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RESEARCH ARTICLE

STUDY OF SERUM LEPTIN LEVELS WITH HISTOLOGICAL GRADING AND RECEPTOR STATUS IN BREAST CANCER PATIENTS WITH METABOLIC SYNDROME

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ABSTRACT

Objectives
1)To measure serum leptin level in patients with carcinoma breast
2)To study the correlation between metabolic syndrome as well as its individual parameters and grading and receptors in patients of carcinoma breast
3)To evaluate rise of serum leptin levels in patients with carcinoma breast with metabolic syndrome(MS) in comparison to values in patients with breast cancer without MS.
Method: A cross sectional study was carried out with 66 patients of proven carcinoma breast. Serum leptin of all the patients were analysed using ELISA. All the parameters of MS were recorded individually as defined according to NCEP-ATP3(National Cholesterol Education Program and Adult Treatment Panel). Histopathological grading was done by using SEER and modified bloom Richardson grading. The data was carefully tabulated in a proforma and statistically analysed by statistician using SPSS. ***Results:*** In our study out of 66 ,38 (57.57%) patients were in TNBC group and 28 (42,42%)in receptor positive group.The mean age in receptor positive group was 49.32= 14.56 and in TNBC 51.16=10.47.in receptor positive group 85.7% had waist circumference >80cm and in TNBC group 73.7% had WC >80 cm . Total 32 (48.48%) patients had MS, in receptorpositive group 13/28(46.43% had MSand 15/28(53.57% did not fall in MS category, however in TNBC 19/38(50%) had MS and equal no 19/38(50%)did not have MS and the P value obtained was 0.716 which was statistically non significant. Inreceptor positive group 28.57% had grade 3 histological grading and in receptor negative group 52.63% patients had grade 3 histology.In receptor positive group 6/28 (21.4%)had serum leptin levels were <11.1 pg/dl and 22/28 (78.6%) had serum leptin level >11.1%.In TNBC group 4/38 (10.5%) patients had serum leptin level <11.1pg/dl and 34/38(89.5%) patients had serum leptin level >11.1 pg/dl and the P value obtained was 0.03 which was statistically significant. ***Conclusion:*** Thus the increased serum leptin levels have strong correlation with TNBC and high grade breast cancers and correlation with MS was equivocal .The correlation with Ki 67 was also statistically significant while comparing both groups.

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INTRODUCTION

Breast cancer is heading towards the leading cause of oncologic morbidity and mortality among women worldwide. According to international consortium of researchers, co-ordinated by Institute of Health Metrics and Evaluation (IHME) at University of Washington showed breast cancer as top killer among women in India. India and China are accountable for one third of the global burden of breast cancer (Statistics of breast cancer in India, 2012). The life time risk of woman being diagnosed with breast cancer is approximately 12 % in the western countries. Many factors known to increase the risk of breast cancer are non modifiable, such as age ,family history ,early menarche and late menopause .Understanding how modifiable life style risk factors affect breast cancer incidence may have important implications for the prevention and management of this malignancy ,especially in countries with a high disease burden (American Cancer Society, 2015).

There are several risk factors for Carcinoma breast such as:

- Female sex
- Increased age
- Race & Ethnicity- Between the ages of 60 and above breast cancer rates are higher in white women. However, black women have a higher incidence rate before age 45 and more likely to die from breast cancer at every age.
- Positive family history
- Genetic predisposition
- Personal history of breast cancer. Women diagnosed with early onset breast cancer (age <40) have almost a 4.5 fold increased risk of subsequent breast cancer.
- Ductal or lobular carcinoma in situ
- Breast density - greater breast density have about a 1.6 or 2.3 times respectively, higher risk of breast cancer. Perhaps more

importantly, mammographic detection of breast cancer is impaired in areas of dense breast tissue.

