



Risk Factors Associated with Delayed Diagnosis of Advanced Breast Cancer

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Abstract

Background: Delay in the detection of breast cancer is an important topic in health care, both due to its frequency of occurrence and its possible negative effects on the survival of patients. A delay in breast cancer diagnosis may increase the risk of metastatic lymph nodes and the progression of tumor size. Although little is known about the nature of missed and delayed diagnosis it has been suggested that the poorer survival from breast cancer can be attributed to more advanced cancer stages at presentation.

Methods: We conducted a systematic review of the literature of the last twenty years on patient, practitioner and system-mediated breast cancer diagnosis and treatment delays, identifying the risk factors that may influence these. We generated hypotheses about the relationship between each risk factor and the delay of diagnosis and treatment. We critically appraised the papers for inclusion in the review according to predefined criteria. The small number of studies of adequate quality did not allow formal meta-analysis. We also registered cases of delayed presentation in our clinic from the last 3 years, trying to determine which risk factors can be influenced, thereby decreasing morbidity associated with delay in diagnosis and treatment of breast cancer.

Results: We identified three types of risk factors: Patient-mediated, practitioner-mediated and health-care mediated delay. Most studies were deemed to be of poor quality and were excluded. Among 18 studies of adequate quality, however, there was strong evidence for an association between older age and delay by patients, and moderate evidence that marital status was related to delays by patients. Older age and presentation with a breast symptom other than a lump were strong risk factors for delays. Moderate evidence was shown for several other factors.

Discussion: The strength of the current evidence is inadequate to allow for the development of specific strategies in order to shorten delays by patients or providers. Clarification of the findings of this review through a major program of primary research is urgently required.

Conclusion: Having sought help for potential cancer symptoms, it is also important that practitioners recognize symptoms, investigate, examine, and refer appropriately, not in a delayed fashion.

Keywords: Risk factors; Delayed diagnosis; Breast cancer

Introduction

Delayed presentation of breast cancer is a problem in both developed and developing countries. Possible issues to address in order to improve this situation include public awareness of cancer and its symptoms, access to screening and diagnostic services, primary care awareness and referral time, and adequate resources at secondary and tertiary cancer care services. The influence of delays in diagnosis and treatment on survival and the risk factors for delay in breast cancer patients has been a subject of interest for many years. Unfortunately, in Romania, there is no national database for monitoring the survival rate for cancer and the percentage of cases with a delayed cancer diagnosis. Consequently, there is a need to ascertain risk factors related to increased time to presentation. Delay can occur at three phases during the diagnostic process: In the interval between the patient first noticing a symptom and first consulting a doctor (patient delay), between first consultation and referral by a practitioner (doctor or practitioner delay) and between referral and diagnosis (system delay). Within the patient delay phase, there are two component intervals; identification of a symptom by the patient (the period between detecting a symptom and deciding to go to the doctor) and help-seeking (the period from perceiving a need to discuss the symptoms with a health care practitioner to the first consultation). In addition to outlining the various points during which extraneous factors might adversely influence time to presentation and referral, considering the delay

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in these phases enables identification of areas where interventions designed to reduce delay might be targeted. However, before such interventions can be developed, we need to better understand the nature and duration of these intervals. Symptom misinterpretation is frequently reported, with patients believing their symptoms are the result of stress connected to pre-existing conditions, aging, or expected bodily changes. This topic is not easily amenable to study by randomized trial, and as such, interpreting data available from observational studies is essential to increase our understanding of the risk factors associated with delay and to facilitate the development of effective new strategies to reduce the time involved. If longer delays have an impact on survival, then such strategies could save a significant number of lives. If a reduction in deaths from breast cancer is to be achieved, a greater understanding of the reasons for late diagnosis and treatment is required [1-3].

Material and Method

In order to gain a more comprehensive understanding of the risk factors for delayed breast cancer patient presentation, relevant papers published in the literature over the course of the past two decades were reviewed. This systematic review followed the methodological approach described in the Cochrane Collaboration's Handbook for Systematic Reviews of Interventions. The Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) statement has been used to ensure transparent and complete reporting (Figure 1). We performed the review according to established principles laid down to protect against potential bias. The research question was translated into inclusion and exclusion criteria using the PICO (Participants-Interventions-Comparator-Outcomes) framework: Patients with advanced breast cancer (P), who didn't have access to specific diagnosis/treatment in an early fashion or the ones who had delayed diagnosis and treatment because of specific risk factors (I), comparison between the reviewed studies regarding the frequency of factors which led to a delayed presentation (C). The outcomes of interest (O)/objectives were the identification of risk factors which lead to the presentation of oncological patients in late stages and the statistical significance of these factors. Because of the large number of possible factors and their likely interactions, we formulated clear hypotheses for each factor at the outset of the review. The risk factors we assessed fell into three main classifications: Patient, practitioner and system delay.

