

Review Article

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Role of Obesity-induced Inflammatory Cytokines on Breast and Thyroid Cancer Therapeutics: A Literature Review

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Abstract

Background: As reported by the Centers for Disease Control and Prevention, cancer is the second leading cause of death in the United States. Several factors are known to be related to causing cancer, obesity is one of them. Currently, the World Health Organization is considering obesity as a “global pandemic”. In the United States, more than 36% of adults are obese. Among them, women are more susceptible to severe obesity (11.5%) compared to men (6.9%). Obesity and overweight have long been associated with several chronic diseases including cancer. According to the International Agency for Research on Cancer, there is substantial evidence that obesity is associated with cancers in 13 anatomical sites such as the endometrium, kidney, gastric, cardiac, colon, rectum, biliary tract, pancreas, breast, esophagus, ovary, thyroid, liver, and meninges. In both men and women, a strong correlation between hormones and obesity-induced inflammatory cytokines is evident in cancer development. Recent studies show that several mechanisms can play a role in obesity-related endocrine cancers, such as alteration of inflammatory, immunological, and metabolic functions, defects in DNA repair, and alteration in gene function. However, a comprehensive picture to show the relationship between obesity-induced inflammatory markers in breast and thyroid cancer is lacking. This review aims to illustrate the link between obesity-induced inflammatory cytokines as well as the occurrence of breast and thyroid cancer and the role of metformin and chemotherapy in the treatment of these cancers.

We provide studies on the expression of novel inflammatory markers that may furnish essential clues for the detection, prognosis, prevention, and therapeutic implications of obesity-linked cancers.

Keywords: Obesity, Inflammatory cytokines, Leptin, Adipokines, Breast Cancer, Thyroid cancer

Abbreviations: IARC: International agency for Research on Cancer; BMI: Body Mass Index; TNF: Tumor necrosis factor; ER: Estrogen receptor; PR: Progesterone receptor; HER2: Human Epidermal Growth Factor Receptor 2; TNBC: Triple Negative Breast Cancer; IBC: Inflammatory Breast Cancer; SHBG: Sex Hormone Binding Globulin; IGF: Insulin-like Growth Factor; MCP: Monocyte Chemoattractant Protein; LEPR: Leptin Receptor Gene; mTOR: Mechanistic Target of Rapamycin; CLS: Crown-like Structure; FFA: Free Fatty Acid; TLR: Toll-like Receptor; SAPRC: Secreted Protein Acidic and Rich in Cysteine; SFRP5: Secreted Frizzled-related Protein 5; CTRPs: C1q/TNF-related Protein; IR: Insulin Resistance; DTC:

Differentiated Thyroid Cancer; JAK2: Janus Activated Kinase 2; STAT3: Signal Transducer and Activator of Transcription 3; ERK: Extracellular Signal-regulated Kinase; PIP3: Inositol-triphosphate 3; PTC: Papillary Thyroid Cancer; AMPK: Adenosine-Monophosphate Activated Protein Kinase; PPAR: Peroxisome Proliferator-Activated Receptor; PGC: Proliferator-Activated Receptor-Gamma Coactivator; NFkB: Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells

Introduction

Cancer is a common cause of death, especially in developed countries. In 2020, there will be an estimated 1.8 million new cancer cases diagnosed and 606,520 cancer deaths in the United States [1]. Several modifiable factors increase the risk of cancer such as obesity, using tobacco and alcohol [2,3]. Among them, obesity has become a devastating health burden over the decades. The number of obese and overweight people has increased significantly both in developing and developed countries. In the recent years, 60-70% of the adult populations in developed countries are obese, and the prevalence is more common in women [4]. According to WHO, in 2016, 39% of the world's adult population were overweight (39% of men and 40% of women), and 13% were obese (11% of men and 15% of women) [5]. In the United States, 38% of adults are obese (BMI) >30 kg/m², and nearly 8% are extremely obese, with a BMI >40 kg/m². Epidemiological data is supporting the part of adiposity/obesity in the carcinogenesis of breast, and thyroid cancer, and studies established the association between these cancers and obesity.

The association of obesity and overweight with postmenopausal breast cancer has been established for a long time [6]. According to some studies, a relationship between breast cancer risk and enhanced BMI has been demonstrated, particularly in premenopausal females, even though some studies did not find such a relationship [7]. Several epidemiological studies have also demonstrated a significant association between obesity and thyroid cancer. Likewise, American Cancer Society shows breast and thyroid cancers as only probably being associated with obesity and overweight.

Obesity increases the risk of cancers by the expansion of adipose tissues. Adipose tissue expansion is associated with infiltration of immune cells such as T-cells, and macrophages with pro-inflammatory phenotypes. These adipocytes and immune cells cause secretion of adipokines, chemokines, cytokines like IL-1,2,6,8, TNF- α etc. lipid with proinflammatory character. Thus, the fat cell is now considered an endocrine tissue and fatty acid an inflammatory mediator. The pathophysiology of obesity involves different changes that may contribute to the development of cancer, such as an excess inflammatory cytokines and chronic inflammation, hyperinsulinemia,

insulin resistance, and raised leptin and estrogens [8].

The aim of this review is to compile the data available both on *in vivo* and *in vitro*, or drugs available for the clinical trials on obesity-induced inflammatory cytokines/chemokines and their pathways involved in breast and thyroid carcinogenesis. We chose breast and thyroid cancer because these cancers share obesity as a common etiologic risk factor.

In this paper, our main contribution is to provide a comprehensive review on the effects of obesity-induced inflammatory cytokines on breast cancer and thyroid cancer while discussing available treatment modalities.

Obesity-induced inflammatory markers in cancer

Obesity increases the number as well as the size of the adipocytes. Adipocytes alter the adipokines-leptin, adiponectin secretion and produce a low-grade inflammatory state. Inflammatory cells such as macrophages and lymphocytes enhance the secretion of inflammatory cytokines and influence this inflammatory process. Adipokines and cytokines are known to initiate and promote tumor development and progression [9-11]. Here, we describe how obesity signals leptin, leptin induced-molecules, adiponectin, cytokines (TNF- α and IL-6) and their probable impact on breast cancer, and thyroid cancer through an exploration of the current literature as shown in figure 1.

