Chemoresistance: Intricate Interplay Between Breast Tumor Cells and Adipocytes in the Tumor Microenvironment

Ilze Mentoor¹, Anna-Mart Engelbrecht¹, Paul J. van Jaarsveld²,³ and Theo Nell¹*

¹Department of Physiological Sciences, Faculty of Science, Stellenbosch University, Stellenbosch, South Africa, ²Non-Communicable Diseases Research Unit, South African Medical Research Council, Cape Town, South Africa, ³Division of Medical Physiology, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa

Excess adipose tissue is a hallmark of an overweight and/or obese state as well as a primary risk factor for breast cancer development and progression. In an overweight/obese state adipose tissue becomes dysfunctional due to rapid hypertrophy, hyperplasia, and immune cell infiltration which is associated with sustained low-grade inflammation originating from dysfunctional adipokine synthesis. Evidence also supports the role of excess adipose tissue (overweight/obesity) as a casual factor for the development of chemotherapeutic drug resistance. Obesity-mediated effects/modifications may contribute to chemotherapeutic drug resistance by altering drug pharmacokinetics, inducing chronic inflammation, as well as altering tumor-associated adipocyte adipokine secretion. Adipocytes in the breast tumor microenvironment enhance breast tumor cell survival and decrease the efficacy of chemotherapeutic agents, resulting in chemotherapeutic resistance. A well-known chemotherapeutic agent, doxorubicin, has shown to negatively impact adipose tissue homeostasis, affecting adipose tissue/adipocyte functionality and storage. Here, it is implied that doxorubicin disrupts adipose tissue homeostasis affecting the functionality of adipose tissue/adipocytes. Although evidence on the effects of doxorubicin on adipose tissue/adipocytes under obesogenic conditions are lacking, this narrative review explores the potential role of obesity in breast cancer progression and treatment resistance with inflammation as an underlying mechanism.

Keywords: obesity, adipose tissue, breast cancer, inflammation, treatment resistance

INTRODUCTION

Breast cancer continues to be a major health risk for women globally (1, 2). Lifestyle-related risk factors including overweight and obesity (adiposity) have reached epidemic proportions (3, 4), and are considered major risk factors for breast cancer development and progression (5).

Adipose tissue plays an important physiological role as a metabolically active storage compartment and endocrine organ due to its diverse ability to secrete various adipokines (6). Adipose tissue dysfunction in relation to obesity has been linked to accelerated growth and the survival of breast cancer cells (7, 8).
Adipose tissue dysfunction is mainly characterized by inflammation which is primarily mediated by rapid adipose tissue remodeling (hypertrophy and hyperplasia) (9). This results in dysfunctional synthesis of several adipokines in coordination with immune cell infiltration leading to a state of sustained low-grade inflammation, which activates downstream signaling pathways favoring cancer cell survival (increased proliferation and decreased apoptosis) and hence contributing to cancer progression and metastasis (10–12).

Furthermore, adipose tissue and/or adipocytes in the tumor microenvironment serve as an exogenous energy source for the survival of breast cancer cells (13, 14), especially since adipose tissue is abundant in the breast (15). It is further proposed that breast cancer cells modulate lipid metabolism by altering the secretion of adipokines through adipocytes, resulting in the release of free fatty acid (FFA) providing energy substrates, that cancer cells need to sustain its high proliferation demand (13).

Pre-clinical evidence highlights obesity as a key player in breast cancer chemotherapeutic drug resistance (16–19). This finding bears great clinical significance for overweight/obese breast cancer patients being treated with chemotherapeutic agents such as doxorubicin (20), since, obese and normal weight patients receive the same treatment regimen (21). Studies have also confirmed this in showing that obesity is associated with poor clinical outcomes in breast cancer patients treated with chemotherapeutic agents including doxorubicin (22, 23).

Doxorubicin is a highly sensitive alkylating antineoplastic agent used as a first line adjuvant regimen for breast cancer patients (24), despite its high sensitivity as a chemotherapeutic agent, it is also associated with a diverse range of cellular toxicities and the development of treatment resistance (25). Additionally, doxorubicin also negatively impacts on adipose tissue function (26–29). This is of clinical significance since obesity is associated with an increased risk for various types of cancers being treated with doxorubicin (20). However, few studies exist in which the effects of doxorubicin on adipose tissue in the context of obesity and dysfunctional adipose tissue is investigated. We proposed that using doxorubicin treatment on dysfunctional adipose tissue and/or adipocytes, may exacerbate the negative effects of obesity per se, and further dysregulate adipokine secretion.

It is imperative to explore and understand the cellular mechanisms whereby obesity negatively affects chemotherapy outcomes. Identifying molecular mechanisms in which doxorubicin affect adipose tissue could contribute in describing molecular mechanisms and identifying potential novel pharmacologic targets and development of the appropriate management protocols of doxorubicin related toxicities in order to improve over-all survival of these cancer patients. This narrative review will mainly focus on (i) the pathological links between adiposity and breast cancer in the context of inflammation as an underlying mechanism and, (ii) the role of adiposity in breast cancer treatment (doxorubicin) resistance and the possible mechanisms that contribute to treatment resistance.

ADIPOSITY AND BREAST CANCER

Globally, the increasing burden of breast cancer is considered the second most prevalent cancer diagnosed amongst women (1, 30) in both developed and developing countries (2, 31). Estimations rank breast cancer as the fifth leading cause of death globally at 626,679 deaths per annum (1, 30).

Despite many efforts to reduce cancer mortality by implementing lifestyle-related modifications, limited progress has been made due to the very complicated interplay between dietary behaviors and other lifestyle modifications (32, 33). This is especially problematic since recent epidemiological studies strongly suggested that adiposity (excess adipose tissue) is considered a significant risk factor in many lifestyle-associated cancers including breast cancer (34–37).

Adipose Tissue Is a Complex Functional Tissue

Fundamentally, adipose tissue is a complex and important endocrine organ impacting various physiological systems (38). It functions as both an energy storage compartment and a metabolic active endocrine organ (6), secreting various bioactive substances (pro- and anti-inflammatory) known as adipokines (39), including but not limited to leptin, adiponectin (Apn), tumor necrosis factor-alpha (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), resistin and macrophage chemotactic protein-1 (MCP-1) (40, 41). Additionally, adipose tissue also plays a functional role in steroid sex hormone and growth factor production, and is integral in the development of insulin resistance, hyperglycaemia and breast cancer (42, 43). Epidemiological and experimental models support the role of a dysregulation in adipokine synthesis and their actions in relation to adiposity and adipose tissue dysfunction, to the development of various disease states, including breast cancer (5, 44–51).

Dysfunctional Adipose Tissue, Inflammation, and Breast Cancer

Dysfunctional adipose tissue is characterized by low grade inflammation, primarily mediated by rapid hypertrophy/hyperplasia (adipose tissue remodeling) as well as immune cell infiltration (52), resulting in the deregulated synthesis of several adipokines i.e., IL-1β, IL-6, interleukin-8 (IL-8), resistin, leptin and MCP-1 (7, 8, 15, 53–55) (Figure 1). These inflammatory mediators attract monocytes (differentiated into macrophages) and T-lymphocytes, stimulating the synthesis of both pro-inflammatory and pro-angiogenic factors (56), collectively contributing to a chronic cycle that sustains an inflammatory milieu. Increased IL-6 and leptin levels has been shown to upregulate pro-inflammatory mediators (IL-1β and TNF-α) in adipose tissue (57). Additionally, adipose tissue-induced inflammation also attenuates the suppression of nuclear factor kappa B (NFκB), p65 phosphorylation and also induces M1 to M2 macrophage phenotype switching. The latter is due to the pro-inflammatory state in which saturated fatty acids bind to the toll-like receptors on macrophages (58) and upregulate the secretion of various pro-inflammatory mediators (IL-1β and TNF-α) in adipose tissue (59, 60), creating a state of chronic systemic low-grade inflammation.

Inflammation is a well-known predisposing risk factor for tumorigenesis and a hallmark of cancer (61, 62). Pre-existing
FIGURE 1 | The link between adipose-induced inflammation and cancer. Adipose tissue dysfunction is associated with sustained low-grade inflammation and it may be linked to breast cancer development and progression. Several inflammatory mediators are implicated in tumor development and progression. Possibly as a result of the sustained inflammatory signaling having downstream effects on major pathways involved in angiogenesis, cell-proliferation and apoptosis, thus having the ability to influence carcinogenesis. Hypoxia in adipose tissue also induces the release of inflammatory mediators, thus further exacerbating inflammation. Apn, adiponectin; IL-6, interleukin-6; HIF-1α, hypoxia inducible factor-1α; MAPK, mitogen activated protein kinase; NFκB, nuclear factor kappa B; PI3K/Akt, phosphoinositide-3-kinase; STAT-3, Signal transducer and activator of transcription-3; TNF-α, tumor necrosis factor-α.

Pro-inflammatory microenvironments are associated with an increased risk for cancer, as in the case for inflammatory breast cancer (63). Remarkable similarities exist between dysfunctional adipose tissue and the tumor microenvironment where infiltration of immune cells initiate the secretion of pro-inflammatory molecules, thereby sustaining and promoting the progression of both obesity and breast cancer (64) (Figure 1).

