

Signals from the Adipose Microenvironment and the Obesity-Cancer Link—A Systematic Review

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Abstract

Obesity and its associated metabolic dysregulation are established risk factors for many cancers. However, the biologic mechanisms underlying this relationship remain incompletely understood. Given the rising rates of both obesity and cancer worldwide, and the challenges for many people to lose excess adipose tissue, a systematic approach to identify potential molecular and metabolic targets is needed to develop effective mechanism-based strategies for the prevention and control of obesity-driven cancer. Epidemiologic, clinical, and preclinical data suggest that within the growth-promoting, proinflammatory microenvironment accompanying obesity, crosstalk between adipose tissue (comprised of adipocytes, macrophages and other cells) and cancer-prone cells may occur via obesity-associated hormones, cytokines, and other mediators that have been linked to increased cancer risk and/or progression. We report here a systematic review on

the direct "crosstalk" between adipose tissue and carcinomas in humans. We identified 4,641 articles with $n = 20$ human clinical studies, which are summarized as: (i) breast ($n = 7$); (ii) colorectal ($n = 4$); (iii) esophageal ($n = 2$); (iv) esophageal/colorectal ($n = 1$); (v) endometrial ($n = 1$); (vi) prostate ($n = 4$); and (vii) ear-nose-throat (ENT) cancer ($n = 1$). Findings from these clinical studies reinforce preclinical data and suggest organ-dependent crosstalk between adipose tissue and carcinomas via VEGF, IL6, TNF α , and other mechanisms. Moreover, visceral white adipose tissue plays a more central role, as it is more bioenergetically active and is associated with a more procancer secretome than subcutaneous adipose tissue. Efforts to eavesdrop and ultimately interfere with this cancer-enhancing crosstalk may lead to new targets and strategies for decreasing the burden of obesity-related cancers. *Cancer Prev Res*; 10(9): 494–506. ©2017 AACR.

Introduction

Obesity is a major global health challenge and is expected to further increase substantially over the next several decades (1). In the United States, 38% of adults are obese, defined as having a body mass index (BMI) >30 kg/m², and nearly 8% are extremely obese, with a BMI > 40 kg/m² (2). A recent summary by the International Agency for Research on Cancer reinforced obesity as a risk factor of many cancer types, including colorectal, postmenopausal breast, liver, endometrial, esophageal, kidney (renal cell), gastric, gall bladder, pancreatic, ovarian, thyroid, and multiple myeloma (3).

With cross-sectional studies investigating tumors in overweight or obese cancer patients, new knowledge can be gained on adipose-associated factors that drive tumor development and growth. The interactions between an evolving tumor and its

microenvironment are known to involve a complex interplay among multiple cells, local and systemic secreted mediators, and other components (4, 5). In particular, emerging evidence suggests that noncancer cell types in the tumor microenvironment, such as adipocytes and macrophages, interact to enhance inflammation, reprogram cancer cell metabolism, and affect processes involved in invasion, metastasis, and immune clearance, all of which can support tumor progression and impact patient outcome (6).

Adipose tissue classification

Adipose tissue can be classified into three different types: white (WAT), brown (BAT), and beige adipose tissue, whose presence differs with development, species, and anatomic location (7). Although BAT and beige adipose tissue have been associated with thermoregulation, WAT is considered the key site for energy storage in the form of triacylglycerides (7). WAT can be further divided into distinct body compartments, which have differential impact on disease risk (8). Visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) are characterized by differences in cellular structure, molecular composition, and secretome, each of which may be altered by the degree of adiposity itself (8). VAT is generally considered to be bioenergetically more active and responsive to substrates of the electron transport chain than SAT due to a higher concentration of mitochondria. However, BAT has even higher mitochondrial density than VAT, so the differences in metabolic activity between VAT and SAT can be influenced by their brown or beige adipocyte content. VAT adipocytes are also more lipolytically active than SAT

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adipocytes and, thus, contribute more to plasma-free fatty acid levels, particularly in obese individuals. In addition, although pro- and anti-inflammatory mediators and immune cells (e.g., Tregs, TH2, eosinophils, ILC2s) maintain immune balance in the lean (healthy) state of adipose tissue (6), increased WAT mass accelerates chronic inflammation through at least three mechanisms: altered generation of secreted inflammatory factors, increased tissue inflammation (immune cell infiltration and formation of crown-like structures by macrophages surrounding dead or dying adipocytes), and adipose tissue remodeling (9). Consequently, the evidence has shown a stronger correlation between WAT and cancer risk compared with BAT and beige adipose tissue (10). Visceral fat area has also been found to be a predictive factor of poor survival and treatment outcomes for different cancer types, such as colon, esophageal, and renal cancers (11–14).

Adipose tissue-induced inflammation

Inflammation, a hallmark of cancer (4), has been linked to obesity and cancer in both epidemiologic and preclinical research (15). Evidence from preclinical *in vitro* and *in vivo* studies is emerging that obesity-associated adipose-derived factors, including the cytokines IL6, IL8, monocyte chemoattractant protein 1 (MCP-1), and TNF α , as well as infiltrating inflammation-inducing cells (e.g., macrophages), can influence cellular metabolism and promote cancer (see Fig. 1; refs. 16–22). This expanded, inflamed adipose tissue appears to increase cancer risk more prominently than obesity itself (6) and may stimulate the hallmark events involved in the development and progression of cancer (23), including cellular transformation, cell survival and proliferation, invasion, angiogenesis, and metastasis (see Fig. 1; ref. 24).

O'Flanagan and colleagues have demonstrated that obesity enhances the development and metastatic spread of orthotopi-

cally transplanted metM-Wnt^{lung} cells, a triple-negative breast cancer cell line that metastasizes to the lung (25). Pascual and colleagues also showed that diet-induced obesity increases the metastatic potential of several types of cancer cells, including oral squamous cell carcinoma, melanoma, luminal breast cancer, bladder cancer, and small-cell lung carcinoma, in a CD36-dependent manner (26). Muller's group found a metabolic symbiosis between tumor-associated adipocytes and cancer cells involving transfer of triglyceride to the cancer cells, resulting in increased availability of free fatty acids for β -oxidation and enhanced metastatic potential (27). They also established that components of the adipocyte secretome, particularly IL6, are able to stimulate the invasive capacity of breast cancer cells, independent of any effect on proliferation (28, 29).

