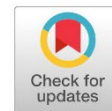


Research Article

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CT Stages of Breast Cancer in Newly Diagnosed Libyan Patients

Nadya Ben Geweref^{1*}, Faiza M. Kutrani², Anas A. Dagman³, Mohamed H. Buzgheia⁴, Mohamed F. S. Alwafi⁵, and Jamila M. Alshrif⁶

*Corresponding author:

Nadya.bengeeref@uob.edu.ly

Department of Radiology,
Faculty of Medicine, Benghazi
University, Benghazi-
Libya.

^{2, 3, 4, 5} Department of Radiology,
Faculty of Medicine,
Benghazi University, Benghazi-
Libya.

⁶ Benghazi Medical Center
,Benghazi, Libya

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Abstract

The main objective of this study was to look into Libyan female breast cancer patients' delayed diagnosis and how it affected their disease stage. The study relied on a multidetector CT scan to check for distant metastases because a PET scan was unavailable. According to the study highlighted in this thesis, 43.9% of patients received a diagnosis more than six months after their initial test, with a median diagnosis time for women with breast cancer being 4.9 months. According to the CT scan stages of breast cancer, the clinical stage distribution was 21% stage IV, 35.9% stage III, 34.4% stage II, and only 8.8% stage I. An important factor contributing to the delay in diagnosis was the recipient's inappropriate reassurance that the lump was benign. The delay in diagnosis was associated with a significantly larger tumor size ($p<0.0001$), positive lymph nodes ($p<0.0001$), and a higher incidence of late clinical stage ($p<0.0001$). According to the results of this study, delay in diagnosis is a major concern in Libya and is related to multifaceted interactions between a set of variables which can result in advanced cancer stages and potentially high mortality rates. To encourage early detection, screening centers must be set up and breast cancer awareness campaigns must be elevated.

Keywords: Libyan, Breast Cancer, Tumor Staging, Diagnosis, CT scan.

INTRODUCTION

Breast cancer is the second most common cancer in the world, with 1.67 million new cases diagnosed in 2012. It is the most frequent cause of cancer death in women in less developed regions (324,000 deaths, 14.3% of all cancer deaths), and it is now the second cause of cancer death in more developed areas (198,000 deaths, 15.4%) after lung cancer (Abulhair, O. et al. 2010). In Libya, breast cancer is the most frequent and fatal neoplasm among females. Breast cancer patients often present with an advanced stage, have early disease recurrence, and are associated with high mortality (DeSantis, C. et al. 2013).

A majority of cancers in Africa are predominantly advanced stage at diagnosis because of a lack of screening and early detection services, as well as limited awareness of early signs and symptoms of cancer among the public and health care providers (CO, C. 2008). In the US, death rates from breast cancer in women have dropped since 1990, due in part to early detection by mammography screening and improvements in treatment. Presently, 60% of breast cancers are diag-



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nosed at an early stage, for that, the five-year survival rate is 98% (Andersen, R. S. et al. 2009). If cancer is detected early, within a comprehensive cancer control plan, a significant number of cancer patients can be cured, or have their lives prolonged significantly. If diagnosis is delayed, treatment costs rise substantially, resources are used inefficiently, and the need for palliative care services increases unnecessarily (Arndt, V. et al. 2002).

MATERIALS AND METHODS

Patients: A retrospective review of the medical records of 262 female Libyan patients, ages 25 to 84, who received a new diagnosis of breast cancer at Benghazi Medical Center between 2013 and 2014, was conducted. **Techniques:** To screen for distant metastasis, the study used a multi-detector CT scan (a 64-slice, third-generation Philips CT scan with 42 detector modules; a PET scan is unavailable). Figures 1 and 2 depict the CT staging of a patient with stage IV distant metastases from breast cancer. On a form (questionnaire), retrospective preclinical and clinical data were gathered from patient medical records.

Social and demographic information, medical and obstetric history, questions about symptoms, and questions about consultations were all part of the data collection process. Dates of the sequential occurrences (first symptom recognition, initial consultation, referral, and initial visit to the hospital) were mentioned. Days were estimated for the diagnosis process and any delays. Initial signs and symptoms included a lump, symptoms other than breast pain, symptoms unrelated to the breast, history of oral contraceptive use, and hormone replacement therapy. Information on tumor stage was gathered from each patient's medical records and was based on histopathological (T, N) and clinical (M) data (Arndt, V. et al. 2003).