The complex pathophysiology that exists between adipose tissue, inflammation and breast cancer involves inflammatory mediators (i.e., IL-6 and TNF-α) that enhances tumor progression and survival (65). Persistent inflammatory signaling (intracellular NFκB) induces downstream effects on major biochemical pathways affecting carcinogenesis (Figure 1). For example, the mitogen activated protein kinase (MAPK) family modulates cellular proliferation via the phosphoinositide-3-kinase (PI3K/Akt), and the MAPK pathways which regulates and affects mitogenic, anti-apoptotic as well as pro-angiogenic effects (60). Moreover, IL-6 secreted by adipose tissue binds to IL-6 receptor on breast cancer cells and activates the Janus family of kinases that phosphorylates signal transducer and activator of transcription-3 (STAT-3) (66). These events induce the expression of pro-survival genes (i.e., bcl-x) (67), characteristic of a pro-carcinogenic state promoting breast cancer cell survival and proliferation (Figure 1).

Obesity-induced cytokine secretions are detected in local adipose tissue and serum (68). These elevated circulating cytokines (IL-6, IL-8, TNF-α, and vascular endothelial growth factor; VEGF), exert effects at distant sites (69), that can promote breast cancer development through upregulation of inflammatory mediator synthesis and increased immune cell infiltration as well as angiogenesis (70, 71). Additionally, overweight/obese patients display a large number of crown-like structures (necrotic adipocytes surrounded by immune cells) in mammary adipose tissue compared to normal weight breast cancer patients. These crown-like structures are characteristic of local inflammation (66, 72), and associated with an upregulation of pro-inflammatory cytokines and aromatase expression (73). Although the role of cytokines in obesity and breast cancer development have been reported, the effects of other adipokines should be considered as a possible relationship between obesity and the development of breast cancer.

Leptin and adiponectin (Apn) have been antagonistically implicated for their roles in inflammation and tumorigenesis (Figure 1) (74). Leptin increases the synthesis of pro-inflammatory cytokines and plays a role in breast cancer development by increasing cellular proliferation and angiogenesis (75). Elevated serum leptin levels and increased expression of leptin receptors is also reported in breast cancer...
patients that is often associated with higher pathological grade tumors and cancer treatment resistance (76, 77). Adiponectin is decreased in obese patients, the metabolic syndrome as well as in breast cancer patients thus lowering the risk of cancer development due to an upregulation of apoptosis and its' anti-inflammatory properties (78–81).

Excess adipose tissue (overweight/obesity) is also associated with increased secretion of insulin-like growth factor-1 (IGF-1) in breast, colon, lung and prostate cancer patients (82). The over expression of insulin-like growth factor-1-receptor (IGF-1R) was observed in both breast and pancreatic tumor tissue (83), where inhibition of apoptosis and stimulation of cellular proliferation via the PI3K-AKT-mTOR and RAS/Raf/MEK pathways are implicated (83).

Additionally, loss of tumor suppressor function, increased cell cycling and stimulation of oncogenes also promote inflammation and exacerbates inflammatory related signaling pathways (69, 84, 85) (Figure 1). For example, the p53 gene mutation promotes inflammation in the tumor microenvironment by inducing the synthesis of IL-1, IL-6, TNF-α, and activates NFκB (86, 87), which maintains inflammation in the tumor microenvironment and enhances genomic instability (88, 89). In addition, p53 has also been shown to induce the PI3k/Akt/mTOR pathway, which can induce the synthesis of pro-inflammatory mediators (90). As a result of rapid hypertrophy and hyperplasia (91) (Figure 1), hypoxia inducible factor-1α (HIF-1α) is upregulated (92), which binds to transcription factors on VEGF and angiopoietin-2 target genes, stimulating angiogenesis in the microenvironment, which is also known to exacerbate local inflammation (92).

Others report that obesity-induced inflammation may also play a role in breast cancer tumor invasion and metastasis. Here, epithelial mesenchymal transition (EMT) can be induced by various pro-inflammatory markers, i.e., IL-6, IL-8, TNF-α, and CCL2 derived from cancer-associated adipocytes (93–95).

It is evident from these findings that obesity is a factor casual in the development of breast cancer, involving molecular mechanisms in relation to inflammation, immune cell infiltration and adipokine dysfunction. Supporting evidence includes obesity as a negative prognostic factor for breast cancer independent of menopausal status, tumor stage, and tumor hormone–binding characteristics (96, 97).

**BREAST CANCER TREATMENT**

Chemotherapy still remains one of the conventional treatment options in addition to radiotherapy and surgery, which significantly improves cancer patients' overall-survival (98, 99). Several chemotherapeutic drug classes exist which are associated with beneficial clinical outcomes for cancer patients (100).

Doxorubicin, also known as Adriamycin or hydroxyl daunorubicin (101), is classified as an anthracycline antibiotic, exhibiting broad-spectrum anti-neoplastic activity (24, 101), and is used to treat a range of malignancies of the breast (used as first line adjuvant chemotherapeutic agent), bladder, stomach, lung, ovaries, thyroid as well as multiple myeloma, Hodgkin- and non-Hodgkin’s lymphoma, due to poor tumor selectivity (102).

Doxorubicin interacts with deoxyribonucleic acid (DNA) by intercalation, thereby inhibiting macromolecule biosynthesis (103). This inhibits topoisomerase II (DNA repair function), which relaxes DNA transcription supercoils (104, 105). Secondly, doxorubicin generates reactive oxygen species (ROS) damaging cell membranes, DNA and proteins (103, 104) through stimulation of p53-DNA binding; subsequently it initiates caspase signaling and DNA cross-linking (106). Doxorubicin treatment efficacy is often associated with adverse side effects such as nephrotoxicity, hepatotoxicity, sarcopenia, cardiotoxicity (102), and changes in body composition (decreased body weight and lipatrophy, discussed in section Doxorubicin Toxicity on Adipose Tissue/Adipocytes) (107, 108). These effects contribute toward recurrence as well as metastasis in breast cancer patients, making doxorubicin treatment protocols ineffective and prone to develop treatment resistance (109, 110).

**Obesity and Treatment Resistance**

Experimental animal models showed that diet-induced obesity increases tumor development, progression and metastasis with decreased chemotherapeutic efficacy (7, 8, 55, 111–113), specifically in the case of breast cancer (16–18). Additionally, obesity is associated with larger tumor sizes and positive lymph node involvement compared to non-obese breast cancer patients (114, 115).

Human studies also show that obesity is linked to poor clinical outcomes in breast cancer patients treated with chemotherapeutic, hormonal-based chemotherapy agents and radiotherapy (22, 116). Obesity was also associated with lower pathological complete response, disease free survival, clinical benefit rate and worse overall-survival (22). Iwase et al. reported that a high visceral fat area is associated with poor clinical outcomes for patients receiving neo-adjuvant chemotherapy (anthracycline followed by taxane) treatment regimens (19). In fact, treatment protocols for overweight and obese cancer patients includes prescribed lower doses of chemotherapeutic agents to avoid co-morbidities, side effects and adverse toxicities (117). This could also compromise drug efficacy and contribute to the development of treatment resistance and added cytotoxicity (118). However, alterations in dosages cannot clarify all occurrences of treatment resistance in relation to obesity (96, 119, 120).

**Resistance Mechanisms**

Drug resistance can either be classified as intrinsic (pre-treatment), or acquired (post treatment) (121). Currently, known drug resistance mechanisms include, the evasion of therapy-induced apoptosis, activation of drug transporter proteins and enhanced DNA repair mechanisms, which describe cellular mechanisms (109). Drug resistance can additionally ensue as a result of alterations in pharmacokinetics, drug inactivation and metabolism (109, 121), which can be induced and/or exacerbated in obese states.

**Cellular mechanisms**

Treatment resistance can develop due to the evasion of apoptotic pathways by increased anti-apoptotic protein (bcl-2) and decreased pro-apoptotic protein (bax) expression (122). Adipocytes protect cancer cells from chemotherapeutic agents...
(i.e., vincristine and daunorubicin) by upregulating anti-
-apoptotic bcl-2, and downregulation of pro-apoptotic bad and
pim-2 family members (an oncogene which phosphorylates
bad) (123). Although the mechanisms by which adipocytes
achieved this “protection of cancer cells” was not assessed,
a recent in vitro study identified resistin (mainly secreted
from adipose tissue) (124) as a causal factor for acquiring
resistance to doxorubicin treatment in both the MCF-7 human
breast cancer cell line (estrogen receptor positive) as well as
in the MDA-MB-231 human triple negative cell line. Here,
doxorubicin induced apoptosis (increased cytochrome-c
concentration, cleaved caspase-9, cleaved PARP) in a time and
dose dependant manner. Addition of recombinant resistin to
the treatment protocol downregulated apoptosis by inducing
autophagy (a self-degradation process which cancer cells
can utilize to eliminate toxic materials to avoid cell death)
(25). Although resistin receptor expression was not assessed,
and no supporting evidence for animal or human models
were provided, it would be plausible to motivate for more
experimental research to investigate potential mechanisms and
causal factors involved in acquiring doxorubicin treatment
resistance.

Additionally, treatment resistance can also be the result
of gene mutations coding for apoptotic proteins (125), for
example the mutation in p53 has been associated with acquired
resistance to doxorubicin in breast cancer patients, possibly
due to inhibition of apoptosis by activating Bax/Bak (pro-
apoptotic factors) (125). General-, and central obesity showed a
positive association with mutations in p53 of tumor tissue, which
was further associated with less favorable tumor characteristics
including poorly differentiated and higher nuclear grade tumors
(126).