IL6 regulates the inflammatory process by inducing the production of acute-phase proteins and other inflammatory molecules [e.g., C-reactive protein (CRP), prostaglandins, and fibrinogen], the recruitment of CD3⁺ T lymphocytes, and the proliferation of B lymphocytes. Recent publications have demonstrated crosstalk between adipose tissue and breast as well as colon cancer cells through IL6 (16–19, 30). For example, Walter and colleagues have reported that IL6 is secreted by adipose stromal cells (ASC) and promotes migration and invasion in breast cancer cells (30). A variety of signaling pathways have been investigated to elucidate how IL6 induces cell proliferation. In colorectal cancer cell lines, for example, IL6 triggers the phosphorylation of ERK, p38 (MAPK), MEK1/2, JAK2, and STAT3 signaling molecules that control cell metabolism and proliferation (18). Obesity-associated systemic IL6 also promotes ASC aromatase expression via direct effects and stimulation of breast cancer cell cyclooxygenase 2 (COX2) expression and prostaglandin E2 (PGE2) production (31). The subsequent elevation in estradiol levels promotes estrogen receptor-positive (ER⁺) breast cancer cell growth (17).

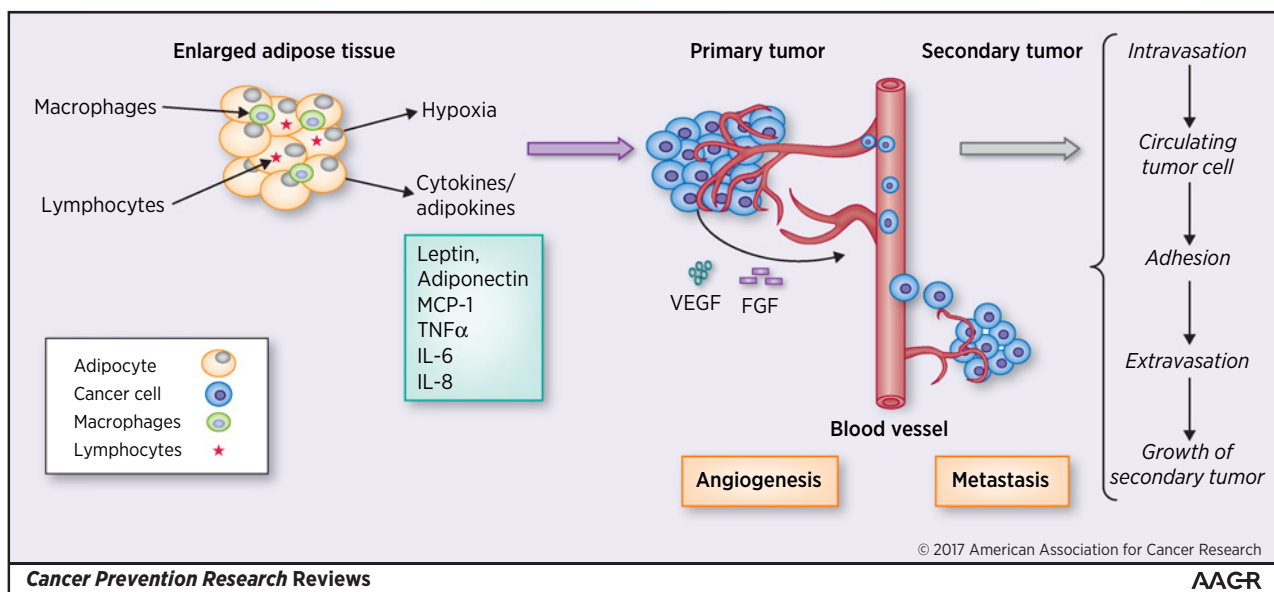


Figure 1.

Adipocyte-secreted cytokines (e.g., leptin, adiponectin, MCP-1, TNF α , IL6, IL8) and adipocyte-induced conditions (e.g., hypoxia) and their impact on the main hallmarks of cancer development: proliferation, angiogenesis, and metastasis.

IL8 shows chemotactic attributes and is particularly involved in the recruitment of leukocytes. Adipocytes in cancer stroma upregulate the expression of IL8, which exerts its effects via the PI3K, JAK/STAT3, ERK, and MAPK signaling pathways, resulting in cell proliferation, survival, angiogenesis, and invasion (20).

MCP-1, also known as chemokine (CC motif) ligand (CCL2), plays a key role in the recruitment and accumulation of proinflammatory macrophages in both adipose and tumor tissues (16). Studies demonstrated elevated adipose tissue MCP-1 in obese mice compared with lean controls, indicating MCP-1 is an important factor for enhanced macrophage recruitment into obesity-associated adipose tissue (32). Consistent with this observation, obesity-induced MCP-1 (and IL1 β) expression in mammary fat depots leads to increased macrophage recruitment (16).

TNF α is a cytokine mainly secreted by macrophages, including those in the adipose tissue. In breast cancer cells lines, TNF α can have either growth-promoting or inhibiting properties depending on cell type (19). Reports also suggest that TNF α contributes to cancer cell proliferation via MAPK and PI3K/AKT signaling pathways (19).

Tumor-infiltrating ASCs

In addition to the protumor para- or endocrine effects of inflammatory factors from dysfunctional adipose tissue, several studies have shown that ASCs from the adipose actually infiltrate cancer lesions and contribute to a tumor-promoting microenvironment via paracrine and contact-dependent effects. Furthermore, the recruitment of ASCs to tumors is enhanced by obesity. Kolonin and colleagues have published several pioneering studies in this area, first demonstrating that GFP-labeled ASCs are recruited to tumors, but not other organs (33). They then found that obesity in mice is associated with increased tumor-infiltrating ASCs that are traceable to an adipose tissue origin and that these ASCs promote tumor growth in multiple cancer models by facilitating tumor vascularization (11, 12). ASCs migrate to tumors in response to tumor production of CXCL1 and CXCL8 (34). The application of these preclinical findings to human disease was evidenced by data indicating that obese prostate cancer patients have increased tumor CXCL1 expression, circulating ASCs, and tumor-infiltrating ASCs (34) and has been further demonstrated by studies indicating an increase in circulating mesenchymal stromal cells (which include ASCs) in obese disease-free donors (35) and colorectal cancer patients (36) as well as an increase in circulating ASCs in obese breast cancer survivors (37).

Others have similarly found that ASCs play a key role in cancer progression via additional mechanisms, including the promotion of metastasis and alterations in extracellular matrix mechanics (38, 39). In addition, obesity has been shown to promote a profibrotic ASC phenotype, leading to a more fibrillar and stiffer extracellular matrix that enhances mammary tumor growth and the tumorigenic potential of premalignant human breast epithelial cells (40). These mechanisms may act in parallel to ASC's effects on tumor vascularization, suggesting that the obesity-associated elevation in tumor ASCs may play a significant role in obesity-induced tumor progression via multiple mechanisms.

Adipokines and hormones

Leptin is a peptide hormone mainly produced within adipose tissue. Beside its neuroendocrine function controlling

food intake, leptin can impact a wide range of biological activities, including angiogenesis, bone formation, and modulation of immune responses (41, 42). The intensity of its production and secretion by adipocytes depends on the body energy status and is highly increased in obese individuals; the resulting leptin resistance causes hyperphagia and increases adipose tissue volume (43).

