ORIGINAL ARTICLE

Association of Leptin and Breast Cancer: A Systematic Review and Metaanalysist

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ABSTRACT
Introduction: The risk factors for breast cancer consist of intrinsic, extrinsic and hormonal factors.
Method: In the last ten years this meta-analysis taken literature based on full-text English journals published. This article aims to discuss the link between leptin levels and the incidence of breast cancer. The databases that we use in writing this article are Sage Pub, Pubmed and Google Schoolar. PICO (Patient, Index, Comparative, and Objective) analysis used in this study included patients with breast cancer, the index examined was the patient's leptin level, and comparisons were made on patients without breast cancer.
Result: When it comes to breast cancer, the hormone leptin has been connected to a number of various phases and processes, including the progression of the disease itself.**Conclusion:** Most of the studies obtained showed that patients with breast cancer had higher levels of leptin with more severe disease grade, metastases, and ER(+).
Keyword: Breast Cancer, Leptin, Obese, Menopaused

INTRODUCTION

As of 2012, cancer killed 8.8 million individuals, with an estimated incidence of 14 million cases; cardiovascular disease was the leading cause of death among noncommunicable diseases (17.7 million people). 2 There are new instances of breast cancer an estimated 252,710 projected to be treated in the United States in 2017, 63,410 new cases of breast cancer, and from breast cancer around 40,610 deaths. 2,3

Surveillance data from the Riset Kesehatan Dasar (Riskesdas) shows that cancer is prevalent in Indonesia at 1.4 out of every 1,000 persons. After cervical cancer, the second most common cancer in Indonesia in 2018 is breast cancer, with a prevalence of 0.5 percent for breast cancer. 4 Breast cancer risk factors include internal, external, and hormonal variables. 5 Identifying modifiable characteristics that can aid in the development of breast cancer prevention measures. 5 Indeed, data from cell and animal models and human breast cancer biopsies support this theory. 6

Oestrogen-positive breast cancer cells are made more tumorigenic by leptin. Many studies have implicated leptin in breast cancer development. Ex vivo studies showed that LEPR and ER expression in breast cancer cell lines was statistically significant, and that the two receptors had bidirectional communication. 7 The leptin hormone has been associated to a number of different processes and stages in breast cancer, including its progression. Because of this, leptin's effects are enhanced by numerous oncogenes, cytokines and growth factors. 8

MATERIAL AND METHODS

To compile the data for this meta-analysis, researchers consulted full-text English articles published during the last decade. It is the goal of this article to study the connection among raised leptin levels and a higher likelihood of developing breast cancer The databases we used to conduct our research and create this work include Sage Pub, Pubmed, and Google Schoolar. Cancer patients' leptin levels were compared to those of cancer patients without the disease using the PICO approach (Patients, Index, Comparative, and Objective). Breast cancer incidence and leptin levels are to be studied. The review includes both clinical investigations and randomised medical trials.

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) paradigm, researchers entered keywords into each database before conducting a search. There were also searches for the terms "Leptin," "Breast Cancer," and "y 10." (("leptin"[MeSH Terms] OR "leptin"[All Fields] OR "leptin s"[All Fields]) OR "leptine"[All Fields] OR "leptines"[All Fields]))) Five publications have been received by researchers, which will be featured in the subsequent debate (Table 1).
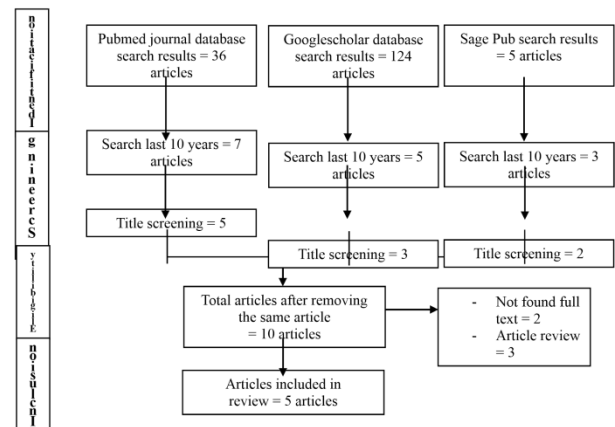

Figure 1: Article search flowchart

RESULT

Figure 1 and Table 1 show studies linking leptin levels to breast cancer. Amir's early research links host factors to breast cancer risk. The leptin assay used a fasting serum

sample taken during trial enrollment (adipocytokine). 231 cases and 856 controls were matched. The study included 49% premenopausal women. Leptin levels did not affect breast cancer risk (all p values less than 0.052). The tamoxifen benefit and leptin levels were unrelated. 9

