ESTIMATION LEVELS OF SOME HORMONES AS BIOMARKER IN BREAST CANCER PATIENTS IN WASIT PROVINCE

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SUMMARY

Objective: Some hormones play an influence on the breast cancer. Leptin is strongly implicated in breast carcinogenesis and may contribute to proinflammatory mechanisms, especially in obese patients. Increased leptin in obesity is implicated in neoplastic transformation and tumor progression. In addition leptin affects the biology of breast cancer in the endocrine glands in the manner of autocrin and paracrine. Estrogen plays an important role in breast cancer carcinogenesis. It either promotes the growth of abnormal cells or the survival of existing mutated cells, or estrogen induces genetic damage that leads to cell transformation. Abnormally high estrogen levels are also associated with an increased incidence of certain types of cancer, particularly breast and endometrial cancers. It is documented in human breast tumors that elevated RANK expression levels are associated with altered mammalian differentiation suggesting that increased RANK signaling may contribute to breast carcinogenesis and that the RANKL/RANK pathway also plays an important role in breast cancer development.

METHODS: This study performed on 70 female patients suffering from breast cancer and 30 healthy individuals as control group. Age of patients ranged from (21-71 yrs.). During the period from November 2019 to the January 2020 at the laboratories College of Science/Wasit University in cooperation with the laboratories of Al-Karama Teaching Hospital and Al-Batool Hospital in the city of Kut/Wasit governorate. Levels of Leptin, Estrogen, and Human Receptor Activator of Nuclear Factor Kappa B (RANK) were estimated by ELISA assay technique according to manufacturer's description.

RESULTS: The age of the patients in this study were arranged from 21-61 years old, older women in patient group more affected than control group. Results of this study showed that Levels of hormones showed significant differences between the breast cancer patients and control group, leptin, Estrogen and Human Receptor Activator of Nuclear Factor Kappa B (RANK) were a significantly increased in patients of breast cancer compared with control group.

CONCLUSION: Estimation levels of some hormones such as, Leptin, Estrogen and Human Receptor Activator of Nuclear Factor Kappa B (RANK) may use as useful marker for detecting breast cancer.

Keywords: Breast cancer, Leptin, Estrogen, and Human Receptor Activator of Nuclear Factor Kappa B (RANK)

I. INTRODUCTION:
Breast cancer is defined as cancer that forms in the breast tissue and is considered invasive if the breast cancer has spread from where it began to surrounding tissues (Ries, 2017). It is a heterogeneous disease that results from a series of genetic and epigenetic events that impair cell growth, circumvent apoptosis and develop the ability to invade lower tissues through the basement membrane (Antonio and Easton, 2006). Signs of breast cancer include dimpling of the skin, a change in the shape of the breast, a lump in the breast, a red, scaly patch of skin, or fluid from the nipple (Ramya and Nanda, 2017). The main risk factors for breast cancer are exposure to ionizing radiation, obesity, long-term consumption of exogenous estrogen, first pregnancy after the age of 25, inequality, delayed menopause, early menstruation, family history and age (Nabi et al., 2016). Breast cancer can be diagnosed through a comprehensive examination through breast self-examination, clinical breast examination and
mammography (Rizalar et al., 2017). The diagnosis also requires a biopsy of the breast tissue if the medical examination indicates the potential for malignant tissue growth (NBCF, 2015).

In Iraq, breast cancer is a very common type of malignant tumor among the population and is responsible for about a third of cancers registered in females and about a quarter of female deaths from the disease (Ebrahim, 2014; Najm, 2018). According to the Iraqi Cancer Registry in 2005, it ranks first in cancer among females with 31.75% of all cancer cases (ICR, 2005).

Leptin is strongly implicated in breast carcinogenesis and may contribute to proinflammatory mechanisms, especially in obese patients. There is a positive association between BMI and leptin levels with increased obesity. Increased leptin in obesity is implicated in neoplastic transformation and tumor progression (Housa et al., 2006). Abnormally high estrogen levels are also associated with an increased incidence of certain types of cancer, particularly breast and endometrial cancers. (Prentice and Anderson, 2008).

It is documented in human breast tumors that elevated RANK expression levels are associated with altered mammalian differentiation suggesting that increased RANK signaling may contribute to breast carcinogenesis (Gonzalez-Suarez and , Sanz-Moreno 2016) and that the RANKL/RANK pathway also plays an important role in breast cancer development ( Palafox et al., 2012).