- Endogenous hormone levels. It has been found that high levels of circulating estrogens and androgens are also associated with a small increased risk of breast cancer in premenopausal women.
- Menstrual cycle:- Breast cancer risk increases slightly for each year earlier menstruation Begins (by about 5%) and for each year later menopause begins(by about 3%)
- Bone mineral density: - High bone mineral density in postmenopausal women has been associated with increased risk for breast cancer in many, but not in all and risk appears to be most strongly related to ER+ disease.
- 12. Reproductive factors Pregnancy, Fertility drugs, Breastfeeding, Hormonal birth control, Post menopausal hormones influences occurence of BC.
- Obesity
- Physical activity
- Diet
- Alcohol
- Environmental and other risk factors

MS is emerging as risk factor for BChowever few studies ,most confinedtopost menopausal women have investigated association between breast cancer risk and metabolic syndrome(3) .Being overweight or obese negatively affects DFS in TNBC for which India is emerging as home (Choi, 2016). TNBC accounts for 10-17% of all BC ,and both TNBC andbasal like breast cancer tend to be of high histological grade with limited therapeutic options and a significant overlap in their biological and clinical characteristics repeatedly shown by moleculartechniques (Thike, 2010). It is well established that elevated levels of leptin plays vitalrole in causation of BC by enhancing BC cell proliferation inhibiting pro-apoptosis signalling pathways and by favouring in vitro sensitivity to oestrogen (Niu, 2013). Higher plasma leptin levels are associated with obesity,insulin resistance and MS. It is a common observation that majority of women with oneor more affected first degree relative seldom develop BC and most women who develop BC do not have a family history of disease .This strengthens the role of environmental factors and life style associated factors in causation of BC (Collaborative group on hormonal factors in breast carcinoma familial breast cancer, 2001). The current study was endeavoured o investigate the association between serum leptin levels with histological grading and receptor status in BC patients with or without MS .If strong correlation found between BC and attributable modifiable risk factors in form of MS ,adapting preventive strategies (guidelines for nutrition and physical activity) would be a key to nail down the increasing incidence and associated morbidity of BC in India.

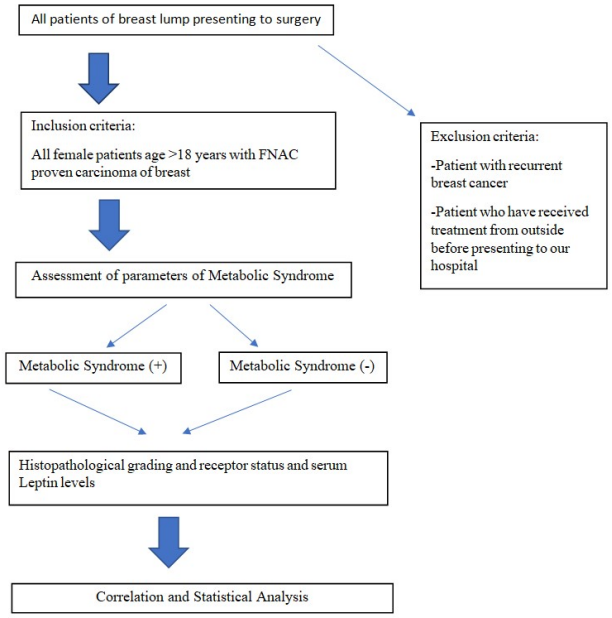
METHODS

This was the cross sectional study carried out in Department of General Surgery, Pathology and Biochemistry, Lady Hardinge Medical College and Associated hospitals, New Delhi from November 2016 to April 2020 with approval from research and ethical committee (LHMC/ECHR/2016/130). The study population n=66 comprised of all female patient >18 years of age with FNAC/TRUCUT biopsy proven BC. The patients with metastatic breast disease were excluded from study. All the patients were subjected to a detailed history, physical examination and biochemical, pathological and radiological evaluation. Serum leptin of all patients were analysed using ELISA (Markowaska, 2004) All the parameters of MS were recorded individually as defined according to the NCEP-ATPIII guidelines with an anthropometric modulation of WC value that is specifically applicable to SouthAsians (Misra, 2005). Patients were defined as having MS when they m*et al* least 3 out of 5 criteria