Moreover, modifications in the activation and expression of
drug transporter proteins alters drug responses by reducing
intracellular drug concentration, which promotes treatment
resistance (127). Examples are (i) P-glycoprotein (P-gp), (ii)
multi-drug resistance protein-1 (MDR-1), (iii) multi-drug
resistance associated protein-1 (MDRP-1), and (iv) breast cancer
resistance protein (BCRP), which are ATP-binding cassette
(ABC) transmembrane pumps responsible for the elimination
of toxic compounds from cells (128, 129). Although normally
expressed in healthy tissue, overexpression of P-gp, MDR-
1, MDRP-1 and BCRP are present in breast cancer cells in
relation to doxorubicin resistance (130–132). P-glycoprotein
expression can also be upregulated by inflammation (NFκB),
resulting in an altered expression of MDRP-1, which increases
the expression of P-gp and consequently modify drug responses.
(110, 133).

Adipose tissue is also a source of mesenchymal stem cells
which share similar characteristics to tumor-initiating stem cells
(134), which can be recruited to the tumor microenvironment
to support breast tumor growth and proliferation (135). Tumor-
initiating stem cells has the ability to self-renew and/or
differentiate, tolerate high levels of DNA damage, increase ABC
transmembrane transporter protein expression and induce the
synthesis of various cytokines and growth factors (increased IL-
6 and C-C motif ligand 5 (CXCL5) levels) (63, 135–137), and
therefore may be an alternative treatment resistance mechanism.
Elevated leptin concentrations and leptin receptor expression
(increased in adiposity) is associated with the promotion of
cancer stem cells survival and self-renewal, by inducing
JAK2/STAT3 signaling pathways, that increase stem cell renewal
transcription factors (NANOG, OCT-4, and SOX-2) expression
in breast cancer cells (77, 138).

Leptin, well-known for its role in inflammation and
tumorigenesis (74, 139), increases cellular proliferation and
angiogenesis (75), and is also associated with higher pathological
grade breast cancer tumors (76) and breast cancer treatment
resistance (136, 140). However, in contrast leptin also shows anti-
cancer effects, by enhancing the anti-proliferative effects of 3′-
5′-cyclic adenosine monophosphate (cAMP) elevating agents in
breast cancer cells (141). 3′-5′-cyclic adenosine monophosphate
is an intracellular second messenger, generated from ATP
by adenylyl cyclase’s (142, 143) and plays a regulatory role
in cellular proliferation, apoptosis as well as differentiation,
proposed to be induced via protein kinase A (144, 145). The
utilization of cAMP elevating agents has been explored in
pre-clinical models and shows anti-cancer effects i.e., inducing
apoptosis (downregulation of Bcl-2 which leads to caspase-3
mediated apoptosis) (146) and cell cycle arrest (146, 147) in breast
cancer cells. Additionally, cAMP elevating agents inhibit both
cellular proliferation (148), and angiogenesis (decreased VEGF)
(149) as well as sensitize breast cancer cells to chemotherapeutic
drug treatments (150). Naviglio et al. showed that co-treatment
of triple negative breast cancer cells (MDA-MB-231 cells) with
leptin and a cAMP elevating agent (forskolin) decreased breast
cancer cell proliferation by inhibiting the activation of the ERK
signaling pathway (141), which is well-known to be over
active in breast cancer cells (151, 152). Interestingly, the authors
also showed that leptin enhanced the anti-proliferative effects
of cAMP elevating agents, by inducing both apoptosis and
cell cycle arrest (141). Additionally, Spina et al. showed that
an increase in cAMP levels inhibits leptin-induced migration
of breast cancer cells (MDA-MB-231) (153). Recently, Illiano
et al. demonstrated that forskolin treatment (cAMP elevating
agent) inhibited ERK1/2 activity via protein kinase A-mediated
inhibition, which induced apoptosis and increased the sensitivity
of breast cancer cells (MDA-MB-231 and MDA-MB-468) to
doxorubicin treatment (154). This finding is significant since,
doxorubicin treatment resistance in breast cancer cells involves
the activation of the RAS/RAF/ERK signaling pathway (152,
155). The anti-proliferative interaction between leptin and
cAMP elevating drugs might provide potentially new strategies
for therapeutic intervention in overweight/obese breast cancer
patients (since leptin levels are elevated in overweight/obese
patients), who are at risk/prone to develop treatment resistance.
However, treatment of breast cancer cells with cAMP elevating
agents under obesogenic conditions, is yet to be explored,
especially considering cAMP can stimulate lipolysis in adipose
tissue (156).

Additional growth factors secreted by adipocytes also
implicated in treatment resistance include IGF-1 and IGF-1R
(increased systemic bioavailability in adiposity and adipocytes
also secrete IGF-1). These growth factors are linked to

decreased apoptosis, increased cancer cell proliferation and pro-inflammatory mediator secretion which are directly associated with breast cancer risk and progression (157–160). Upregulation of IGF-1R was associated with poor disease prognosis and chemotherapy resistance through increased expression of MDR-1 and MDRP-1 affecting drug transportation and delivery in cancer cells (161).

Acquired resistance to doxorubicin and docetaxel in breast cancer cells was also attributed to the transfer of microRNA present in exosomes (nanovesicles which mediates cell-cell transfer of DNA, mRNA, microRNA, proteins and lipids) (162). Adipocyte derived exosomes has been associated with increased migration in breast cancer cells (163), immune cell recruitment of macrophages and chronic inflammation (164, 165). Resistance to paclitaxel in ovarian cancer cells was attributed to the transfer of microRNA (miR21) present in adipocyte derived exosomes (166, 167), which downregulated the expression of apoptotic protease activating factor-1, a key protein involved in apoptosis formation (166). In addition, adipocyte derived exosomes increased the invasion of melanoma cancer cells and induced metabolic reprogramming by transferring proteins (ECHA (subunit of mitochondrial trifunctional protein) and hydroxyacyl-coenzyme A dehydrogenase), involved in fatty acid oxidation to these cancer cells. In addition, these effects were found to be worsened by obese adipocytes (168). However, evidence on the role of adipocyte and/or obese adipocytes derived exosomes in treatment resistance on breast cancer cells are lacking and therefore motivates experimental models to investigate potential mechanisms and causal factors involved in acquiring doxorubicin treatment resistance.

**Drug metabolism mechanisms**

Adiposity alters chemotherapeutic pharmacokinetics by; (i) increasing drug distribution, (ii) altering drug clearance, and (iii) modifying the drug-protein binding process (169). For example, obesity increases the distribution volume of lipolytic drugs by increasing its accumulation in excess adipose tissue (169), thereby decreasing exposure of cancer cells to treatment agents. Behan et al. showed that excess adipose tissue could act as a "shelter" for protection against treatment toxicity, as cancer cells migrate into adipose tissue (123).

Obesity affects drug clearance via the liver, which primarily metabolizes, detoxifies and clears drugs from circulation (170). Hepatosteatosis decreases hepatic microcirculation, whereas the glomerular filtration and tubular secretion, and reabsorption in the kidneys, leads to increased drug clearance (117). Ghose et al. reported that mice fed a high fat diet, showed a decreased expression of key hepatic drug metabolizing enzymes (i.e.,

![Proposed effects of breast cancer cells on adipocytes and its role in treatment resistance. Breast cancer cells dysregulate metabolic pathways, by altering the secretion of adipokines from adipocytes which results in inflammation. This, could result in morphological and phenotypical changes (delipidation) and thereby increase the release of FFA. These FFA provide energy substrates for cancer cells to sustain its high proliferation demand, contributing to cancer treatment resistance.](frontiersin.org)
CYP3A11, CYP2B10 and CYP2A4), which could be the result of the high levels of pro-inflammatory mediators (IL-1β, IL-6 and TNF-α), increased phosphorylation of JNK and increased activation of NFκB (171). CYP34 activity, has also been found to be increased in a lepim knockout obesity model (172). In addition, the elimination, or the half-life of a drug may also be altered in obese individuals (173). Lastly, obesity is also associated with an increase in alpha-1 acid glycoprotein concentration, which could increase the binding of drugs in the plasma, thereby decreasing its bioavailability (174).

Furthermore, cytarabine, a treatment agent used in acute myeloid leukemia, is only toxic to cancer cells in its phosphorylated form (cytarabine triphosphate) (129). Cancer cells disrupt the phosphorylation reactions by altering the expression of enzymes involved in the metabolic activation of cytarabine i.e., aldo-keto reductase (AKR) and carbonyl reductase (CBR) (122). Sheng et al. showed that adipocytes metabolized daunorubicin (by increasing the expression of daunorubicin-metabolizing enzymes i.e., AKR-1C1, AKR-1C2, AKR-1C3 and CBR-1), which lead to the inactivation of daunorubicin and acquired resistance (175). This could implicate adipocytes/adipose tissue as a co-factor to decrease certain drug concentration in lipid-enriched tumor microenvironments (175). Evidence now also suggest that cancer cells “manipulate” adipocytes in the tumor microenvironment, in order to survive, but also alter drug pharmacokinetics and induce drug resistance by disrupting lipid storage and metabolism (13, 176).

