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IMPACT AND ASSOCIATION OF BREAST FEEDING WITH BONE AND LIVER METASTASIS IN DIFFERENT STAGES OF BREAST CANCER

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Abstract

Aims: *Goals of this study was to analyze the effect and correlation of breast-feeding practice upon breast cancer patients in the metastatic involvement of bones and liver.*

Breast cancer is the most common cancer diagnosis in women globally and the second-leading cause of cancer-related death of women.

Research Design: *Cross Sectional Study. (Observational Study)*

Methodology: *Study was carried out on 250 patients taken from Jinnah Post Graduate Medical Centre, (department of oncology) clinically and histopathologically diagnosed cases of breast cancer were selected for the study. Study design was approved by Board of Advance Studies, University of Karachi and ethical committee of Jinnah Post Graduate Medical Centre. TNM staging by IHC based on ASCO classification 2008 was done. For detection of liver and bone metastasis C.T scan bone scan and ultrasound was done.*

Results: *Frequency of breast cancer occurrence was found more in patients who did not breast fed their children. Significant correlation was noted between breast feeding practice and tendency to metastasize in bones and liver among all stages.*

Conclusions: *Breast feeding practice as appeared more protective tool from breast cancer development as well as it prevents metastasis to distant organs and slows progress of disease.*

INTRODUCTION

Breast cancer is the most common cancer diagnosis in women, and the second-leading cause of cancer-related death of women in the United States. In 2021, 284,200 novel cases of invasive disease are estimated and 44,130 women and 530 men are estimated to succumb to the disease. Breast cancer mortality is attributable to complications arising from the formation and growth of distant metastases, most commonly that of the liver, lungs, and bone. Only 50–70% of metastatic breast cancer cases involve the liver.

Prognosis is poor following metastasis to the liver, with the median survival rate being only 2–3 years [1 2 3 4 5 6].The most common site of primary lesion for women (age 20–50) was breast, wherein 1.4% of breast cancer patients assessed harbored liver metastasis at the time of primary diagnosis, and that the presence of liver metastasis significantly reduced patient overall survival (OS) compared to patients without liver metastasis (HR 1.94 [1.86, 2.02]). These results were corroborated by univariate logistic regression analyses, confirming the significant impact of liver metastasis on OS in patients with stage IV disease [7]. Basal-like breast cancers frequently metastasize to the lungs and brain, luminal breast cancers tend to metastasize to the bone, and HER2+ breast cancers aggressively colonize the liver. Relative to the other frequent sites of metastasis, liver is one of the most common sites of metastatic relapse [8 9 10 11 12].

Presence of liver metastasis significantly reduced patient overall survival (OS) compared to patients without liver metastasis [13]. The most common site of metastasis in breast cancer is the bone, where the balance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation is disrupted. This imbalance causes osteolytic bone metastasis in breast cancer, which leads to bone pain, pathological fractures, spinal cord compression, and other skeletal-related events (SREs). These complications reduce patients' quality of life significantly and have a profound impact on prognosis. In this review, we begin by providing a brief overview of the epidemiology of bone metastasis in breast cancer, including current diagnostic tools, treatment approaches, and existing challenges. Then, we will introduce the pathophysiology of breast cancer bone metastasis (BCBM) and the animal models involved in the study of BCBM. We then come to the focus of this paper: a discussion of several biomarkers that have the potential to provide predictive and prognostic value in the context of BCBM some of which may be particularly compatible with more comprehensive liquid biopsies. Biomarkers emerge as invaluable tools, offering decision support for the precise selection of treatments tailored to individual patients. Research into the molecular underpinnings of BCBM continually enriches our comprehension of prospective therapeutic targets and clinically significant biomarkers [14].

Ultrasound imaging is a commonly used modality for breast cancer detection and diagnosis. In this review, we summarize ultrasound imaging technologies and their clinical applications for the management of breast cancer patients. The technologies include ultrasound elastography, contrast-enhanced ultrasound, 3-D ultrasound, automatic breast ultrasound and computer-aided detection of breast ultrasound. We summarize the study results seen in the literature and discuss their future directions. We also provide a review of ultrasound-guided, breast biopsy and the fusion of ultrasound with other imaging modalities, especially magnetic resonance imaging (MRI). For comparison, we also discuss the diagnostic performance of mammography, MRI, positron emission tomography and computed tomography for breast cancer diagnosis at the end of this review. New ultrasound imaging techniques, ultrasound-guided biopsy and the fusion of ultrasound with other modalities provide important tools for the management of breast patients [15].

Staging and repeated evaluation of patients with metastatic breast cancer are central to the accurate assessment of disease extent at diagnosis and during treatment; guiding ongoing clinical management. Advances have been made in the diagnostic and therapeutic fields, particularly with new targeted therapies. In parallel, oncological imaging has evolved exponentially with the development of functional and anatomical imaging techniques. Consistent, reproducible and validated methods of assessing response to therapy are critical in effectively managing patients with metastatic breast cancer. Major progress has been made in ontological imaging over the last few decades. Accurate disease assessment at diagnosis and during treatment is important in the management of metastatic breast cancer. CT (and BS if appropriate) is generally widely available, relatively cheap and sufficient in many cases.