Based either on FNAC (fine needle aspiration cytology) or histopathological examination (including needle biopsy or excisional biopsy), the diagnosis time was calculated from the date of the first symptoms to the date of the final breast cancer diagnosis. Consultation time was the time spent seeing a general practitioner following the onset of symptoms.

Statistical analysis

We used three months as the cut-off point of delay and divided the diagnosis time into three periods: less than three months, three to six months, and more than six months (Ahmed, S. B. et al. 2002). If the final diagnosis of breast cancer was made more than three months after the onset of symptoms, the diagnosis was deemed to have been delayed (diagnosis delay).

Sociodemographic factors such as age, education level, and work status were thought to be potential predictors of diagnosis delay. Health factors that were believed to have an impact on how long it took to diagnose someone included being menopausal, using oral contraceptives, self-examination of the breast, having a history of fibrocystic disease, and having a family history of breast cancer. SPSS for Windows (version 18, SPSS, Inc., Chicago, USA) was used to analyze the data.

To determine the significance of the data, the Fisher's exact test, the Chi-square test with likelihood ratio (LR) was used. We aimed to identify independent determinants of diagnosis delay of 3 to 6 months and more than 6 months versus less than 3 months, as well as the relationship between possible predictor factors and diagnosis delay. Based on the results of the CT scan, the relationship between the clinical stage and diagnosis delay was investigated for each patient. Values $p < 0.05$ were considered statistically significant in all tests.

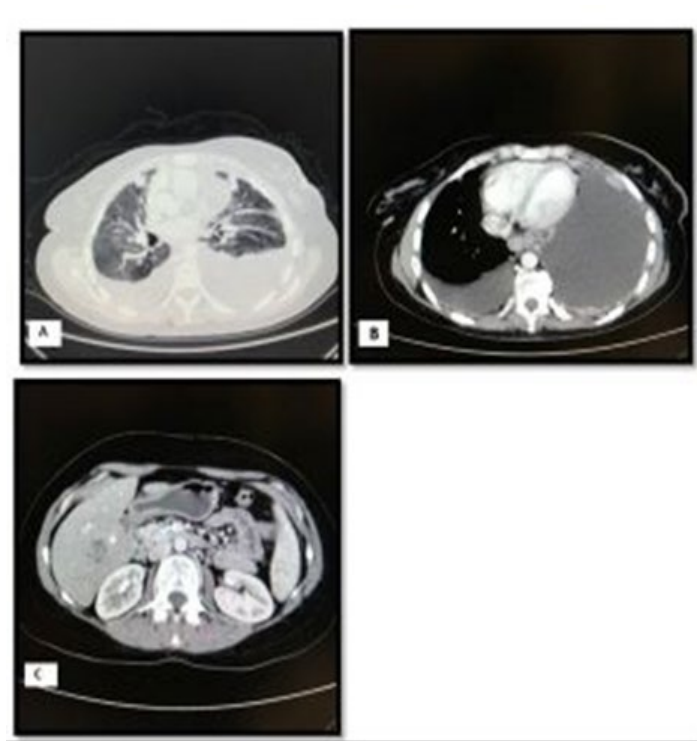


Figure (1). Selected images from the CT examination of a left-sided breast cancer patient with distant metastasis (Stage IV). These axial images through the lower chest and upper abdomen reveal bilateral lung nodules representing lung metastasis (A). Bilateral pleural effusion with nodular pleural thickening is more evident on the left side representing pleural metastasis (B). Heterogeneous enhanced mass in the liver represents liver metastasis (C).