Obesity-associated hyperleptinemia also promotes chronic low-grade inflammation by stimulating the production of IL1, IL6, IL12, and TNF α (43, 44). In a murine model of preneoplastic (Apc^{Min/+}; IMCE) colon epithelial cells, leptin treatment induced the production of IL6 (18). Consequently, leptin seems to be an important initiating mediator in the proinflammatory cascade in adipose tissue (45). Multiple studies have reported that leptin-induced cell signaling cascades are associated with an enhanced risk for different types of cancer, such as colorectal, hepatocellular, renal, breast, ovarian, endometrial, and prostate (46).

Adiponectin, another major adipokine, antagonizes the oncogenic actions of leptin in several tissues. Also secreted by adipocytes, but at reduced levels in the obese versus nonobese state, adiponectin regulates the effects of insulin on adipocytes and attenuates inflammation (6, 47). There is *in vitro* evidence of a protective effect of adiponectin on the development of cancer by inhibiting proliferation and metastasis (48–52). Particularly in breast cancer cells, it has been shown that adiponectin signaling results in antiproliferative responses (48–50). The peptide hormone stimulates AMPK and PPAR α signaling and inhibits MAP kinase pathways via two types of receptors (AdipoR1 and R2; refs. 49, 52).

Increased levels of the steroid hormone estradiol have been associated with breast and gynecologic cancers, such as cervical, endometrial, and ovarian cancer. The conversion of androgen to estradiol by aromatase (a key step in estradiol synthesis) in adipose tissue is the major source of circulating estradiol in postmenopausal women (53). Estradiol's effects are mediated by ER's transcription factor activity as well as its stimulation of PI3K/Akt and MAPK signaling pathways (54). Several *in vitro* studies have demonstrated that obesity-associated factors (e.g., leptin, IL6, TNF α) increase the expression and activation of aromatase and estrogen receptors in ASCs and cancer cells (e.g., breast and endometrial; refs. 55–60).

IGF-1 is a growth factor with similar molecular structure and signaling pathways to insulin and is mutagenic in many cancer cell lines (21, 61). For example, crosstalk between leptin and IGF-1 has been reported to induce invasion and migration of breast cancer cells (21). Findings from fatless A-Zip/F1 transgenic mice, which lack WAT and have aliprotrophic diabetes, suggest that leptin and adiponectin may be less critical to tumorigenesis when insulin and/or IGF-1 are elevated. Tumor growth in these mice following topical application of a carcinogen or crossbreeding with a transgenic model of breast cancer was enhanced despite the total lack of adipose tissue and associated adipokines (62).

The current report systematically reviews the evidence regarding crosstalk between the adipose tissue (as an entity, comprised of adipocytes, macrophages, and other cells) and carcinomas. We characterize the dimensions of this crosstalk in the context of mechanisms highlighted above. In contrast to prior reviews, we describe the direct interactions that occur between tumor cells and adipose tissue compartments in multiple cancer types, where

adipose tissue can be adjacent to the tumor or part of the peritumoral microenvironment. Our focus on cross-sectional studies investigating the adipose–tumor crosstalk provides insight into direct adipose–stroma–associated factors that drive tumor development and growth.

Materials and Methods

We conducted a systematic literature search in PubMed/Medline covering publications from January 1946 to March 2017 with the goal to identify literature characterizing crosstalk between adipose tissue and carcinomas.

Two researchers (C. Himbert and M. Delphan) independently performed two searches with the following search terms: (i) (adipose OR fat OR obese) AND (tissue OR cell) AND (cancer OR tumor) AND (crosstalk OR microenvironment OR paracrine OR milieu OR interaction); and (ii) adipose tissue in cancer patients. The queries resulted in 4,641 article publications.

At the identification stage, abstracts were read, and the articles were selected according to the following inclusion criteria: English language, prospective human clinical studies, adults (>18 years), and solid tumor types (in addition to "cancer" overall, we searched specifically for, e.g., breast, gastrointestinal, reproductive, melanoma, and renal cancer).

At the screening stage, articles were screened on the basis of the following criteria: crosstalk (e.g., paracrine influence, adipocytes as cancer microenvironment) between adipose tissue and carcinoma in cancer patients. Studies investigating solely the systematic effects of secreted products of either adipose tissue or carcinoma (e.g., inflammation markers, adipokines, hormones measured in plasma or serum) were not included. Because the diverse publications on this topic could not be identified with simple search terms, we used the above described broad search strategy. The primary reasons for exclusion were (i) no cancer patients, (ii) animal study, (iii) intervention study, and (iv) review.

Finally, $n = 20$ primary research publications of human clinical studies were found to be directly relevant as describing adipose tissue/tumor interactions and are summarized in Table 1: (i) breast cancer ($n = 7$); (ii) colorectal cancer ($n = 4$); (iii) esophageal cancer ($n = 2$); (iv) esophageal and colorectal cancer ($n = 1$); (v) endometrial ($n = 1$); (vi) prostate cancer ($n = 4$); and (vii) ear-nose-throat (ENT) cancer ($n = 1$). Disagreements relating to data extraction were discussed between authors and resolved. The overall process is outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) flow diagram (Fig. 2; ref. 63).

Results

Adipose tissue in cancer—human clinical studies

$N = 20$ studies have been identified that were conducted in patients with different cancer types (breast, colorectal, esophageal, endometrial, prostate, and ENT) to investigate the crosstalk between patients' adipose tissue and carcinomas (see Table 1; refs. 8, 64–75).

The majority of human studies have been conducted in breast cancer patients ($n = 7$; refs. 66, 68, 70, 75–78). Other studies have been implemented in cancers of the gastrointestinal tract [colorectal cancer ($n = 4$; refs. 8, 64, 71, 73),

esophageal cancer ($n = 2$; refs. 65, 79), combined (colorectal and esophageal; $n = 1$; ref. 80)], reproductive cancer [endometrial ($n = 1$; ref. 72), prostate ($n = 4$; refs. 69, 74, 81, 82)], or ENT tract [tongue ($n = 1$; ref. 83)].

Breast cancer. The tumor stroma, consisting of immune cells, fibroblasts, extracellular matrix, and other cells, may have profound tumor-promoting effects and plays an important role when investigating the tumor microenvironment. Of interest, although the risk for breast cancer is increased for obese postmenopausal women, premenopausal obese women have a lower incidence of breast cancer (84). Adipocytes comprise about 90% of the normal breast tissue and, thus, the question of adipocytes contributing directly to tumor progression as part of the tumor stroma has been addressed in several studies (66, 68, 70, 75, 76). Breast cancer stroma can be classified into adipose stroma cancer (>50% of cells are adipocytes), and fibrous stroma cancer (100% of cells are fibroblasts) or a combination of both stroma types (<100% of cells are fibroblasts, <50% are adipocytes; ref. 76).

