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MASTERS' THESIS

Jamil DEBEL



T.R.

ANKARA YILDIRIM BEYAZIT UNIVERSITY
PUBLIC HEALTH INSTITUTE

**DELAY DIAGNOSIS OF BREAST CANCER IN THE NORTH
WEST SYRIA: INFLUENCING FACTORS AND ASSOCIATED
NEGATIVE OUTCOMES**

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Thesis Supervisor

Prof. Dr. Salih MOLLAHALILOĞLU

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Ankara 2025

APPROVAL of the THESIS
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I certify that this thesis meets all the requirements for a Master's Degree

PLAGIARISM

I declare here that everything in this thesis is my unique work. I have explicitly referenced Ankara Yildirim Beyazit University guidelines, academic rules, and ethical conduct and I accept full legal responsibility for the academic procedure of my thesis.
(06/02/2025)

Jamil DEBEL



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ABSTRACT

Master's Thesis

DELAY DIAGNOSIS OF BREAST CANCER IN THE NORTH WEST SYRIA: INFLUENCING FACTORS AND ASSOCIATED NEGATIVE OUTCOMES

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Background: Breast cancer is a major global health issue and the most common cancer among women, significantly contributing to morbidity and mortality. According to the World Health Organization, breast cancer accounts for a substantial percentage of cancer-related deaths worldwide, with the burden being particularly pronounced in low- and middle-income countries (LMICs). Early diagnosis and timely treatment are critical to improving survival rates; however, in resource-constrained settings, delays in diagnosis are a persistent challenge. In conflict-affected regions like Northwest Syria, the situation is exacerbated by the fragile healthcare infrastructure, ongoing political instability, and limited access to essential healthcare services. Women in these areas face significant barriers to early detection, including a lack of awareness about breast cancer symptoms, cultural stigmas, financial constraints, and logistical issues in accessing healthcare facilities. Delays in diagnosis often result in advanced-stage presentation, leading to poor prognosis and increased mortality. Healthcare delays can be categorized into two main types: patient-related delays, where individuals fail to seek medical attention promptly after noticing symptoms, and system-related delays, which occur within the healthcare system due to inefficiencies in diagnostic pathways, lack of resources, and inadequate healthcare provider training. These delays not only impact individual outcomes but also strain already overburdened healthcare systems. While breast cancer diagnosis and management have been extensively studied in high-income countries, there is limited research focusing on LMICs, particularly conflict-affected regions such as Northwest Syria. The unique challenges posed by the ongoing conflict, including displacement, poverty, and disrupted healthcare services, underscore the need for context-specific research to address delays in diagnosis and improve outcomes for breast cancer patients. This study aims to investigate the factors contributing to diagnostic delays in breast cancer among women in Northwest Syria and their associated negative outcomes. By identifying these barriers and providing actionable recommendations, the research seeks to contribute to the development of effective strategies for improving early detection and treatment in resource-limited and conflict-affected settings.

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Key Words: Breast Cancer, Delay Diagnosis, Screening Program, Northwest Syria