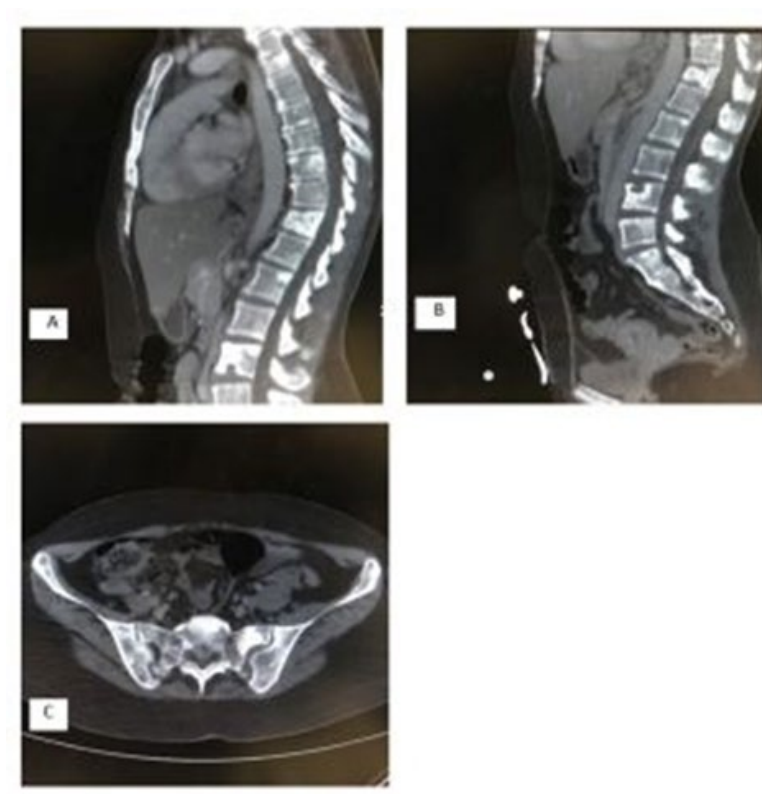


Figure (2). Other selected images from the same patient. Sagittal reformatted images from a CT scan of the spine and axial image of the pelvis reveal diffuse osteosclerotic lesions representing bony metastasis (A, B, and C).

RESULTS

A total of 395 patients with primary breast cancer that had been histopathologically confirmed were admitted to Benghazi Medical Center during the study period. A total of 262 breast cancer patients were included in the study after 133 patients were excluded, 26 patients who were not from Libya, 61 patients with incomplete data, 44 patients who were referred from other cities and had incomplete data with stop follow-up, and two patients who were dead (diagnosed as late stage at age > 50) but had incomplete data. Table 2 displays the characteristics of the study population (n = 262). Women's ages ranged from 25 to 84 years old, with a mean age of 47.8. 166 of the patients, or 63.4%, were literate. Among the 199 patients, 76% were married. Out of 73 patients, 27.8% had used oral contraceptives, and 35.9% of them had gone through menopause. While 7.6% had a history of benign breast disease, only 16% had a family history of breast cancer. In this study, 255 patients (97.3%) who had breast cancer reported discovering a lump or lumps by accident, whereas 7 patients (2.7%) found a lump or lumps while doing a self-examination. Less frequently (19.5%) were reports of other breast symptoms, such as skin changes, nipple discharge, or bleeding. Systemic involvements were the initial symptom in 19 (7.3%) of the patients.

Table (1). Description of the study population (n = 262)

Social demographic characteristics of the patients			
		No. of patients	Percentage %
Age (years)	<50	170	64.9%
	≥50	92	35.1%
Education	Literate	166	63.4%
	Illiterate	96	36.6%
Occupation	Housewife	172	65.6%
	Employed	90	34.4%
Marital status	Married	199	76%
	Single	63	24%
Medical history of the patients			
Menopausal status	Pre-menopausal	168	64.1%
	Post-menopausal	94	35.9%
Breastfeeding	Yes	160	61%
	No	39	14.9%
Oral contraceptive	Yes <5 years	36	13.7%
	Yes > 5 years	37	14.1%
	No	189	72.1%
	Yes	7	2.7%
Breast self examination	No	255	97.3%
Family history	Positive	42	16%
	Negative	220	84%
History of benign breast disease 7.6	Yes	20	7.6%
	No	242	92.4%
Clinical presentations of the patients			
Symptoms	Lump	192	73.3%
	Nipple discharge	17	7.5%
	Skin changes	34	13%
	Systemic	19	7.3%
Symptoms	lump	192	73.3%
	Others	70	26.7%

Diagnosis delay and consultation time

The diagnosis time is displayed in Figure 3. The maximum diagnosis time was 25 months, with a median of 4.9 months. Within three months of the onset of symptoms, 36.6% (n = 96) of the patients received a diagnosis. Diagnoses were made for 19.5% (n = 51) of patients in less than three to six months and 43.9% (n = 115) in more than six months. Four months was the median consultation duration, with a maximum of twenty-four months. In the month following the onset of symptoms, 25.2% (n = 66) of patients saw a doctor, and in the month following symptoms, 39.7% (n = 104) went to the doctor. 92 patients, or 35.1% of the total, saw a doctor more than six months after the onset of symptoms. Most patients (97.3%; n = 255) received their diagnoses within a month of seeing their general practitioners. 2.3% of patients (n = 6) received a diagnosis between one and six months following their initial visit to the physician; 4.4% of patients had to wait longer than six months following their initial medical consultation to receive a diagnosis.