- 1)Elevated WC:>90cm in men >80 cm in women
- 2) Elevated BP:SBP>130&DBP >85mmHg
- 3) Reduced HDL Ch <40mg/dl in men<50 mg/dl in women
- Elevated fasting glucose :>110mg/dl
- Elevated TG :>150 mg/dl

Histopathological grading was done by using SEER and modified Bloom Richardson grading was taken in to consideration ER, PR and HER 2 Neu and Ki 67 were documented for all patients (Fitzgibbons, 2019).

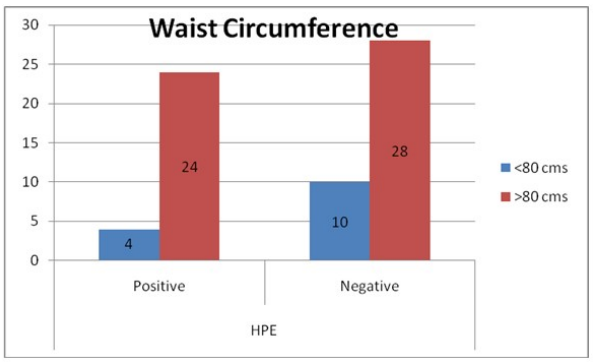
Flow chart



RESULTS

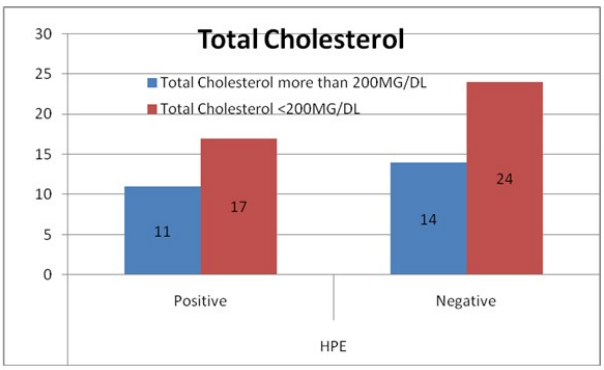
Table 1. The distribution of the study group according to the demographic and body habitus group

PARAMETERS	HPE		P Value
	Positive	Negative	
	Mean ± SD	Mean ± SD	
Age	49.32 ± 14.56	51.16 ± 10.47	0.573
Height	152.21 ± 11.02	153.29 ± 7.99	0.663
Weight	65.82 ± 12.35	63.66 ± 11.71	0.471
BSA	1.62 ± 0.19	1.62 ± 0.16	0.953
Waist Circumference	89.5 ± 9.43	87.89 ± 9.32	0.494



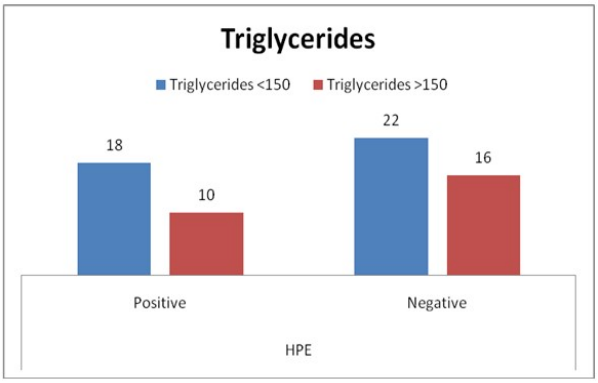
Graph 1. Waist Circumference

The mean age in receptor positive group was 49.32+ 14.56 years while in receptor negative group 51.16+10.47 years. The mean height was 152.21+11.02 cm and 153.29+7.99 cm in respective groups. The mean weight was 65.82+12.35 kg in receptor positive group while 63.66+11.71kg in receptor negative group. The mean waist circumference was 89.5+9.43cm in receptor positive group and 87.89+9.32 cm in receptor negative group.