Obesity-linked inflammatory markers in breast cancer: Breast cancer is the second leading cause of cancer mortality in women and shows a higher prevalence in women compared to men. Less than 1% of all cancers in men are breast cancer and only 1% of breast cancer patients are men. Despite genetic factors and other risk factors, obesity increases the breast cancer mortality rate by up to 30% compared to a normal-weight woman with breast cancer. In this part, we mainly focus on obesity-linked cytokines' impact on cancer, specifically on breast cancer.

Obesity and breast cancer: The WHO considers obesity as a "global epidemic" [12] and uses BMI, a ratio

between weight and the squared height (kg/m^2) of a subject, for classification; with multiple subtypes for stratification (**Table 1**) [13]. Despite its prevalence as a metric of the body, BMI has a major limitation – it cannot differentiate between mass derived from fat tissue and muscle tissue. This can inappropriately categorize individuals with the same BMI. Hence, the obesity classification should be focused on body fat distribution and composition instead of considering bodyweight only. Sometimes waist circumference is included with BMI to make it a more reliable indicator of overall health. In addition to genetic predisposition, obesity itself has a significant role in the risk and outcome of breast cancer [14]. Several studies show how obesity creates a pro-growth environment for breast cancer. Joao et al. [15], showed obesity provides a high energy level metabolic state with an increased number of ATP that influences the excessive cell turnover causing tumor growth.

Breast is mainly composed of adipose, glandular, and connective tissues [16]. Among them, adipose tissues are one of the vital components of breast structure, which varies in the amount in different ages and has a potential role in developing breast cancer [17]. Besides these tissues, there are also three different types of receptors in the breast including the estrogen receptor (ER), progesterone receptor (PR), and the human epidermal growth factor receptor 2 (HER2). In obese women, the risk of breast cancer varies according to receptor expression and ethnicity (Table 2) [14].

Premenopausal women: Studies show that obesity lowers the risk of estrogen receptor (ER) positive breast cancer among Hispanic and non-Hispanic white before menopause [14]. On the other hand, another study shows no association between obesity and ER-positive risk factors in African American women. Inversely, obesity increases the risk of ER-negative and Triple-negative (lack of ER, PR, HER2 receptors) breast cancer (TNBC). In India, a case-control study shows increased waist circumference and waist-hip ratio influences the risk of TNBC, independent of BMI [14],[18]. In the case of inflammatory breast cancer obesity aggravates the risk of both ER-positive and ER-negative breast cancer.

Postmenopausal women: Although in premenopausal women obesity has a negative effect on receptor-positive breast cancer, obesity increases the risk of receptor-positive breast cancer in postmenopausal women [16]. This influence is more in women from Asia-pacific than North America, Europe, and Australia. Though BMI is the most popular indicator of obesity, the waist-hip ratio is also used as an indicator in this case. Regarding ER/PR negative

and TNBC, obesity decreases the risk in some studies but also contributes to a 3 to 5-fold risk of inflammatory breast cancer [14],[18].

Obesity and recurrence of breast cancer: Obesity increases the risk of recurrence and has a negative effect on the survival rate. In addition to obesity, a weight gain of 10% also increased the risk of late recurrence [19]. Obesity mainly escalates the recurrence risk of contralateral breast cancer and distant metastasis. However, there is no relation between the recurrence of lymph node-negative, ER-positive breast cancer, and local recurrence with obesity. The circulating level of estradiol and IL-6 receptors are the primary indicators of recurrence. Estradiol level is higher in recurred patients. In terms of ER-positive breast cancer, high levels of IL-6 receptors indicate shorter relapse-free survival.

Inflammatory pathways in breast cancer: The relationship between chronic inflammation and cancer has been known for a long time [20]. Obesity contributes to breast cancer by low-grade chronic inflammation. When a person becomes obese, there is an increase in the number of adipocytes. Excessive adipocytes produce an excess of pro-inflammatory cytokines (IL-6, TNF- α mainly) and mediators which produce a favorable environment for cancer growth, invasion, and metastasis. Normally inflammation and autophagy are body's defense mechanisms causing tissue repair by eliminating the injured cells, when dysregulated, pathological effects such as oxidative stress, metabolic impairment, and cell death can occur [21]. These pathological effects can lead to breast cancer.

Obesity-induced cytokines in breast cancer: The number of adipocytes with the immune cells is increased in obese people. These cells produce cytokines having inflammatory activities and cause chronic inflammation, insulin resistance, etc. Through different inflammatory changes, obesity can lead to cancers-mainly endocrine cancers. In lean persons normal adipocytes produce more anti-inflammatory adiponectin and a very small amount of proinflammatory, pro-mitogenic and proangiogenic leptin. On the other hand, in obese persons the maturation of immature adipocytes (preadipocytes) to mature adipocytes is slowed and there is an accumulation of preadipocytes. Excessive preadipocytes produce a large amount of leptin and reduce adiponectin production. This preadipocyte accumulation causes hypoxia in cells and leads to activation of inflammatory processes [14].

Obesity-induced inflammatory cytokines and breast cancer in vivo (humans) model:

Obesity increases breast cancer risk in several ways by interfering with intracellular signaling pathways (Figure 2). Adipose tissue increases body estrogen levels by enhancing the aromatization of circulating androgens. In premenopausal obese women, the low level of circulating SHBG (sex hormone-binding globulin) leads to a high level of unbound androgen which is converted into and causes the accumulation of estrogens. Increased secretion of proinflammatory cytokines occurs when there is a communication between adipocytes and cancer cells. Immature adipocytes increase the number of cancer cells with tumor-forming and metastatic potentials. Increased insulin resistance presents with a high level of insulin in the blood and enhances the activity of aromatase in adipocytes. Insulin also reduces apoptosis [22]. Additionally, obesity stimulates insulin-like growth factor (IGF) pathways.

Hypercholesterolemia, a high plasma cholesterol level, aggravates tumor formation and accelerates their aggressiveness. Oxidative stress causes DNA damage and increases breast cancer risk [19].

Leptin and breast cancer: Adipokines, mainly leptin, are released from adipocytes which activate proinflammatory cells to produce proinflammatory cytokines such as cyclooxygenase-2 (COX-2), TNF- α , IL-6, interleukin (IL)-1 β , monocyte chemoattractant protein-1 (MCP-1), etc. around tumor sites.