The most recent study collected benign breast tissue of $n = 83$ postmenopausal women who were recently diagnosed with invasive breast cancer (75). Mullooly and colleagues focused on the association between crown-like structures and steroid hormones in breast adipose tissue (75). In about 36% of the tissue samples, crown-like structures were detected, and the frequency was increased in obese individuals (75). Women with a high ratio of estrone:androstendione were more likely to exhibit crown-like structures; individual hormone levels or tumor characteristics were not associated (75).

Another study investigated the association between the densities of tumor-associated macrophages with or without crown-like structures with patient survival (78). Furthermore, the authors assessed whether there are differences between the racial/ethnicity groups (Caucasian, black, non-black Latinas). Densities of tumor-associated macrophages in black breast cancer patients were the highest (mean = 142.21 cells/mm²) compared with Caucasian (62.72 cells/mm²) and non-black Latinas (110.16 cells/mm²; ref. 78). Caucasian patients presented with a significantly lower density of tumor-associated macrophages than the other ethnicities ($P < 0.0001$; ref. 78). Tumor-associated macrophages detected in the tissue of black patients showed a higher proliferation activity of tumor-associated macrophages, and survival rates for black patients were lower than for other ethnicities (78).

In a large study, $n = 939$ breast cancer cases were classified depending on the adipose tissue and fibroblast content within the tumor stroma into adipose stroma type and fibrous stroma type (76). The differences between these two cancer types were investigated regarding the breast cancer subtypes, molecular tumor characteristics, and the patients' outcome (76). Cases with cancer of "adipose stroma type" showed higher expression of cancer-associated and fibroblast-related proteins [e.g., fibroblast activation protein α (FAP α), prolyl 4-hydroxylase] compared with cases with "fibrous stroma type." For example, FAP α , which is reported to be involved in extracellular matrix modulation and tumor cell invasion, was higher expressed in stroma ($P < 0.001$) and tumor ($P < 0.001$) cells in "adipose stroma type" patients (76). Furthermore, among cases of "adipose stroma type," high tumor expression of prolyl 4-hydroxylase was associated with longer disease-free survival ($P = 0.03$;

Table 1. Clinical studies of adipose tissue and tumor crosstalk

Author (year, journal)	Study population/tissue type	Focus	Results
Breast cancer			
Mullooly et al (2017, Breast Cancer Res; ref. 75)	Postmenopausal women (<i>n</i> = 83) Benign breast tissue	<ul style="list-style-type: none"> Crown-like structures and sex steroid hormones in breast adipose tissue 	<ul style="list-style-type: none"> Crown-like structures were observed in 36% of the tissue samples and increased in obese patients (<i>P</i> = 0.03) Crown-like structures were not related to hormone levels or tumor characteristics, but were associated with hormone ratios
Koru-Sengul et al (2016, Breast Cancer Res Treat; ref. 78)	Women (<i>n</i> = 150) Caucasian (CA), non-black Latinas (NBLA), blacks (BL); each Breast tissue	<ul style="list-style-type: none"> Association between the number of TAM and/or crown-like structures with patient survival Differences among ethnicities (Caucasian, non-black Latinas, blacks) 	<ul style="list-style-type: none"> Significantly different density of TAMs among ethnicities, with black patients having the highest, followed by non-black Latinas, and Caucasian presenting the lowest density. The majority of TAMs presented an immunosuppressive, with black patients showing the highest density
Jung et al (2015, Tumour Biol; ref. 76)	Women (<i>n</i> = 939) <i>n</i> = 642 fibrous stroma type (100% fibrous stroma) <i>n</i> = 297 adipose stroma (>50% adipose tissue in tumor) Breast tissue	<ul style="list-style-type: none"> Relationship between stroma type and tumor phenotype classification Effect of stroma type on gene expression of tumor cell 	<ul style="list-style-type: none"> Luminal A subtype was more prevalent in adipose stroma breast cancer type (<i>P</i> < 0.001) Tumor cell expression of podoplanin and FAPα was higher in adipose stroma type, while higher expression of prolyl 4-hydroxylase and PDGFRα in fibrous stroma type
Iyengar et al (2015, Clin Cancer Res; ref. 66)	Women (<i>n</i> = 227) Cohort 1: cross-sectional prospective study (<i>n</i> = 100) who undergo mastectomy for breast cancer risk reduction (<i>n</i> = 10) or treatment (<i>n</i> = 90) Cohort 2: retrospective study (<i>n</i> = 127) who developed metastatic cancer Breast WAT	<ul style="list-style-type: none"> Breast WAT inflammation Circulating inflammatory factors 	<ul style="list-style-type: none"> Breast WAT inflammation was detected in 52 of 100 patients (52%) of cohort 1 and 52 of 127 patients (41%) of cohort 2
Iyengar et al (2015, Cancer Prev Res; ref. 77)	Women (<i>n</i> = 237) Breast WAT	<ul style="list-style-type: none"> Association of breast WAT inflammation with BMI and menopause 	<ul style="list-style-type: none"> WAT inflammation was significantly associated with menopausal status (<i>P</i> < 0.001) and BMI (<i>P</i> < 0.001)
Savolainen-Peltonen et al (2014, J Clin Endocrinol metab; ref. 70)	Postmenopausal women (<i>n</i> = 14) with ER-positive breast tumor Women undergoing breast reduction mammoplasty (<i>n</i> = 14) Breast subcutaneous adipose tissue	<ul style="list-style-type: none"> Estrone, estradiol, and estradiol fatty acyl ester concentrations in breast adipose tissue mRNA expression levels of estrogen-converting enzymes in breast adipose tissue 	<ul style="list-style-type: none"> Estradiol concentration in breast subcutaneous adipose tissue was lower in women with cancer compared with controls (<i>P</i> = 0.002), whereas the serum concentrations did not differ mRNA expression for 17β-hydroxysteroid dehydrogenase type 12 was lower in cancer patients (<i>P</i> = 0.018)
Morris et al (2011, Cancer Prev Res; ref. 68)	Obese (BMI \geq 30 kg/m ²) women (<i>n</i> = 30) Breast adipose tissue	<ul style="list-style-type: none"> Aromatase activity Adipocyte size Serum inflammation marker 	<ul style="list-style-type: none"> The severity of breast inflammation, defined as the CLS (crown-like structures)-B index, correlated with both BMI (<i>P</i> < 0.001) and adipocyte size (<i>P</i> = 0.01) Increased NF-κB binding activity and elevated aromatase expression and activity were found in the inflamed breast tissue of overweight and obese women
Colorectal cancer			
Liesenfeld et al (2015, Am J Clin Nutr; ref. 8)	Women or men (<i>n</i> = 59) VAT and SAT	<ul style="list-style-type: none"> VAT and SAT: 1,065 metabolites Serum: 1,810 metabolites Anthropometric measurements 	<ul style="list-style-type: none"> VAT displayed elevated markers of inflammatory lipid metabolism, free arachidonic acid, phospholipases (PLA2G10), and prostaglandin synthesis-related enzymes (PTGD/PTGS2S) Plasmalogen concentrations were lower in VAT than in SAT, which was supported by lower gene expression of FAR1, the rate-limiting enzyme for ether-lipid synthesis in VAT Serum sphingomyelin concentrations were inversely correlated (<i>P</i> = 0.0001) with SAT adipose triglycerides Logistic regression identified lipids in patients' adipose tissues, which were associated with tumor stage