The aim of the study is estimation levels of some hormones leptin , estrogen as well as RANK (Receptor Activator Nuclear Kappa-B) as biomarker in breast cancer patients.

II. MATERIALS AND METHODS

**Study design:** The study was conducted at the College of Science/Wasit University in cooperation with the laboratories of Al-Karama Teaching Hospital and Al-Batool Hospital in the city of Kut/Wasit governorate for women arriving at the two hospitals and within the period from (1/11/2019) to (7/1/2020) as sample collection centers, as it included. The study sample was women, with a total of 70 women, their ages ranged from (21 - 71 years), and they were divided into three age groups: (21 - 40 years), (41 - 60 years) and (<61 years), woman and the second section of the sample included the test group of women patients with breast cancer who did not undergo treatment (40) women and they were diagnosed with breast cancer by the specialized physician.

**Sample Collection:** The samples were females with age range (21-71) all patients and control were from the same ethnic group. The present study include (70) blood samples which grouped as following: control group (30) samples, patients group including (40) blood samples. Breast cancer was diagnosed by physicians.(10) ml of venous blood was withdrawn from patients and healthy people in the current study in a state of fasting and both using 5 ml medical syringes twice, after sterilizing the brachial vein area with ethyl alcohol (76%), from which blood will be drawn , to include the first blood sample (5 ml in anticoagulant tubes and leave for (20) minutes to be placed in the centrifuge at a speed (4000 cycles / minute) for (12) minutes to obtain the serum to be kept in the eppendorf tubes at a temperature of (-40° C) Until the metabolic criteria tests are performed, while the second blood sample (5) ml is kept in the eppendorf tubes at a temperature of (-80°C) until the biochemical criteria tests are performed.

**Methods**

**Estimation Hormones level**

Ten ml of blood was collected from each patient put in gel tube and allow the sample to clot for a few minutes at room temperature, followed by serum separation from the clot by centrifugation for 15 minutes at 1000 g. Then the serum was divided into several eppendorf tubes, labeled and stored at -40 °C . levels of Leptin, Estrogen and Human Receptor Activator of Nuclear Factor Kappa B was estimated by ELISA assay technique . Reagent preparation and procedure prepared according to manufacturer's description (Melson Medical, China)

**Statistical analysis:** Statistical Package for Social Sciences version 23 (SSPS 23) computer software was depended for statistical analysis .Descriptive statistics were used in addition to the analysis of the results using the one-way variance analysis test (ANOVA) to compare the averages of the samples, and the significant differences of the study sample were determined between the data of the control group and the group of breast cancer patients using the least significant difference (LSD) test. (Least significant difference) at the probability level (0.05).
### III. RESULTS

#### Biomarkers assays

##### Leptin level (LPT)

The results indicated a significant increase (P ≤ 0.05) in the level of LPT biomarker (ng/ml) in the serum of breast cancer patients of the third age group (<61 years) (0.37±5.75 ng/ml) compared to its level in the healthy group of the two age groups. (40-21 years) and (60-41 years) (0.12 ± 0.92 and 0.36 ± 0.91 ng/ml), respectively. While the data of the current study did not record the level of the leptin bio-criterion (LPT) on the presence of any significant differences (P > 0.05) between the age groups of the group of patients.

Table (1) the level of leptin (ng/mL) in the serum of the two groups of breast cancer patients and the control group.

<table>
<thead>
<tr>
<th>The group</th>
<th>BC-Patients group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 – 40</td>
<td>4.19 ± 0.41 bcd</td>
<td>0.62 ± 1.91*</td>
</tr>
<tr>
<td>41 – 60</td>
<td>0.20 ± 4.60 bcd</td>
<td>0.44 ± 3.96bc</td>
</tr>
<tr>
<td>&gt; 61</td>
<td>0.37 ± 5.75d</td>
<td>0.68 ± 4.08acd</td>
</tr>
</tbody>
</table>

LSD= 1.261

Data = Mean + S. E. M*  
* Different uppercast indicate for significant difference at the level of (P ≤ 0.05).  
* Similar uppercast indicate that there is no significant difference at the of (P> 0.05).

##### Estrogen level (Es)

The results of the statistical analysis of the bio-standard estrogen showed a significant (P ≤ 0.05) increase in the serum of breast cancer patients compared to healthy controls. It reached its highest height in the age group (60-41 years) (166.53 ± 9.95 pg/ml) compared to the control groups and for all age groups (40-21 years), (60-41 years) and (<61 years) (96.32 ± 4.55 and 62 91 years). .±6.50 and 134.62±8.68 pg/mL), respectively. While the data of the current study did not record any significant differences (p > 0.05) for the mean (Es) for both groups of patients and control for the three age groups.