However, several additional imaging modalities are emerging and can be used as adjuncts, particularly in pregnancy or other diagnostically challenging cases [16].

RESEARCH DESIGN:
Cross Sectional Study. (Observational Study)

METHODOLOGY
Selection of Patients: The present study was carried out on 250 patients taken from Jinnah Post Graduate Medical Centre, (department of oncology) randomly selected from community. Consent form was described orally to every patient and signature was taken. Demographic data regarding age, parity, breast feeding, marital status, BMI was taken. Study design was approved by Board of Advance Studies, University of Karachi and ethical committee of Jinnah Post Graduate Medical Centre.

Inclusion Criteria: Clinically and histopathologically diagnosed cases of breast cancer were selected for the study. Selected patients belong to different stages like stage 1, stage II, stage III and stage IV. Patients were adult females from 18 years to onward, premenopausal, peri-menopausal and postmenopausal. Cases of all four stages of cancer, married, unmarried, lactating, non-lactating, having different body mass index. Chemotherapy and radiotherapy was allowed accordingly.

Exclusion Criteria: Male patients, Patients suffering from primary Bone diseases, Diabetes, Hepatobiliary disease and previous history of any other type of malignancy were excluded from the study.

Methods: The staging was done on the basis of TNM staging criteria of breast cancer. TNM staging criteria describes observations related to tumor size (T), degree of involvement of regional lymph nodes (N) and metastasis (M). For liver and bone metastasis dectection ultrasound, bone scan and C.T scan were done.

TNM Staging: Specimen received in formalin coded as tru cut biopsy or mastectomy, submitted in single cassette. Tissues were examined for tumor characteristics at chromosome and molecular level at JPMC and BMSI. Histological staging was performed on formalin-fixed paraffin embedded sections from mastectomy specimens. TNM staging system was used for that purpose 0.44 mm diameter of microscopic field was used. Three parameters were taken into consideration: cancerous tissue size and local or distant metastasis, nodal involvement. Each parameter was scored between one and four. Breast cancer is typically described in stages, according to the presence and size of the tumor and its metastasis in the axillary lymph nodes, and other factors. T refers to the tumor size. For breast tumors, bigger than 2cm changes the T category. N refers to 'node status ', that change as the tumor spreads into lymph nodes. M refers to 'metastasis', which indicates that the cancer has spread to places beyond the breast. The TNM classifications were developed by the American Joint Committee on Cancer.

Ultrasound: The B-mode **ultrasound** was performed on Canon - Xario 200 to check liver metastasis. A center frequency between 7-10 MHz was used for adequate spatial resolution.

C.T Scan: CT examination were scanned using a GE Light speed 64-row CT machine with a tube voltage of 120 kV and a tube current of 150–350 mA, and the non-ionic contrast agent (iodine content 300 mg/mL) was infused into the peripheral vein at an infusion rate of 3 mL/s and an infusion dose of 80–100. Images were obtained in multiple planes with HRCT protocol and viewed at appropriate window settings.

Bone Scan: Done on Siemen E Cam scanner with accessories. Intravenous dye technicium 99 MDP was used. This test helps to see if a cancer has metastasized to bones and is useful because it provides a picture of the entire skeleton. For this purpose, 20/mci (dose) of radioactive material (technetium 99) would be injected into a vein (intravenously or IV). The substance settles in

areas of damaged bone throughout the entire skeleton over the course of a couple of hours. (Six hours to twenty four hours). Patient lies on a table for about 30 minutes while a special camera detects the radioactivity and created a picture of the skeleton.

Statistical analysis: For statistical analysis, software SPSS was used. Frequency tables and histograms are used to describe distribution. Regression correlation analysis was applied to characterize the association and strength of association among quantitative variables. A value of $P < 0.05$ was considered significant, and $P < 0.01$ was considered as statistically significant.

RESULTS:

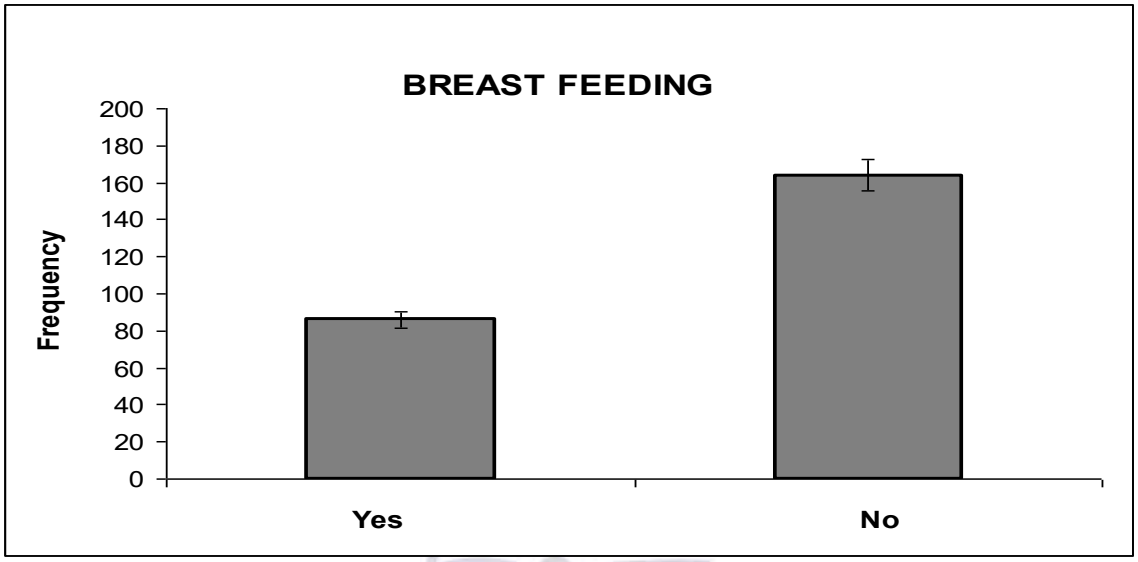

Figure 1: Bar diagram showing frequency of breast cancer occurrence is more in cases who did not breast fed their children.

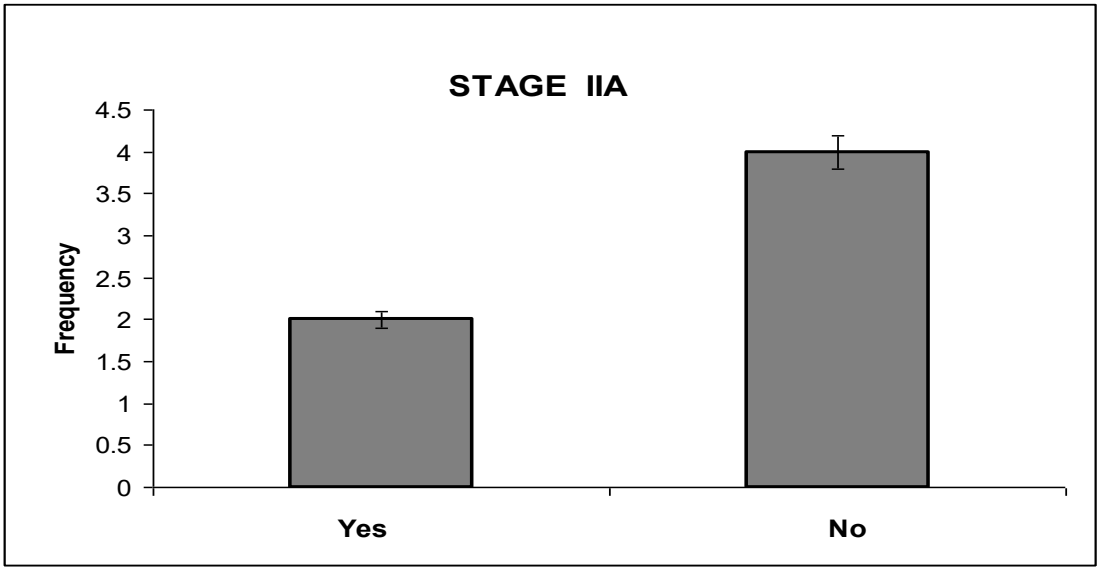

Figure 2: Bar diagram showing frequency of breast cancer occurrence found more in stage IIA cases who did not breast fed their children.