Original reports published between January 2000 and December 2020 was searched in PubMed. All citations retrieved from the systematic literature search were screened based on title and abstract. Relevant citations were evaluated based on the full text. Following full-text screening, we included studies with diagnosis and treatment delay regarding breast cancer patients. We included only records published in English. We confined the review to studies involving patients with breast cancer and excluded patients with benign breast disease. We included studies based on consecutive-cohort or case-control designs and excluded those based on small case series or unrepresentative samples. We included evidence related to a particular factor if the analysis involved appropriate univariate, multivariate analysis, or both. If the analysis was inappropriate or potentially misleading, we excluded the evidence. Inclusion and exclusion criteria of the studies are described in Table 1. The literature was reviewed and from 229 studies, we selected eighteen studies that concerned the debated topic; keywords for searching were: Risk factors, delayed diagnosis, breast cancer. Eighteen papers were reviewed and detailed analysis

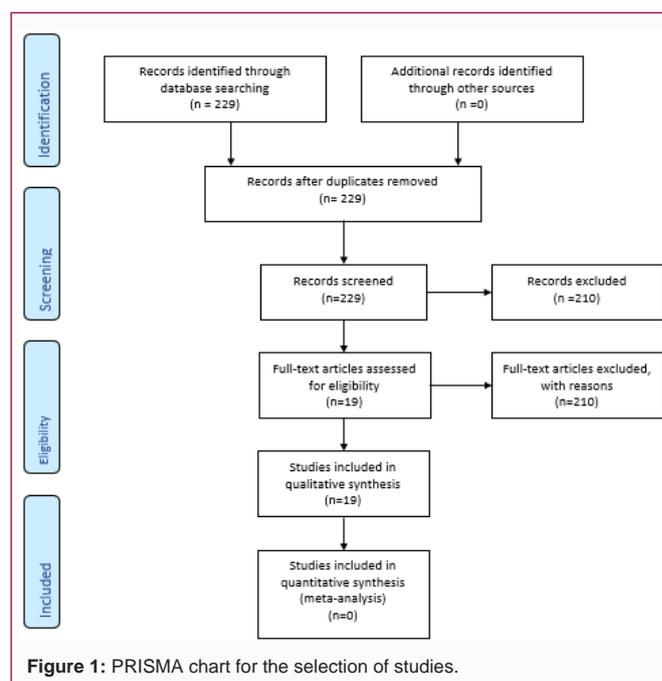


Figure 1: PRISMA chart for the selection of studies.

and debate of risk factors leading to delay diagnosis and treatment of advanced stages of breast cancer at presentation were extracted and presented in our paper. This paper reports on and discusses risk factors for patients, primary care practitioners, and health-care system delays. It combines, summarizes and debates earlier reported results for breast cancer and risk factors associated with delayed diagnosis and treatment. Studies were eligible for inclusion if they were based on a clear description of a discrete interval of delay-by patients or providers. We defined diagnosis delay as the time between the onset of initial symptoms and the first medical consultation. Treatment delay by practitioner was defined as any discrete interval between first medical consultation and treatment. A meta-analysis of factors predicting delay was not possible because of the small number of studies of adequate quality related to individual factors, inconsistencies in the definition of factors or differences in cut-off values (age for example). For each factor, we summarized data into three categories: Studies supporting the hypothesis (supportive, with an effect at $p < 0.05$ in the direction of the hypothesis); studies not supporting the hypothesis (non-supportive) and studies that refuted the hypothesis (with an effect at $p < 0.05$ in the direction opposite to that of the hypothesis). We assigned the strength of evidence for each factor according to a combination of the number and size of studies supporting, not supporting or refuting the hypothesis. The number of studies in each category was counted. However, given the low intrinsic probability under the null hypothesis of any study showing a significant ($p < 0.005$) effect in either direction, more weight was given to these studies. We also surveyed five patients from our clinic with advanced breast cancer for the last three years about risk factors mentioned by them which led to delay diagnosis. We assessed time from symptom onset to first presentation and different types of risk factors which contributed to delayed presentation.