Table 1: The litelature include in this study

Author	Origin	Method	Sample Size and Population	Period	Result	Outcome
Amir, 2012⁹	Canada	Case–control study design	Two hundred and thirty-one cases were matched with 856 controls	1992 and 1997	Mean leptin level in patient with breast cancer invasive and not is 53.1 vs 9.8, r = 0,12	Leptin levels were not associated with breast cancer risk (all p > 0.052)
Hosney, 2017¹⁰	Egypt	Clinical Trial	A total of 44 female patients diagnosed with breast cancer and 24 healthy donors	February 2013 and August 2014	Association between leptin expression and breast cancer patient (r=0.916, p <0.001)	The results demonstrated a statistically significant increase in the level of leptin in plasma samples from the tumor microenvironment of obese patients with estrogen receptor positive (ER+) breast cancer, compared with peripheral plasma samples.
Assiri, 2015¹¹	KSA	Clinical Trial	A total of 82 BC newly diagnosed and histologically confirmed	March 2011 till December 2013	Serum levels of leptin were significantly higher in BC patients than controls (p <0,001). No significant difference between premenopausal BC patients and premenopausal controls for leptin (p = 0.52).	Leptin serum levels as risk factors for postmenopausal BC
Author	Origin	Method	Sample Size and Population	Period	Result	Outcome
Liu, 2018¹²	China	Clinical Trial	794 cases and 805 matched controls were sequentially enrolled	No date	The unconditional logistic regression model showed that persistent overweight (BMI ≥24 kg/m2) over the preceding 10 years was associated with increased breast cancer risk in premenopausal women (odds ratio [OR] =1.67, 95% confidence interval [CI]: 1.19–2.35).	In premenopausal women, persistent overweight (BMI =24 kg/m2) over the preceding 10 years increases breast cancer risk. Persistent overweight along with LEPrs7799039 AA or LEPRrs1137100 GG genotypes synergistically increase risk of breast cancer among premenopausal women.
Matini, 2015¹³	Iran	Cross-sectional study	130 patients (Sixty-five patients with breast cancer)	2010 and 2011	Circulating levels of leptin were 20.05±14.69 vs. 14.74±10.16 mL in malignant and benign groups, respectively (P=0.011). A positive correlation was observed between BMI and leptin concentration (r = 0.431, P < 0.001). Leptins levels were not associated with the patients' age (P = 0.108), menstrual status (P = 0.214), and history of OCP use (P = 0.269).	Patients with breast cancer have significantly higher levels of leptin compared to those with benign lesions.

Hosney researches leptin and the cell proliferation signalling pathway. and At Ain Shams University Hospitals (Cairo, Egypt) healthy donors and breast cancer patients. Obese breast cancer tissue had increased leptin expression than overweight and normal samples (P0.001). Oncogenic ER+ leptin+ breast cancer cells. ¹⁰

Table 2: Summary of study results

Study	Mean	SD	OR	Lowest CI	Higest CI	R	p
Amir (2012)	53	7	1,38	0,99	1,93	0,122	0,052
Hosney (2017)	60	6				0,916	0,001
Assiri (2015), Premenopaused	20	2				0,083	0,52
Assiri (2015), Postmenopaused	30	5	0,24	1,3	3,8	0,762	0,001
Liu (2018), Premenopause			1,67	1,19	2,35		0,001
Matini (2015)	25	17				0,431	0,001

According to Assiri, premenopausal BC patients exhibited higher serum levels of leptin than premenopausal controls (p = 0.52). Postmenopausal BC grade, onset, and lymph node metastasis are increased by leptin, but not premenopausal BC. 11 Chronic overweight (BMI 24 kg/m2) was linked to an elevated risk in premenopausal women of breast cancer (OR 1.67, 95 percent CI 1.19–2.35).
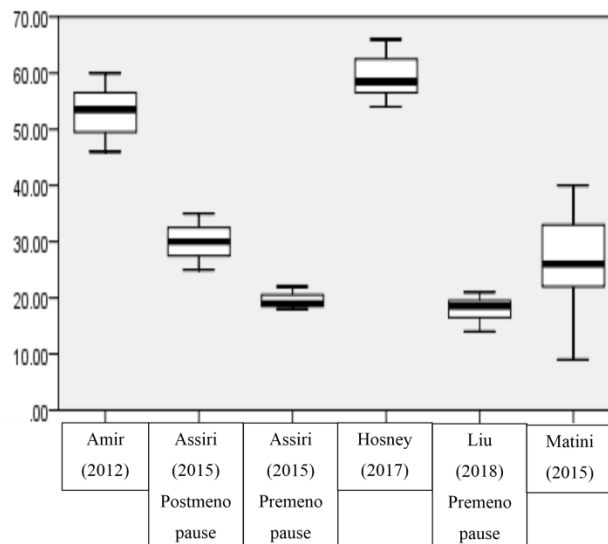

Figure 2: Boxplot for Table 2.