Several mechanisms exist which can result in the modification of drug metabolism, drug transport and the failure of tumor cells to respond to chemotherapeutic drugs, due to overexpression of drug export proteins in cancer cells (169). It should be emphasized that limited evidence, investigating the role of overweight/obesity on pharmacokinetics of the majority of anti-cancer drugs in clinical trials, exists (170, 177). This is mainly attributed to participant inclusion criteria into phase I clinical trials and pharmacokinetic analyses, that exclude patients with co-morbidities, which is highly prevalent in overweight and obese cases (177).

**Adipocytes in the Tumor Microenvironment: Lipid-Related Mechanisms**

Breast cancer cells co-exist in a sophisticated microenvironment with various adjacent cell types including adipocytes, macrophages, fibroblast and endothelial cells (178). Evidence exist on the beneficial roles of fibroblasts, endothelial cells and macrophages in the tumor microenvironment (179–181). The exact role of adipocytes in the breast tumor microenvironment in treatment resistance remains unclear.

The presence of adipocytes in the tumor microenvironment revealed that breast tumors utilize adipocytes to function as a survival advantage to promote its survival, growth as well as proliferation and metastasis (13, 176). In addition, the presence of adipocytes in the tumor microenvironment also reduces the toxic effects of breast cancer treatment agents (18). For example, Trastuzumab® treatment (a monoclonal antibody targeting human epidermal growth factor-2) inhibited breast cancer cell growth in the absence of a lipoma. However, this inhibition was hindered in the presence of a lipoma suggesting that adipose tissue/adipocytes may have an impact on resistance to cancer therapy (176).

Adipocytes in the breast tumor microenvironment is characterized by both morphological and phenotypical changes. Histological analysis of human mammary tumor biopsies shows no, or very few adipocytes present (174), with characteristic smaller cell size (14). Adipocytes in the breast tumor microenvironment also display a more fibroblast like morphology known as cancer-associated adipocytes (127, 182). These phenotypical and morphological alterations induce functional changes in adipocytes to yield free fatty acids (FFA) from triglycerides (TG) stored in lipid droplets (Figure 2) (73). This is proposed to be as a result of tumor growth inducing lipolysis in adipocytes, which can result in adipose tissue mass reduction (183).

Previously it was shown that breast cancer cells induce lipolysis by increasing the expression of hormone sensitive lipase (HSL) and adipose triglyceride lipase enzymes in adipocytes (13). It is proposed that adipocyte-derived fatty acids are either used as metabolic substrates for energy (β-oxidation) (184), or stored in lipid droplets and/or membranes within tumors (185), to sustain survival. Fatty acids and its derivatives serve as building blocks for various membrane lipids (i.e., phospholipids and sterol esters) and signaling molecules, both implicated in carcinogenesis and treatment resistance (186–188).

Additional supporting evidence include breast cancer cells increasing exogenous fatty acid uptake and utilization (FFA derived from adipocytes), by altering the expression of various enzymes in fatty acid uptake (i.e., increased fatty acid binding protein-4 (FABP-4) and fatty acid translocase (CD36) expression) (189–191) and β-oxidation (i.e., increased carnitine palmitoyltransferase I expression) (13, 192, 193). In addition, “obese” adipocytes provided higher concentrations of FFA to breast cancer cells to sustain survival and migration (13), however treatment resistance was not assessed in this obese breast cancer model.

Furthermore, adipocytes also provide FFA to breast cancer cells by dedifferentiation and/or inhibition of adipogenesis (13) (Figure 2), evident by adipocytes showing decreased expression of adipogenic markers including peroxisome proliferator-activated receptor-γ (PPAR-γ), FABP-4 and cytosine-cytosine-adenosine-adenosine-thymidine (CCAA) enhancer binding protein-α (CEBP-α) (14). Breast cancer cells can also alter fatty acid metabolism by increasing de novo synthesis of fatty acids, by altering the expression of fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), and stearoyl-CoA-desaturase-1 (SCD-1) enzymes (194–198). The result of this alteration is lipid saturation of cancer cell membranes, which protects against the cytotoxic effects of chemotherapy and anti-cancer drugs (199). Increased FFA are also stored in tumors in the form of lipid droplets in order to avert lipotoxicity and/or to serve as an energy reserve (200). This is also supported by lipid depositions found in tumors (185), including breast tumors which is considered a characteristic of cancer aggressiveness (201).

It is proposed that the dysregulation of cytokines (increased IL-6, TNF-α and IL-1β), adipokines (increased leptin and
DOXORUBICIN TOXICITY ON ADIPOSE TISSUE/ADIPOCYTES

Doxorubicin treatment has been shown to negatively impact adipose tissue/adiocytes (26, 29), ranging from metabolic dysfunction to phenotypical changes (27, 106, 210–212), which contribute toward the disruption of adipose tissue homeostasis and lipid storage (Table 1).

The molecular mechanisms underlying doxorubicin’s negative effects on adipose tissue/adiocytes is proposed to involve adipokine dysregulation, which in turn affects factors regulating lipid metabolism pathways. For example, decreasing and/or inhibition of adipogenesis (decreased PPAR-γ and FABP expression) and lipogenesis (decreased FAS expression) as well as the induction of lipolysis (increased HSL expression) (27, 29) (Figure 3). This in turn induces an increase in FFA release as the result of the phenotypical changes (27, 29), thereby disrupting lipid storage. Doxorubicin induced metabolic dysfunction (increased FFA levels), could potentially increase the availability of energy substrates (FFA) for cancer cells to utilize to sustain both its survival and proliferation demands (26, 27, 29, 106), and thereby indirectly contribute to breast cancer treatment resistance itself. However, it should be stressed that evidence on the effects of doxorubicin on adipose tissue/adiocytes (Table 1) is based on normal functioning adipose tissue/adiocytes, and not on an obesity model, where adipose tissue is dysfunctional.

Evidence on the effects of doxorubicin on adipose tissue/adiocytes in the context of obesity, where adipose tissue is dysfunctional is lacking. In light of this, we proposed that doxorubicin treatment on dysfunctional adipose tissue and/or adiocytes, may further exacerbate the negative effects of obesity itself, toward cancer treatment by further dysregulating adipokines secretion, which in turn affects the factors regulates lipogenesis, adipogenesis and lipolysis, thereby further implicating obesity in the context of breast cancer treatment (Figure 3).

FUTURE RESEARCH AND CONCLUSION

Adipose tissue plays an important physiological role as a metabolically active storage compartment and endocrine organ. A disruption in adipose tissue homeostasis results in potentially serious health and clinical-related outcomes. Obesity induced adipose-dysfunction is associated with an increased risk for breast tumor development and progression.

Obesity is associated with chronic low grade inflammation as a result of adipokine secretion (immune cell infiltration), which results in a sustained inflammatory milieu. These inflammatory mediators activate downstream signaling pathways (MAPK and PI3K) in breast cancer cells that favors cancer cell survival (increased proliferation and decreased apoptosis), and contribute to breast cancer development and progression (Figure 3).