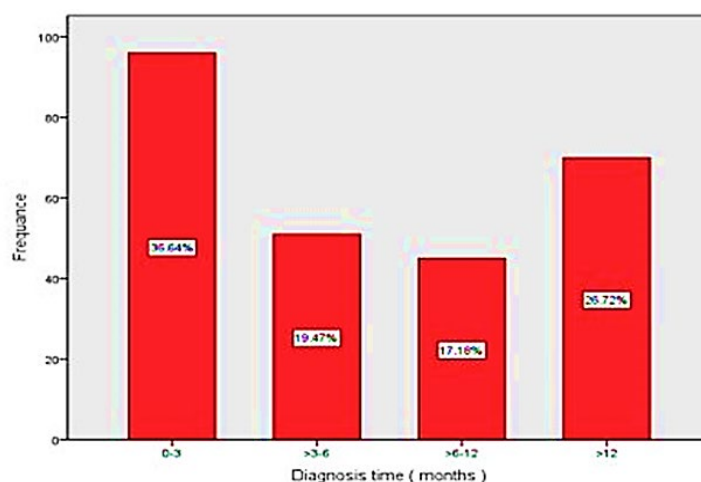


Figure (3). Diagnosis time (from first symptoms) among 262 Libyan breast cancer patients (2013–2014). Diagnosis time (months).

Clinical staging at diagnosis:

8.8% of patients in stage I, 34.4% in stage II, 35.9% in stage III, and 21% in stage IV at the time of diagnosis. Figure 4 displays the clinical stage distribution at diagnosis, and Table 2 shows the TNM staging.

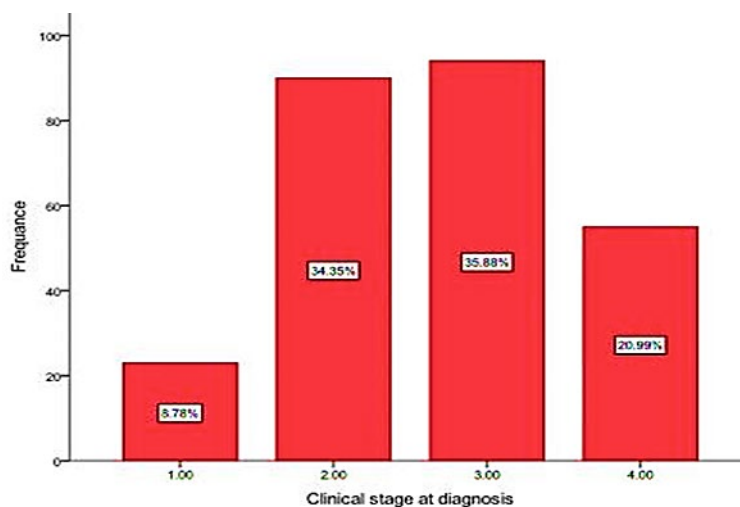


Figure (4). Stage distributions at diagnosis in 262 Libyan breast cancer patients (2013-2014).

Table (2). Clinical staging and TNM classification at the diagnosis in 262 Libyan breast cancer patients 2013-2014

	Tumor characteristics	No. of patients	Percentage %
Clinical stages	Stage 1	23	8.8
	Stage 2	90	34.4
	Stage 3	94	35.9
	Stage 4	55	21
Clinical stages	Early (1 and 2)	113	43.1
	Late (3 and 4)	149	56.9
T	T1	31	11.8
	T2	85	32.4
	T3	108	41.2
	T4	38	14.5
N 2.7	NO	67	25.6
	N1	99	37.8
	N2	76	29
	N3	20	7.6
M	M0	207	79
	M1	55	21