Leptin also maintains the interaction between energy metabolism and immune cells, creates an inflammatory microenvironment that facilitates the survival, proliferation, and the metastatic potential of the cancer cells, impairs immune response against cancerous cells, and decreases adiponectin levels [15,22,23]. Leptin controls appetite and energy balance by acting on the brain. Obesity causes leptin resistance, which leads to increased levels of leptin in circulation [24,25]. Leptin receptors are present in breast cancer and stimulate several signaling pathways, such as Janus kinase/ signal transducer and activator of transcription. This stimulation accelerates cancer cell proliferation, survival, invasion, and metastasis.

IL-6 enhances the prostaglandin E2 formation from the breast cancer cells which ultimately escalates the preadipocyte aromatase expression [19]. Leptin and IL-6 together influence the cancer growth and metastasis.

TNF- α enhances estrogen metabolism through an

oxidative process, which can lead to DNA mutation related to breast cancer [19]. The effect of TNF- α on breast cancer is shown in figure 3.

Adiponectin and breast cancer: Adiponectin is another adipokine released from adipose tissue that has anti-inflammatory activities. It stimulates AMP-activated protein kinase, peroxisome proliferator-activated receptor pathways and inhibits leptin pathways. As a result, it hinders the cancer cell progression, invasion, and metastasis. However, adiponectin level is decreased in post-menopausal women with breast cancer compared to women without cancer [24].

Obesity-induced inflammatory cytokines and breast cancer in vivo (mice) model:

Some studies have been implemented in mice models to observe the effect of obesity on breast cancer. Leptin receptor gene (LEPR) is found in several human solid tumors. A study using mice models shows tumor progression and metastatic potentials are reduced in mice that have fewer peripheral leptin receptors with intact central leptin signaling. Tumor growth is also reduced in the case of transplanted tumors from LEPR deficient mice to wild animals compared to the transplanted tumor from intact LEPR mice. Another in vitro study using mice models shows, adiponectin inhibits breast cancer cell survival and proliferation. An additional study shows the size of the mammary gland in obese mice is double with 6-fold higher level of aromatase mRNA compared to lean mice and has a higher risk of developing breast cancer [24]. In addition, weight loss lowers the aromatase activity and decreases breast cancer risk [24,26].

Leptin antagonist and Adiponectin agonist: Another preclinical trial using a leptin antagonist and adiponectin agonist also shows promising results in the treatment of breast cancer in mice models.

Pitavastatin: Pitavastatin is found to reduce the production of a liver produced carcinogenic agent diethyl nitrosamine in obese mice [14]. As a result, the FDA has approved lipid lowering agents as a treatment option for obesity-related breast cancers.

Prevention of breast cancer in obese patients:

Besides different treatment modalities, several studies show lifestyle modifications, especially weight loss, have a great impact on prevention, reducing recurrence of breast cancer, and overall survival rate. However, without weight loss, diet and exercise have very little impact [14]. A person with a low BMI has a reduced amount of circulating sex

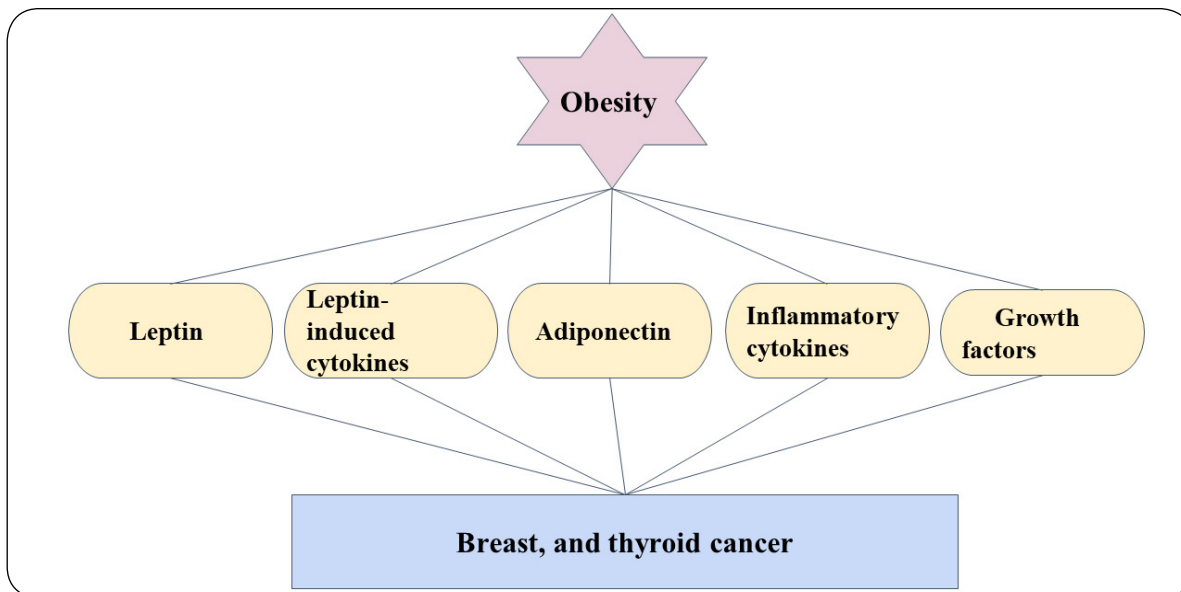


Figure 1: Association of obesity-linked inflammatory molecules to female endocrine cancer.