Table (2) the Estrogen biomarker level (pg/ml) in the serum of the two groups of breast cancer patients and the control group.

<table>
<thead>
<tr>
<th>The group</th>
<th>BC-Patients group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 – 40</td>
<td>23.19 ± 142.12bc</td>
<td>4.55 ± 96.32bc</td>
</tr>
<tr>
<td>41 – 60</td>
<td>9.95 ± 166.53bd</td>
<td>6.50 ± 62.91+</td>
</tr>
<tr>
<td>&gt; 61</td>
<td>8.45 ± 161.63bd</td>
<td>8.68 ± 134.62acd</td>
</tr>
</tbody>
</table>

LSD= 23.729

Data = Mean + S. E. M*  
* Different uppercast indicate for significant difference at the level of (P ≤ 0.05).  
* Similar uppercast indicate that there is no significant difference at the of (P> 0.05).

##### Human Receptor Activator of Nuclear Factor Kappa B level (RANK)

The statistical results in the current work and shown in Table (3) recorded a significant increase (P ≤ 0.05) in the serum of breast cancer patients compared to the healthy ones, as the highest significant level (P ≤ 0.05) was recorded for the three age groups (40-21 years) and (60). -41 years) and (<61 years) (31.89 ± 190.58, 9.92 ±
169.72, and 20.64 ± 152.99 pg/ml) respectively in the patient group compared to the control groups for the same three age groups (45.28 ± 4.01, 45.51 ± 2.08 and 43.13 ± 10.10) respectively, pg/ml) respectively, while the data of the current study indicated that there were no significant differences (P > 0.05) for the two groups of patients and control and for all age groups.

Table (3) Level of human receptor activator of nuclear factor Kappa B (RANK) (pg/mL) in the serum of the two breast cancer groups and the control group.

<table>
<thead>
<tr>
<th>The group (Age)</th>
<th>BC-Patients group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>21 – 40</td>
<td>31.89 ± 190.58^b</td>
<td>4.01 ± 45.28^a</td>
</tr>
<tr>
<td>41 – 60</td>
<td>9.92 ± 169.72^b</td>
<td>2.08 ± 45.51^a</td>
</tr>
<tr>
<td>&gt; 61</td>
<td>20.64 ± 152.99^b</td>
<td>10.10 ± 43.13^a</td>
</tr>
</tbody>
</table>

LSD= 24.909

Data = Mean + S. E. M*

* Different uppercast indicate for significant difference at the level of (P ≤ 0.05).

* Similar uppercast indicate that there is no significant difference at the of (P> 0.05).

IV. DISCUSSION

Leptin level (LPT)
The increase in the level of leptin (LPT) among the group of patients compared to the control group may be due to the high percentage of body fat, and it is possible that the positive correlation between body fat and the level of leptin may be explained, as leptin is mainly produced by adipose tissue in proportion to the amount of fat stores in the body (Rodríguez et al., 2015). Leptin is a hormone that is produced by adipose tissue (normal and malignant tissue) and is secreted excessively in obese and overweight people (Park et al., 2015). As such, leptin sends signals to the brain to reduce appetite, and in the case of obesity, excessive production of leptin by adipose tissue leads to resistance to this signal causing anorexia. Lipids and inflammation (Gautron et al., 2011).

Leptin also affects immune function, cytokine production, angiogenesis, and carcinogenesis. Leptin exerts an oncogenic effect on ER+ tumors by regulating aromatase gene expression and estrogen synthesis (Catalano et al., 2003). It is encoded by the obese gene (Ob) which maintains energy balance through a central feedback mechanism at the level of the hypothalamus. It controls adipose tissue, growth and proliferation of cells including breast tissue where leptin levels have been associated with breast cancer aggressiveness and can predict the type, grade, stage, lymph node and hormone receptor involvement, and recurrence of breast cancer (Gu et al., 2019).

In addition, leptin affects the biology of breast cancer in the endocrine glands in the manner of autocrine and paracrine (Andò et al., 2014). It is a multidirectional molecule that influences energy balance, appetite control, angiogenesis, immune response, bone development (Jarde et al., 2011; Ando et al., 2014) and proliferation of various cell types including breast cells. Leptin has been shown to exert oncogenic effects in breast cancer by acting directly on tumor growth, migration and invasion signaling pathways, by decreasing tissue sensitivity to insulin, or regulating inflammatory responses and neoplastic angiogenesis (Moon et al., 2013; Crisostomo et al., 2016).