Graph 2. Total Cholesterol

There was no statistical significance in between two groups with a p value more than 0.05 hence the two groups were comparable. In receptor positive group only 4 patient (14.3%) had WC < 80 cm and 24 patients (85.7%) had WC >80 cm.



Graph 3. Triglycerides

Table 2. HDL

	frequency	%	frequency	%	
hdl >50	14	50.0%	12	31.6%	0.130
hdl <50	14	50.0%	26	68.4%	
total	28	100%	38	100%	

In receptor negative group 10 patients had WC <80 cm and 28 had WC >80 cm with p value 0.362. In receptor positive group 11(39.3%) patients had total cholesterol >200mg/dl and 17(60.7%) had <200mg/dl, however in receptor negative group the number was 14 (36.8%) and 24(63.2%) in respective groups with p value 0.840.

Table 3. Blood pressure

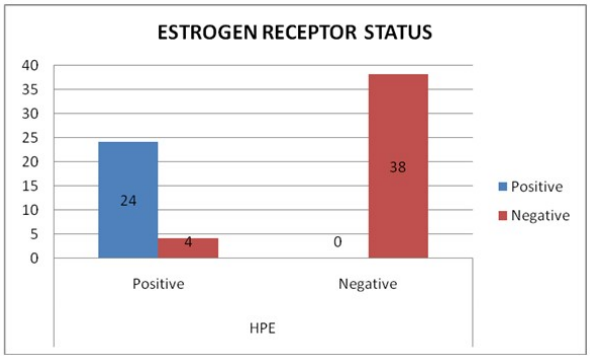
BP	HPE				P Value
	Positive		Negative		
	Frequency	%	Frequency	%	
Normal	16	57.1%	18	47.4%	0.432
Increased	12	42.9%	20	52.6%	
Total	28	100%	38	100%	

In receptor positive group 18 patients (64.3%) had TG <150mg/dl and 10 (35.7%) had >150 mg/dl and in receptor negative group 22(57.9%) had TG < 150 and 16(42.1%) had TG >150mg/dl wih p value 0.599.

METABOLIC SYNDROME

Table 5. Metabolic Syndrome

Metabolic Syndrome	HPE				P Value
	Positive		Negative		
	Frequency	%	Frequency	%	
No metabolic syndrome	15	53.57%	19	50%	0.716
Metabolic Syndrome Present	13	46.43%	19	50%	
Total	28	100%	38	100%	



Graph 4. Estrogen Receptor Status

The number of patients having HDL>50 was 14 in receptor positive group and 12 in receptor negative group.14 patients had HDL < 50 were in receptor positive group and 26 (68.4%) were in receptor negative group with p value o.130. In receptor positive group 16(57.1%) patients had normal BP and 12(42.9%) had raised BP .In receptor negative group 18 patients had normal BP and 20 had raised BP with p value 0.432. In receptor positive group 16 (57.1%) patients had normal FBS levels and 12 (42.9%) had >110mg/dl. In receptor negative group 22(57.9%) had normal FBS and 16 (42.1%) had raised levels with p value 0.748. I our study out of 66 patients 32 were found to have MS and 34 patients were not fiting in to the criteria of MS. The p value obtained for correlation between receptor positive and negative group was 0.716which was statistically non significant. Total number of patients in receptor positive group was 28 out of which 24(85.7%) showed ER positive status and 4(14.3%) did not show ER expression. The number of Triple negative was 38.The p value obtained for this correlation was (o.001) which was statistically significant. Statistically significant correlation was found with progeateron receptor too.