Recent evidence also implicate obesity as a causal factor for reduced chemotherapy efficacy, resulting in treatment resistance. Obesity-driven changes may contribute to chemotherapy
| Model | Findings | Proposed Mechanism | References |
|-------|----------|--------------------|------------|
| **In vivo**<br>Rat retroperitoneal adipose tissue<br>Doxorubicin: 15 mg/kg/body weight, 72 hours before sacrifice. | In vivo: Doxorubicin (10 and 100 nM) was toxic to adipocytes, thereby inducing over 90% cellular apoptosis. In vitro: Doxorubicin disrupted adipocyte homeostasis: ↓ lipogenesis, ↑ glucose uptake and ↑ lipolysis thereby increasing free fatty acids (FFA) availability. | Disrupt lipid-related pathways: The molecular mechanism by which doxorubicin exerts its toxic effects on adipose tissue was still unknown at this point and warranted further investigation. | (210) |
| **In vitro**<br>3T3-L1 cells (differentiated into mature adipocytes) | Doxorubicin was found to be a negative regulator of body weight as it resulted in a significant decrease in the body weight of animals on doxorubicin vs. untreated controls. The decrease in body weight was specifically due to a loss in adipose tissue. | Necrosis: Adipose tissue undergoes necrosis as a result of chemotherapy. However, there is very limited proposed molecular mechanisms by which doxorubicin exerts its effects on a molecular level and to what extent the damage is and is unclear if it is only due to necrosis or not. | (29) |
| **In vivo**<br>Male dawley Sprague rats<br>epididymal fat<br>Doxorubicin: 2.5 mg/kg/body weight, once a week for 4 weeks. | Both in vivo and in vitro models: doxorubicin treatment ↓ adipocyte size compared to controls. In vivo: doxorubicin treatment disrupted lipogenesis, i.e., ↓ fatty acid synthase (FAS) and Acetyl-CoA carboxylase (ACC) expression. In addition, primary adipocytes treated with doxorubicin showed a decrease in insulin-stimulated glucose uptake. | Phenotypical and metabolic dysfunction: This may have been the result of decreased expression of proteins regulating lipogenesis and therefore decreased lipid storage. | (27) |
| **In vitro**<br>Primary adipocytes isolated from retroperitoneal fat and 3T3-L1 cells (differentiated into mature adipocytes) | Doxorubicin treatment resulted in a significant ↓ in bodyweight and serum triglyceride (TG) concentration compared to saline treated mice. | Changes in body composition: Proposed by authors to be the underlying reason for cardio-dysfunction in this animal model. | (28) |
| **In vivo**<br>Mice<br>Doxorubicin: 8 mg/kg body weight, for 4 weeks. | A significant increase in fatty acid binding protein (FABP) concentration was observed in rats treated with doxorubicin compared to control animals, treated mice. | Disrupt lipid-related pathways: Doxorubicin treatment affects markers regulating adipogenesis. | (211) |
| **In vivo**<br>Male wistar albino rats<br>Doxorubicin: 2 mg/kg/body weight for 7 weeks. | Doxorubicin treatment resulted in the inhibition of adipogenesis i.e., ↓ expression of PPAR-α, and ↓ PPAR-γ and FABP-4 expression in a dose-dependent manner. Adipocytes which over expressed PPAR-γ and were treated with doxorubicin counter-acted all the above effects of doxorubicin. | Disrupt lipid-related pathways: Doxorubicin acts as an inhibitor of adipogenesis, by being an antagonist to PPAR-γ expression, which may ultimately lead to a lack of fat accumulation. | (26, 105) |
| **In vivo**<br>3T3-L1 cells (differentiated into mature adipocytes) | Doxorubicin treatment caused a significant ↓ epididymal adipose tissue weight and adiponectin an increase in serum insulin, glucose, FFA concentration levels compared to saline controls. Doxorubicin treatment caused a decreased HOMA-IR (measurement of insulin resistance) and glucose uptake vs. control animals, which is indicative of impaired insulin sensitivity, and these animals displayed insulin resistance, hyperglycaemia, and hyperinsulinemia. | Metabolic Dysfunction: These findings were the result of decreased expression of both AMPK and GLUT-4 in skeletal muscle, which was confirmed by the in vitro experiments. The authors concluded that doxorubicin treatment caused hyperglycaemia and insulin resistance, mediated by inhibition of AMPK. | (106) |
| **In vivo**<br>Male wistar rats treated with doxorubicin (15 mg/kg/body weight, 72 h before sacrifice). | Doxorubicin treatment caused a significant ↓ epididymal adipose tissue weight and adiponectin an increase in serum insulin, glucose, FFA concentration levels compared to saline controls. Doxorubicin treatment caused a decreased HOMA-IR (measurement of insulin resistance) and glucose uptake vs. control animals, which is indicative of impaired insulin sensitivity, and these animals displayed insulin resistance, hyperglycaemia, and hyperinsulinemia. | Metabolic Dysfunction: These findings were the result of decreased expression of both AMPK and GLUT-4 in skeletal muscle, which was confirmed by the in vitro experiments. The authors concluded that doxorubicin treatment caused hyperglycaemia and insulin resistance, mediated by inhibition of AMPK. | (106) |
| **In vivo**<br>T2DM mice model (db/db, leptin knockout) treated with doxorubicin (15 mg/kg/body weight, 5 days before sacrifice) | Doxorubicin treatment induced an inflammatory milieu in diabetic muscle by exacerbating a pro-inflammatory microenvironment (upregulating transcription factor HIF-1α, NFκB, and TNF-α) as well as decreasing anti-inflammatory actions (downregulating regulatory molecule AMPK and IL-15). Doxorubicin treatment induced a dysregulation in glycolytic metabolism in diabetic skeletal muscle by upregulating pyruvate dehydrogenase kinase-4 and lactate dehydrogenase and downregulating phosphorylation of ACC. | Metabolic Dysfunction: Results suggest that doxorubicin treatment in the context of diabetes may cause an environment, which can worsen diabetes related effects. | (212) |

ACC: Acetyl-CoA carboxylase; AMPK, AMP-activated protein kinase; FABP-4, fatty acid binding protein-4; FAS, fatty acid synthase; FFA, free fatty acids; GLUT-4, glucose transporter-4; HOMA-IR, homeostatic model assessment of insulin resistance; HIF-1α, hypoxia inducible factor-1α; IL-15, interleukin-15; NFκB, nuclear factor kappa B; PPAR-α, peroxisome proliferator-activated receptor-α; PPAR-γ, peroxisome proliferator-activated receptor-γ; TAGs, triglycerides; TNF-α, tumor necrosis factor-α; ↑, Increased; ↓, Decreased.
resistance by altering drug pharmacokinetics, impairing drug metabolism and delivery, and inducing chronic inflammation as well as altering tumor-associated adipocyte adipokine secretion. However, the exact underlying mechanisms by which obesity achieves this remains unclear.

It is suggested that adipose tissue/adipocytes, serve as a potential energy source for cancer cells to sustain their survival thereby promoting cell growth and proliferation (Figure 3). This is especially significant in the case of breast cancer; as adipose tissue is the most abundant tissue type in the breast. Breast cancer cells dysregulate lipid related metabolic pathways i.e., lipolysis, adipogenesis, de novo fatty acid synthesis and exogenous lipid uptake by altering the secretion of adipokines by adipocytes, which in turn results in the release of FFA (Figure 3). These fatty acids can then serve as energy substrates for breast cancer cells to sustain its high proliferation rates or can be stored in tumors in the form of lipid droplets and/or in membrane lipids in order to avoid lipotoxicity, which protects against the cytotoxic effects of anti-cancer drugs.

Additionally, doxorubicin treatment itself has also been shown to modify adipose tissue/adipocytes through inhibition of adipogenesis, downregulating lipogenesis, inducing lipolysis, and subsequently disrupting lipid storage. Resulting in phenotypical changes in adipocytes (Figure 3), which in turn produces more “bioavailable” energy substrates (increased FFA), which cancer cells can potentially utilize to sustain survival and proliferation demands and thereby could indirectly contribute to chemotherapeutic treatment resistance (Figure 3).

It should be stressed that studies investigating the effects of doxorubicin on adipose tissue/adipocytes and lipid metabolism in the context of obesity, where adipose tissue is dysfunctional are lacking. We thus propose that doxorubicin treatment in patients with dysfunctional adipose tissue and/or adipocytes, may further exacerbate the tumor promoting effects of obesity itself. This may be achieved by further dysregulating adipokine secretion, which in turn affects lipogenesis, adipogenesis and lipolysis, linking adiposity to breast cancer treatment resistance (Figure 3). It is thus of importance to investigate the effect of doxorubicin in the context of obesity, and how obesity may aggregate factors playing a role in the development of doxorubicin treatment resistance, as there is an increase in the prevalence of breast cancer patients who are either overweight or obese, treated with doxorubicin. Specifically, since, obese and normal weight patients receive the same treatment regimens. Therefore, extensive investigation is needed to elucidate the
underlying mechanism by which obesity contributes to treatment resistance.

The role of lipid metabolism in breast cancer also remains understudied as well as the cytotoxic effects of chemotherapeutic drugs on adipose tissue/adipocytes, both of which may contribute to the promotion of breast cancer cell survival and treatment resistance. Therefore, the identification of molecular mechanisms underlying both the effects of a neoplastic state and doxorubicin treatment on adipose tissue, will promote the identification of novel pharmacologic targets as well as the development of appropriate management protocols for adipose tissue driven chemotherapeutic drug resistance as well as doxorubicin related toxicities in order to improve overall survival of breast cancer patients.

AUTHOR CONTRIBUTIONS
IM wrote the first draft of the manuscript. TN, A-ME, and PVJ contributed to critical revision and intellectual input of the manuscript. All authors read and approved the final manuscript.

FUNDING
Work in this laboratory is supported by research grants from the Cancer Association of South Africa (Cansa), the South African Medical Research Council (SAMRC) and the National Research Foundation (NRF) of South Africa. Funding bodies had no role in the preparation of this manuscript.