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Table 1. Clinical studies of adipose tissue and tumor crosstalk (Cont'd)

Author (year, journal)	Study population/tissue type	Focus	Results
Amor et al (2015, Int J Colorectal Dis; ref. 73)	Women or men ($n = 36$) Visceral peritumoral and nontumoral adipose tissue	• Differences between obese and lean patients' adipose tissue secretion	• Peritumoral adipose tissue secreted higher amounts of nitrites and nitrates than nontumoral • Peritumoral adipose tissue secretion was increased in obese cancer patients
Notarnicola et al (2012, Lipids; ref. 64)	Women or men ($n = 32$) Adipose tissue (10 cm distance from tumor location)	• Enzymes (LPL and FAS) activity and gene expression	• Significant reduction in both LPL and FAS gene expression and activity levels in adipose tissue adjacent to tumor lesion compared with those detected in paired tissue distant from the cancer
Catalan et al (2011, J Nutr Biochem; ref. 71)	Women or men with colorectal cancer ($n = 11$) Healthy women or men ($n = 18$) VAT	• mRNA levels of proinflammatory adipokines (lipocalin-2, chitinase-3 like-1 and osteopontin, IGF1, IGFBP3) and angiogenic-related factors (HIF-1, VAGF, and MMP2 and MMP9) in VAT	• Increased mRNA expression levels of lipocalin-2 ($P = 0.014$), osteopontin ($P = 0.027$), TNF α ($P = 0.016$), and chitinase-3 like-1 ($P = 0.006$) in patients with colorectal cancer • Significantly higher levels of HIF-1, VAGF, and MMP2 ($P < 0.001$) in patients with colorectal cancer • Expression of IGF-1, IGFBP3, and MMP9 followed same, but not significant ($P > 0.001$)
Esophageal cancer			
Trevellin et al (2015, Oncotarget; ref. 65)	Women or men ($n = 60$) Peritumoral and distal adipose tissue of esophageal cancer patients	• Peritumoral adipose tissue: adipocyte and adipokine expression • BMI and obesity-related parameters (e.g., leptin mRNA levels)	• Increased adipocyte size was directly associated with leptin expression, angiogenesis (CD31), and lymph angiogenesis (podoplanin); however, these parameters were associated with nodal metastasis only in peritumoral but not distal adipose tissue of patients
Lysaght et al (2011, Br J Surg; ref. 79)	Women or men ($n = 35$) Omental adipose tissue	• T-cell activation status and cytokine production in omental adipose tissue	• Omental CD4 ⁺ and CD8 ⁺ T cells displayed significantly enhanced expression of the T-cell activation markers CD69 ($P < 0.001$) and CD107a (CD8 ⁺ T cells: $P < 0.01$), and significantly decreased CD62L expression ($P < 0.05$), compared with blood • IFN γ was the most abundant cytokine expressed by omental T cells
Colorectal and esophageal cancer			
Lysaght et al (2011, Br J Surg; ref. 79)	Women or men ($n = 35$) SAT and VAT of colorectal or esophageal patients	• Effect of SAT or VAT conditioned media on colorectal or esophageal cancer cells • Levels of proinflammatory and tumor proliferative properties in VAT and SAT	• Significantly higher levels of VEGF and IL6, and higher proportions of CD8 T cells and NKT cells in VAT • Cancer cells cultured with VAT conditioned media showed significant increase in cell proliferation
Endometrial cancer			
Modesitt et al (2012 Int J Gynaecol Cancer; ref. 72)	Women ($n = 8$) with endometrial cancer ($n = 4$) without endometrial cancer ($n = 4$) VAT, SAT, and endometrium	• Gene expression in VAT and SAT	• $n = 19$ gene sets were regulated in in VAT and SAT • $n = 47$ gene set pathways in in VAT • $n = 38$ gene set pathways in SAT • $n = 5$ pathways were significantly regulated in all three tissues, including glycolysis/ribosome, peroxisome proliferator activator receptor signaling, pathogenic <i>Escherichia coli</i> infection, and natural killer-mediated cytotoxicity
Prostate cancer			
Zhang et al (2016, Cytokine; ref. 82)	Women or men ($n = 30$) Periprostatic adipose tissue	• Gene expression of IL6, leptin, and adiponectin in per-prostatic adipose tissue	• IL6 and leptin were positively associated with the aggressiveness of prostate cancer, whether adiponectin was negatively associated
Venkatasubramanian et al (2014, Prostate; ref. 81)	Men ($n = 40$) Periprostatic adipose tissue and SAT	• Levels of secreted in periprostatic adipose tissue	• Periprostatic adipose tissue secretions were significantly more proliferative in both prostate cancer cells and endothelial cells compared with lean or overweight men and SAT
Ribeiro et al (2012, BMC Med; ref. 69)	Men ($n = 18$) Periprostatic adipose tissue	• Gene expression in human periprostatic adipose tissue	• In obese and overweight patient samples increased expression of proliferative, adipogenic, and immunoinflammatory genes (e.g., <i>LEP</i> and <i>ANGPT1</i>)

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Table 1. Clinical studies of adipose tissue and tumor crosstalk (Cont'd)

Author (year, journal)	Study population/tissue type	Focus	Results
Finley et al (2009, J Urology; ref. 74)	Men ($n = 7$) Periprostatic adipose tissue	<ul style="list-style-type: none"> Cytokine expression in periprostatic adipose tissue Inflammatory infiltrates in periprostatic adipose tissue 	<ul style="list-style-type: none"> IL6 in periprostatic adipose tissue conditioned medium was about 375 times greater compared with patients' serum Periprostatic adipose tissue showed a greater phosphorylation on STAT3 with high-grade tumors.
ENT cancer			
Iyengar et al (2016, Cancer; ref. 83)	Women or men ($n = 125$) Tongue and neck tissue	<ul style="list-style-type: none"> Association between WAT inflammation and cancer-specific survival 	<ul style="list-style-type: none"> WAT inflammation was associated with BMI, increased tumor thickness, and vascular invasion ($P < 0.05$) WAT inflammation was associated with worse cancer-specific and overall survival in early-stage cancer patients

Abbreviations: CLS, crown-like-structures; FAS, fatty acid synthase; FERKO, fat-specific ER α knockout mouse; Lcn2, lipocalin 2; LPL; lipoprotein lipase; Ob-R, leptin receptor; PDGFR α , platelet-derived growth factor receptor α ; PLA2G10, phospholipase A2 G10; PTGD/PTGS2S, prostaglandin synthesis-related enzymes; TAM, tumor-associated macrophages.

ref. 76). However, stromal expression of prolyl 4-hydroxylase was associated with shorter disease-free ($P = 0.005$) and overall ($P < 0.001$) survival (76). Taken together, the results show that breast cancer of "adipose stroma type" presents a distinct expression profile that may lead to an increase in cancer growth, invasion, and metastasis compared with the "fibrous stroma type."