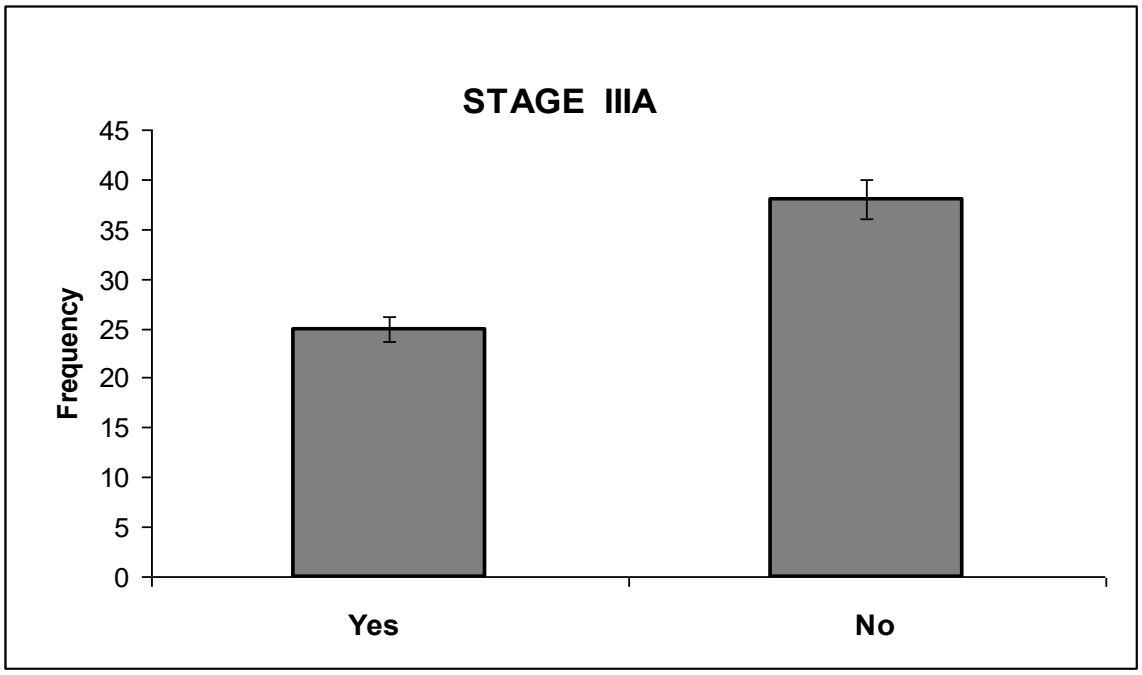

Figure 3: Bar diagram showing frequency of breast cancer occurrence found more in stage IIIAcases who did not breast fed their children.

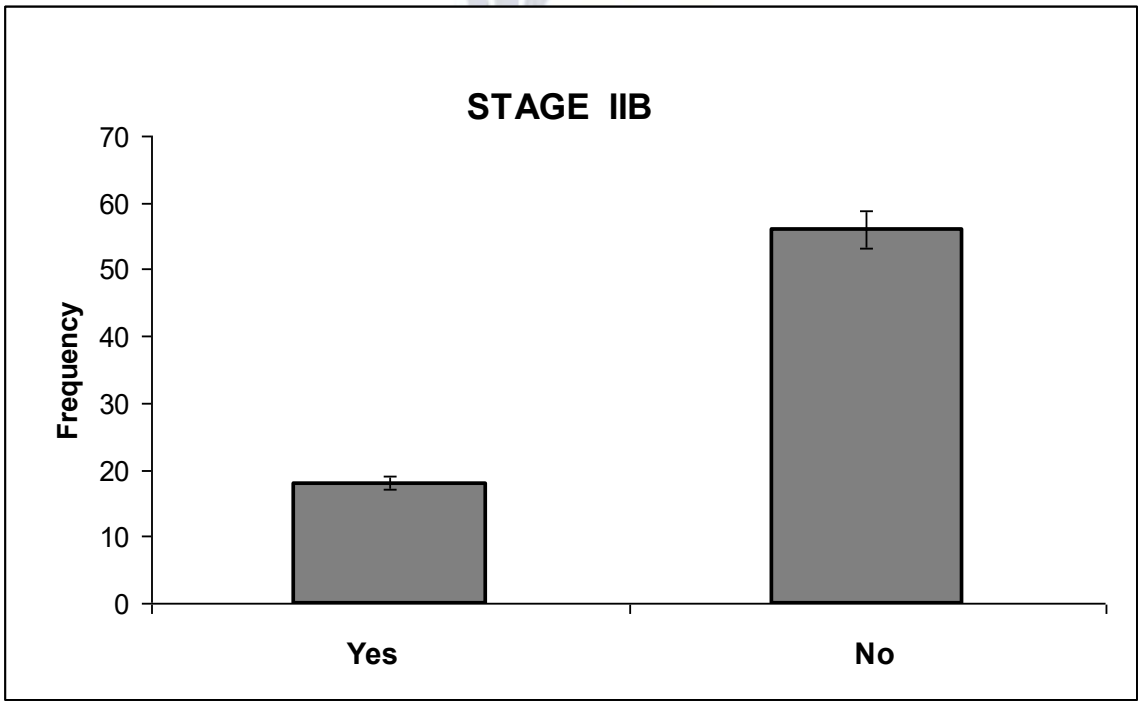

Figure 4: Bar diagram showing frequency of breast cancer occurrence found more in stage IIB cases who did not breast fed their children.