Diagnosis delay and associated factors: Delays in diagnosis were predicted by several factors: Of the patients, 139 (53.1%) did not consider their symptoms serious. In 9.2% of the patients, alternative therapy was used. For 9.2% and 0.8% of the patients, respectively, fear and shame kept them from seeing a doctor. After their initial visit to the doctor, 5 patients (1.9%) were not appropriately reassured that the lump was benign. Early breast symptoms in the absence of a lump were significantly linked to delayed diagnosis ($p < 0.0001$). Figure 5 displays the distribution of symptoms according to the diagnosis time (months). Women who did not report monthly breast self-examination tended to have longer diagnosis delays ($p = 0.002$). Before presenting their symptoms to a doctor, older women waited longer than younger women ($p > 0.0001$). Additionally, women who had taken oral contraceptives for more than five years ($p = 0.001$) and those who were illiterate ($p > 0.0001$) had a significantly higher risk of delay. Table 3 displays the diagnosis delay and related variables.

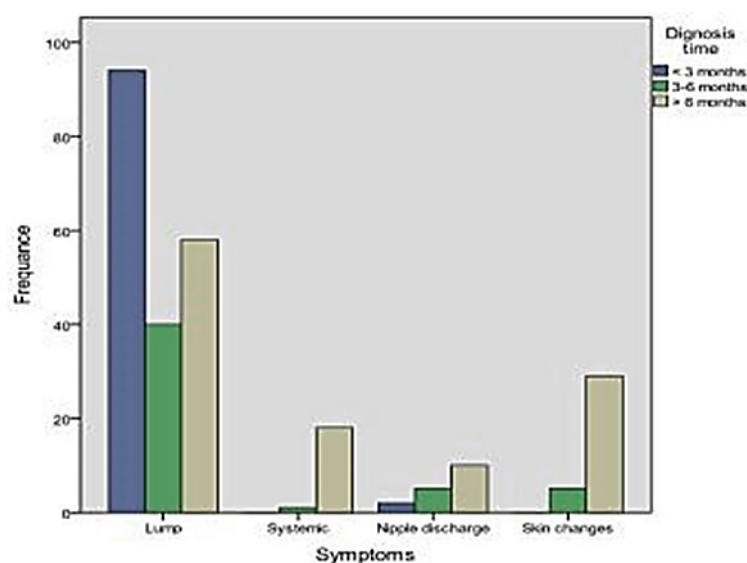
**Figure: (5).** Symptoms distribution according to diagnosis time (months) in 262 Libyan breast cancer patients (2013-2014).

Table: (3). Diagnosis delay in Libyan breast cancer in relation to socio-economic factors, health behaviors, and tumor-related factors

Predicting factors		Proportion of patients according to diagnosis time (percent)				P -value
		No. of patients	<3 months	3-6	>6months	
Age (years)	<50	170	45.3	17.6	37.1	<0.0001
	≥50	92	20.7	22.8	56.5	
Education	Literate	166	32.6	19.8	47.7	0.140
	Illiterate	96	44.4	18.9	36.7	
Occupation	Housewife	172	53	13.9	33.1	<0.0001
	Employed	90	8.3	29.2	62.5	
Marital status	Married	199	45.2	17.9	36.9	<0.0001
	Single	63	21.3	22.3	56.4	
Menopausal status	Pre- menopausal	168	35.7	17.6	46.7	0.199
	Post- menopausal	94	39.7	25.4	34.9	
Breastfeeding	Yes	160	38.8	16.9	44.4	0.251
	No	39	25.6	20.5	53.8	
Oral contraceptive	Yes <5 years	36	36.1	11.1	52.8	0.001
	Yes > 5 years	37	8.1	29.7	62.2	
Breast self Examination	No	189	42.3	19	38.6	0.027
	Yes	7	54.8	4.9	33.3	
Family history	Positive	255	33.2	20.9	45.9	0.021
	Negative	42	60	25	15	
History of benign breast disease	Yes	220	34.7	19	48.3	0.002
	No	20	100	0	0	
Symptoms	lump	242	34.9	20	45.1	<0.0001
	Others	192	49	20.8	30.2	
		70	2.9	15.7	81.4	

Association between diagnosis delay and clinical staging

Table 3 shows that 56.9% of patients had a late clinical stage of breast cancer. This stage was found in more women who had a diagnosis delay of more than six months (76.5%) than in those who had received a diagnosis less than three months after the onset of symptoms (1.3%; $p < 0.0001$). There was a significant correlation between large tumor size (T3 and T4; $p < 0.0001$) and positive lymph nodes (N2, N3; $P < 0.0001$) and diagnosis delay.