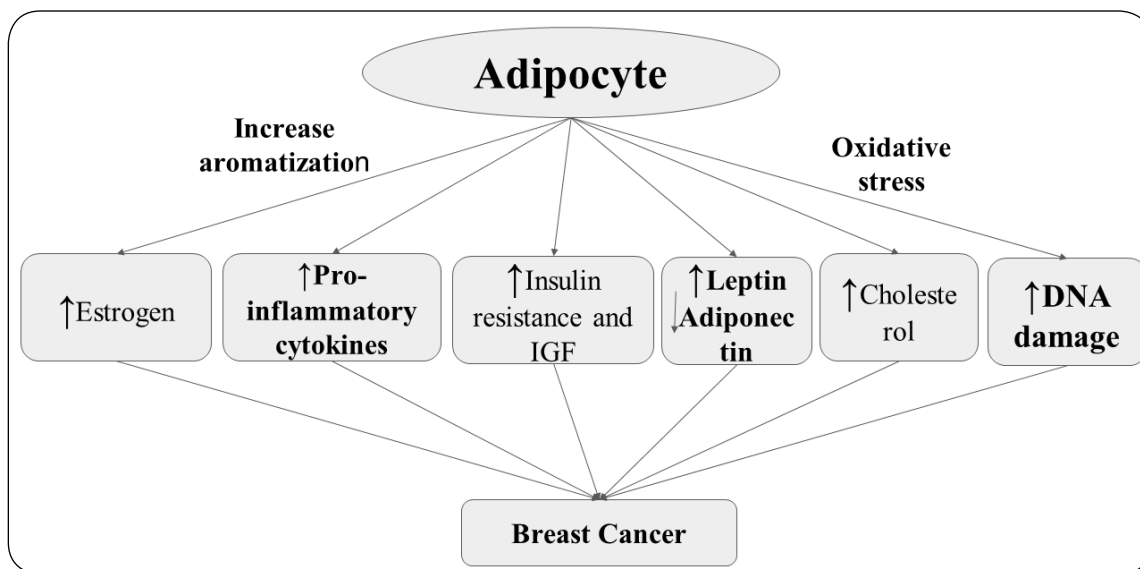


Figure 2: Adipocytes-linked pathways in breast cancer.

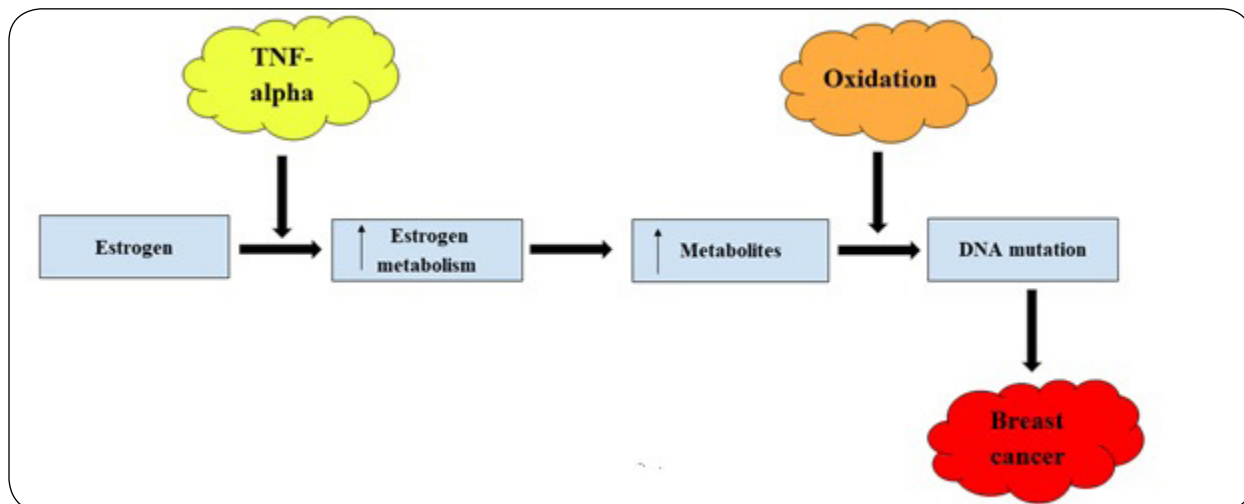


Figure 3: Effect Of TNF-alpha on breast cancer.

Table 1: Classification of BMI.

Body Mass Index (BMI)	Classes/Subtypes
40 or over	Extreme obesity (Class 3 obesity)
35-39.9	Class 2 obesity
30-34.9	Class 1 obesity
25.0-29.9	Overweight
18.5-24.9	Normal
18.5 or less	Underweight

Table 2: Influence of obesity over risk of breast cancer (↑ means increase, ↓ means decrease and - means unknown means no association).

Name of receptor	Hispanic/ Non-Hispanic white	African American	Indian	Asia-pa- cific	North American	European
ER +ve	↓	∅	-	↑↑	↑	↑
ER -ve	↑	↑	↑	↓	↓	↓
PR +ve	-	-	-	-	-	-
PR -ve	-	-	-	↓	↓	↓
TNBC -ve	↑	↑	↑	↓	↓	↓
IBC	↑			↑		

ER, estrogen receptor; PR, progesterone receptor; TNBC, triple negative breast cancer; IBC, inflammatory breast cancer.

hormones compared to a person with a high BMI.

Clinical trial in obesity-induced breast cancer:

There are different treatment modalities for breast cancer, such as chemotherapy, radiotherapy, hormonal and targeted therapy, and others [25].

Chemotherapy: Different chemotherapeutics are available. Among them, anthracyclines (e.g. Doxorubicin) and taxanes (e.g. Docetaxel) are popular chemotherapeutic agents used for breast cancer treatment.

Metformin: Recent preclinical studies show metformin has a positive effect on the treatment of breast cancer. Metformin inhibits the IL-6 mRNA expression and activates the IL-1R expression which acts as an anti-inflammatory cytokine. In breast cancer cells metformin interferes with mTOR pathway signaling and decreases the expression of HER-2 protein.

Targeted and hormonal therapy: Nowadays, targeted and hormonal therapies are exhibiting better outcomes in the prognosis of breast cancer. Commonly used targeted and hormonal therapies are showing in tables 3 and 4.

Recent studies reveal combination therapy is more successful compared to monotherapy.

Aromatase inhibitor: Adipocytes contain the aromatase enzyme, which helps in peripheral conversion of androgen into estrogen. Aromatase inhibitor (e.g., letrozole) blocks peripheral estrogen conversion and helps to inhibit tumor growth in both ER-positive and ER-negative breast cancers.

In summary, the treatment outcome and prognosis of breast cancer is influenced by the presence of hormone receptors. As obesity has a negative impact on treatment outcome and recurrence rate, during the treatment period women with breast cancer should stay away from weight gain and after completion of treatment should try to lose weight. After the diagnosis of breast cancer weight gain is usual. In such instances, chemotherapy would be the treatment of choice, as it decreases metabolism. However, obesity is usually associated with comorbid conditions, to reduce the toxic effects of chemotherapeutic agents, a subtherapeutic dose is sometimes given to the patients which ultimately affects the treatment responses.

Table 3: Targeted therapy used in breast cancer.

Targeted therapy	Mechanism of action
Epidermal growth factor family inhibitor (Gefitinib, erlotinib)	Inhibit tyrosine kinase receptors
Nonreceptor tyrosine kinase	Inhibit intracellular signaling pathways
Angiogenesis inhibitor (PARP inhibitor)	Inhibit DNA repair

Table 4: Hormonal therapy used in breast cancer.

