RESEARCH ARTICLE

Factors Associated with Diagnostic Delays among Tunisian Breast Cancer Patients

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Abstract

   Background: Breast cancer (BC) remains one of the most common and deadliest cancer among women worldwide and in Tunisia. The lethality of BC is particularly high in developing countries, such as Tunisia, due to late diagnosis in the majority of cases. The objective of this study was to analyze factors associated with delayed presentation among women followed at the Salah Azaiez institute of Tunis during the year 2021. **Methods:** It was a retrospective cohort study, including patients with primary BC, consulting at the Salah Azaiez institute of Tunis over a period of six months, from january 1st to june, 30th, 2021. The total diagnostic interval (DI) was divided into patient interval (PI) and healthcare system interval (HSI). Diagnosis delay due to patient (PD) was defined as a delay more than three months between the discovery of symptoms and the first medical consultation. Data were collected using a valid questionnaire "the breast cancer questionnaire delay" and from patients' medical records. The calculation of crude and adjusted Odds Ratios using a stepwise descending binary logistic regression model was performed to measure the association of the studied factors with the delayed presentation. **Results:** A total, 146 patients were included. The mean age of the patients was 50.1 ± 10.9 years. More than a half of patients had a primary education (56.8%). Majority of patients were married (86.3%) and unemployed (90.4%). The median of patient interval (PI) and HSI were 31 days [IQR: 12.5-151.5] and 53 days [IQR: 33.0-88.7] respectively. About three quarter of patients (76.4%) presented a healthcare system delay (HSD). After univariate analysis, factors significantly associated with PD were the low level of education (illiterate/primary) (RR: 2.7; 95% CI [1.1-6.4]; p=0.02) and the lack of knowledge about BC symptoms by patients (RR: 15.0; 95% CI [6.0-37.4]; p<10-3). The only variable that remained associated with PD, after multivariate analysis, was lack of initial knowledge of symptoms (OR: 15.0; 95% CI [6.0-37.4]; p<10-3). **Conclusion:** Lack of knowledge of symptoms was the main factor associated with delayed presentation among BC women.This study shows the need to inform women about performing breast self-examination as well as clinical signs of BC.

   Keywords: Breast cancer- delayed presentation- risk factors- Tunisia

Introduction

   Breast cancer (BC) is a major public health problem worldwide. According to the Global Cancer Observatory, in2020, BC represented 24.5% of all cancers among women with an age standardized incidence rate (ASIR) of 47.8/100,000 inhabitants (i.e. 2.3 million new cases) (Sung et al., 2020). In Tunisia, BC is also the most frequent and deadliest cancer among women (Sung et al., 2020). According to the NorthernTunisia Cancer Registry (Hsairi, 2021), this cancer ranked first among womenwith an estimated ASIR of 51.7 per 100,000 inhabitants in 2020 with a significant increasing trend in terms of incidence.

   Despite the considerable progress in the fight against BC, delayed diagnosis (DD) remains problematic in Tunisia with an advanced tumor stage at diagnosis (12.7%

at stage IV; 25.6% at stage III; 47.3% at stage II) (Hsairi, 2021). According to the littérature, DD is associated with a poor prognosis and lower survival (Richards et al., 1999; Caplan, 2014). A systematic review including 87 studies (Richards et al., 1999) showed that an interval more than three months between the beginning of symptoms and the onset of the treatment were associated with poorer survival. DD depends essentially on the patient himself, which correspond to the Patient Delay (PD)(Caplan, 2014), but also maybe related to the healthcare system called as, healthcare system delay (HSD). Understanding barriers causing PD is important to develop strategies to shorten this delay and to improve prognosis of BC in Tunisia. In this way the aim of this study was to analyze factors associated with PD among female patients diagnosed with BC and attending the Salah Azaiez Institute of cancer

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(SAI) in Tunisia during the year 2021.

Materials and Methods

Study design

It was a retrospective cohort study conducted in the medical oncology department of the SAI of Tunis,over a six-month period from January 1st through June 30th, 2021. The SAI is the reference center of oncology in Tunisia. It drains the northern Tunisia region.

StudyPopulation

Included in this study were all women over 18 years old with a confirmed diagnosis of BC within one year of the date of the survey and attending the SAI during the study period. Exclusion criteria were patients who presented any history of BC or other cancer, refused to participate to the study and couldn't remember the different dates of the beginning of symptoms and the first medical visit, and women whose BC symptoms were fortuitous.