Out of the 55 patients who had metastases at the time of diagnosis, 96.4% had a diagnosis delay of more than six months ($p < 0.0001$) following symptoms. Table 4 displays the clinical stages of breast cancer at the time of diagnosis along with the associated diagnosis delay.

Table (4). Diagnosis delay and risk of late-stage breast cancer at the time of diagnosis

Tumor characteristics			Proportion of patients according to diagnosis time (percent)			
		No. of patients	<3 months	3-6	>6months	P -value
Clinical stages	Stage 1	23	100	0	0	<0.0001
	Stage 2	90	78.9	20	1.1	
	Stage 3	94	2.1	33	64.9	
	Stage 4	55	0	3.6	96.4	
Clinical stages	Early (1 and 2)	113	83.8	15.9	0.9	<0.0001
	Late (3 and 4)	149	1.3	22.1	76.5	
T	T1	31	90.3	9.7	0	<0.0001
	T2	85	70.6	17.6	11.8	
	T3	108	7.4	25	67.6	
	T4	38	0	15.8	84.2	
N 2.7	NO	67	97	3	0	<0.0001
	N1	99	29.3	22.2	48.5	
	N2	76	2.6	32.9	64.5	
	N3	20	0	10	90	
M	M0	207	46.4	23.7	30	<0.0001
	M1	55	0	3.6	96.4	

DISCUSSION

The most common and deadly tumor in women in Libya is breast cancer. Patients with breast cancer frequently have advanced stages at diagnosis, experience early disease recurrence, and have high death rates (Boder, J. et al. 2011). The majority of research in the developed world indicates that a delay of more than three months (total delay) between the onset of symptoms and the initiation of treatment is associated with an advanced clinical stage of breast cancer (El Mistiri, M. et al. 2007). Furthermore, there is a correlation between decreased survival and delays longer than three months.

(Ferlay, J. et al. 2012). Investigating diagnosis delay and comprehending its causes is essential to cut down on delays and enhance early diagnosis since delays are avoidable and have a significant impact on a patient's prognosis and outcomes. This study demonstrates that a major issue in Libya is the delay in breast cancer diagnosis. The length of time it took on average to receive medical advice and a diagnosis was greater than it was in developed or developing nations (Goodson, W. et al. 2002). This study reported several factors that are predictive of delayed diagnosis, which is consistent with other studies (Green, M. et al. 2008; Grunfeld, E et al. 2003). An important predictor of delay was the association between the patient-associated factors (psychology and/or sociology) and the delayed presentation of symptoms. According to some research, delays may have occurred when patients believed their symptoms would go away on their own without the need for medical

intervention (Najjar, H. et al. 2010). We discovered that many patients thought their symptoms were harmless and would go away on their own without the need for treatment. This was the main justification for delaying consulting a physician. The majority of patients sought out non-surgical treatments to avoid surgery. Certain patients held the belief that conventional medicines are more efficacious than contemporary medications, or that there are no effective treatments available for breast cancer. The majority of patients reported worsening symptoms while on alternative treatments, which ultimately resulted in a more advanced stage. Compared to 41.5% in other studies, 9.2% of respondents in this study reported using alternative therapies rather than going to the doctor (Jones, R. et al. 2007).

This study demonstrated that delays were caused by unfavorable information regarding breast cancer diagnosis and treatment. Some patients thought there was no use in getting diagnosed and treated for breast cancer because it could not be cured (Keen, J. et al. 2009). Some women may choose not to get their symptoms checked out if they suspect breast cancer because they are afraid of their husbands divorcing them or getting remarried. Negative information about chemotherapy's side effects and anticipated toxicity caused patients to become afraid of the treatment and refuse it. Delays in diagnosis were also linked to the perception that mastectomy results in disability and disfigurement (Montella, M. et al. 2001). Moreover, stigma and the individual desire to conceal symptoms were factors contributing to the delay in diagnosis, especially for older women in this study who were over 50. There are some "alarm symptoms," significant prediction of cancer diagnosis. But nurses and physicians don't always know about these. Even though the majority of lumps in young patients are benign, doctors should encourage diagnostic tissue sampling from all palpable breast masses as a simple way to avoid delays in diagnosis. In this study, respondents were unnecessarily reassured that a lump could be deemed benign without a biopsy following the initial visit. This mindset is untrue and played a significant role in the length of the diagnosis period in this investigation. Remarkable outcomes were documented by (Nadia, M. et al. 2007).