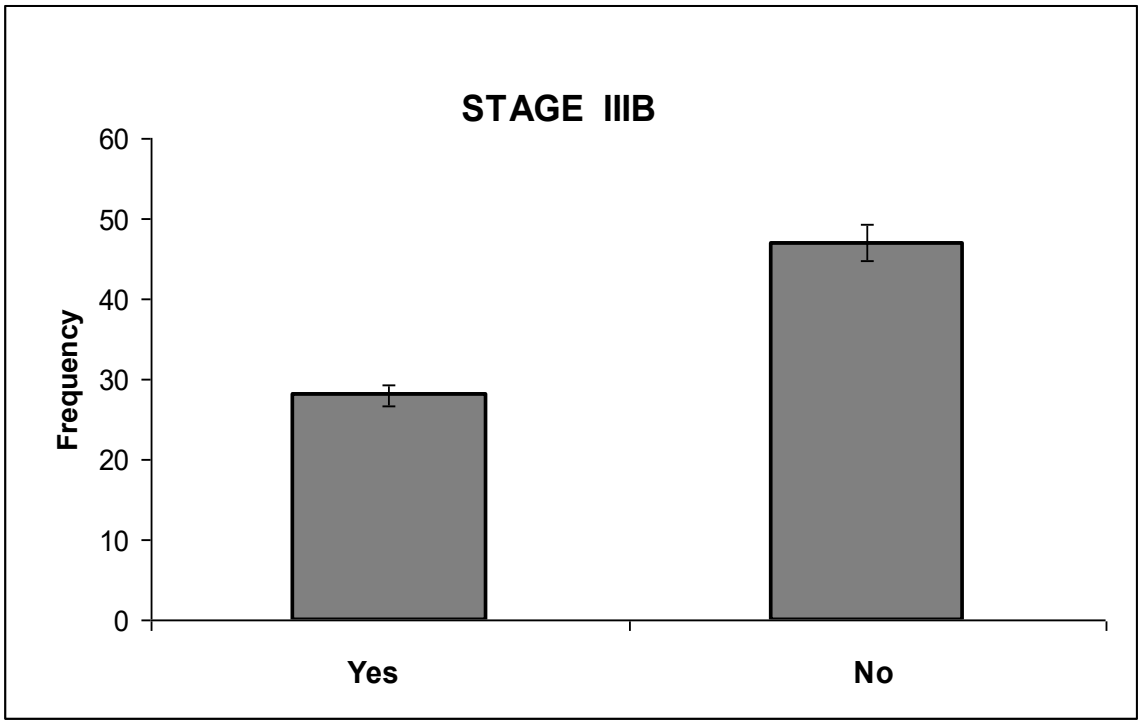

Figure 5: Bar diagram showing frequency of breast cancer occurrence found more in stage IIIB cases who did not breast fed their children.

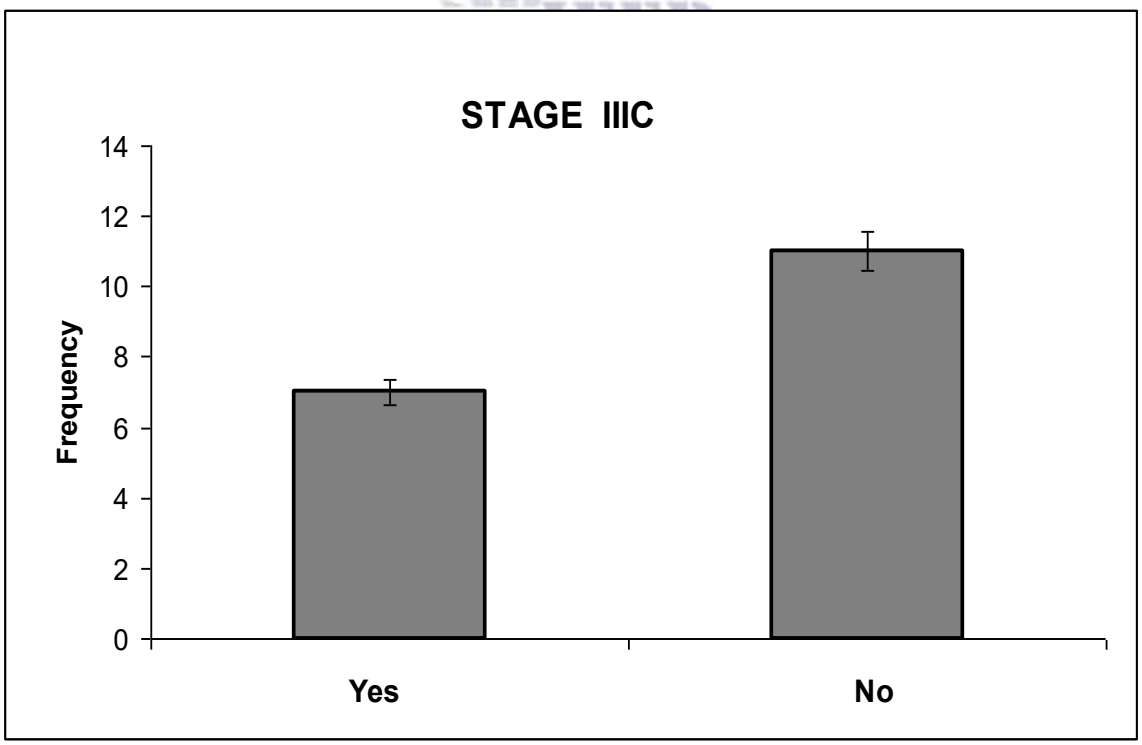

Figure 6: Bar diagram showing frequency of breast cancer occurrence found more in stage IIIC cases who did not breast fed their children.