SERUM LEPTIN LEVELS

S LEPTIN	HPE				P Value
	Positive		Negative		
	Frequency	%	Frequency	%	
<11.1pg/dl	6	21.4%	4	10.5%	0.0302
>11.1pg/dl	22	78.6%	34	89.5%	
Total	28	100%	38	100%	

HER2neu RECEPTOR STATUS

Table 7. Her2neu Receptor Status

HER2Neu	HPE				P Value
	Positive		Negative		
	Frequency	%	Frequency	%	
Positive	12	42.9%	4	10.5%	0.004
Negative	16	57.1%	34	89.5%	
Total	28	100%	38	100%	

The correlation between two groups was statistically significant with p value of 0.04.

Table 8. Distribution according to histological grading

	Receptor +ve		Receptor -ve	
	Number	%age	Number	%age
Grade-I	2	7.14	3	7.89
Grade-II	18	64.28	15	39.47
Grade-III	8	28.57	20	52.63
	28		38	

In receptor positive group 22 patients (78.6%) had serum leptin >11.1pg.dl and the number in receptor negative group was 34patients (89.5%).Six paients in receptor positive group and 4 in receptor negative group had serum leptin <11.1pg/dl.The p value obtained for this correlation was 0.03 which was statistically significant.

Ki 67 Proliferative Index

Table 8. Ki 67 proliferative index

KI 67	HPE				P Value
	Positive		Negative		
	Frequency	%	Frequency	%	
<35	20	71.4%	7	18.4%	<0.001
>=35	8	28.6%	31	81.6%	
Total	28	100%	38	100%	
Sensitivity	Specificity	PPV	NPV	Accuracy	
81.6%	71.4%	79.5%	74.1%	77.3%	

The correlation between two groups was statistically significant with p value of 0.04. In receptor positive group 2/28 (7.14%) had grade 1 and 8/28(28.57%) had grade 3 histology. In receptor negative group 3/38 had grade 1 and 20/38(52.63%) had grade 3 histology. In receptor positive group 20 patients (71.4%) had Ki 67 proliferative index <35 8 (28.6%) had >35.In receptor negative group 7(18.4%) had Ki 67 proliferative index <35 and 31(81.6%) had >35.P value obtained for this correlation was 0.001which was statistically significant.

DISCUSSION

Breast cancer incidence: GLOBOCON 2020 states the number of BC cases 178361(26.3%) of all cancers in women in India. India has faced an epidemic of disease with 11.54% increase in incidence and 13.82% mortality due to BC during 2008-12.BC is most common cancer in women in all population based registries of India (Mathur, 2020; Ferlay, 2010) TNBC. The TNBC has become the root cause of poor prognosis not only in premenopausal but in postmenopausal ladies too. TNBCs lack expression of the steroid receptors ER,PR and tyrosine kinase HER 2 ,therefore TNBCS are a diagnosis of exclusion ,typically characterized by upregulation of cytokeratines 5,14 and 17 and elevation of the EGFR and only 15-20% BCs meet these criteria. Compared to other BC subtypes these are aggressive, invasive (ductal, medullary, or metaplastic) grade 3 tumours with high rates of mitotic division ,of which nearly half contain high rate of P 53 mutation and account for high metastasis ,recurrence and death. TNBC in west has been reported at 12.2-13% but in several Indian reports it is up to 31 % (13,14 ,15). With the advances that have been taking place in the field of medical research, numerous markers have been found to be substantial both in diagnosis and in the therapeutic armamentarium for BC, however the price and limited accessibility of such amenities makes an obstacle for the use of these modalities especially in resource poor countries. In our study TNBCs were 57.57% which is much higher then the incidence reported in literature,this can be explained on the fact that estimated rate of BC in India is 80 new cases per 100000 population per year and in Delhi, it is estimated to be 146,and in last decade there is rapid increase in TNBCs with geographical concern (Hauner, 2014).