Name of medication	Target receptor	Mechanism of action
Tamoxifen, fulvestrant	ER receptor	Antagonizes the action of estrogen
Trastuzumab	HER-2 receptor	Interfere signaling pathway through HER-2 receptors
Everolimus	mTOR inhibitor	Interfere mTOR pathway

Obesity-linked inflammatory markers in thyroid cancer

Thyroid cancer is the most common endocrine neoplasm. It represents 2.9% of all new cancer cases and is the 12th most common cancer in the United States [27]. Age, sex, ethnicity, and genetic predisposition are well known non-modifiable risk factors for thyroid cancer. However, epidemiological studies have shown that several environmental factors, such as dietary habits, obesity, environmental carcinogens, and pollutants can also play a significant role [28,29]. In this chapter, our goal is to determine the association between obesity-induced inflammatory cytokines and thyroid cancer.

Obesity and thyroid cancer: The prevalence of obesity has increased significantly both in developing and developed countries in recent years. 60-70% of the adult populations in developed countries are obese, and the prevalence is more common in women [4]. The incidence of thyroid cancer has also increased in the past several decades. From 1992 to 2017, the incidence rate has increased from 5.8 to 13.3 [27]. The rising incidence of thyroid cancer has been attributed to increased surveillance and improvement in diagnostic tests such as USG and FNAC, which have made it possible to detect small papillary tumors. However, technological advancement and increased surveillance do not fully explain the rising incidence of thyroid cancer, as large tumors have also increased. This indicates, it is highly likely that some other environmental factors are playing a role as well [29-31]. According to epidemiological studies, a significant portion of thyroid cancer (> 40% in the USA) results from several environmental factors such as obesity and cigarette smoking [32]. Several studies have demonstrated an association between obesity and thyroid cancer. Another pooled analysis of five prospective cohort studies showed that increased BMI was associated with an increased risk of

thyroid cancer both in men and women [31].

A prospective cohort study on 90,713 US radiologic technologists, followed for 23 years, found an elevated risk of thyroid cancer for women with RR of 1.74 (95% CI: 1.03-2.94, P: 0.04) for BMI over 35 [28]. Some studies have also demonstrated that study subjects who have gained weight over time compared to those who maintained stable weight are also at an increased risk of developing thyroid cancer [33]. A large case-control study demonstrated subjects who gained weight (10 kg or more) had higher chance of developing thyroid cancer than those who maintained a stable weight (loss or gain < 5 kg) [Men, OR 5.39, 95% CI 3.88-7.49; women, OR 3.36, 95% CI 2.87-3.93] [34]. Thyroid cancer is prevalent in both men and women, but the increased risk in men was reported by Zhang et al., whereas Ma et al. found a stronger association in obese women than men [35]. So, the role of gender in increasing the propensity to thyroid cancer should be explored for more information.

Although the exact pathophysiology by which obesity contributes to thyroid cancer is not yet well understood, several complex pathways are suspected and seems to play a role, such as chronic inflammation, insulin resistance, and increased production of pro-inflammatory cytokines [31,33,35]. The relationship between thyroid cancer and obesity-induced cytokines is displayed in figure 4.

Inflammatory pathways in thyroid cancer: Epidemiological studies have shown that systemic subclinical inflammation can promote the development and progression of several cancers, including thyroid cancer. These pathways are mediated by several molecular mechanisms, which result in the formation of reactive oxygen species, inactivation of tumor suppressor genes, and increase in cell turnover. In addition, infiltrative inflammatory cells maintain the

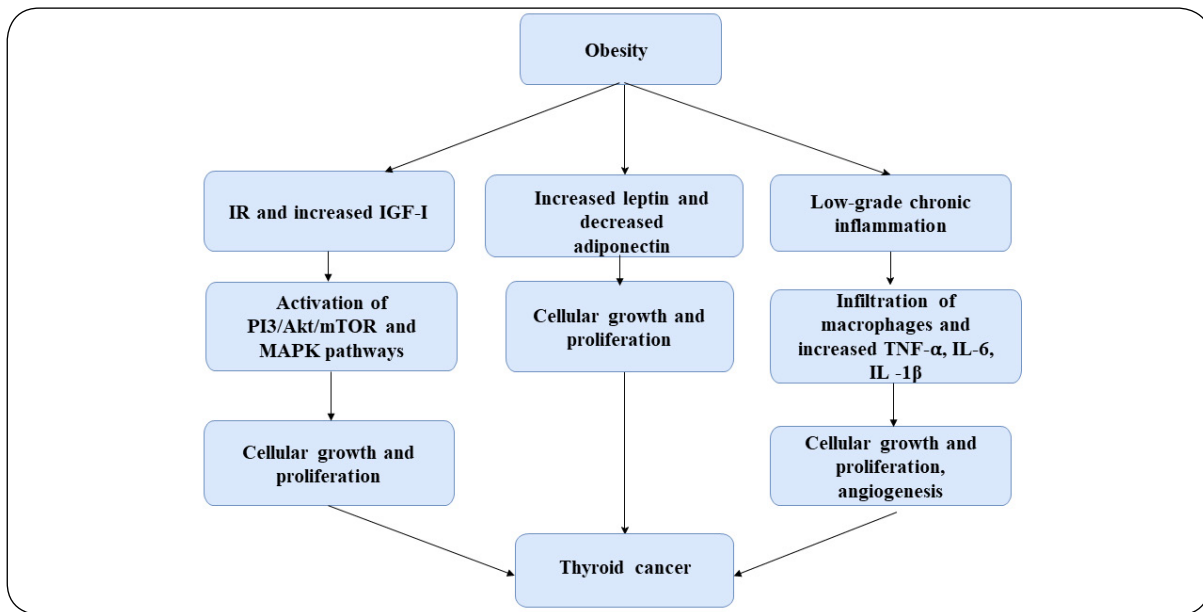


Figure 4: Obesity-signaling pathway in thyroid cancer. IR, Insulin resistance; IGF-I, insulin-like growth factor.

microenvironment that is necessary for tumor growth and progression [36,37]. A perfect example of an association between thyroid cancer and inflammation would be Hashimoto thyroiditis and the risk of developing differentiated thyroid carcinoma, and lymphoma, in the long run. Many clinical studies provided even more specific evidence of the association between thyroid cancer and inflammation. For example, an Italian cross-sectional study found a higher percentage of inflammatory and immunological cells were present in the follicular carcinoma than in the adenoma. To be more specific, the expression of CD1a (a marker of dendritic cells) and CD68 (a marker of macrophages) were higher in follicular carcinoma than adenoma. Expansion of adipose tissue due to obesity leads to chronic subclinical inflammation and facilitates tumorigenesis predominantly by producing proinflammatory cytokines (TNF- α , IL-6) and inducing the inflammatory cells' migration [36,37].