ÖZET

Yüksek Lisans Tezi

KUZEY BATI SURIYE'DE MEME KANSERİNİN GECİKMİŞ TANISI: ETKİLEYEN FAKTÖRLER VE İLİŞKİLİ OLUMSUZ SONUÇLAR

Jamil DEBEL

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Arka Plan: Meme kanseri, önemli bir küresel sağlık sorunudur ve kadınlar arasında en yaygın kanser türüdür ve morbidite ve mortaliteye önemli ölçüde katkıda bulunur. Dünya Sağlık Örgütü'ne göre, meme kanseri dünya çapında kanserle ilişkili ölümlerin önemli bir yüzdesini oluşturur ve yük özellikle düşük ve orta gelirli ülkelerde (LMIC'ler) belirgindir. Erken teşhis ve zamanında tedavi, sağ kalım oranlarını iyileştirmek için kritik öneme sahiptir; ancak kaynak kısıtlı ortamlarda, teşhis gecikmeleri sürekli bir zorluktur. Kuzeybatı Suriye gibi çatışmalardan etkilenen bölgelerde, durum kırılgan sağlık altyapısı, devam eden siyasi istikrarsızlık ve temel sağlık hizmetlerine sınırlı erişim nedeniyle daha da kötüleşmektedir. Bu bölgelerdeki kadınlar, meme kanseri semptomları hakkında farkındalık eksikliği, kültürel damgalar, mali kısıtlamalar ve sağlık tesislerine erişimde lojistik sorunlar dahil olmak üzere erken teşhis için önemli engellerle karşı karşıyadır. Teşhis gecikmeleri genellikle ileri evre sunumuna neden olur ve bu da kötü prognoza ve artan mortaliteye yol açar. Sağlık hizmetlerindeki gecikmeler iki ana türe ayrılabilir: Hasta kaynaklı gecikmeler, bireylerin semptomları fark ettikten sonra derhal tıbbi yardım almaması ve sağlık sisteminde tanı yollarındaki yetersizlikler, kaynak eksikliği ve yetersiz sağlık hizmeti sağlayıcısı eğitimi nedeniyle oluşan sistem kaynaklı gecikmeler. Bu gecikmeler yalnızca bireysel sonuçları etkilemekle kalmaz, aynı zamanda zaten aşırı yüklenmiş sağlık sistemlerini de zorlar. Meme kanseri teşhisi ve yönetimi yüksek gelirli ülkelerde kapsamlı bir şekilde incelenmiş olsa da, özellikle Kuzeybatı Suriye gibi çatışmadan etkilenen bölgeler olmak üzere düşük ve orta gelirli ülkelere odaklanan sınırlı sayıda araştırma bulunmaktadır. Yerinden edilme, yoksulluk ve kesintiye uğrayan sağlık hizmetleri gibi devam eden çatışmanın getirdiği benzersiz zorluklar, tanı gecikmelerini ele almak ve meme kanseri hastaları için sonuçları iyileştirmek için bağlama özgü araştırmalara olan ihtiyacı vurgulamaktadır. Bu çalışma, Kuzeybatı Suriye'deki kadınlarda meme kanserinde teşhis gecikmelerine katkıda bulunan faktörleri ve bunlarla ilişkili olumsuz sonuçları araştırmayı amaçlamaktadır. Bu engelleri belirleyerek ve uygulanabilir öneriler sunarak araştırma, kaynakların sınırlı olduğu ve çatışmalardan etkilenen ortamlarda erken teşhis ve tedaviyi iyileştirmek için etkili stratejilerin geliştirilmesine katkıda bulunmayı amaçlamaktadır.

Şubat 2025, 69 sayfa

Anahtar Kelimeler: Meme Kanseri, Gecikmiş Tanı, Tarama Programı, Kuzeybatı Suriye

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LIST OF ABBREVIATIONS

AS	Advanced Stage
BC	Breast Cancer
BCR	Breast Cancer Risk
BMI	Body Mass Index
BRCA1	BReast CAncer gene 1
BRCA2	BReast CAncer gene 2
CI	Confidential Interval
COVID 19	COrona VIRus Disease of 2019
CRP	C-Reactive Protein
CS	Clinical Stage
DALYs	Disability-Adjusted Life Years
DCIS	Ductal Carcinoma In Situ
DD	Diagnosis Delay
DFS	Disease Free Survival
DNA	DeoxyriboNucleic Acid
DV	Dependent Variables
ER	Estrogen Receptor
ER	Danger-Associated Molecular Patterns
ET	Estrogen Therapy
GFR	Glomerular Filtration Rate
HCW	Healthcare Worker
HeR-2	Human Epidermal growth factor Receptor 2
HNAP	Humanitarian Needs Assessment Programme
HR	Hormone Receptor
HRT	Hormone Replacement Therapy
HT	Hormone Therapy
ICU	Intensive Care Unit
LCIS	Lobular Carcinoma In Situ
LMICs	low-income or middle-income economies
M	Metastasis
N	Lymph Node Involvement
NWS	Northwest Syria
OR	Odds Ratio
OS	Overall Survival