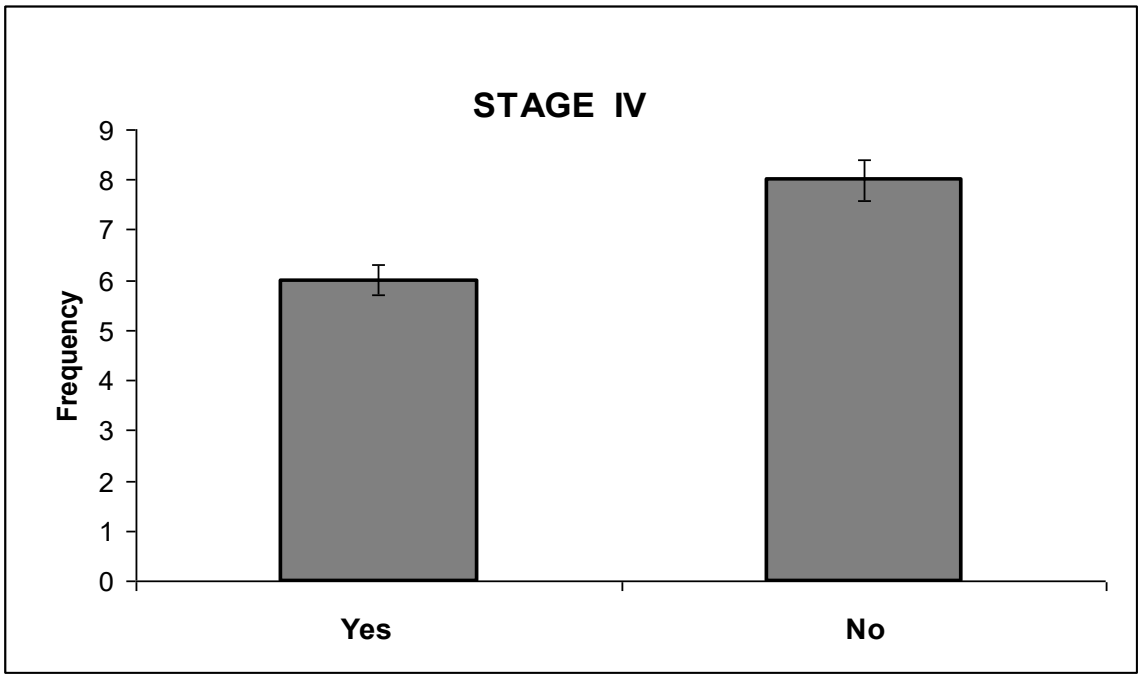

Figure 7: Bar diagram showing frequency of breast cancer occurrence found more in stage IV cases who did not breast fed their children.

Table 1-: Showing coefficient correlation that is a numerical measure of correlation, meaning a statistical relationship between two variables. Significant correlation was noted between breast feeding practice and tendency to metastasize in bones and liver.

Coefficients

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	321.424	54.917		5.853	.000
	L Mets	-21.722	19.943	-.064	-1.089	.277
	Bone Scan	-53.738	20.059	-.162	-2.679	.008
	Brest Feed	24.819	17.252	.087	1.439	.151

Table 2-: Showing descriptive analysis of TNM staging and breast feeding in terms of mean and standard deviation. Standard deviation of all variables except M is below 1 showing that data is not widely spread.

Descriptive Statistics

	Mean	Std. Deviation	N
Brest Feed	1.54	.499	283
Stage T	2.80	.974	283
Stage N	1.05	.907	283
Stage M	1.39	1.713	283

Table 3-: Showing the parametric Pearson association and significance among TNM staging and breast feed. Association of breast feed with stage and nodal metastasis is weak positive and significant only with N, not with T. Breast feed showed a negative and significant association with M. Stage T showed a weak positive and non- significant association with breast feed while a weak negative but significant association with N. M showed a weak negative but significant association with breast feed while a weak positive association with T and N. Association is significant with N. Nodal metastasis showed a weak negative but significant association with T while a weak positive and significant association with M and breast feed.

Correlations

		Brest Feed	Stage T	Stage N	Stage M
Brest Feed	Correlation	1	.101	.117	-.137*
	Sig. (2-tailed)		.091	.050	.022
	N	283	283	283	283
Stage T	Correlation	.101	1	-.148*	.208**
	Sig. (2-tailed)	.091		.012	.000
	N	283	283	283	283
Stage N	Correlation	.117	-.148*	1	.185**
	Sig. (2-tailed)	.050	.012		.002
	N	283	283	283	283

Stage M	Correlation	-.137*	.208**	.185**	1
	Sig. (2-tailed)	.022	.000	.002	
	N	283	283	283	283

Table 4-: Showing descriptive analysis of TNM staging and metastatic burden to bones, lungs, liver and brain in terms of mean and standard deviation. Mean of metastasis to liver, bone is approximately equal. Standard deviation is higher for "M" (metastasis) in comparison to T and N. Standard deviation is same for bone and liver metastasis.