Obesity-induced cytokines in thyroid cancer:

Adipose tissue is not just a collection of fat cells. It is a central metabolic organ that works as an energy reservoir and secretes various hormones, cytokines, extracellular matrix proteins, and metabolites (known as adipokines). These adipokines play a crucial role in regulating insulin sensitivity, blood pressure homeostasis, angiogenesis, and inflammation [30,38].

Adipose tissue is also considered a part of the immune system as it produces receptors for immune cells and secretes several immune molecules into circulation. In addition to adipocytes, stromal cells in the adipose tissue also produce immune cells, which can play a role

in angiogenesis, adipogenesis [30,39,40]. These cells can provide a favorable microenvironment for tumorigenesis.

Weisberg and Colleague (2014) studied the transcript expression in adipose tissue from a mice model to see what happens when there is increased adiposity. They found 1304 transcripts, and among them, many have similar characteristics to that of macrophages. Further immunohistochemical analysis reveals that the percentage of expression of macrophage was positively correlated with adiposity and increased body mass [30]. Another study demonstrated that macrophages comprise 40% of adipose tissue in obese mice and humans compared to 18% of lean control [41].

Recruitment of macrophages in adipose tissue is enhanced by several factors, including fatty acid influx, cell free DNA from adipocytes, and abnormal adipokine secretion. The most recent hypothesis is that adipocyte death from obesity can play a pivotal role in recruiting macrophages [40]. When there is increased adipose tissue, there is a mismatch of the blood supply, which leads to hypoxia and adipocyte death. In turn, dead adipocytes secrete monocyte chemotactic factors (MCP-1), which are responsible for the infiltration of blood monocytes into adipose and transformation into macrophages [37,41]. After infiltration, macrophages form a crown-like structure (CLS) in the dead adipose tissue, which serves as a biomarker for adipose tissue inflammation [37]. CLS have been demonstrated in breast cancer, tongue cancer, and are associated with reduced disease-specific and overall survival. Infiltrated macrophages produce different pro-inflammatory cytokines IL-1 β , IL-6, TNF- α [42].

FFA (free fatty acid) from entrapped adipocytes can also stimulate the production of pro-inflammatory cytokines from macrophages by binding with toll-like receptors (TLR) 4 on the plasma membrane of macrophages [37]. These inflammatory cells and pro-inflammatory cytokines play a key role in obesity-induced cancer by promoting tumor cells' growth and differentiation and maintaining angiogenesis.

Again, adipose tissue produces adipokines, which are bioactive polypeptides released either by adipocytes, pre-adipocytes, or various immune cells and play a crucial role in maintaining insulin sensitivity, energy balance, blood pressure homeostasis, appetite, and inflammation [30,34,43,44]. There are several types of adipokines such as leptin, adiponectin, resistin, chemerin, lipocalin -2, vaspin, progranulin, secreted protein acidic and rich in cysteine (SAPRC), secreted frizzled-related protein 5 (SFRP5), and C1q/TNF-related protein (CTRPs). Some of these adipokines have anti-inflammatory properties, and some of them have pro-inflammatory properties. However, in obesity, which can be considered a chronic inflammatory state, there is a shifting of the balance between these two groups. So, this results in more pro-inflammatory cytokine (e.g., leptin) than anti-inflammatory cytokines (adiponectin), which creates a microenvironment that is optimal for tumor growth and differentiation [30].

Obesity-induced inflammatory cytokines and thyroid cancer in vivo (humans) model: Obesity aggravates the risk of thyroid cancer by altering the normal physiologic process of the thyroid gland.

Obesity can lead to insulin resistance (IR). IR is a condition when there is enough insulin in the body, but tissues have difficulty utilizing it because of impaired insulin sensitivity. To compensate for that, pancreatic beta-cells increase the synthesis of insulin and lead to hyperinsulinemia [30,42]. Several clinical studies link hyperinsulinemia and insulin resistance to colorectal, pancreatic, liver esophageal, breast, and endometrial cancers [30]. Its role in thyroid cancer has also been studied. A case-control study by Rezzonico et al. found that IR was present in 50% of patients with differentiated thyroid cancer (DTC) compared to 10% of the control group [45]. In a systematic review and meta-analysis, it was found that insulin resistance was associated with an increased risk of thyroid cancer, RR= 1.59, 95% CI= 1.12-2.27, P =0.01 [35].

Hyperinsulinemia in insulin resistance reduces the production of insulin-like growth factor-1 binding proteins, thus increasing the level of insulin-like growth factor-1

(IGF-1). Increased expression of IGF-1 and its receptor is observed in differentiated thyroid cancer, suggesting its significant thyroid tumorigenesis role [42].

Both insulin and IGF-1 have mitogenic properties; they can regulate cell growth and proliferation by activating PI3K/Akt/mTOR and Ras/Raf/MAPK pathways [37,45,46].

Leptin and thyroid cancer: Leptin is a multifunctional cytokine produced mainly by adipose tissue and skeletal muscle enterocytes and plasma cells. It plays a central role in maintaining body weight and energy expenditure by acting on the leptin receptor in the ventromedial nucleus of the hypothalamus. Apart from its role in maintaining body weight, it also participates in immune surveillance, exerts mitogenic effect, enhances the proliferation and invasion of malignant cells, and causes angiogenesis. Synthesis and release of leptin is regulated by different hormones and cytokines such as insulin, TNF alpha, and glucocorticoids [30,45,47]. Leptin mediates its effect by acting on leptin (Ob-R), an external tyrosine kinase receptor, and leads to activation of several downstream signaling pathways such as JAK2/STAT3, erbB2, ERK, IRS, and rho/rac pathways. The binding of leptin to its receptor (Ob-R) initiates conformational changes, leading to the recruitment of JAK2 and activation by phosphorylation. Activated JAK2 phosphorylates the tyrosine kinase residue of the receptor's intracellular domain, which acts as a docking unit for various protein molecules; one such molecule is STAT3. Upon docking, STAT3 gets phosphorylated by JAK2 and then dissociates from the receptor and dimerizes to enter the nucleus and to activate gene transcription [30,47-49].

