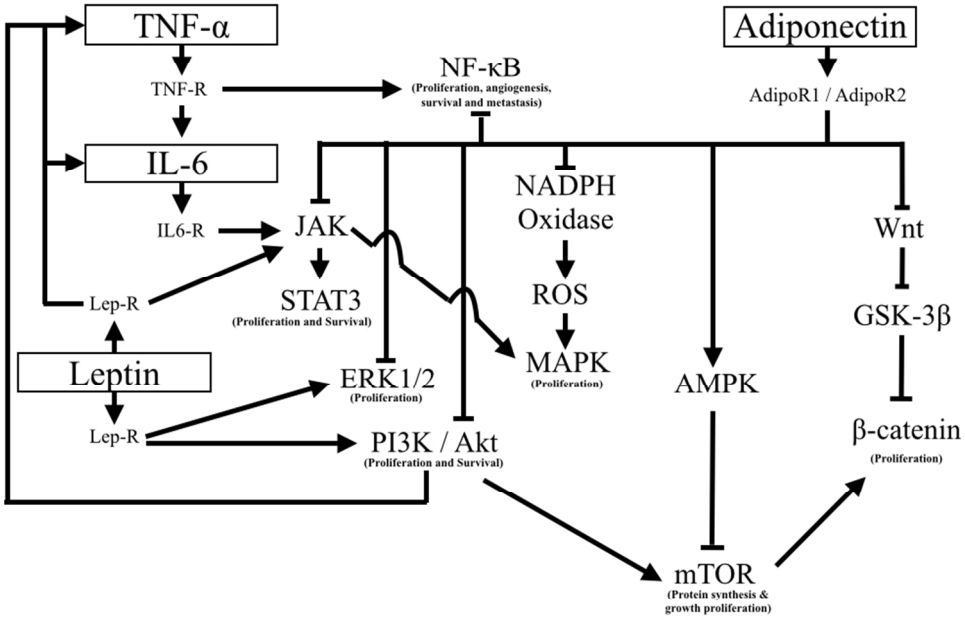


Figure 1: Schematic diagram showing the interaction of various major adipokines and their downstream signaling pathways
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