Descriptive Statistics

	Mean	Std. Deviation	N
Stage T	2.80	.974	283
Stage N	1.05	.907	283
Stage M	1.39	1.713	283
Bone Scan	1.76	.430	283
L Mets	1.77	.424	283

Parameteric Correlation:

Table 4-: Showing linear association and significance among different variables in breast cancer patients. T showing nonlinear but significant relation to N, bone metastasis and liver metastasis. M showing a linear and significant relation to N and T but nonlinear and significant relation to liver and bone metastasis. N showing nonlinear but significant correlation to T and liver metastasis but linear and significant to bone metastasis. A nonlinear and significant relation was noted among liver and bone metastasis.

Correlation

		Stage T	Stage N	Stage M	Bone Scan	L Mets
Stage T	Correlation	1	-.148*	.208**	-.185**	-.235**
	Sig. (2-tailed)		.012	.000	.002	.000
	N	283	283	283	283	283
Stage N	Correlation	-.148*	1	.185**	.060	-.208**
	Sig. (2-tailed)	.012		.002	.311	.000
	N	283	283	283	283	283
Stage M	Correlation	.208**	.185**	1	-.503**	-.179**
	Sig. (2-tailed)	.000	.002		.000	.003
	N	283	283	283	283	283
Bone Scan	Correlation	-.185**	.060	-.503**	1	-.060

	Sig. (2-tailed)	.002	.311	.000		.313
	N	283	283	283	283	283
L Mets	Pearson Correlation	-.235**	-.208**	-.179**	-.060	1
	Sig. (2-tailed)	.000	.000	.003	.313	
	N	283	283	283	283	283

RESULT:

Analysis shows that the frequency of breast cancer occurrence was more in cases who never breast feed their children as compare to those who breast feed their children. **Table 1** showing significant coefficient correlation between breast feeding practice and tendency to metastasize in bones and liver. Cases who did not breast feed to their children showing more metastasis ti liver and bone. **Table 2** showing descriptive analysis of TNM staging and breast feeding in terms of mean and standard deviation. Standard deviation of all variables except M are below 1 showing that data is not widely spread. **Table 3** showing the association and significance among TNM staging and breast feed. Association of breast feed with stage and nodal metastasis is weak positive and significant only with N, not with T. Breast feed showed a negative and significant association with M. Stage T showing a weak positive and non- significant association with breast feed while a weak negative but significant association with N. M showed a weak negative but significant association with breast feed while a weak positive association with T and N. Association is significant with N. Nodal metastasis showing a weak negative but significant association with T while a weak positive and significant association with M and breast feed. **Table 4** showing linear association and significance among different variables in breast cancer patients. T showing nonlinear but significant relation to N, bone metastasis and liver metastasis. M showing a linear and significant relation to N and T but nonlinear and significant relation to liver and bone metastasis. N showing nonlinear but significant correlation to T and liver metastasis but linear and significant to bone metastasis. A nonlinear and significant relation was noted among liver and bone metastasis.

DISCUSSION

Breast cancer diagnosis is based on histopathological assessment of the primary tumor or metastases according to the American Joint Committee on Cancer (AJCC) TMN system; whereas staging - evaluating the extent of visceral, nodal and bone disease, is determined largely on imaging. Due to the heterogeneity of breast cancer, consensus on the optimal imaging modality or interval frequency is however currently lacking. Initial staging and restaging imaging protocols are based upon both national and international guidelines, which are varied. The Royal College of Radiologists (RCR) clinical practice guidelines for breast cancer do not advocate routine staging imaging for asymptomatic patients with early stage (T1/T2) disease, rather imaging is usually reserved for those patients with more advanced cancers at higher risk of metastasis (T3/T4). RCR guidelines further recommend computerised tomography (CT) of the thorax, abdomen and pelvis with or without bone scintigraphy (BS) for staging of patients with large (T4) tumors, heavy burden of nodal disease (N2/N3)6 or symptoms attributable to metastatic disease. Positron emission tomography fused with CT (PET/CT) is recommended in cases of suspected inflammatory breast cancer. This is supported by van Uden et al. in their recent systematic review demonstrating that 2-deoxy-2 [18 F] fluoro-D-glucose PET/CT (FDG-PET/CT) outperforms conventional imaging in the detection of locoregional and distant metastases in the initial diagnostic workup of locally advanced and inflammatory breast cancers. The North American National Comprehensive Cancer Network (NCCN) recommends CT and BS to assess metastatic disease primarily. National Institute for Health and Care Excellence (NICE) guidelines recommend CT, magnetic resonance

imaging (MRI), ultrasound and plain radiography to assess the extent of visceral disease. For bone disease, BS, CT or MRI is recommended [9]. The NCCN also advise that FDG-PET/CT in this setting should be employed only when conventional image findings are inconclusive or suspicious. Current evidence does not support the routine use of FDG-PET/CT in the staging of loco-regional disease. The European Society for Medical Oncology (ESMO) guidelines recommend clinical history, physical examination, hematology and biochemistry tests together with imaging of the skeleton, chest and abdomen as the minimal staging work-up in patients at high risk of developing metastatic disease (i.e. those with heavy disease burden or aggressive tumoral biology). Other options include ultrasound, particularly in resource-poor countries. Further, the ESMO recommends the application of validated gene expression profiles as complement to other staging tools, where these may assist with prognostication and clinical management. Staging and risk assessment recommendations outlined by the ESMO have in addition been agreed and accepted by the Pan-Asian ESMO adapted Clinical Practice guidelines. In cases where staging imaging is indicated, there is consensus that the initial minimum imaging work-up should include CT evaluation of the thorax and abdomen as well as BS. Conversely, CT evaluation of the pelvis is not routinely indicated. In a study of 2426 women with metastatic breast cancer, pelvic metastases were the only known site of disease in 0.5% (n = 13) of cases, of which the majority were osseous in origin. Pelvic CT led to 204 additional imaging procedures and 50 surgical procedures of which 84.6% yielded normal, benign or indeterminate results [17 18 19 20 21 22 23 24 25].