The expression of leptin and leptin receptors is one of the mechanisms linking obesity with breast cancer, as leptin is involved in the initiation, progression and progression of breast cancer through a signal transduction network. (2020) and is partially responsible for the inflammatory state associated with obesity (Pérez-Pérez et al., 2017). Chronic sebaceous inflammation promotes cancer growth and angiogenesis and alters immune responses as the pro-inflammatory microenvironment at the tumor site promotes cytokines and pro-inflammatory mediators. Tumor-nearing leptin stimulates proinflammatory cytokines and enhances T-helper 1 responses (Atoum et al., 2020).
In addition, leptin secretion causes circadian rhythm fluctuations and changes with nutritional status as circulating leptin levels transmit an energy storage state to the brain and these levels reflect the amount of adipose tissue present and increase in proportion to BMI. In addition, serum leptin levels have been shown to be higher in women than in men even after body weight correction and this can be explained by subcutaneous synthesis and regulation of estrogen and androgen hormones (Ahima and Osei, 2004).

The main function of leptin is to maintain energy balance and participate in the anorexia pathway through a central feedback mechanism at the level of the hypothalamus and in this way it controls the growth of adipose tissue through intermediate hormonal mechanisms that regulate food intake. In addition to this main function, leptin is known to have effects on fetal growth, reproduction, lactation, bone growth, hematopoiesis, immune response, angiogenesis, and the proliferation of many different cell types, including breast tissue cells (Barone et al., 2016). One of the peripheral functions of leptin is its regulatory role in the interaction between energy metabolism and the immune system (Pérez-Pérez et al., 2017).

Furthermore, elevated leptin levels have been linked to breast cancer aggressiveness and poor prognosis (Guo et al., 2012). It has recently been proposed as a biomarker that can be associated with type, class, stage, lymph node and hormone receptor involvement, and breast cancer recurrence (Kabaz et al., 2017).

Besides, leptin can regulate processes such as inflammation, metabolism and autophagy (Delort et al., 2015; Park, 2018). Autophagy has an important role in the pro-tumor effects induced by leptin. It has been shown that ER-negative breast cancer cells are more dependent on autophagy for survival than ER+ -positive breast cancer cells even under nutrient-rich conditions (Maycotte et al., 2014).

Leptin can also promote breast cancer recurrence and metastasis, which ultimately leads to poor overall survival in late-stage breast cancer patients (Goodwin et al., 2012). And leptin expression can promote aggressive phenotypes and tumor metastases. By promoting (epithelial- mesenchymal transition) EMT is a process associated with more malignant cell phenotypes and closely associated with tumor metastases (Liang et al., 2014). Non-motile epithelial cells acquire the characteristics of mesenchymal cells and lose cell polarity and cell- to-cell adhesion allowing for increased migration and invasion (Yang et al., 2020). As well as promoting peritoneal metastases of ovarian cancer (Wei et al., 2017).

Studies by Assiri et al. (2016) in breast cancer patients revealed an association between elevated serum leptin levels and characteristics of aggressive malignancy. Leptin expression in normal breast tissue adjacent to ductal carcinoma and its absence in breast tissue of healthy adults suggest that leptin is involved. In the early stages of the formation of breast cancer tumors, while another study reported that there was no association between the hormone leptin in the blood and the development of breast cancer (Aliustaoglu et al., 2010).

Gu et al. (2019) demonstrated in their study to assess the relationship between serum leptin levels and breast cancer risk that the apparent discrepancies between the results were related to heterogeneity across studies due to different genetic backgrounds, different stages and types of breast cancer, and different analytical methods for measuring leptin levels in Blood, menstrual status, different treatment of breast cancer patients, different demographics and clinical characteristics as well as the difference in tumor tissue expression of leptin.

Leptin exhibits multidirectional effects that include inhibition of pro-apoptotic signaling in breast cancer cells, estrogen sensitization, and modulation of the microenvironment contributing to local pro-inflammatory mechanisms and promotion of breast tumor growth (Delort et al., 2015).