Recently, Iyengar and colleagues focused on breast WAT-induced inflammation, which was defined by the presence of crown-like structures within WAT (66). Using biospecimens from two cohorts [cohort 1, prospective ($n = 100$), cohort 2, retrospective ($n = 127$)], they reported that 52 of 100 (52%) and 52 of 127 (41%) patients had breast WAT inflammation, respectively (66). Cohort 1 patients with WAT inflammation experienced increased levels of insulin, glucose, leptin, CRP, and IL6 and lower high-density lipoprotein cholesterol and adiponectin ($P < 0.05$). In cohort 2, WAT-induced inflammation correlated with hyperlipidemia, hypertension, and diabetes ($P < 0.05$). In both cohorts, WAT inflammation was associated with reduced recurrence-free survival, suggesting that WAT inflammation may, at least in part, explain the relationship between metabolic syndrome and worse breast cancer prognosis (66).

The same study presented results on the association between breast WAT inflammation and menopausal status or BMI in $n = 237$ breast cancer patients (77). They reported a significant association between breast tissue-associated crown-like structures (CLS-B) or the crown-like structures' density (CLS-B/cm²; indicating WAT inflammation) with menopausal status ($P = 0.008$ and $P < 0.001$) and BMI (both $P < 0.001$; ref. 77). Furthermore, the average size of adipocytes was correlated with crown-like structures in breast tissue ($P < 0.001$; ref. 77).

In a small study, Savolainen-Peltonen and colleagues examined the concentrations of estrone, estradiol, and estradiol fatty acyl ester and the mRNA expression of estrogen-converting enzymes in subcutaneous breast adipose tissue (70). Samples were collected from postmenopausal women either with ER⁺ breast cancer ($n = 14$) or undergoing breast reduction mastoplasty (controls; $n = 14$; ref. 70). The concentration of estradiol in breast subcutaneous adipose tissue was reduced in women with cancer compared with controls ($P = 0.002$; ref. 70). Expression of 17 β -hydroxysteroid dehydrogenase type 12 was also lower in the adipose tissue of breast cancer

patients compared with controls ($P = 0.018$; ref. 70). This suggests that estradiol metabolism may be differentially regulated in the adipose tissue of women with breast cancer.

Confirming their initial results of links between adiposity and inflammation in a mouse model (85), Morris and colleagues showed in breast tissue of $n = 30$ breast cancer patients that the severity of breast inflammation, defined as the crown-like structures of the breast index (CLS-B; number of breast WAT slides with evidence of crown-like structures/number of breast WAT slides examined), correlated with BMI ($P < 0.001$) and adipocyte size ($P = 0.01$; ref. 68). In addition, increased NF- κ B-binding activity and elevated aromatase expression and enzyme activity were found in the inflamed breast tissue of overweight and obese women (68).

In summary, the current evidence on the local interaction between breast WAT and breast cancer cells supports the hypothesis that adipose tissue inflammation, defined by the presence of crown-like structures, is a key player in cancer growth and progression. However, the involvement of steroid hormones as drivers of tumor progression represents an additional important aspect of the adipose-cancer link, particularly in hormone-dependent cancers, such as breast or endometrial cancer (17, 86–88).

Colorectal cancer. Four studies were identified that have investigated the crosstalk between adipose tissue and colorectal cancer (8, 64, 71). Nested in the international cohort study ColoCare, Liesenfeld and colleagues used a multiomic approach to investigate differences between VAT compared with SAT in patients with colorectal cancer (8). They comprehensively assessed differences in metabolic, lipidomic, and transcriptomic profiles in paired human VAT and SAT samples and their association with colorectal cancer tumor stage (8). Mass spectrometry was used to measure 1,065 metabolites in adipose tissue and 1,810 metabolites in serum of $n = 59$ patients, and parallel genome-wide gene expression data were used to perform integrated analyses of candidate metabolites (8). Compared with SAT, VAT was characterized by elevated markers of inflammatory lipid metabolism, phospholipases (PLA2G10), free arachidonic acid, and prostaglandin synthesis-related enzymes (PTGD/PTGS2S; ref. 8). Several lipids showed a linear association with increasing tumor stage (not significant after correction for multiple testing; ref. 8).