Sample size calculation

The sample size was calculated using the following data: an alpha risk fixed at 5%, a statistical power equal to 80% and an Odds Ratio (OR) estimated at 4. An estimation of the proportion of a lack of knowledge of BCsymptoms of 11.4% and a proportion of PD of 38.3%,were both obtained from previous unpublished study in the SAI.

Using the statcalc program of Epi Info 7, the minimum required number of patients was 139 patients.

Data collection

Patients were selected from medical records which were used to verify inclusion criteria and to collect some needed informations.Then, patients were interviewed by the same investigator using a validated and standardized questionnaire "The breast cancer questionnaire delay", in order to analyze the different dates from the recognition of symptoms to the onset of the treatment and to collect factors that may be linked to a delayed consultation.

Definitions of delays in the pathway for patients with breast cancer

According to the literature, the diagnosis delay (DD) is defined as the time interval between the discovery of first symptoms by the patient and the diagnosis or the onset of the treatment (Richards et al., 1999; Walter et al., 2012; Scott et al., 2013; Maghous et al., 2016; Grosse Frie et al., 2018). The DD is composed of two periods: the interval between the discovery of symptoms and the first consultation (when this duration is more than three months it is called a PD) (Maghous et al., 2016; Li et al., 2019; Unger-Saldaña et al., 2019) and the interval between the first consultation and the diagnosis or the onset of the treatment (when it is more than one month it is called a HSD) (Maghous et al., 2016; Li et al., 2019) (Figure 1).

The breast cancer questionnaire delay

It was a standardized questionnaire validated in English which has been carried out to analyze the pathway of patients with BC (Unger-Saldaña et al., 2012). This questionnaire has been used by several other studies in Mexico (Unger-Saldaña et al., 2019), Morocco (Benbakhta et al., 2013), Mali (Grosse Frie et al., 2018),and Peru (Romanoff et al., 2017). The translation of the Arabic version of the questionnaire was carried out using the double translation method (translation, back translation) by three translators.The final version was discussed and agreed by the work team. When the meaning of an item appeared to be lost or altered, the translation process was repeated for that item. The Cronbach alpha analysis was used to measure the degree of internal consistency.

Concerning patients who had difficulties to remember different dates, we used the calendar technique (Martynand Belli, 2002), which helps patients to remember dates more accurately. Events of the year, such as religious and national holidays and school vacations, were evoked to help patients to remember the exact date of the first symptoms. Using this technique, if the patient only remembered the month, without any other details, the 15th day of the month was used as the date of the event. If the patient alluded to the beginning of the month, the 5th day was used. If the patient was referring to the end of the month, the 25th day was used.

Lack of knowledge was defined as women who do not link their BC symptoms with a potential cancer, women who confused their symptoms with others begnin diseases like breastfeeding, taking contraceptive pills and women who were not initially bothered by their illnesses.

Statistical analysis

Statistical analysis was performed using IBM SPSS (Statistical Package for the Social Science) version 25.0.

Quantitative variables were described by means and standard deviations (SD). If the normality condition was not respected (kolmogorov-smirnov test significantly < 0.05), data were described through medians and interquartile ranges (IQR) at 25% and 75%. Categorical variables were described by percentages. The PD was convered into a categorical variables : presence of PD when the time interval was higher than 91 days and absence of PD, if the time interval was less or equeal than 91 days.

Concerning the univariate analysis, chi-square test and Fisher's exact test were used for the comparison of percentages. To compare means, we used the Student T-test. We calculated the relative risk (RR) and its 95% confidence interval (95% CI) to measure the strength of the association between the dependent variable (PD) and other independent variables.

We performed a binary logistic regression using the top-down stepwise likelihood ratio method to identify factors independently associated with PD. Final results were quantified by calculating the adjusted ORs and their 95% CIs. Statistical significance level was set at 5%.

Ethical considerations

This study was approved by the Reviewer Board of The Faculty of Medecine of Tunis; this approval includes ethical consideration. Oral consent was obtained from each participant. Clear and appropriate information was communicated to each patient, including a description of the survey process and its scientific purpose. Patients

were included if they clearly indicated their willingness to participate to this study, including participation in the interview, use of medical records, and possible telephone contact. Anonymity and confidentiality of data were respected.