Metabolic syndrome: In the recent past there is insurgence in cases of MS specifically in south-east Asia region and various studies have been conducted to understand the association between MS and increase risk of cancers and other diseases (Bhandari, 2014). Individual components of MS specifically central obesity, diabetes and hypertension have been associated with increased risk of BC, aggressive phenotype and distant metastasis. However in our study MS was found in 32(48.48%) patients but insignificant correlation found between receptor positive and receptor negative group but the exact role of MS in causation of BC needs more specific studies (Hauner, 2014; Maiti, 2010).

Serum leptin: Leptin a protein hormone produced mainly by adipocytes placenta and mammary epithelium plays a significant role in control of metabolism, reproductive process, immune processes, angiogenesis. Circulating leptin is an essential factor regulating fat metabolism and involved in the development BC, having promoting effect on the carcinogenesis and metastasis of breast cancer in autocrine manner.

Functional inhibition of leptin can be effective for the prevention and treatment of BC. In systematic analysis by Li Gu (Li, 2019) of 43 studies serum leptin were higher in BC patients and study by Bhandari *et al* also found positive association between two (Bhandari, 2014). Pathophysiology of the association between MS serum leptins & BC. Insulin resistance is frequent phenomenon with MS resulting in increased insulin secretion and hyperinsulinemia and also leads to subacute inflammation caused by accumulation of immune cells in adipose tissue. An impaired secretion of 'adipokines'including a pro inflammatory cytokines, TNF alpha ,IL 1 beta ,IL-6,IL -8,MCP-1exerting mitogenic, angiogenic, antiapoptotic action lead to tumour progression. Adipose tissue is a major component of tumour environment in breast tissue and there are interactions between cancer cells and adjacent adipocyte leading to formation of cancer associated adipocytes (CAA). These adipocytes in direct contact with BC cells show delipidation and loss of terminal differentiation markers and increased expression of pro-inflammatory cytokines and intensive cross linking between two and it is proposed increased lipolytic activity serve to supply energy to the growing cancer cells (Khandekar, 2011; Park, 2011; Nieman, 2013; Ishikawa, 2004). High level of serum insulin and oestrogen derived from increased adipose tissue are considered to contribute to pathogenesis of BC in obese patient. Serum leptin has been documented to be higher in patients withBC as compared to controls .Higher serum leptin ,intratumoral leptin mRNA and intratumoral ObR isoform mRNA level have been observed to be poor prognosis predictors in patients withBC.Note has been made of increased leptinwith leptin receptor expression in both primary and metastatic BC tissues along with observations that expression of these protein correlated with ER status,tumour size and higher tumour grade irrespective of BMI of patients.Leptin plays an important role in breast carcinogenesis by modulating ER signalling and aromatase activity. Obesity is a well known risk factor for BC and obesity is associated with elevated serum leptin level along with decreased adiponectin. Studies have shown that low levels of adiponectin in the background of increased leptin increases the risk of BC.

Hence a balance between leptin and adiponectin may have a more important role in breast carcinogenesis than either of them alone (Nieman, 2013; Ishikawa, 2004). In a study done by Assiri *et al*. (2015) serum leptin levels were raised in BC patients along with resistin and visfatin and positively correlated with TNM staging ,tumour size, lymph node metastasis in postmenopausal women. In a study by Madhav Danthala *et al*. (2018) serum leptin levels were raised and adiponectin levels were low in BC patients when compared to controls. Study by Claudia Angoli *et al*. (2015) stated that presence of MSwas associated with increased risk of BC. Study by Karaduman *et al*(26) showed significantly higher mean tissue leptin levels in cancer tissue as compared to normal breast tissue. All these studies supported the role of raised serum leptin in BC. The overall prognosis of BC is generally considered superior to other cancers, but some variants like TNBC have poor prognosis. In line with available literature, in our study it was detected that there was agood association with raised serum leptin with detecting cancer and levels were higher in TNBC as compared to receptor positive group we conclude that as the results were positive for association with TNBC ,the levels may be done to screen high risk individuals .And can be used as evidence in explaining prognosis. Nonetheless bigger studies with larger sample size with a longer follow up should be conducted for further evaluation.