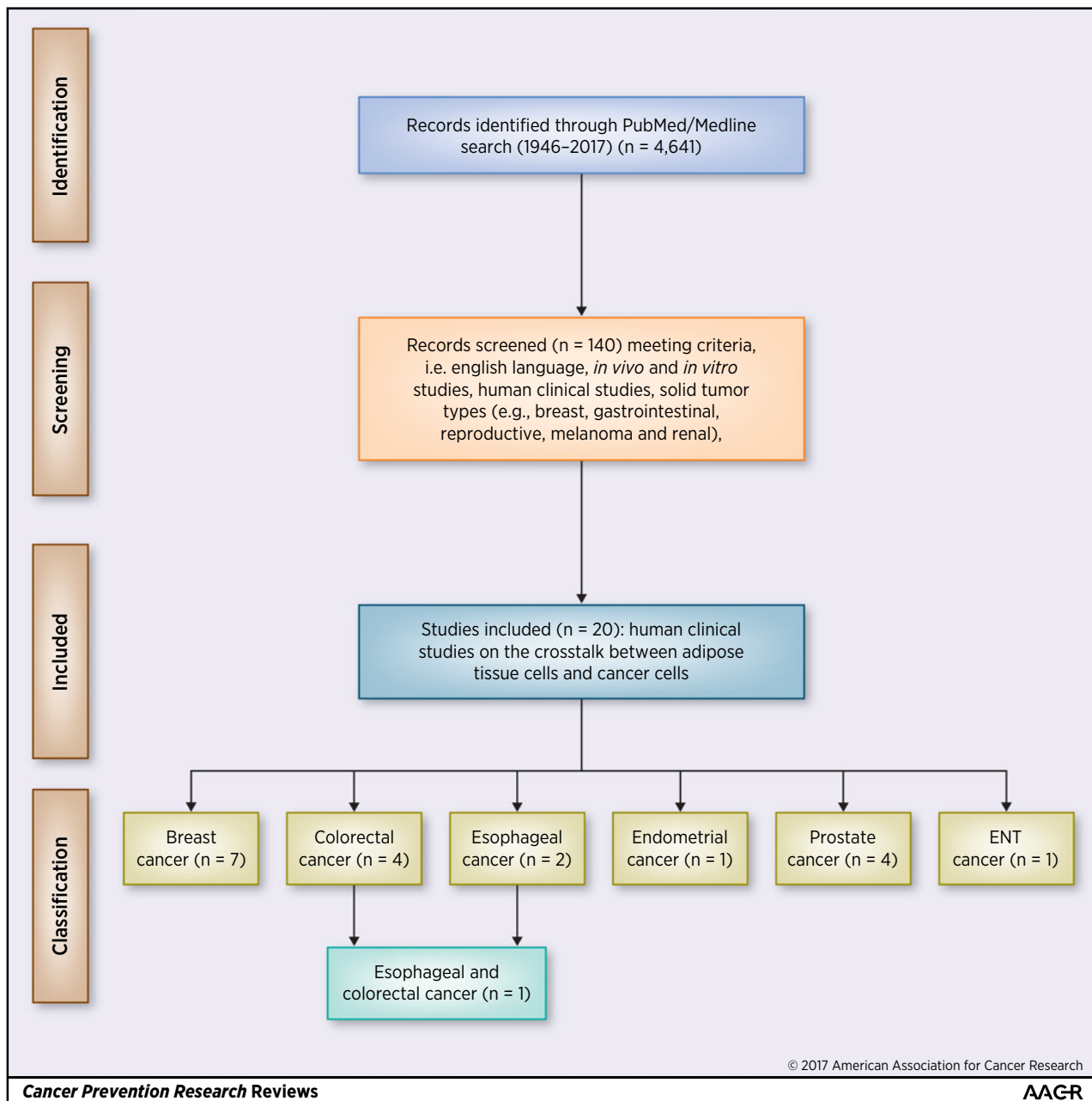


Figure 2. Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols (PRISMA) flow diagram (63).

In the same year, Amor and colleagues collected VAT of $n = 18$ colorectal cancer patients and $n = 18$ healthy controls (73). Participants were classified into four groups: (i) obese with cancer; (ii) lean with cancer; (iii) obese without cancer; and (iv) lean without cancer (73). Tissue samples were divided into peritumoral and nontumoral fat. Their results showed that the secretion activity of peritumoral adipose tissue in cancer patients was higher compared with the control groups and nontumoral tissue samples (73). Tissue samples from obese cancer patients also had an increased rate of secretion compared with lean patients (73).

Another study examined regional differences (peritumoral and distant from neoplasia) in the expression of lipogenic enzymes (e.g., lipoprotein lipase and fatty acid synthase) and their influence on events that sustain colorectal cancer growth (64). The evaluation of $n = 32$ adipose tissue samples of colorectal cancer patients [adjacent (not defined) and distant (about 10 cm)] to neoplasia showed that lipoprotein lipase as well as fatty acid synthase were less expressed in adipose tissue adjacent to the tumor compared with adipose tissue distant from the cancer (64). The results underline the influence of

cancer cells on environmental adipose tissue's lipid metabolism, demonstrating a cancer-induced impairment in the formation and lipid-storing capacity of adjacent adipose tissue in patients with colorectal cancer (64).

In a small case-control study, differences in VAT gene expression of proinflammatory and angiogenesis-related factors between 11 colorectal cancer patients and 18 healthy individuals were assessed (71). Gene expression of lipocalin-2, osteopontin, chitinase-3 like-1, *TNF α* , *HIF1A*, and *VEGFA* was significantly elevated in VAT of colorectal cancer patients.

These results suggest that inflammatory factors in VAT of colorectal cancer patients are elevated and may accelerate cancer development or progression (71).

In summary, the inflammatory features of the adipose tissue environment embedding the colon and rectum seem to play a crucial role when investigating the tumor-promoting effects of adipose tissue. Only one study considered the reciprocal influence of the tumor on the surrounding adipose tissue. Focusing on only lipogenic enzymes, this study illustrates that the adipose tissue-tumor interaction needs to be considered in both directions.

Esophageal cancer. A recent study reported that esophageal peritumoral adipose tissue and its secretion of tumor-promoting factors are directly correlated with increased tumor growth (65). Studying the morphologic, histologic, and molecular characteristics of peritumoral and omental adipose tissue in esophageal cancer patients ($n = 60$), the study was designed to investigate whether adipose depot-specific differences affect tumor behavior (65). Only in peritumoral adipose tissue, increased adipocyte size was directly associated with leptin expression, angiogenesis (CD31), and lymph angiogenesis (podoplanin; ref. 65). Thus, peritumoral adipose tissue may directly accelerate the progression of esophageal cancer by secreting paracrine factors; the adipokine leptin seems to be a key player in this crosstalk (65).

Lysaght and colleagues performed flow cytometry to assess the activation of T cells and cytokine production in VAT (omental adipose tissue) of $n = 35$ esophageal cancer patients (79). A large number of lymphocytes were observed in the omentum (79). Both CD4⁺ and CD8⁺ T cells showed significantly increased expression of the T-cell activation markers CD69 ($P < 0.001$) and CD107a (CD8⁺ T cells: $P < 0.01$) compared with blood, as well as reduced CD62L expression ($P < 0.05$). Similarly, higher proportions of CD45RO⁺ T cells compared with CD45RA⁺ T cells were present. IFN γ was significantly elevated in VAT, compared with blood and subcutaneous adipose tissue ($P < 0.01$; ref. 79). Overall, this study confirmed that VAT is a major source of activated proinflammatory lymphocytes, which may help fuel chronic inflammation (79).

Although the number of studies in esophageal cancer is limited, they highlight two important aspects. First, the theme of inflammatory mechanisms as a key player in the adipose-cancer link is also prominent in this cancer type; second, the fascinating work by Travellin and colleagues (65) highlights the role of peritumoral adipocytes as a carcinogenic driver in esophageal cancer and possibly beyond.

Colorectal and esophageal cancer (combined). In 2011, one study investigated the differences in cytokine and adipokine expression of VAT and SAT from normal-weight and centrally obese

gastrointestinal cancer patients (including colorectal and esophageal cancer) and their effects on colorectal and esophageal cancer cell lines (80). They observed a higher *IL6*, *VEGF*, and *LEP* gene expression in VAT compared with SAT and a higher IL6 and VEGF protein secretion from VAT into conditioned media compared with SAT (80). Adipose tissue-conditioned media from centrally obese patients induced significantly more proliferation in both esophageal and colorectal cancer cell lines, compared with adipose tissue-conditioned media from nonobese patients. Greater proliferation of cancer cell lines was observed after culture with VAT-conditioned media, compared with SAT-conditioned media. (80). This study illustrates the elevated expression of inflammatory and angiogenesis-related factors in VAT compared with SAT of cancer patients and translates it directly back to impact gastrointestinal cancer cell lines. In particular, the link via VEGF highlights a potential mechanism whereby VAT from centrally obese patients may drive carcinogenic progression (80).