Results

We identified 229 studies containing data directly linking risk factors and delay in breast cancer. Eighteen of these papers met the inclusion criteria and contributed to the findings of the review. These

Table 1: Inclusion and exclusion criteria.

Review question: What are the main risk factors which predispose to delayed presentation in breast cancer patients?	
Inclusion criteria	Exclusion criteria
Studies investigating factors for delayed diagnosis and treatment	Other topics related to breast cancer
Advanced breast cancer	Benign breast disease
Definition of treatment/diagnosis delay (all)	
English	Other than English
Full text available	No full text available

Table 2: Studies included in the review and type of delay.

Study	Country	No. of patients	Type of delay	Type of cancer	Year of pub
Ruiz et al. [1]	Spain	1236	Treatment delay	Breast	2020
Maghous et al. [2]	Morocco	137	Diagnosis delay	Breast	2016
Poum et al. [3]	Thailand	180	Diagnosis delay	Breast	2014
Bachok et al. [4]	Malaysia	3525	Diagnosis delay	Breast	2011
Zhang et al. [5]	China	312	Diagnosis delay	Breast	2019
Medeiros et al. [6]	Brazilia	814	Diagnosis delay	Breast	2019
Medeiros et al. [7]	Brazilia	662	Diagnosis delay	Breast	2018
Pace et al. [8]	Rwanda	144	Diagnosis delay	Breast	2015
Williams et al. [9]	Texas	247	Diagnosis delay	Breast	2013
Lopes et al. [10]	Brazilia	82	Diagnosis delay	Breast	2017
Huo et al. [11]	China	1431	Diagnosis delay	Breast	2014
Stuver et al. [12]	Boston	938	Diagnosis delay	Breast	2011
Burgess et al. [13]	UK	100	Diagnosis delay	Breast	2005
Burgess et al. [14]	UK	196	Diagnosis delay	Breast	2000
Rabia et al. [15]	India	1386	Diagnosis delay	Breast	2008
Salih et al. [16]	Sudan	153	Diagnosis delay	Breast	2016
Ghazali et al. [17]	Malaysia	246	Diagnosis delay	Breast	2013
Ermiah et al. [18]	Lyban	200	Diagnosis delay	Breast	2012

papers underwent data extraction and were critically appraised. Studies were conducted in different countries across Europe and other continents. For each factor, we identified the country of origin, the number of patients enrolled and the type of delay (diagnosis or treatment delay) (Table 2). According to whether the data was non-supportive, supportive, or refuted the hypothesis we also recorded the risk factors which we found relevant regarding delay in breast cancer (Table 3a, 3b). Although many of these factors are likely to be inter-related, they were mainly assessed univariately. Regarding demographic risk factors, evidence was found in six studies to support the hypothesis that older age (over 60 years old) is associated with longer delay by patients (Table 3a). The twelve non-supportive studies were generally smaller than the supportive studies. The total number of patients in one of the supportive studies conducted in China was more than ten times larger than certain non-supportive studies. There was strong evidence that socio-economic status was related to patient delay. Eight studies supported this hypothesis. Ethnicity (non-white ethnic origin) was also identified as a risk factor for delayed diagnosis in two studies (1,184 patients in total), so there was moderate evidence against non-white ethnic origin influencing delay by providers. The strength of evidence supporting the hypotheses related to other factors such as marital status was moderate, sustained by only four studies. Two of them reported significant findings supporting the hypotheses which outweighed the

number of patients in non-supportive studies (Table 3a). For each factor, the total number of patients in the supportive studies was at least twice that of the non-supportive studies. The hypothesis related to area of residency was sustained by four studies. Clinical risk factors such as comorbidities, type of symptom and family history were also analyzed. We found that the presence of comorbidity and family history did not influence delay in women with breast cancer (one and respectively two studies, some of them with a high number of patients, supported these hypotheses). Ten studies supported the hypothesis related to type of symptom and delay. Psychosocial factors such as emotional response, life events and mood disorders were found to be statistically significant in only three studies (one study with a large number of patients and two others with a small number of patients). Our main concern is that factors related to health care system and practitioner delay are not registered and not taken into consideration in the studies that we reviewed. There was insufficient evidence for us to draw conclusions about these types of risk factors since only two papers contributed to the review, despite their large sample size.