SUMMARY AND CONCLUSION

This cross sectional study was conceived and conducted based on our observation of metabolic syndrome had a higher incidence of triple negative breast cancer and higher grade of histology. Our study was a cross sectional study that was done to investigate the association between serum leptin levels with histological grading and receptor status in FNAC proven carcinoma breast with and without metabolic syndrome. We were not able to find the correlation between metabolic syndrome as well as its individual parameters and Grading and receptor status in patients of Carcinoma Breast.

We found that there was s statistical significant risein the serum leptin which is considered as a marker for metabolic syndrome levels in those patients with carcinoma breast having metabolic syndrome in comparison to patients with breast cancer without metabolic syndrome. In our hospital, a large number of female patients coming to surgery outdoor patient department, belong to a both low and socio-economic status, who are overweight or obese and/ or have two or more components of metabolic syndrome are hardly concerned about the problems that can be caused by their body habitus or the metabolic syndrome. Most are unaware that the components of metabolic syndrome are associated with breast cancer .And even in surgery outdoors we have seen there is rapid increase in number of patients with metabolic syndrome. Still there is need for health awareness program to increase awareness among general population in India as more and more people are now facing the problem of metabolic syndrome as a result of the changes in the life style that have taken place. With increasing incidence of breast cancer in females especially at a younger age and efforts should be made to detect the disease early so that the best conservative modalities be done. We feel that, adequate training of the health care workers and awareness of the general public to pay attention to the other modifiable risk factors of breast cancer be made so that the incidence be reduced or disease be detected early in its stage so the a better cure rate with a functional and aesthetic result be done.

CONCLUSION

In our cross sectional study that was done to investigate the association between serum leptin levels with histological grading and receptor status in FNAC, we found that statistical significant risein the serum leptin levels occurred in those with poorer histology or a receptor negative disease This is in concurrence with existing literature and validates our hypothesis. Further studies with a larger study population are recommended to give more information.

REFERENCES

Statistics of breast cancer in India: Global comparison. 2012 A report by International Agency for Research on Cancer.www. breastcancerindia.net/statistic/stat-global.html.

American Cancer Society. Breast Cancer Facts &Figures2015-2016. Atlanta: American Cancer Society, Inc .2015.

Bhandari R, Kelley GA, Hartley TA, Rockett IR. Metabolic syndrome is associated with increased breast cancer risk: a systematic review with meta-analysis. International journal of breast cancer. 2014;2014:189384 doi: 10.1155/2014/189384.

Choi Y, Park SK, Ahn KJ, Cho H, Kim TH, Yoon HK, Lee YH. Being overweight or obese increases the risk of progression in triple negative breast cancer after surgical resection. J Korean Med Sci 2016;31:886-891.

Thike AA, Cheok PY, Jara-Lazaro AR, Tan B, Tan P, Tan PH. Triple-negative breast cancer: clinicopathological characteristics and relationship with basal-like breast cancer. Modern pathology. 2010 Jan;23(1):123-133.

Niu J, Le Jiang WG, Shao L, Liu Y, Wang L. The association between leptin level and breast cancer: a meta-analysis. PLOS one. 2013;8(6).

Collaborative group on hormonal factors in breast carcinoma familial breast cancer: collaborative reanalysis of individual data from 52 epidemiological studies including 58,209 women with breast cancer and 101986 women without disease. Lancet 2001:358:1389-1399.