**Estrogen level (Es)**

The current study indicates that the increase in the level of vital criteria (Es) in patients with breast cancer may be attributed to the increase in body mass index and the source of estrogen synthesis, as there is a positive relationship between body mass index and breast cancer (Wada et al., 2014), as well as the tendency to obesity. Weight gain may positively bind to the estrogen receptor (Ahn et al., 2007), as estrogen has an important role in stimulating the growth and development of obesity-related breast cancer, especially among obese postmenopausal women (Renehan et al., 2008) that postmenopausal circulating estradiol levels are proportional to fat mass and directly correlated with breast cancer risk, as a 50% lower risk of breast cancer was observed among women who lost more than 10 kg and maintained it after menopause (Stewart et al., 2009) In addition,
body mass index (BMI) is positively correlated with tissue levels of estrogen (schaier et al., 2016; Kakugawa et al., 2017).

As for the source of estrogen synthesis, estrogen biosynthesis differs between pre-menopausal and post-menopausal women. Pre-menopausal women produce estrogen from the ovaries (Cui et al., 2013). In postmenopausal obese women, adipose tissue is the main source of estrogen biosynthesis (Brown et al., 2012). The main mediator of postmenopausal estrogen biosynthesis is aromatase, a rate-limiting enzyme in estrogen biosynthesis and its expression is assumed to be in Adipose stromal cells of the breast drive the growth of breast tumors and confer endocrine therapy resistance in postmenopausal obese women (Bhardwaj et al., 2019). Therefore, with increased fat mass and body weight, aromatase expression and consequently estrogen levels increase (Morris et al., 2011; Brown et al., 2017).

In addition, peripheral estrogen production in postmenopausal women plays a critical role in regulating local and circulating estrogen concentrations (Li et al., 2015). Estrone (E1) and 17β-estradiol (E2) levels in adipose tissue (AT) are several times higher than in circulation reflecting active local estrogen synthesis in adipose tissue (AT) (Savolainen-Peltonen et al. 2014; Vihma et al., 2016). Visceral obesity is more associated with subcutaneous obesity than with chronic inflammation and AT dysfunction which increases the risk of estrogen receptor positive postmenopausal breast cancer (Rose and Vona-Davis, 2010) and metabolic disorders (Smith et al., 2012; Lee et al., 2013). Obesity stimulates neoplastic environments through multiple biological pathways including endogenous sex hormone synthesis, inflammation and insulin resistance (Healy et al., 2010). Obese women have large amounts of fat cells that serve as primary sources of hormone production. Estrogen after menopause. For example, androgens originating from the adrenal glands are converted to estrogen by adipose cells (Clemons and Goss, 2001). Therefore, women with higher amounts of body fat tend to have higher levels of circulating estrogen and this stimulates breast tissue that is more sensitive to estrogen and which may already have a tendency to hyperstimulate which ultimately promotes tumor formation and development (Dal Maso et al., 2008) In addition, adipose tissue produces many cytokines, growth factors, and inflammatory factors that may in turn lead to the activation of sex hormones. Moreover, insulin resistance, adipocytokines and leptin are also important factors for the formation and progression of obesity-inducible breast cancer (Maccio et al., 2010; Rock et al., 2012).

Estrogen plays an important role in breast cancer carcinogenesis. It either promotes the growth of abnormal cells or the survival of existing mutated cells, or estrogen induces genetic damage that leads to cell transformation (Clarke et al., 2003). Two types of estrogen receptors (ERs) have been identified, ERα and ERβ receptors (Banerjee et al., 2014; Simons et al., 2014). ERα in the beneficial effect of estrogen on adipose tissue distribution, glucose metabolism, and inflammation (Luglio, 2014).

In breast cancer, estrogen can act via genomic and non-genomic mechanisms. The genomic actions of estrogen receptors (ERs) are associated with the regulation of estrogen responsive gene expression (ERE) (Deroo and Korach, 2006) in estrogen-dependent genomic activation. (ERE) Estrogen binding to its receptors increases interaction with activator proteins for ERE binding in DNA, leading to changes in gene expression that regulate growth, differentiation, apoptosis and angiogenesis (Hall et al., 2001). However, estrogen can also facilitate gene transcription via pathways that do not require ERs. In gene activation-independent ERE, the estrogen-ER complex can also interact with other DNA-binding transcription factors such as Fos/Jun in order to bind to AP-1 (Activating protein-1) sites in the inducible regions of target genes, resulting in the activation of gene transcription. (Deroo and Korach, 2006) Non-genomic effects are actions that are mediated by activation of a site close to or on the plasma membrane (Marino and Ascenzi, 2008).