Endometrial cancer. To identify obesity-related endometrial cancer genes via microarray analysis in endometrial and adipose tissues, Modesitt and colleagues collected endometrial tissue, VAT, and SAT in $n = 8$ ($n = 4$ with endometrial cancer, $n = 4$ without endometrial cancer) individuals undergoing hysterectomy (72). The authors noted no differences in hormone/metabolite levels between groups (72). Gene set enrichment analysis contrasting patients with and without endometrial cancer showed that endometrial, VAT, and SAT displayed 40, 47, and 38 alternatively regulated gene set pathways, respectively (72). Eighteen pathways were regulated in opposite directions between VAT and SAT (72).

The results from this pilot study suggest that SAT and VAT have opposite patterns of gene expression in obese patients with and without endometrial cancer and may provide new potential targets for cancer treatment and prevention for obese women. However, considering the small sample size of this first study, more research is needed.

Prostate cancer. Although visceral obesity has been associated with worse prognosis for prostate cancer patients, periprostatic adipose tissue may lead to an increase in the aggressive growth of this disease (69, 74, 81, 82). A recent study analyzed the expression of IL6, leptin, and adiponectin in periprostatic adipose tissues specimens from $n = 30$ prostate patients and $n = 10$ noncancer controls (82). IL6, leptin, and adiponectin gene expression was higher in the samples from prostate cancer patients compared with controls ($P < 0.001$; ref. 82). Furthermore, IL6 expression in adipose tissue was associated with increased aggressiveness of prostate cancer ($P = 0.001$; ref. 82).

One study collected periprostatic and subcutaneous adipose tissue in $n = 40$ prostate cancer patients (81). In culture with either prostate cancer cells or endothelial cells, the periprostatic adipose tissue showed higher proliferative effects compared with SAT (81). Furthermore, this result was more significant in samples of obese patients (BMI ≥ 30 kg/m²) compared with overweight (25–30 kg/m²) or lean (<25 kg/m²) patients (81).

Ribeiro and colleagues (69) conducted a study with $n = 18$ periprostatic adipose tissue samples, which were categorized into three groups based on postsurgical diagnosis and pathologic

analysis. Differentially expressed genes in the periprostatic tissue were investigated by microarrays (69). In the tissues of obese and overweight individuals, an increased expression was observed in genes that are involved in adipogenic, proliferative, and mild immunoinflammatory processes (e.g., *LEP*, *ANGPT1*; ref. 69). In patients with prostate cancer, the expression profile of periprostatic adipose tissue was consistent with hypercellularity and reduced immunosurveillance (69). The authors concluded that their findings are consistent with periprostatic adipose tissue among obese individuals providing a favorable environment for prostate cancer progression (69).

In 2009, another study collected periprostatic adipose tissue samples from $n = 7$ patients undergoing surgery treatment (74). Analyzing the cytokine expression in the tissue samples, their results showed a 375 times higher expression of IL6 in the per-prostatic adipose tissue compared with the patients' serum sample (74). Furthermore, the phosphorylation cell signaling of STAT3 in periprostatic adipose tissue was greater with high-grade tumors (74).

All studies of prostate cancer collected periprostatic adipose tissue and suggest that altered adipose tissue metabolism in obese individuals forms a more auspicious microenvironment for prostate cancer development. An increase in cell proliferation and expression of proliferative genes, as well as IL6, has been detected in expanded periprostatic adipose tissue of obese individuals. However, the results need to be confirmed in studies with larger sample sizes.

ENT cancer. To assess the association between WAT inflammation of the tongue environmental adipose tissue and squamous cell carcinoma (SCC) of the tongue, Iyengar and colleagues analyzed $n = 125$ tissue samples from oral cancer patients (83). The presence of dead or dying adipocytes surrounded by macrophages forming crown-like structures was defined as WAT inflammation (83). Thirty-nine percent of the patients presented WAT inflammation, and this was statistically significantly associated with BMI, increased tumor thickness, and vascular invasion ($P < 0.05$; ref. 83). The cancer-specific survival rate was with 59% [95% confidence interval (CI), 46–76] lower for patients presenting WAT inflammation compared with patients without (82%; 95% CI, 72–92; ref. 83). In $n = 70$ patients with early-stage SCC (without lymph node involvement, no indication for adjuvant therapy), tongue WAT inflammation was significantly associated with both decreased cancer-specific and overall survival ($P < 0.05$; ref. 83).

The results of this study suggest that inflammation of neck and tongue WAT plays an important role in the development and growth of oral cancers. However, considering that this is the first study of this cancer type, further investigations are needed to confirm the results.

Conclusions

Obesity is an established risk and progression factor for many cancers (e.g., breast, colorectal, esophageal), but the underlying mechanisms are incompletely understood. A potential crosstalk between adipose tissue and carcinomas may contribute importantly to the observed associations between obesity and increased cancer risk and/or progression.

In vitro and *in vivo* studies have shown that adipose tissue is enriched for hormones, cytokines, and other mediators (e.g.,

leptin, adiponectin). This milieu has already been characterized as a growth-promoting and proinflammatory microenvironment. More recent investigations have used a set of multiomic techniques, including transcriptomics and metabolomics, yielding novel signals, as well as integrated effects on pathways (10). They also demonstrated clear distinctions of the adipose tissue type (visceral vs. subcutaneous) by these -omic characterizations.

Here, results of $n = 20$ human clinical studies indicate that (i) there is a direct/specific crosstalk between adipose tissue and carcinomas, likely with different mechanisms and different directions depending on the organ system; (ii) WAT is more important than other adipose pools in this pattern of cellular communication; and (iii) VAT plays a central role, as it is metabolically more active than SAT. In addition, peritumoral adipose tissue that is directly present in the organ may provide an imminently present microenvironment that fosters carcinogenic progression. Whether the mediators and intensity of crosstalk between adipose tissue and cancer is affected by the tissue distance is an important but currently unanswered question.

Despite the intriguing results of studies presented within this systematic review, we still miss the complete picture that elucidates the mechanisms underlying the adipose-tumor crosstalk. In addition to the limitation of small sample sizes in most studies, other aspects that are relevant in inflammatory processes were often not reported or assessed. Inflammation can be modified by several environmental factors, such as age, smoking, medication use, and diet. Even though adding another layer of complexity, such variability in the investigated study populations should be considered. Furthermore, as detailed above, distinct adipose tissue compartments have different metabolic capabilities. These potentially generate adipose tissue-specific forces that affect the tumor, locally or systemically. However, only a limited number of studies assessed or have the means to assess the distribution of adipose tissue compartments in individuals. Rather than relying on BMI, the amount of adipose tissue in a patient and its distribution would be much more informative to investigate the effect of adipose tissues on carcinogenesis to identify means of specific intervention.

Consequently, there is a clear need for larger and more comprehensive investigations of the adipose tissue as a central player in explaining the obesity-cancer link. Overall, data of the human clinical studies, as well as *in vitro* and *in vivo* studies, suggest that efforts to eavesdrop and ultimately interfere with this cancer-enhancing crosstalk between adipose tissue and carcinomas may lead to new targets and strategies for decreasing the burden of obesity-related cancers.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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