Leptin/Ob-R complex can also activate the PI3/AKT pathway, which plays a major role in carcinogenesis by regulating cell survival and proliferation. This leptin/ Ob-R receptor complex causes phosphorylation of the IRS domain by receptor tyrosine kinase. Activated IRS then recruits other signaling molecules to initiate downstream signaling pathways, such as the enzyme phosphatidylinositol 3 kinase, which generates inositol-triphosphate (PIP3) from membrane phospholipid. PIP3, in turn, recruits a serine/ threonine kinase called PDK1, which can directly activate AKT by phosphorylating threonine 308, or indirectly by activating mTORC2 (by phosphorylating Serine 473). AKT then activates mTORC1, which increases protein synthesis and inhibits autophagy. AKT also increases cell survival and proliferation by inhibiting a downstream molecule called FOXO [47,48].

Leptin receptors are expressed in diverse cancer cells,

including thyroid follicular cells, where they maintain growth and proliferation of malignant cells. A translational study examined the effect of leptin on thyroid cancer cells (TPC-1 and K-1) and found that there was a mild increase in proliferation of K-1 cell type (20% over the control only in K-1 cells, $p < 0.05$) after prolonged exposure and increase in migration in both types of cells [50].

In another study, the researcher performed immunohistochemical staining with the Ob-R antibody in a large cohort of PTC (Papillary Thyroid Cancer) tumors and found that Ob-R protein was expressed in 80% of cases. This study also demonstrated that PTC tumors associated with elevated level Ob-R (leptin receptor) were larger in size, metastasized early, invaded lymph nodes and extra thyroid tissue, and had higher grades. This indicates that leptin receptor expression is not only associated with increased thyroid cancer risk but also with poorer prognosis [47,48].

IL-6 is a multifaceted cytokine that induces a host immune defense mechanism. It also stimulates the growth and differentiation of malignant cells by inhibiting apoptosis, inducing angiogenesis, and facilitating drug resistance. Several molecular pathways mediate these effects, particularly the signal transducer and transcription activator 3 (STAT-3) [51,52]. IL-6 increases the risk of several cancers, including breast cancer and prostate and colon cancer. However, very little evidence is present at this moment to link IL-6 and thyroid cancer directly, but its ability to maintain the tumor microenvironment can play a pivotal role in tumorigenesis [30].

TNF- α is a cytokine that is responsible for inflammatory and immune responses. It exists in 2 forms: a membrane integrated form and a soluble form and mediates its effect by binding with either TNFI or TNFII receptor. TNF I receptor is found in most immune cells. TNF II receptor is present in immune cells and other subtypes of cells such as neurons, oligodendrocytes, astrocytes, endothelial cells, and T lymphocytes' subpopulation. Activation of the TNF I receptor leads to two opposite effects: proliferation or apoptosis of the cells, depending on the signaling molecules. On the other hand, activation of the TNF II receptor only causes activation, proliferation, and cell migration [53]. TNF- α also induces blood vessels' proliferation (angiogenesis), which is necessary for tumor growth and progression. An elevated level of TNF- α has been found in several malignancies. Liu et al. found an elevated TNF- α level in a patient with colorectal cancer. The effect of TNF- α in thyroid follicular cells is different from that of other cell types. At a physiological level, it has an antiproliferative effect on

thyroid follicular cells. However, chronic overproduction of TNF- α in obese patients leads to resistance. As a result, it exerts a proliferative effect on thyroid follicular cells and enhances tumorigenesis [30,53].

Adiponectin and thyroid cancer: Adiponectin is the most abundant of the adipokines with anti-inflammatory, anti-atherogenic properties. It plays a pivotal role in maintaining insulin sensitivity, promoting cellular growth and proliferation, and maintaining the balance between anti and proinflammatory cytokines. These biological effects of adiponectin are mediated by two types of receptors – AdipoR1 and AdipoR2 [30,36,44]. Insulin inversely regulates the expression of adiponectin receptors [54]. Binding to its receptor activates various downstream signaling pathways to mediate the effects. For instance, insulin sensitivity is maintained by an increase in AMPK activity and PPAR alpha and PGC alpha, cell proliferation is regulated by AKT/mTOR/PI3K and MAPK pathways and immune surveillance is mediated by NFkB pathways [30].

Recent studies have shown a significant association between adiponectin and different types of cancer. Gelsomino et al. report that adiponectin has an antiproliferative effect in obesity-associated female cancers (such as cervical, ovarian, endometrial, and breast cancer) [54]. Mitsiades and colleagues found an inverse relationship between adiponectin and differentiated thyroid cancer. They have also demonstrated that ADIPOR1 and ADIPOR2 receptors are expressed in the thyroid follicular cell, supporting that adiponectin has effect in thyroid follicular cells [30]. However, significant data/research is absent to show the association between the adiponectin receptor expression and clinicopathological varieties of thyroid cancer. According to one study, adiponectin level was similar between patients with a localized or advanced thyroid cancer stage [36]. However, another study reported a clinicopathological variation of thyroid cancer per adiponectin receptor expression. Cheng et al. in 2013 reported a study on the significance of the biological importance of adiponectin receptor in Papillary thyroid cancer (PTC), showed that 27% of the primary PTC expressed ADIPOR1, and ADIPOR2 in 47% cases. They had seen when the tissue was negative for both the receptor, tumors were more prone to metastasize, involve the lymph nodes and extrathyroidal structure [30,55].

Obesity-induced inflammatory cytokines and thyroid cancer in vivo (mice) model: Some studies have been conducted on ThrbPV/PV Pten+/-mice to understand the role of inflammation in thyroid cancer.

These mice have a deletion of one allele of the Pten gene (a tumor suppressor gene) and mutation in thyroid hormone receptor beta (denoted as PV), making them more susceptible to developing thyroid cancer. The effect of obesity-related inflammation on thyroid tumorigenesis was analyzed after giving them a high-fat diet. It was found that inflammatory immune cells (e.g., monocytes, macrophages) were 7 times more prevalent in the thyroid tumor cell of ThrbPV/PV Pten+/-mice than wild-type control. A 10.3-fold increase in expression of a protein of TNF- α and increased activation of PI3-AKT pathway was also evident [56].