Results

Sociodemographic characteristics of patients

A total of 146 patients were included in this study. The average age was of 50.1± 10.9 years wich ranging from 27 to 84 years. More than a half of patients had a primary education (56.8%). The majority of patients were married (86.3%), unemployed (90.4%) and had a healthcare coverage (87.7%) (Table 1).

Description of different delays

The median time between the discovery of symptoms and the first medical consultation was of 31 days [IQR: 12.5-151.5]. However the median of the interval time between the first consultation and the beginning of the treatment was of 53 days [IQR: 33.0-88.7] (Figure 2). Results of this study have also shown that the PD and the HSD was observed respectively among 34.9% [IC 95%:27.2-43.3] and 76.4% of patients [95% CI: 68.5-83.2].

Factors associated with patient delay

Univariate analysis showed that factors significantly associated with PD were a low level of education (illiterate/primary) (RR:2.7; 95% CI [1.1-6.4]; p=0.02) and the lack of knowledge about BC symptoms by patients (RR: 15.0; 95% CI [6.0-37.4]; p<10-3). However,

Table 1. Sociodemographic Characteristics of Patients

| Characteristics	(n = 146)	Percentage (%)	Mean ± SD
Age (years)			
20-30	2	1.4	
30-40	32	21.9	
40-50	45	30.8	
50-60	43	29.4	
> 60	24	16.5	50.1 ± 10.9
Marital status			
Married	126	86.3	
Single	14	9.6	
Widow/divorced	6	4.1	
Educational level			
Illiterate	23	15.8	
Primary	83	56.8	
Secondairy	29	19.9	
University	11	7.5	
Professional status			
Housewife	132	90.4	
Employed	14	9.6	
Residence areas			
Urban	124	84.9	
Rural	22	15.1	
Distance from SAI			
< 100 Km	90	61.9	
≥ 100 Km	56	38.4	
Medical insurance :			
Yes	128	87.7	
No	18	12.3	
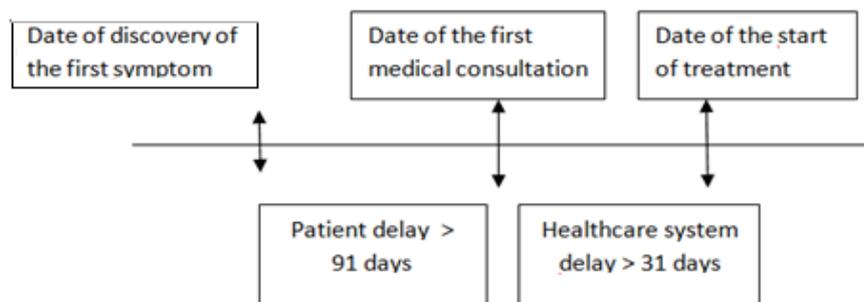
Figure 1. Patient Pathway among Breast Cancer Women
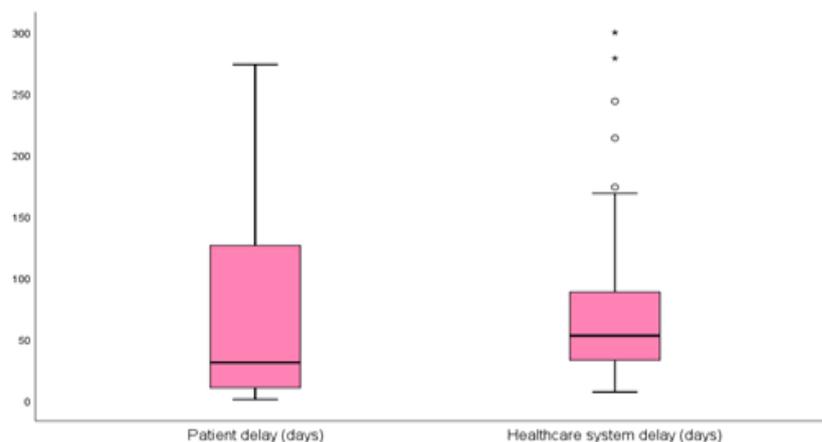
Figure 2. Box Plot of Different Delays

Table 2. Study of the Association between Patient Delay and the Independant Factors (Univariate Analysis)