REFERENCES
1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. (2018) 68:394–424. doi: 10.3322/caac.21492
2. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: Sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer (2015) 136:E359–386. doi: 10.1002/jic.29210
3. Nagrani R, Mhatre S, Rajaraman P, Soerjomataram I, Boffetta P, Gupta S, et al. Central obesity increases risk of breast cancer irrespective of menopausal and hormonal receptor status in women of South Asian ethnicity. Eur J Cancer (2016) 66:153–161. doi: 10.1016/j.ejca.2016.07.022
4. Ng M, Fleming T, Robinson M, Thomson B, Graetz N, Margono C, et al. Global, regional and national prevalence of overweight and obesity in children and adults 1980–2013: A systematic analysis. Lancet (2014) 384:766–81. doi: 10.1016/S0140-6736(14)60460-8
5. Sparano JA, Wang M, Zhao F, Stearns V, Martino S, Ligibel JA, et al. Obesity at diagnosis is associated with inferior outcomes in hormone receptor-positive operable breast cancer. Cancer (2012) 118:9397–46. doi: 10.1002/cncr.27527
6. Rezaee F, Dashzy S. Role of adipose tissue in metabolic system disorders: adipose tissue is the initiator of Metabolic diseases. J Diabetes Meta (2013) 5:13:008. doi: 10.4172/2155-6156.S13-008
7. Cowen S, McLaughlin S, Hobbs G, Coad J, Martin KH, Olfert IM, et al. Evidence for a tumor promoting effect of high-fat diet independent of insulin resistance in HER2/Neu mammary carcinogenesis. Breast Cancer Res Treat. (2010) 122:647–59. doi: 10.1007/s10549-009-0386-8
8. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose tissue remodeling: its role in energy metabolism and metabolic disorders. Front Endocrinol. (2016) 7:30. doi: 10.3389/fendo.2016.00030
9. Calle EE, Kaaks R. Overweight, obesity and cancer: epidemiological evidence and proposed mechanisms. Nat Rev Cancer (2004) 4:579–91. doi: 10.1038/nrc1408
10. Toren P, Mora BC, Venkateswaran V. Diet, obesity, and cancer progression: are adipocytes the link. Lipid Insights (2013) 6:37–45. doi: 10.4137/LPSI00871
11. Mahon KL, Lin H-M, Castillo L, Lee BY, Lee-Ng M, Chatfield MD, et al. Cytokine profiling of docetaxel-resistant castration-resistant prostate cancer. Br J Cancer (2015) 112:1340–8. doi: 10.1038/bjc.2015.74
12. Balaban S, Shearer RE, Lee LS, van Geldermalsen M, Schreuder M, Shein HC, et al. Adipocyte lipolysis links obesity to breast cancer growth: adipocyte-derived fatty acids drive breast cancer cell proliferation and migration. Cancer Metab. (2017) 5:1. doi: 10.1186/s40470-016-0163-7
13. Dirat B, Bochet L, Dabeck M, Daviaud D, Dauvillier S, Majed B, et al. Cancer-associated adipocytes exhibit an activated phenotype and contribute to breast cancer invasion. Cancer Res. (2011) 71:2455–65. doi: 10.1158/0008-5472.CAN-10-3233
14. Liu E, Sanad F, Mueller BM. Local adipocytes enable estrogen-dependent breast cancer growth: role of leptin and aromatase. Adipocyte (2013) 2:165–9. doi: 10.4161/adip.23645
15. Bousquenau M, Fico F, Solinas G, Rüegg C, Santamaria-Martínez A. Obesity promotes the expansion of metastasis-initiating cells in breast cancer. Breast Cancer Res. (2018) 20:104. doi: 10.1186/s13058-018-1029-4
16. Dong L, Yuan Y, Opsansky C, Chen Y, Aguiler a-Barrantes I, Wu S, et al. Diet-induced obesity links to ER positive breast cancer progression via LPA/PKD-1-CD36 signaling-mediated microvascular remodeling. Oncotarget (2017) 8:22550–62. doi: 10.18632/oncotarget.15123
17. Dong L, Yuan Y, Opsansky C, Chen Y, Aguiler a-Barrantes I, Wu S, et al. Diet-induced obesity links to ER positive breast cancer progression via LPA/PKD-1-CD36 signaling-mediated microvascular remodeling. Oncotarget (2017) 8:22550–62. doi: 10.18632/oncotarget.15123
18. Incio J, Ligibel JA, McManus DT, Suboj P, Jung K, Kawaguchi K, et al. Obesity promotes resistance to anti-VEGF therapy in breast cancer by up-regulating IL-6 and potentially FGF-2. Sci Transl Med. (2018) 10:eaag0945. doi: 10.1126/scitranslmed.aag0945
19. Iwase T, Sangai T, Nagashima T, Sakakibara M, Sakakibara J, Hayama S, et al. Impact of body fat distribution on neoadjuvant chemotherapy outcomes in advanced breast cancer patients. Cancer Med. (2016) 5:41–48. doi: 10.1002/cam4.571
20. Hydock DS, Lien CT, Jensen BT, Schneider CM, Hayward R. Switching to a low-fat diet attenuates the intensified doxorubicin cardiotoxicity associated with high-fat feeding. Cancer Chemother Pharmacol. (2013) 71:1551–60. doi: 10.1007/s00028-013-2154-5
21. Sirin O, Kolonin MG. Treatment of obesity as a potential complementary approach to cancer therapy. Drug Discov Today (2013) 18:567–73. doi: 10.1016/j.drudis.2012.05.008
22. Gevorgyan A, Bregni G, Galli G, Ganzinelli M, Martinetti A, Lo Vullo S, et al. Body mass index and clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer. Tumori (2016) 102:11–4. doi: 10.5301/t.5000515
23. Karpinska A, Safarow K, Kladny J, Sulzyc-Bielicka V. The influence of obesity on results of AT (doxorubicin plus doxetacel) neoadjuvant chemotherapy in locally advanced breast cancer patients. Pol Przegl Chir. (2013) 85:237–8. doi: 10.1126/scitranslmed.aag0945
24. Guenancia C, Ladoire S, Ghiringelli F, Rochette L, Vergely C, Cottin Y. Implications of excess weight in the cardiotoxicity of anthracyclines and trastuzumab in breast cancer. Arch Cardiovasc Dis. (2017) 110:69–71. doi: 10.1016/j.acvd.2016.12.004
25. Liu Z, Shi A, Song D, Han B, Zhang Z, Ma L, et al. Resistin confers resistance to doxorubicin-induced apoptosis in human breast cancer cells through autophagy induction. Am J Cancer Res. (2017) 7:574–83. eCollection 2017.
26. Arunachalam S, Kim SY, Kim MS, Vi HK, Yun BS, Lee DY, et al. Adriamycin inhibits adipogenesis through the modulation of PPARy and restoration of...
adriamycin-mediated inhibition of adiogenesis by PPARy over-expression. *Toxicol Mech Methods* (2012) 22:540–6. doi: 10.3109/13573651.2012.692110

27. Bonnito LA, Lima Junior EA, Souza CO, Cruz MM, Cunha R, Alonso-Vale MI, et al. Impact of doxorubicin treatment on the physiological functions of white adipose tissue. *PLoS ONE* (2016) 11:e015148. doi: 10.1371/journal.pone.015148

28. Nagendran J, Kienesberger PC, Pulnilkunnil T, Zordoky BN, Sung MM, Kim T, et al. Cardiomyocyte specific adipose triglyceride lipase overexpression prevents doxorubicin induced cardiac dysfunction in female mice. *Heart* (2013) 99:1041–7. doi: 10.1136/heartjnl-2013-303843

29. Xiang P, Deng HY, Li K, Huang GY, Chen Y, Tu L, et al. Dexrazoxane prevents doxorubicin-induced cardiac myopathy: upregulation of Akt and Erk phosphorylation in a rat model. *Cancer Chemother Pharmacol.* (2009) 63:343–9. doi: 10.1007/s00280-008-0744-4

30. Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. *Global Cancer Statistics, 2012.* CA Cancer J Clin. (2015) 65:87–108. doi: 10.3322/caac.21262

31. Moodley J, Cairncross L, Naiker T, Monberg M. Understanding pathways to breast cancer diagnosis among women in the Western Cape Province, South Africa: a qualitative study. *BMJ Open* (2016) 6:e009905. doi: 10.1136/bmjopen-2015-009905

32. Biondo LA, Lima Junior EA, Souza CO, Cruz MM, Cunha R, Alonso-Vale MI, et al. Doxorubicin-induced effects on adipose tissue and metabolic syndrome. *Mediators Inflamm.* (2013) 2013:136584. doi: 10.1155/2013/136584

33. Ghoncheh M, Momenimovahed Z, Salehiniya H. Epidemiology, incidence and cancer risk of chronic state of inflammation as mediators that link obese adipose tissue and metabolic syndrome. *Diabetol Metab Syndr.* (2011) 3:12. doi: 10.1186/2046-3347-3-12

34. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and breast cancer risk. *Diabetes* (2015) 64:645–57. doi: 10.1111/dia.12700

35. Divella R, De Luca R, Abbate I, Naglieri E, Daniele A. *Obesity and cancer at major anatomical sites: umbrella review of the literature.* BMJ (2017) 356:j4777. doi: 10.1136/bmj.j4777

36. Sun X, Nichols HB, Robinson W, Sherman ME, Olshan AF, Troester MA. Post-diagnosis adiposity and survival among breast cancer patients: influence of breast cancer subtype. *Cancer Causes Control.* (2015) 26:1803–11. doi: 10.1007/s10552-015-0673-6

37. Zhu QL, Xu WH, Tao MH. Biomarkers of the metabolic syndrome and breast cancer. *Cancers* (2016) 8. doi: 10.3390/cancers8010017

38. Diabetol Metab Syndr.* (2013) 17:47–52. doi: 10.7314/APJCP.2016.17.53.47

39. Donohoe CL, Doyle SL, Reynolds JV. Visceral adiposity, insulin resistance and breast cancer risk. *Diabetol Metab Syndr.* (2011) 3:12. doi: 10.1186/1758-5996-3-12

40. O’Neill S, O’Driscoll L. Metabolic syndrome: a closer look at the pathophysiology of metabolic syndrome. *Clin Lab Sci.* (2010) 23:51–61; quiz 2010:25–115. doi: 10.1016/j.jcy.2010.07.031

41. Mendonça FM, de Sousa FR, Barbosa AL, Martins SC, Araújo RL, Soares R, et al. Effect of Obesity on Prognosis after early-stage breast cancer. *Best Pract Res Clin Endocrinol Metab.* (2013) 27:163–77. doi: 10.1016/j.beem.2013.02.005

42. Cefalu WT. Inflammation, insulin resistance, and type 2 diabetes: back to the future? *Diabetes* (2009) 58:3077–8. doi: 10.2337/db08-1656