PD	Patient Delay
PFS	Progression Free Survival
PR	Progesterone Receptor
RNA	Ribonucleic Acid
SD	Standard Deviation
SD	System Delay
SPSS	Statistical Package for the Social Sciences
T	Tumor Size
TD	Treatment Delay
TFR	Total Fertility Rate
TN	Triple-Negative
TNBT	Triple Negative Breast Cancer
TNM	Tumor Nodes Metastases
UNFPA	United Nations Fund for Population
WHO	World Health Organization

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1. INTRODUCTION

1.1. Background

Breast cancer is a disease of great public health importance. About 40,000 female breast cancer deaths and 232,670 new instances of the disease diagnosed in the United States in 2014, making breast cancer the second most common cause of cancer-related deaths among women (1). Efforts to promote early diagnosis remains the focus in the fight against breast cancer because primary prevention of the disease is still not possible except through drastic procedures like preventive mastectomy for women who are genetically at high risk (2). Early detection aims to successfully treat breast cancer patients when their chances of long-term survival are at their highest (3).

If a delay results in stage advancement, worsening of the illness, or treatment problems, longer waiting periods between the diagnosis of breast cancer and the start of therapy are of prognostic significance. Two main categories of delays exist. Patient delay is the failure to follow appointments or the delay in seeking medical help after self-discovering a possible breast cancer symptom. System delays occur when appointments, diagnostic test scheduling, gaining a conclusive diagnosis, and starting therapy are delayed within the health care system. Women with breast cancer may have a worse prognosis because of both factors since they may cause delays in diagnosis and treatment.

Several components made up a thorough evaluation of the literature on breast cancer delay conducted in the early 1990s (4). The review's first section looked at research that investigated the connection between prognosis and delay. The significance of patient delay and the variables linked to prolonged patient delay were therefore the focus of the review. With system delay, it had the same effect. Numerous review articles examining the factors linked to protracted delays have been published since then (5, 6). As a result, the author chose to concentrate this review on how delays affect breast cancer survival.

1.2. Early Studies

Prior research on the effects of delay on prognosis tended to indicate that longer wait times are linked to tumors that are diagnosed at a later stage, which lowers survival rates.

Women who start therapy 3–6 months after the onset of breast cancer-related symptoms actually have a much lower survival rate than those who wait less than 3 months, according to a meta-analysis of 87 studies (7).

However, most of that research was conducted before 1970, making them outdated. Among the recent investigations, two conducted in the late 1990s that were included of the evaluation are detailed below (8,9).

Increased delay was also linked to more advanced malignancies at diagnosis and/or lower survival, according to many other 1980s studies that were left out of Richards et al.'s study. Those with delays of at least 6 weeks had more advanced disease (35% stage I, 52% stage II, and 12% stage III) than those with delays of less than 6 weeks (52% stage I, 42% stage II, and 5% stage III), according to Robinson et al.'s study on diagnosis delays among patients with breast cancer (10).

This study did not determine survival. At Houston's M.D. Anderson Hospital, Neale et al. showed that patients with delays of more than 6 months had significantly worse cumulative survival after 10 years compared to patients with delays of 3–6 or <3 months, even when tumor grade was not taken into account (11). In 1970–1971 and 1980–1981 combined, patients treated with radical or modified radical mastectomy were about twice as likely to have tumors of at least 4 cm and about 40% more likely to have axillary metastases if they delayed more than 6 months, according to a study of breast cancer patients at New York's Memorial Sloan-Kettering Cancer Center by Robbins et al. (12).

Increased relative risks for regional disease were noted in a study of 274 women with breast cancer in Los Angeles over the five months between self-discovery of the symptom and initial contact with the doctor (13). Furthermore, the time between self-discovery of the symptom and biopsy was linked to regional disease, but not the time between initial contact with the doctor and biopsy. The authors discovered no proof that additional delays had a negative impact on the patient's chance of receiving a regional illness diagnosis after the patient saw the physician.