	Patient delay ≥ (3 months)			
	(n =146)	Percentage (%)	RR	95% CI
Age (years)				
Age ≤ 45	56	37.5	1.4	0.5-3.8
45 < Age ≤ 60	63	34.9	1.3	0,5-3.6
Age > 60	27	29.6	1	
Marital status:married				
Yes	126	35	0.9	0.3-2.6
Others(single, widow, divorced)	20	34.9	1	
Educational leval				
Illiterate / primary	106	40.6	2.7	1.1-6.4
Secondary / university	40	20	1	
Pofessional Status				
Housewife	125	40.8	4.1	0.8-19.2
Employed	14	14.3	1	
Residence areas				
Urban	124	33.1	1.6	0.6-4.2
Rural	22	45.5	1	
Distance from SAI				
≤ 100 km	90	33.3	1,2	0.5-2.4
> 100 Km	56	37.5	1	
First symptôme of discovery				
Nodule or tumefaction	118	31.4	0.3	0.0-1.1
Inflammation	18	44.4	1	
Pain	10	60	0.3	0.1-2.5
Reasons not to consult				
Lack ok knowledge of breast cancer symptoms	72	61.1	15	6.0-37.4
Others	74	9.5	1	
Traditional healer consulted				
Yes	6	33.3	1	
No	140	35	0.9	0.1-5.2

RR, Relative risk; 95% CI, 95% of confidence interval

no significant associations were found between PD and others socio-demographic characteristics (age, marital status, residence areas, distance from the ISA) (Table 2).

Multivariate analysis showed that only the lack of knowledge about BC symptoms remains independently associated with PD (OR: 15.0; 95% CI [6.0-37.4]; p<10-3) (Table 3).

Discussion

According to this study, about one third of patients presented a PD (34.9%). Factors associated with PD, in univariate analysis, where the low level of education (illiterate/primary) and the lack of knowledge about BC symptoms. In multivariate analysis, only the lack of initial knowledge of BC symptoms was independedtly associated with PD.

According to « The Global Breast Cancer Initiative » taken by the World Health Organization (2021), to reduce global BC mortality by 2.5% per year (i.e., 2.5 million deaths prevented worldwide between 2020 and 2040). It is recommended to increase the proportion of women diagnosed at a local stage (I and II) through the promotion of early detection via population-based awareness programs. This study is part of this context. It is a relevant study, which provided updated data to guide decision-makers on actions to take to improve early detection of BC. It is also the first Tunisian study

Table 3. Study of the Association between Patient Delay and the Independant Factors (Multivariate Analysis)

	Patient delay (≥ 3 months)		
Factor	OR	95% CI	P
Lack of initial knowlege about breast cancer symptoms	15	6.0-37.4	<10-3

OR. Odds Ratio; 95% CI, 95% Confidence Interval; p, p-value

which used a validated and standardized questionnaire to analyze the patient 's care pathway. However, this study presented some limits that should be discussed. First, this study could expose to a recall bias in the estimation of the proportion of patients with a long PD. However, according to the literature, women with BC easily remembered the date of first symptom discovery (Facione et al., 2002). Moreover, we used the calendar technique which helps patients to remember the exact date. Secondary, our results showed that most of patients were housewives with a low level of instruction (illiterate/primary level), this category is usually observed in public health care services, which could suggest a lack of representativeness of the study population. However it was not possible to include patients from the private sector.

In the present study, the median delay between the discovery of symptoms and the first medical consultation was of one month. This delay is much higher than results of studies conducted in developed countries such as Australia (11 days) (Youl et al., 2016), the United States of America (14 days) (Ruddy et al., 2014). However, it remains lower than delays in developing countries such as Libya (120 days) (Ermiah et al., 2012), Morocco (65 days) (Benbakhta et al., 2015) and India (60 days) (Kumar et al., 2019). Results of our study were in accordance with a systematic reviewconducted by Espina et al., (2017) who found that the duration between recognition of symptoms and the first consultation of a healthcare professional varied from one to four months in North Africa. This study also showed that about the third of patients (34.9%) presented a PD. This percentage is higher than those reported by other countries such as the United States of America (17%) (Ruddy et al., 2014), Germany (Arndt et al., 2002),and Mexico (20%) (Unger-Saldaña et al., 2009). However, it is still lower than that reported by some developing countries such as India (38.7%) (Somanna et al., 2020), Ethiopia, (35.7%) (Gebremariam et al., 2019), and China (40.4%) (Li et al., 2019).