Matini et al. looked at the serum levels of leptin in patients with malignant and benign breast tumours. The cancer group had 20.0514.69 mL of leptin circulating while the benign group had 14.7410.16 mL (P=0.011). The BMI and leptin levels correlated positively (r = 0.43, P = 0.001). There was no association between Leptin levels and age, menstrual status, or OCP use history. The study found that breast cancer patients have higher levels of leptin than benign tumours. 13

DISCUSSION

Over 400,000 individuals die each year from breast cancer, and one million new cases are discovered. In postmenopausal women, being overweight or obese is a contributing factor to the onset of this disease. The importance of adipokines, which are produced by adipose tissue and released into the bloodstream, is now widely understood. Changes in plasma adipokine levels caused by obesity may have "remote" effects on breast cancer development. 14,15

Premenopausal breast cancer patients had lower leptin levels than postmenopausal breast cancer patients, according to a new study. 11 Obesity in postmenopausal women can have a variety of negative effects on their health. Aromatase, a hormone-converting enzyme found in adipose tissue, is thought to increase oestrogen levels in those who have more adipose tissue than the average person. Obese postmenopausal women have lower levels of sex hormone-binding globulins (SHBGs), which increases their risk of breast cancer and free/bioavailable oestrogen. Fats and pro-inflammatory cytokines may play a role in disease progression through excess adipose tissue, according to some researchers. 16

Many ideas relate obesity to ailments like diabetes, heart disease, and cancer. Adipose tissue is an endocrine organ that produces hormone-like substances (cytokines) such as leptin, resistin, and adiponectin. These adipokines, including leptin, contribute to obesity-related inflammation and insulin resistance. Obese folks have higher levels of

leptin in their blood. Many studies show that leptin promotes breast cancer cell growth. 16

Obesity is often associated with diseases like diabetes, heart disease, and cancer. Leptin, resistin, and adiponectin are hormone-like molecules (cytokines) produced by adipose tissue. Obesity-related inflammation and insulin resistance are caused by adipokines, particularly leptin. The hormone leptin is more prevalent in the blood of obese people. Leptin has been shown to increase breast cancer cell proliferation in a number of research studies. 16

Locally, an adipocyte microenvironment surrounds and influences breast cancer cells, which is more common in obese people. In obese people Leptin may contribute to local pro-inflammatory processes, who are at higher risk to develop metastases and from the disease they die. Leptin regulates energy levels in the body and has a function in anorexigenic processes via hypothalamic feedback. 14,15

It is able to control calorie intake and hence fat tissue production through the employment of hormonal intermediates. Additional studies have revealed that leptin can affect fertility, lactation, reproduction, bone mineral density hematopoiesis proliferation and immune response angiogenesis of a variety of cell types, including those found in breast tissue. 16 When leptin stimulates the activation of the AKT and ERK signalling pathways, ER-positive breast cancer cells become susceptible to cytochrome P450 1B1 (CYP1B1). 17

In ER-positive breast cancer cells, leptin from adipose stem/stromal cells also causes a unique pattern of gene expression. Leptin's actions are also mediated through ER-alpha crosstalk. Leptin-induced STAT3 activation and subsequent ERK1/ERK2 signalling activation have both been linked to ER-dependent breast cancer progression. 18

Using a new method in ER-positive cells the function of leptin in breast cancer growth has recently been hypothesised. CCN5, a cancer anti-invasive protein found in the extracellular matrix, is inhibited by JAK/STAT3-Akt signalling pathways. Other investigations have shown that oestrogen receptor signalling plays a vital role in the development of breast cancer cells induced by leptin via activation of autophagy. 19,20

When leptin activates matrix metalloproteinase (MMP-2) and epidermal growth factor receptor (EGFR) in MCF-7 cell lines, the adhesion, migration, and invasion processes are accelerated (EGFR). Chronic inflammation in adipose tissue in obese people may account for the greater amounts of leptin found in the breast tumour microenvironment of obese patients. 21,22

Obese women's breast cancer samples had significantly higher leptin levels (P 0.001) than did those of normal weight women and healthy controls. 10 Obese women are more likely to have advanced breast cancer metastases if they had increased adipo-triglyceride lipase expression and decreased pigment epithelium-derived factor expression. The breast tumour microenvironment of obese persons is activated by insulin and insulin-like growth factors, inflammatory cytokines, and VEGF. 21,22

Leptin increases the expression of MAPK and STAT3, which activates aromatase and increases oestrogen synthesis in breast cancer patients who are obese and have oestrogen receptor positive (ER+) cells. Oestrogen activates a variety of processes in breast cancer, including cell division, angiogenesis, and proliferation. According to the findings of this study, obese females having ER+ breast cancer are at a high risk to produce leptin, a hormone that promotes breast cancer growth. 15

CONCLUSIN

Most of the studies obtained showed that patients with breast cancer have highr levels of leptin with more severe disease grade, metastases, and ER(+).

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