Discussion

Risk factors for delayed diagnosis and treatment of breast cancer were identified among the papers selected in order to facilitate the action leading to the early detection of the disease, crucial for improving survival rates. Most studies have examined patient delay risk factors,

Table 3a: P-values for demographic factors influencing the diagnosis/treatment delay.

Study	BMI	Age	Gender	Socio-economic status	Ethnicity	Marital status	Area of residence
Ruiz et al. [1]	0.018	ns	-	0.001	-	0.016	-
Maghous et al. [2]	-	ns	-	Ns	-	ns	<0.001
Poum et al. [3]	-	0.04	-	0.01	-	-	0.01
Bachok et al. [4]	-	-	-	-	-	-	-
Zhang et al. [5]	-	0.049	-	-	-	-	-
Medeiros et al. [6]	ns	ns	-	0.03	ns	ns	ns
Medeiros et al. [7]	ns	ns	-	0.04	ns	ns	ns
Pace et al. [8]	-	ns	-	0.001	-	ns	-
Williams et al. [9]	-	0.0025	-	-	ns	-	-
Lopes et al. [10]	-	ns	-	0.01	ns	0.04	ns
Huo et al. [11]	-	0.009	-	Ns	-	-	0.002
Stuver et al. [12]	-	<0.001	-	Ns	0.03	-	0.001
Burgess et al. [13]	-	ns	-	-	-	ns	-
Burgess et al. [14]	-	-	-	-	-	-	-
Rabia et al. [15]	-	ns	-	0.045	-	0.045	ns
Salih et al. [16]	-	ns	-	Ns	-	Ns	ns
Ghazali et al. [17]	-	ns	-	Ns	0.033	0.014	ns
Ermiah et al. [18]	-	0.033	-	0.009	-	Ns	-

Ns: Not statistically Significant

Table 3b: P-values for clinical and psychosocial factors influencing the diagnosis/treatment delay.

Studies	Clinical factors			Psychosocial factors			
	Comorbidity	Symptom	Family history	Emotional response	Common superstitions	Support	Life events
Ruiz, et al. [1]	0.011	0.029	-	-	-	0.005	0.002
Maghous, et al. [2]	-	<0.001	<0.001	-	-	-	-
Poum, et al. [3]	-	0.01	-	-	-	-	-
Bachok, et al. [4]	-	0.008	-	-	0.029	-	-
Zhang, et al. [5]	-	0	-	-	-	0.013	-
Medeiros, et al. [6]	-	0.02	0.02	ns	-	0.004	ns
Medeiros, et al. [7]	-	0.001	ns	-	-	-	-
Pace, et al. [7]	ns	ns	ns	-	<0.001	-	-
Williams, et al. [8]	-	ns	-	-	-	-	-
Lopes, et al. [9]	-	ns	ns	-	-	-	-
Huo, et al. [10]	ns	0.004	ns	-	-	-	-
Stuver, et al. [11]	-	<0.001	-	-	-	ns	-
Burgess, et al. [12]	-	0.003	-	ns	-	-	ns
Burgess, et al. [14]	-	-	-	<0.001	-	-	<0.001
Rabia, et al. [15]	-	-	-	-	-	-	-
Salih, et al. [16]	-	-	ns	-	-	-	-
Ghazali, et al. [17]	ns	ns	ns	-	-	-	-
Ermiah, et al. [18]	-	<0.0001	ns	-	-	-	-

ns: not statistically significant

but our study also attempted to examine causes for healthcare system and practitioner delay, which are likely to be significant. Older patient age was found to be a risk factor for delayed presentation with symptoms of breast cancer. A UK general population survey suggested that knowledge about the risks and symptoms of breast cancer was poorer among older women [4]. A better understanding of the risk factors for delayed presentation of breast cancer in older

women may allow for the development of effective interventions to promote early help-seeking in this high-risk group. Most breast cancers occurred in older women and survival from breast cancer was reduced among women over 70 years, compared with younger women. Older age was found to be a strong risk factor for delayed presentation and also there was a high chance that symptoms in older women were associated with breast cancer, while the majority of

Table 4: Case series from our department of general surgery.