Bone metastasis in breast cancer is challenging to treat and can lead to complications including bone pain, pathological fractures, hypercalcemia, and spinal cord compression, which are collectively known as skeletal-related events (SREs). SREs significantly impact patients' quality of life and reduce survival rates. It is worth noting that breast cancer metastasis can have a long dormant period, and some patients may experience recurrence and metastasis, especially bone metastasis, up to 20 years after the diagnosis of the primary tumor. Considering the profound consequences of bone metastasis and the potential for late recurrence, early detection of bone metastasis and identification of patients at elevated risk of bone metastasis are of utmost importance. Improved screening with biomarkers creates opportunities to provide personalized strategies for early prevention, diagnosis, and treatment [26 27 28].

Diagnostic guidelines for BCBM recommend timely imaging evaluation and biopsy in cases of suspected bone metastasis based on symptoms such as bone pain, pathological fractures, elevated alkaline phosphatase levels, or hypercalcemia [11]. Commonly used imaging modalities include whole-body bone scintigraphy (Emission computed tomography, ECT), X-rays, computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography-computed tomography (PET-CT). ECT is the most commonly used method for bone metastasis screening despite having a lower sensitivity and specificity than the more suitable PET-CT [29 30 31]. Exosomal miRNA-21 derived from breast cancer cells directly targets osteoclasts, increasing their differentiation and bone-resorbing ability. These factors play important roles in the formation of the bone microenvironment for osteolytic bone metastasis in breast cancer [32].

Bone is the most common site of metastasis in patients with metastatic breast cancer, and 60–75% of patients with metastatic breast cancer are first diagnosed with bone metastasis. A population-based study showed that from 2010 to 2013, patients with an initial diagnosis of metastatic breast cancer involving the bone accounted for 3.6% of all patients with an initial diagnosis of breast cancer and 62.5% of patients with an initial diagnosis of metastatic breast cancer. Additionally, 70.5% of patients with bone metastases were hormone receptor-positive (HR+/human epidermal growth factor receptor 2 (HER2-): 57.6%; HR+/HER2+: 12.9%). In one systematic review and meta-analysis, 12% of

patients with stage I–III breast cancer developed bone metastases during a 5-year follow-up, and a median of 55% of the patients who developed distant metastases during follow-up had bone metastases. Studies have used bone scans and sophisticated imaging techniques such as magnetic resonance imaging (MRI) or computed tomography (CT) to screen for the presence of bone metastases [33 34].

BS in combination with CT is considered the gold standard for BC staging. However, the use and relevance of PET/CT in this context have increased in recent years. Even though BS and PET/CT have been applied to the detection of bone metastasis, no consensus has been established on the most suitable imaging modality for this purpose. International Guidelines recommend PET/CT for staging in patients with locally advanced disease and inflammatory carcinomas [35].

The implications of this study are far-reaching, proposing a paradigm shift in clinical practice. The evidence presented strongly advocates for revising the current standard of care, emphasizing the judicious and targeted use of BS. By aligning with established guidelines, hospitals can curtail unnecessary healthcare expenses, expedite preoperative processes, and, importantly, spare patients from undue exposure to radioisotope without significant diagnostic yield. This tailored approach, supported by our data, not only streamlines healthcare delivery but also ensures efficient resource allocation, optimizing patient care and contributing to a more sustainable healthcare system [36].

Ultrasound is frequently used to evaluate suspicious masses in breasts. These evaluations could be improved by taking advantage of advanced imaging algorithms, which become feasible for low frequencies if accurate knowledge about the phase and amplitude of the wave field illuminating the volume of interest is available [37]. The addition of screening ultrasound or MRI to mammography in women at increased risk of breast cancer resulted in not only a higher cancer detection yield but also an increase in false-positive findings [38].

CONCLUSIONS

Breast feeding practice appeared more protective tool from breast cancer development as well as it prevents metastasis to distant organs and slows progress of disease too. Number of cases who practiced breast feeding was counted low in frequency and in metastasis to organs as compared to those did not.

AUTHOR'S CONTRIBUTION

All authors have equal contribution. All authors read and approved the manuscript. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

ORIGINALITY OF THE MANUSCRIPT

It is declared that the submitted manuscript is original, unpublished and not under simultaneous consideration by any other journal.

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