Median time interval for the healthcare systeme was 53 days [IQR: 33.0-88.7]. A delay was noted among about three quarter of patients. These results remain closed to those reported in a previous Tunisian study where 62.6% of patients had access to a first therapeutic management (interval between radiological diagnosis and first management (Limam et al., 2016). This can explained by the lack of reference centers specializing in oncology in Tunisia (only four centers) and the long duration of coverage by the healthcare insurance.Our results contrast with some other studies, such as in China, where an HSD of more than one month represents only 15.5% of all delays (Li et al., 2019). However, the evaluation of the HSD remains difficult to interpret due to the methodological differences between studies (Kumar et al., 2019).

Factors associated with patient delay

This study showed that lack of knowledge about initial BC symptoms was the only variable independently associated with PD. Same result, was reported by a previousTunisian study, which showed that 35% of patients did not make the link between abnormal breast

symptomatology and a potential cancer (Landolsi et al., 2010). According to the literature, barriers to early presentation depend, essentially, on the lack of knowledge and awarness about BC symptoms (Benbakhta et al., 2013; Pace et al., 2015;Grosse Frie et al., 2018; Unger-Saldaña et al., 2018; Kumar et al., 2019; Xolisile et al., 2022). It has been also reported that many women tend to attribute their symptoms to physiological conditions such as aging, use of oral contraceptives, breastfeeding and a history of benign breast disease (Moodley et al., 2016; Kumar et al., 2019; Getachew et al., 2020).Thus, lack of awareness of BC symptoms remains problematic even in developed countries. An Australian study conducted by Youl et al. (2016) reported that 48% of women attributed their delayed medical presentation to lack of awareness. Similar results were reported also in Germany (Arndt et al., 2002), where 72% of patients attributed their delays to misinterpretation of initial symptoms (painlessness symptoms, thinking that tumefactions were temporary). The present study also showed that women whose main reason for consultation delay was the lack of knowledge about BC symptoms had a 18.0 increased risk of PD compared with other patients. Similar results were reported in Mali (Grosse Frie et al., 2018), where patients who interpreted the first symptoms as "infection" or "nothing serious" had 10 increased risk of PD. This study lead us to conclud that the level of education and awareness of the Tunisian female about BC symptoms would be insufficient. According to the "Global breast cancer initiative"(WHO, 2021), the promotion of early detection of BC requires culturally appropriate educational messages for the entire population. Media can playa key role in educating and raising awareness among women, especially in developing countries (Pruittet al., 2020). According to Zelle et al., (2012) media appears to be a cost-effective intervention. Thus, a systematic review conducted by Donnelly et al., (2015) to assess the effectiveness of BC screening interventions in the Arab countries, recommended a simple and clear educational program, adapted to the language and the culture of the country, to overcome the psychosocial barriers and disparity in knowledge among Arab women (Donnelly et al., 2015).

The current study found that low literacy was associated with PD in univariate analysis. However, this association didn't remain significant in multivariate analysis. This result is not consistent with other studies on which low educational level was among the main reasons for delayed presentation (Espina et al., 2017). This difference maybe due to a lack of statistical power in our study. In addition to educational level, this study did not find an association between areas of residence (urban versus rural) and PD. However, living onrural areas has been reported by several studies as an important factor of PD (Kumar et al., 2019; Getachewet al., 2020). Likewise, it would be recommended, to focus more rural areas through information and awareness campaigns. Mobile clinics would be an interesting alternative to reach rural and distant geographical areas (Hsairi, 2021).

In conclusion, patient delay was relatively common in this study. Lack of knowledge of symptoms was the main

factor associated with delayed consultation among BC women. Appropriate education about breast self-screening and BC symptoms would be recommended.

Author Contribution Statement

In this study, all authors contributed to the concept, design and write of the manuscript. All authors have read and approved the final manuscript.

H.Mconceived the idea of this work, managed and supervised the study, and carried out final revision of manuscript.

B.S collected the data, contributed in data analysis, interpretation and darft the manuscript.

K.H contributed in data analysis and revision of the manuscript.

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