Economic status	Ethnicity	Marital status	Comorbidity	Symptom	Emotional response	Common superstitions	Area of residence
low	Ro	Widow	No	breast ulcer	fear of malignancy	Naturist treatment	R
high	Ro	Married	No	breast ulcer	fear of chemotherapy	Naturist treatment	U
low	Ro	Unmarried	No	breast ulcer	fear of biopsy	-	R
high	Ro	Widow	No	breast ulcer	fear of malignancy	Naturist treatment	U
low	Hun	Married	HBP, HF	breast mass	other health problems	-	R

Ro: Romanian; Hun: Hungarian; HBP: High Blood Pressure; HF: Heart Failure; R: Rural; U: Urban

symptoms in younger women revealed a benign condition. Giving the fact that mammographic screening stops at seventy years old, the message being transmitted is that this category is no longer at risk of developing breast cancer [4-6]. Lower socioeconomic status and low education were associated with increased delay for breast cancer. A large proportion of women with breast cancer in the higher-income category reported increased symptom awareness compared to patients with a lower-income. Specific educational approaches, such as breast self-examination, should be tailored to the target group to achieve the greatest effect. Financial incapacity and residence in a rural area have been found to deter patients with breast cancer from seeking medical help, due to the fact that they have to spend more time and effort to arrange visits for diagnosis and treatment, and also because medical services in urban areas are considered superior to services located in rural settings. Negative information, such as the side-effects and the expected toxicity of chemotherapy led to fear and refusal of therapy. Some patients believed that the effects and expected toxicity were worse than breast cancer itself. Non-white ethnic origin was a risk factor for delay in presenting with breast cancer. In most of the studies conducted on the topic of breast cancer in different regions (India, Sudan, Malaysia, Iran, Lebanon, Brazil, Rwanda, Thailand, Morocco) several factors besides ethnicity, such as fear of being diagnosed with cancer or lack of knowledge concerning the disease, led to delayed diagnosis and therefore increased morbidity. As the capacity of low-income countries to treat breast cancer expands, efforts to promote earlier detection of the disease could have a substantial impact on disease stage and curability, but racial and language minorities, with lower educational attainment, are more likely to experience process failures [7-9]. These efforts should target communities and healthcare providers to address patient and system delays. Marital status or living with a partner was found to be also related to presentation patterns for cancer. The protective role of marriage is based on the encouragement of the spouse to seek medical attention, to adhere to treatments that could potentially influence disease outcomes. The presence of co-morbidity was associated with a delay in patients with breast cancer. Some women are aware of breast symptoms but feel more troubled by other medical conditions. This is mainly because women, especially the elderly, prioritize their symptoms according to the influence these symptoms have on their daily functioning.

Risk factors for delayed presentation of breast cancer in women of all ages included discovering an initial symptom which does not include a breast lump, not disclosing symptom discovery to someone else, being prompted by someone else to seek help, presenting indirectly to the doctor with a non-breast symptom. Patients diagnosed with breast cancer were more likely to delay if they had an atypical symptom. Across the cancer groups, patients were typically less likely to delay if they experienced an alarming symptom. For the majority of cancer groups studied, patients were more likely to present when symptoms impacted daily life and activities. If a symptom was vague, the risk of a delayed presentation can be increased and,

conversely, if the symptom was more serious or alarming then the risk of delayed presentation was typically reduced. Where symptoms were understood and thought to be serious, there was a reduced time to presentation. However, women with breast cancer would only seek medical advice earlier upon noticing a sudden or rapid increase in lump size, having additional symptoms, or starting feeling pain. Also, women who never performed breast self-examination were more likely to delay presentation. Many patients with breast cancer presented after having discovered a lump themselves, but women's knowledge and experience about symptoms and risk factors of breast diseases influenced their understanding about the symptoms and subsequent action. Symptom awareness and particularly patients' interpretation of symptoms, was a commonly reported theme. Non-recognition of the seriousness of symptoms related to lack of knowledge about the disease was the predominant risk factor for delay reported across all cancer sites. Delay was often related to patients adopting a 'wait and see' approach, denying their symptoms or, self-medicating before presentation to a practitioner. The difficulty is that common cancer symptoms are often attributable to benign condition. The complexity of this process can be illustrated by considering breast cancer, where there is robust evidence that patients delay less with the well-known symptom of lump, compared with the less recognized non-lump symptoms, which result in greater delay. The impact of a family history of cancers on help-seeking behavior was investigated across several studies but there was no conclusive evidence as to its impact. On the other hand, there are studies that associate family history with delayed diagnosis in breast cancer and they show that because of no history of cancer in the family some participants thought it unlikely to get breast cancer themselves. Fear that a symptom was indicative of cancer, fear of investigation or treatment, embarrassment was also found to be a factor in increasing time to presentation for breast cancers. Shyness, fear of mastectomy, embarrassment, reluctance to bother the general practitioner, nihilism about cancer treatments were cited as risk factors for delay of diagnosis in breast cancer patients. The lesion must not be touched widespread superstition is a reason for avoidance of practitioner consultation. Alternative, spiritual therapies, consultation obtained from a traditional healer were also significantly more likely to have delayed presentations for breast cancer. Social and also family support and the availability of advice were influential factors in patients' decisions to present with cancer symptoms. Patients with breast cancer, who did not disclose their symptoms to someone close to them, were more likely to delay help-seeking. Also, social networks were identified as a potentially important factor in reducing delay, when patients made decisions based on the experience of others. Family responsibilities, severe life events, social problems, domestic adversity, depression, anxiety were not risk factors associated with the delayed presentation for patients with breast cancer [10-13]. Improper physicians' approach in the face of breast cancer was also found. Misdiagnosis occurring either through treating patients symptomatically or by relating symptoms to a health problem other than cancer resulted in increased time