Another study was done on ThrbPV/PV Pten+/- mice to see the effect of leptin on thyroid cancer. It showed that the leptin level was elevated in high fat-induced thyroid cancer, which subsequently led to the activation of downstream JAK-2/STAT3 (Janus kinase-2/signaling transducer and activator of transcription), which mediated the growth and progression of thyroid cancer [57]. These studies provided molecular evidence of the association between obesity and thyroid cancer.

In table 5, we show the name of available targeted therapy in the preclinical models with their molecular pathways.

Metformin: Metformin is a widely used first-line medication for type II diabetes. In addition to controlling blood glucose, it effectively reduces the risk of developing several solid tumors such as liver, pancreatic, stomach, thyroid, and breast cancer in a patient with type II diabetes mellitus. Several in vitro studies in ThrbPV/PV Pten+/- mice have unraveled the underlying molecular mechanism of obesity-induced thyroid cancer and allowed the researchers to explore targeted therapy against them [58].

A study using a mice model showed that metformin effectively prevents the capsular and vascular invasion of thyroid cancer cells and inhibits aplastic transformation, although it did not affect overall survival [58,59]. Metformin inhibits cell growth and proliferation by blocking the leptin-STAT3-ERK pathway and prevents the invasion and distant metastasis by blocking the synthesis of extracellular matrix

components and cytoskeleton structures, such as vimentin, fibronectin, and integrin [58].

STAT-3 inhibitor (SI3-201): Activation of leptin-STAT-3 pathways in obesity plays a key role in tumor growth and progression. So, the efficacy of STAT-3 inhibitor, SI3-201, was studied in mice models, which reported compelling evidence that SI3-201 was able to block the activation of STAT-3 and downstream signaling effectively, thus preventing the proliferation of thyroid tumor cells. SI3-201 was also able to prevent invasion and metastasis by reducing the synthesis of vimentin and matrix metalloproteinases [58,60].

PI3K inhibitor (LY 294002): PI3K-Akt-mTOR pathway plays a significant role in the pathogenesis of different malignancies, including thyroid cancer. LY, a potent inhibitor of PI3K, inhibited PI3K-Akt-mTOR signaling and thus growth and proliferation of thyroid tumor cells in a mice model. It also increased the level of caspase 3, thus promoted apoptosis and prevented unchecked cellular growth [61].

Prevention of thyroid cancer in obese patients:

Extensive nationwide efforts are required to reduce the prevalence of obesity and overweight. Health care providers can play a crucial role in encouraging patients to maintain a healthy weight through a nutritious diet and physical exercise. In addition to providing individual-level support, population-based strategies should be implemented that promote active living and healthy eating in different settings such as at the workplace, school, and communities. Apart from a lifestyle change, medication such as metformin can reduce thyroid cancer risk, especially for cases where IR is the predominant underlying mechanism [36]. Although a strong association between thyroid cancer and obesity is evident, increased vigilance for thyroid cancer among obese and overweight individuals is not recommended [31].

Clinical trial in obesity-induced thyroid cancer:

Metformin: One study explored the effect of metformin in the conventional treatment of thyroid cancer on a study population divided into three groups, diabetic patients treated with metformin, diabetic patients not treated with metformin, and control non-diabetic patients. It was found

Table 5: Targeted therapy used in thyroid cancer.

Targeted therapy	Molecular signaling pathway
Metformin	JAK-2/STAT-3
Rapamycin, everolimus	PI3K/Akt/mTOR
STAT-3 inhibitor (SI3-201)	JAK-2/STAT-3
PI3K inhibitor	PI3K/Akt/mTOR

that tumor size was notably smaller in patients treated with metformin than the patients without metformin and the control group.

To illustrate the exact molecular mechanism affected by metformin, an in - vitro analysis of thyroid cancer cell line was also done. It was reported that metformin exerts its effect by AMPK (5'-AMP-activated protein kinase) dependent downregulation of mTOR/p70S6K/pS6 pathway [61-63].

The PI3K/Akt signaling pathway plays a significant role in cellular proliferation, growth, transformation, and tumor progression. Several drugs that block this pathway, including rapamycin, temsirolimus, everolimus, INK-128, have been tested in phase I-III clinical trial, among which everolimus and temsirolimus manifested significant efficacies in treating thyroid cancer [64].

In conclusion, the incidence of thyroid cancer is increasing, and emerging clinical evidence further establishes the association between obesity and thyroid cancer. We still need more studies to show a causal link between these two, as it can serve as another motivation to maintain a healthy weight and reduce the disease burden of thyroid cancer. Moreover, several molecular mechanisms postulated as a cause of thyroid cancer in obese patients could be explored further as effective targeted therapies.

Conclusion

Obesity is an established causal factor for many cancers including breast, and thyroid carcinoma. In this paper we clearly delineate the relationship between obesity, enhanced activity of cytokines and other mediators (e.g., leptin, adiponectin), and the development of breast and thyroid cancers. Review of in vivo both human and mice models and preclinical models are also done to clarify the obesity-associated cytokines, and adipokines in the breast, and thyroid carcinoma.

In terms of breast cancer, obesity aggravates the chance of having ductal breast carcinoma and ER-positive PR-positive breast cancer. Weight loss with exercise and reduced calorie intake reduces the risk of breast cancer in both premenopausal and postmenopausal women by reducing the circulating level of estrogen and testosterone.

In addition, the role of Metformin to treat both breast and thyroid cancer is discussed. The identification of inflammatory biomarkers released by adipose tissue, and alterations in their pathway in the pathogenesis of these cancers, could be useful in improving diagnostic accuracy, identifying targets of therapy, and suggesting useful lifestyle

behaviors. Future studies based on long-term evaluations of precancerous inflammatory marker levels are required to clarify the relationships between obesity, inflammation, and the risk of breast and thyroid cancer. Prospective studies, along with longitudinal repeated weight analyses will be specifically vital in investigating adiposity at various times frames of life and paths of weight variation over time. These researches can also be utilized to investigate how adiposity at different time frames may impact the survival rate in the patients of breast and thyroid cancer. Detailed case treatment data and methodological rigor can further boost our knowledge of this association.

Declaration

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