Markowaska A, Malendowictz K, Drews K(2004).The role of leptin in breast cancer. Eur J Gynaecol Oncol 25:192-194

9)Misra A,Wasir JS,Pandey RM.An evaluation of candidates definition of the metabolic syndrome in adults Asian Indian .Diabetes Care .2005;28(2):398-403

Fitzgibbons PL, Connolly JL, Edgerton M, Simpson R. Protocol for examination of biopsy specimen from patients with invasive carcinoma of breast. Version: Breast Invasive Biopsy1.0.0.0 College of American Pathologists Available at htpp://documents.cap.org/protocols/cp/breast-invasive-biopsy-19-1000.pd.fFebruary 2019

Mathur P,Satish Kumar K,Chaturvedi M,Das P,Sudarshan KL,Santhappan S,etal Cancer Statistics .2020:Report from National Cancer Registry Programme India JCO Glob Oncol .2020 July;(6):1063-75

Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM,. Estimates of worldwide burden of cancer in 2008:GLOBOCON 2008.Int J Cancer .2010Dec15;127(12):2893-917

Cheang MC, Voduc D, Bajdik C, Leung S, McKinney S, Chia SK, Perou CM, Nielsen TO. Basal-like breast cancer defined by five biomarkers has superior prognostic value than triple-negative phenotype. Clinical cancer research. 2008 Mar 1;14(5):1368-1376.

Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)-negative, progesterone receptor (PR)-negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California cancer Registry. Cancer. 2007 May 1;109(9):1721-1728.

Gogia A, Raina V, Deo S, Shukla NK, Mohanti BK. Triple negative breast cancer :An institutional analysis. Indian J Cancer.2014;51(2):163-166

Hauner D, Hauner H. Metabolic syndrome and breast cancer :Is there a link?Breast Care .2014Apr ;9(4)277-281

Maiti B, Kundranda M.N, Spiro T.P, Daw H.A. The association of metabolic syndrome with triple-negative breast cancer. Breast Cancer Res. Tr. 2010;121:479–483.

Li Gu, Wang CD, Cao C, Cai LR, Li DH, Zheng YZ. Association of serum leptin with breast cancer: A metaanalysis. 2019. February. Medicine 98(5):e14094DOI :10.1097/MD.0000000000014094

Khandekar MJ, Cohen P, Spiegelman BM. Molecular mechanism of cancer development in obesity. Nat Rev Cancer.2011;11:886-895.

Park J, Euhus DM, Scherer PE. Paracrine and endocrine effects of adipose tissue on cancer development and progression. Endocr Rev .2011;32:550-570.

Nieman KM, Romero IL, Van Houten B, Lengyel E. Adipose tissue and adipocyte support tumorigenesis and metastasis. Biochem Biophys Acta.2013;1831:1533-1541.

Ishikawa M1, Kitayama J, Nagawa H. Enhanced expression of leptin and leptin receptor (OB-R) in human breast cancer. Clin Cancer Res. 2004 Jul 1;10(13):4325-4331

Adel M.A. Assiri,, Hala F.M. Kamel, Hassanien MF,. Resistin, visfatin, adiponectinand leptin: risk of breast cancer in preand post enopausal Saudi femalesand their possible diagnostic and predictive implicationsas noval biomarkers. Disease markers .2015/Article ID 253519 9 Pages http://doi.org /10.1155/2015/253519

Danthala M, Rajesh GR, Gundeti S, Raju GS, Chandran P, Srinivas ML. Obesity and breast cancer .Association of serum adiponectin ,leptin, adiponectin -leptin ratio as risk biomarkers. *Indian Journal of Medical and Paediatric Oncology*.2018 july1;39(3):292

Angoli C, Grioni S, Sieri S, Sacerdote C, Ricceri F, Tumino R,Frasca G, Pala V, Mattiello A, Chiodini P, Iacoviello L. Metabolic syndrome and breast cancer risk :A case cohort study nested in amulticentre Italian cohort .PLoS ONE2015;10(6)e0128891 doi .1371/journal .pone .012889110

Karaduman M, Bilici A, Ozet A, Sengul A, Musabak U, Alomeroglu M. Tissue leptinlevels in patients with breast cancer Journal of BUON: official journal of the Balkan Union of Oncology.2010;15(2):369-372.

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