43. Friedrich N, Thüeser R, Jorgensen T, Juul A, Spillichagen C, Wallaschofski H, et al. The association between IGF-I and insulin resistance: a general population study in Danish adults. *Diabetes Care* (2012) 35:768–73. doi: 10.2337/dc11-1833

44. Blüher M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. *Best Pract Res Clin Endocrinol Metab.* (2013) 27:163–77. doi: 10.1016/j.beem.2013.02.005

45. Ewertz M, Jensen M-B, Gunnarsdóttir KÁ, Højris I, Jakobsen E H, Nielsen MA, et al. Adipokines and cytokines in obesity-associated breast cancer: therapeutic targets. *Cytokine Growth Factor Rev.* (2013) 24:503–13. doi: 10.1016/j.cytogfr.2013.10.001

46. Murray PJ. The JAK-STAT signaling pathway: input and output integration. *Immunity* (2007) 178:2623–9. doi: 10.1016/j.immuni.2007.5.2623
68. Balistreri CR, Caruso C, Candore G. The role of adipose tissue and adipokines in obesity-related inflammatory diseases. *Mediators Inflamm.* (2010) 2010:802078. doi: 10.1155/2010/802078

69. Landskron G, De la Fuente M, Thuwajit P, Thuwajit C, Hermoso MA, et al. Chronic inflammation and cytokines in the tumor microenvironment. *J Immunol. Res.* (2014) 2014:149185. doi: 10.1155/2014/149185

70. Guo D, Bell EH, Mischel P, Chakravarti A. Targeting SREBP-1-driven lipid metabolism to treat cancer. *Curr Pharm Des.* (2014) 20: 2619–26. doi: 10.2174/1381612181319990486

71. Gupta S, Roy A, Dwarakanath BS. Metabolic cooperation and competition in the tumor microenvironment: implications for therapy. *Front Oncol.* (2017) 7:68. doi: 10.3389/fonc.2017.00668

72. Vayse C, Lemo J, Garred Ø, Fjeldheim F, Løfteroed T, Schlichting E, et al. Inflammation of mammary adipose tissue occurs in overweight and obese patients exhibiting early-stage breast cancer. *NPJ Breast Cancer* (2017) 3:35. doi: 10.1038/s41523-017-0030-x

73. Choi J, Cha YJ, Koo JS. Adipocyte biology in breast cancer: from silent bystander to active facilitator. *Prog Lipid Res.* (2018) 69:11–20. doi: 10.1016/j.plipres.2017.11.002

74. Surmacz E. Leptin and adiponectin: emerging therapeutic targets in breast cancer. *J Mammary Gland Biol Neoplasia* (2013) 18:321–32. doi: 10.1007/s10911-013-9302-8

75. Rodriguez AJ, Mastronardi C, Paz-Filho G. Leptin as a risk factor for the development of colorectal cancer. *Trans Gastroint Cancer* (2013) 2:211–22. doi: 10.3978/j.issn.2224-4778.2013.10.04

76. Aleksandrova K, Boening H, Jenab M, Bueno-de-Mesquita HB, Jansen A, et al. Decreased levels of plasma adiponectin associated with increased risk of colorectal cancer. *Nutr Cancer* (2010) 621:51–58. doi: 10.1080/00071145.2017.1293339

77. Sultana R, Kataki AC, Borthakur BB, Basumatary TK, Bose S, et al. Chronic inflammation and cytokines in the tumor microenvironment. *Front Oncol.* (2017) 621:51–58. doi: 10.1016/j.gene.2017.04.021

78. Otake S, Takeda H, Fujishima S, Fukui T, Orii T, Sato T, et al. Chronic inflammation in the tumor microenvironment: implications for therapy. *Front Oncol.* (2017) 7:68. doi: 10.3389/fonc.2017.00668

79. Rausch LS, Netzter NC, Hoegel J, Pramsohler S. The linkage between breast cancer, hypoxia, and adipose tissue. *Front Oncol.* (2017) 7:211. doi: 10.3389/fonc.2017.00211

80. Wang X, Simpson ER, Brown KA. p53: protection against tumor growth beyond effects on cell cycle and apoptosis. *Cancer Res.* (2015) 75:9501–7. doi: 10.1158/0008-5472.CAN-15-0563

81. Komarov P. Hypoxia and adipose tissue function and dysfunction in obesity. *Phys Rev. (2013)* 93:1–21. doi: 10.1152/physrevs.00017.2012

82. Rausch LS, Netzter NC, Hoegel J, Pramsohler S. The linkage between breast cancer, hypoxia, and adipose tissue. *Front Oncol.* (2017) 7:211. doi: 10.3389/fonc.2017.00211

83. Xie G, Yao Q, Liu Y, Du S, Liu A, Guo Z, et al. IL-6-induced epithelial-mesenchymal transition promotes the generation of breast cancer stem-like cells analogous to mammosphere cultures. *Int J Oncol.* (2012) 40:1171–9. doi: 10.3892/ijo.2012.1275

84. Chen H, Ding A, Wang M. Impact of central obesity on prognostic outcomes of triple negative breast cancer in Chinese women. *Springer Plus* (2016) 5:594. doi: 10.1186/s40064-016-2200-y

85. Pierobon M, Frankenfield CL. Obesity as a risk factor for triple-negative breast cancers: a systematic review and meta-analysis. *Breast Cancer Res Treat.* (2013) 137:307–314. doi: 10.1007/s10549-012-2339-3

86. Kabel AM, Baal FF. Breast cancer: insights into risk factors, pathogenesis, diagnosis and management. *J Can Res Treat.* (2015) 3:28–33. doi: 10.12691/jcrt-3-2-3

87. Matsen CB, Neumayer LA. Breast Cancer. *JAMA Surg.* (2013) 148:971–9. doi: 10.1001/jamasurg.2013.3393

88. Meredith AM, Dass CR. Increasing role of the cancer chemotherapeutic doxorubicin in cellular metabolism. *J Pharm Pharmacol.* (2016) 68:729–41. doi: 10.1111/jphp.12539

89. Rivankar S. An overview of doxorubicin formulations in cancer therapy. *J Cancer Res Ther.* (2014) 10:853–8. doi: 10.4103/0973-1482.139267

90. Thorn CF, Oshiro C, Marsh S, Hernandez-Bousard T, McLeod H, Klein TE, et al. Doxorubicin pathways: pharmacodynamics and adverse effects. *Pharmacogenet Genomics* (2011) 21:440–6. doi: 10.1097/PGX.0b0133a80037f6236

91. Anampa J, Makower D, Sparano JA. Progress in adjuvant chemotherapy for breast cancer: an overview. *BMC Med.* (2015) 13:195. doi: 10.1186/s12916-015-0439-8

92. Arunachalam S, Tirupathi Pichia PB, Achiraman S. Doxorubicin treatment inhibits PPARγ and may induce lipotoxicity by mimicking a type 2 diabetes-like condition in rodent models. *FEBS Lett.* (2013) 587:105–10. doi: 10.1016/j.febslet.2012.11.019

93. de Lima Junior EA, Yamashita AS, Pimentel GD, De Sousa LG, Santos RV, Gonçalves CL, et al. Doxorubicin caused severe hyperglycaemia and insulin resistance, mediated by inhibition in AMPK signalling in skeletal muscle. *J Cachexia Sarcopenia Muscle* (2016) 7:615–25. doi: 10.1002/jcsm.12104

94. Thivat E, Thérondel S, Lapirot O, Abrial C, Gimbergues P, Gadéa E, et al. Weight change during chemotherapy changes the prognosis in non metastatic breast cancer for the worse. *BMC Cancer* (2010) 10:648. doi: 10.1186/1471-2407-10-648

95. de Vissers KE, Jonkers J. Towards understanding the role of cancer-associated inflammation in chemoresistance. *Curr Pharm Des.* (2009) 15:1844–53. doi: 10.2174/13816120978453239
110. Xu F, Wang F, Yang T, Sheng Y, Zhong T, Chen Y, et al. Differential drug resistance acquisition to doxorubicin and paclitaxel in breast cancer cells. Can Cell Int. (2014) 14:538. doi: 10.1186/s12955-014-0142-4

111. Guiz B, Petit JM, Bonnetain F, Ladoire S, Guiz S, Cercueil JP, et al. Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. Gut (2010) 59:341–7. doi: 10.1136/gut.2009.188946

112. Lashinger LM, Rossi EL, Hursting SD. Obesity and resistance to cancer chemotherapy: interacting roles of inflammation and metabolic dysregulation. Clin Pharmacol Ther. (2014) 96:458–63. doi: 10.1038/clpt.2014.136

113. Thomas AP, Hoang J, Vongbunyong K, Nguyen A, Rakshit K, Matveyenko AV. Administration of melatonin and metformin prevents deleterious effects of circadian disruption and obesity in male rats. Endocrinology (2016) 157:4720–31. doi: 10.1210/endo.2016-1309

114. De Azambuja E, McCaskill-Stevens W, Francis P, Quinones E, Crown JP, et al. The impact of obesity on cancer: a retrospective review. Ann Surg Oncol. (2012) 19:3012–8. doi: 10.1245/s10434-012-2220-8

115. Bochet L, Meulle A, Imbert S, Salles B, Valet P, Muller C. Cancer-associated adipocytes promote breast tumor radioreistance. Biochim Biophys Res Commun. (2011) 411:102–6. doi: 10.1016/j.bbrc.2011.06.101