to referral for breast and gynecological studies. Use of inadequate diagnostic tools, failing to follow-up inconclusive and adequately examine patients, false-negative test results, all were found to be main predictors of doctor delay regarding breast cancer [14,15]. Lack of medical referral system, patient's indecision about choosing the doctor, some problems associated with system factors, including the irregular presence of doctors, official holidays, prolonged admission time, contributed to delays in diagnosis for breast cancer. As to the factors possibly associated with delays in diagnosis, one study suggested little sensitization to women's health matters, poor information campaigns, and lack of screening programs based on mammograms or other techniques for early diagnosis of breast cancer. One study conducted in Brazil concluded that delays in breast cancer diagnosis were attributed to the user's difficulty in accessing the various levels of health professionals [16-18]. We will next present briefly delayed diagnosis of cancer in our clinic for the last 3 years. Among our patients, we highlighted on risk factors reviewed above that contributed to delay presentation and diagnosis (Table 4). Given the fact that our clinic is not treating only cancer cases and the percentage of advanced breast cancer surgery is very small (0.01%) we couldn't summarize a high number of patients with advanced breast cancer diagnosis on the last 3 years. Four from five patients were above 60 years, also two patients out of five with high-income. Regarding marital status, 3 out of five were unmarried. All patients ignored symptoms until they interfered with social life and ulcerations in four cases and mass in one case were so deep and voluminous that they became visually disturbing for patients. None of the patients were with positive family history of breast cancer. Our patients did receive a questionnaire regarding the reasons for delayed presentation. Four out of five patients invoked for delay presentation fear either for diagnostic of malignancy or of potential biopsy, mastectomy and chemotherapy and one patient told she couldn't come earlier because of other health conditions concerning her husband. Three out of five patients also self-treated themselves with alternative therapy (based on plants). Another potential factor for delaying presentation was the long distance between house and clinic, and that is because three out of five patients were living in rural area, far away from any city with hospitals. Of course, our database is limited by the small number of cases, and this is because our clinic is not exclusively oncologic surgery unit and besides because there are strong regional campaigns regarding mammographic annual screening.

Conclusion

Awareness of these issues could help focus efforts to develop algorithms that identify patients at risk for a delay and build programs that facilitate their timely access to care. Follow-up intervention and patient education, could serve to ensure that the vulnerable population receive cancer screening, facilitated access for cancer-related symptoms, and interventions designed to assist patients with abnormal findings to complete recommended consultations and treatment. Research into the risk factors for diagnostic delay indicates that presentation with cancer is not a straightforward process. Knowledge of symptoms and risk factors may be necessary, but not sufficient to determine help-seeking for cancer and further studies are necessary to determine whether accreditation of hospitals and/or centralization of cancer may lower the number of diagnostic delays, especially in hospitals with a large proportion of patients facing a diagnostic delay. These aids understanding of the complexity of the delay process and highlights where and how interventions could be targeted. To impact on presentation with cancer symptoms, we

need a greater understanding of the psychological and sociological factors influencing patients' help-seeking behavior. Besides, we need to devise culturally sensitive strategies, not only to improve awareness of cancer but also to aid interpretation of symptom seriousness by patients. On the behalf of our study, we want to establish an oncological patient profile which delay presentation at the doctor, the importance of medical education, and also raise awareness of the health care professionals for avoidance of delaying the diagnosis and also provide a health system which could permit rapid assessment of patients with facile access to treatment, even in difficult times like COVID-19 pandemics which we are confronting at the moment.

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