Additionally, endogenous sex hormones can influence the lipid profile of premenopausal and postmenopausal women because estrogen and androgen receptors are expressed in both visceral and subcutaneous adipocytes so changes in levels of endogenous sex hormones may affect lipid metabolism in adipose tissue in middle-aged women (Marchand et al., 2015). and that postmenopausal women

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exhibit higher total body fat mass, lipid ratio and higher central fat accumulation than premenopausal women (Razmjou et al., 2018).

About 70% of breast cancer patients are ER+ positive. Estrogen receptor alpha (ERα) is a major driver of tumor growth in ER+ breast cancer as ERα cooperates with several other transcription factors to control gene expression and ultimately tumor growth (Salhia et al., 2011).

**Human Receptor Activator of Nuclear Factor Kappa B (RANK)**

The observed increase in the RANK level in breast cancer patients in the current study may be due to the changes in the levels of the sex hormones estrogen.

Progesterone and the pro-carcinogen RANKL and RANK have been implicated in the emergence of hormone-induced breast cancer (Rao et al., 2018).

Higher concentrations of soluble RANKL are positively associated with an increased risk of estrogen receptor-positive (ER+) breast cancer (Sarink et al., 2017) and a study (Vidula et al., 2017) revealed that RANK expression is increased in ER-negative breast cancer, to estrogen receptor (ER-) and is associated with recurrence-free metastasis. Because RANK and RANKL are essential molecules downstream of sex hormones in the mammary gland, it has been speculated that the RANKL/RANK pathway also plays a major role in the aetiology of breast cancer caused by BRCA1 mutation (BRBreast Cancer gene 1, which are genes that produce proteins that help repair acid damage). Nuclear and everyone has two copies of these genes - one copy inherited from each parent BRCA1 and BRCA2 are sometimes called tumor suppressor genes because when there are certain changes called harmful or pathogenic variants or mutations cancer can develop (Tung et al., 2018). The BRCA1 gene is expressed in many tissues such as breast and ovarian tissue (Oh et al., 2019). And women with mutations in the BRCA1 germline had higher levels of progesterone and estrogen than women without such mutations, indicating a connection between RANKL/RANK activity, which is increased in the progesterone-driven luteal phase (Widschwendter et al., 2013) and in carcinomas. Primary breasts expressing a BRCA1 mutation we observe significantly increased expression of RANK and an enhanced tumor invasiveness and increased tumor potential and metastases (Palafox et al., 2012).

In addition, RANKL in bone tissue can attract RANK-expressing breast cancer cells to the bone matrix (Jacob et al., 2011), and that osteoblasts and bone marrow stromal cells that produced RANKL could not only attract RANK-expressing tumor cells but also stimulate their migration. This mechanism has been observed in many types of cancer including breast cancer and that about 25% of breast cancer cells express RANK (Chawla et al., 2013). Cells that overexpress RANK when injected intra-arterially have shown faster tumor progression and a lower overall survival rate due to their enhanced colonization of bone and that overexpression of RANK reduces intercellular contact and enhances migration (Palafox et al., 2012). Enhanced migration of RANKL activates specific signaling cascades such as the MAP (Mitogen-activated protein (MAP) kinases) pathways. Next, the RANKL/RANK axis regulates breast cancer cell migration and RANKL acts as a chemoattractant on cancer cells that overexpress one of its receptors (Sousa et al., 2018).

In addition to directly attracting RANK-expressing breast cancer cells RANKL can also modulate the microenvironment of the metastatic site. RANKL is not only expressed by breast epithelial cells but is also expressed on the surface of breast cancer cells and RANKL can promote the survival and proliferation of epithelial cell precursors during breast development while simultaneously regulating the expression of RANK. Through its interaction with RANK, RANKL can facilitate new formation of vascular tubes and then stimulate angiogenesis. Blood vessels provide nutrients necessary for the proliferation of cancer cells and act as one of the most widespread means of cell migration. Additionally, RANKL increases vascular permeability which helps breast tumor cells escape from the blood vessels into regular circulation (Wu et al., 2020).

RANKL/RANK confers resistance to radiation causing cell death in breast epithelial cells, altering cell adhesion and regulating the self-renewal capacity of tumor stem cells, all of which can contribute to the development of breast cancer (Schramek et al., 2010).
Estimation levels of some hormones such as, Leptin, Estrogen and Human Receptor Activator of Nuclear Factor Kappa B (RANK) may use as useful biomarker for detecting breast cancer.

REFERENCES