116. Lyman GH, Sparreboom A. Chemotherapy dosing in overweight and obese patients with cancer. Nat Rev Clin Oncol. (2013) 10:451–9. doi: 10.1038/rcnoc1013.108

117. Ritzmo C, Söderhäll S, Karlén J, Nygren H, Eksborg S. Pharmacokinetics of bevacizumab-based treatment in metastatic colorectal cancer. Can Cell Int. (2013) 3:135–41. doi: 10.4239/wjd.v3.i7.135

118. Fuentes-Mattei E. Obesity and cancer: jet fuel accelerating cancer hallmarks and increasing the economic burden of cancer. Adv Obes Weight Manag. (2017) 3:106–19. doi: 10.1016/j.wom.2017.10.010

119. Schweizer R, Tsiip W, Gorantla VS, Marra KG, Rubin JP, Plock JA. The role of adipose-derived stem cells in breast cancer progression and metastasis. Stem Cells Int. (2015) 2015:120949. doi: 10.1155/2015/120949

120. Zheng Q, Banaszk A, Fracci S, Basali D, Dunlap SM, Hursting SD, et al. Leptin receptor maintains cancer stem-like properties in triple negative breast cancer cells. Endocr Relat Cancer (2016) 20:797–808. doi: 10.1530/ERC-13-0329

121. Candelaria PV, Rampoldi A, Harbuzariu A, Gonzalez-Perez RR. Leptin signaling and cancer chemoresistance: perspectives. World J Clin Oncol. (2017) 8:106–19. doi: 10.5306/wjco.v8i2.106

122. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The role of cAMP in resistance of breast cells to apoptosis of MDA-MB-231 breast cancer cells. Front Biosci. (2013) 4:28. doi: 10.3389/fphar.2013.00028

123. Naviglio S, Caraglia M, Abbruzzese A, Chiosi E, Di Gesto D, Mari D, et al. Protein kinase A as a biological target in cancer therapy. Expert Opin Ther Targets (2009) 13:83–92. doi: 10.1517/14728220820602349

124. Bahreyni A, Samani SS, Rahman F, Behnam-Rassouli R, Khazaei M, Ryzhikov M, et al. Role of adenosine signaling in the pathogenesis of breast cancer. J Cell Physiol. (2018) 233:1836–43. doi: 10.1002/jcp.25944

125. Nvasani E, Munir I, Perez M, Payne K, Khan S. Linking obesity-induced leptin-signaling pathways to common endocrine-related cancers in women. Endocrine (2018). doi: 10.1007/s12020-018-1748-4. [Epub ahead of print].

126. Vitale G, Dicitore A, Mari D, Cavagnini F. A new therapeutic strategy against cancer: cAMP elevating drugs and leptin. Cancer Biol Ther. (2010) 9:750–7. doi: 10.4161/cbt.8.12.8937

127. Oerlecke I, Bauer E, Dittmer A, Leyh B, Dittmer J. Cyclic AMP analogs inhibit TGF beta1-induced cell proliferation and subsequent cell migration. FEBS Lett. (2007) 569:105–11. doi: 10.1016/j.febslet.2004.05.097

128. Och-Balcom HM, Marian C, Nie J, Brasky TM, Goerlitz DS, Terris M, et al. Role of drug transporters and drug accumulation in the temporal acquisition of drug resistance. BMC Cancer (2008) 8:318. doi: 10.1186/1471-2407-8-318

129. Oerlecke I, Bauer E, Dittmer A, Leyh B, Dittmer J. Cyclic AMP enhances TGFβ1 responses of breast cancer cells by upregulating TGFβ1 receptor expression. J Cell Physiol. (2013) 228:569–77. doi: 10.1002/jcp.23461

130. Del Valle-Pérez B, Martínez-Estrada OM, Vilaró S, Ventura F, Viríals F. CAMP inhibits beta1-induced in vitro angiogenesis. FEBS Lett. (2004) 569:105–11. doi: 10.1016/j.febslet.2004.05.058
We have been able to analyze the data and come to some conclusions. The data suggests that the prevalence of obesity is on the rise, and this trend is likely to continue. Furthermore, obesity is associated with a number of health problems, including type 2 diabetes, cardiovascular disease, and certain types of cancer.

One of the main ways that obesity affects health is through its impact on insulin resistance. Insulin resistance is a condition in which the body becomes resistant to the effects of insulin, and it is a key factor in the development of type 2 diabetes and cardiovascular disease.

Another important factor in the relationship between obesity and health is the role of adipose tissue. Adipose tissue is the body's primary site of fat storage, and it also plays an important role in regulating energy metabolism and inflammation. In obesity, the number of adipose tissue cells increases, leading to a state of chronic inflammation.

In conclusion, obesity is a growing problem, and its impact on health is significant. Further research is needed to better understand the mechanisms behind obesity and to develop effective interventions to prevent and treat it.
its clinical implications. *Tumour Biol.* (2017) 39:1010428317699133. doi: 10.1177/1010428317699133

188. Rysman E, Brusselmans K, Scheys K, Timmermans L, Derua R, Munck S, et al. *De novo* lipogenesis protects cancer cells from free radicals and chemotherapeutics by promoting membrane lipid saturation. *Cancer Res.* (2010) 70:8117–26. doi: 10.1158/0008-5472.CAN-09-3871

189. Guaita-Esteruelas S, Bosquet A, Saavedra P, Gumà J, Girona J, Lam EW, et al. Exogenous FA-BP4 increases breast cancer cell proliferation and activates the expression of fatty acid transport proteins. *Mol Cancerog.* (2017) 56:208–17. doi: 10.1002/mc.22485

190. Nath A, Li I, Roberts LR, Chan C. Elevated free fatty acid uptake via CD36 promotes epithelial-mesenchymal transition in hepatocellular carcinoma. *Sci Rep.* (2015) 5:14752. doi: 10.1038/srep14752

191. Nieman KM, Kenny HA, Penicka CV, Ladanyi A, Buell-Guthrood R, Zillhardt MR, et al. Adipocytes promote ovarian cancer metastasis and provide energy or rapid tumor growth. *Nat Med.* (2011) 17:1498–503. doi: 10.1038/nm.2492

192. Luo X, Cheng C, Tan Z, Li N, Tang M, Yang L, et al. Emerging roles of lipid metabolism in cancer metastasis. *Molecular Cancer* (2017) 16:76. doi: 10.1186/s12943-017-0646-3

193. Wang T, Fahrmann JF, Lee H, Li YJ, Tripathi SC, Yue C, et al. Autocrine production of interleukin 6 causes multidrug resistance in breast cancer cells. *Cancer Res.*, (2001) 61:8851–8.

194. Shi Z, Yang WM, Chen LP, Yang DH, Zhou Q, Zhu J, et al. Enhanced chemosensitization in multidrug-resistant human breast cancer cells by inhibition of IL-6 and IL-8 production. *Breast Cancer Res Treat.* (2012) 135:737–47. doi: 10.1007/s10549-012-1916-0

195. Nagarseth N, Wicha MS, Zou W. Chemokines in the cancer microenvironment and their relevance in cancer immunotherapy. *Nat Rev Immunol.* (2017) 17:559–572. doi: 10.1038/tnri.2017.49

196. Conze D, Weiss L, Regen PS, Bhushan A, Weaver D, Johnson P, et al. Autocrine signalling in breast cancer cells. *Oncogene* (2017) 36:2105–15. doi: 10.1080/02612105.2017.5864

197. Veigel D, Wagner R, Stübiger G, Wuczkowski M, Filipits M, Horvat R, et al. Fatty acid synthase is a marker of cell proliferation rather than malignancy in ovarian cancer and its precursor cells. *Int J Cancer* (2015) 136:2078–90. doi: 10.1002/ijc.29261

198. Yoon S, Lee MY, Park SW, Moon JS, Koh YK, Ahn YH, et al. Up-regulation of acetyl-CoA carboxylase alpha and fatty acid synthase by human epidermal growth factor receptor 2 at the translational level in breast cancer cells. *J Biol Chem.* (2007) 282:26122–31. doi: 10.1074/jbc.M702854200

199. Zhao J, Zhi Z, Wang C, Xing H, Song G, Yu X, et al. Exogenous lipids promote the growth of breast cancer cells via CD36. *Oncol Rep.* (2017) 38:2105–15. doi: 10.3829/ore.2017.5864

200. Beloribi-Djefallah S, Vasseur S, Guillaumond F. Lipid metabolic reprogramming in cancer cells. *Oncogenesis* (2016) 5:e189. doi: 10.1080/20493002.2015.10549

201. Scalì-Hopp C, Udart M, Hauser C, Rück A. Investigation of lipid bodies in a colon carcinoma cell line by confocal Raman microscopy. *Med Laser Appl.* (2011) 26:152–7. doi: 10.1016/j mjla.2011.08.002

202. de Gonzalez-Calvo D, López-Viláro L, Nasarre L, Perez-Olabarri M, Vázquez T, Escuin D, et al. Intratumor cholesterol ester accumulation is associated with human breast cancer proliferation and aggressive potential: a molecular and clinicopathological study. *BMC Cancer* (2015) 15:460. doi: 10.1186/s12885-015-1469-5