One of the study's key findings demonstrated a strong correlation between the early symptoms of breast cancer (which did not include a lump) and the delay in receiving a diagnosis. According to other studies, finding a breast lump shortens the time patients must wait. The findings imply that education regarding the various forms of breast cancer symptoms is necessary for both physicians and patients. According to this study, patients who performed monthly self-examinations were younger, more educated, and requested medical assistance more quickly than older or less educated patients. Although clinical breast examination (CBE) and breast self-examination (BSE) can both improve the diagnosis of breast cancer without incurring the costs of a mammography facility, mammography remains a sensitive method for early detection of breast cancer (Neal, R. et al. 2008). Additionally, this study found that older women delayed seeing a doctor about their symptoms longer than younger women. Numerous studies have found that receiving a diagnosis later in life is correlated with older age. As such, any intervention program addressing this issue should focus on older women. Numerous studies have reported on the impact of education on symptoms of breast cancer (Norsa'adah, B. et al. 2011).

This work highlights the significant issue of breast cancer ignorance in Libya. Public education campaigns are necessary, particularly for women with lower levels of education. A higher likelihood of delayed diagnosis was seen in women with a history of fibrocystic disease. The explanation is that if previously benign breast tissue alterations are still deemed benign by medical professionals. Therefore, it might be beneficial to advise women who have a known benign breast disease to report any new breast symptoms as soon as possible. Doctors should also be aware that any new symptoms should be considered as possible risks for breast cancer. According to this work, there is

a significant impact of diagnosis delay on the disease's stage and potentially on survival. Additionally, there was a significant correlation between lymph node involvement and diagnosis delay, greater tumor size, a high rate of metastatic disease, and advanced clinical stages. 59.9% of Libyan patients waited more than three months to seek medical advice, with a median consultation duration of 120 days. Just 18% of patients in Europe waited longer than three months before seeking medical advice, with a median consultation duration of 16 days. However, 56.9% of Libyan patients presented with an advanced stage, with a mean age of 47.8 years. In contrast, 57.5 years was the average age of patients in Europe, and 51% were in a late stage. The variations in these outcomes could be due to variations in healthcare or other patient-related, societal, and/or demographic factors. Additionally, compared to European women, Libyan women with breast cancer appear to have a lower mean age and a more advanced stage at the time of diagnosis.

The discovery that patients in Libya have a low mean age at diagnosis, indicating that premenopausal cancers are more common than in Europe, is one of the study's key findings. These also support findings from other Libyan studies (Richards, M. et al. 1999). The age distribution of breast cancer patients in Africa or the Middle and North Africa (MENA) region is consistent with this age distribution (Stapleton, J. et al. 2011). These findings imply that premenopausal type predominates among breast cancer patients from Libya and other African countries. When diagnosed with breast cancer, the majority of patients in the US and Europe are postmenopausal. According to our research, patients in Libya typically present with an advanced stage, an early disease recurrence, and a possible high mortality rate. Our results support other earlier findings regarding the high proportion of patients in advanced stages. As observed in this study, the study on breast cancer in Nigeria (Velikova, G. et al. 2004), and other studies conducted in North African countries, suggest delayed presentation and late diagnosis. This trend may be explained by women's low health awareness, ineffective information campaigns, and Libya's lack of mammography or other screening programs for early breast cancer detection. Although mammography is not included in Libya's screening program, its potential is possibly limited due to the challenges associated with achieving an early mammographic diagnosis of premenopausal breast cancer (Weiss, N. et al. 2003).

CONCLUSION

In Libya, delayed diagnosis is a major issue. Delays in diagnosis have been linked to intricate interactions between medical, social, and other patient-related factors that progress symptoms and may increase mortality. In order to promote early detection, it is necessary to raise public awareness of breast cancer and establish screening facilities.

ETHICS

The study was approved by the Research Ethics Board (REB) at Benghazi Medical Center (BMC) before its commencement.

Duality of interest: The authors declare that they have no duality of interest associated with this manuscript.

Author contributions: A.B. developed the theoretical formalism, performed the analytic calculations, and performed the numerical simulations. Both A.B. and B.C. authors contributed to the final version of the manuscript. B.C. supervised the project.

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