Notably, the anticipated inverse link between delay and survival had not been seen in a number of very early investigations conducted between the 1940s and 1950s (14).

Bloom responded by demonstrating that this was mostly caused by confounding by histologic grade or the tumors' innate malignant propensity (15). According to a study of breast cancer cases from London's Middlesex Hospital, women who experienced a lengthy wait seemed to have a higher likelihood of developing less malignant tumors.

1.3. Recent Studies

The findings of the more recent research are not entirely consistent. One set of research examines the connection between the tumor stage at the time of therapy commencement and the delay. It is reasonable to assume that women with more advanced malignancies will typically live short lives. Other research examines the connection between survival time and delay, sometimes without taking tumor stage into account. Separate reviews are given to these two categories of research.

1.4. Studies on Tumor Stage and Delay

In two trials, Plotogea et al. discovered that a longer delay was linked to a poorer stage at diagnosis. In one study, 2,065 women with invasive breast cancer diagnosed between January 1, 1995, and December 31, 2003, who were randomly selected from a sample of 2,615 women aged 50–69, were divided into three groups: Interval breast cancer, which occurs between 6 and 12 months after a mammogram; screen-detected breast cancer, which occurs if the patient had a mammogram during the study period and her breast cancer was diagnosed within 6 months of that screen; and symptomatic breast cancer, which is found in a woman who did not have a screening mammogram during the study period before being diagnosed (16).

Diagnostic wait times (the interval between imaging or biopsy and breast cancer diagnosis) were significantly shorter for screen-detected breast cancers diagnosed at stage II and symptomatic cancers diagnosed at stage III or IV than for those diagnosed at stage I (OR = 0.66, 95% CI = 0.50–0.87 and OR = 0.46, 95% CI = 0.25–0.85, respectively). 1,760 women between the ages of 50 and 69 who were diagnosed with invasive breast cancer in Ontario between 1995 and 2003 were included in Plotogea's other study (17). Delays from diagnosis to definitive surgery were 17 days on average, from final surgery to postoperative chemotherapy they were 44 days, and from final surgery to postoperative radiation they were 75 days. One noteworthy finding is that, in comparison to 1995–1999, diagnoses made

between 2000 and 2003 were linked to noticeably longer delays for each stage of the treatment route.

Shorter wait periods between diagnosis and definitive surgery were linked to higher diagnosis stage (stage III versus I: OR = 0.49, 95% CI = 0.34–0.71).

At a National Comprehensive Cancer Network Center, Warner et al. studied 21,427 White, Asian, Black, and Hispanic women who were diagnosed with stage I–IV breast cancer between January 1, 2000, and December 31, 2007 (18). The median time to diagnosis for symptomatic women was 36 days for White women and 53.6 days for Black women. The median time to diagnosis for women with abnormal mammography was 21 days for White women and 29 days for Black women. Stage III or IV cancers were most common in Black people (26%). Although estimates remained statistically significant, the observed elevated incidence of stage III and IV breast cancer decreased from 40 to 28% among Hispanics and from 113 to 100% among Blacks after taking time to diagnosis into consideration. The observed disparities in stage between racial/ethnic groups were not entirely explained by longer time to diagnosis.

Interviews were conducted with 200 Libyan women, ages 22 to 75, who had been diagnosed with breast cancer in 2008–2009 regarding the delay in diagnosis [the time between the onset of symptoms and the ultimate diagnosis of breast cancer based on histological examination (19)]. With 30.0% of patients receiving a diagnosis within three months of symptom onset, 14% receiving a diagnosis within three to six months, and 56% receiving a diagnostic more than six months later, the median diagnosis delay was 7.5 months. Greater tumor size, positive lymph nodes, a higher incidence of late clinical stages, and metastatic illness were all linked to a diagnosis delay of more than three months.

African-American women with self-detected breast alterations were the subjects of a study that looked at the associations between breast cancer stage, marital status, delay to seek medical attention, spirituality, breast cancer fatalism, and disclosure of symptoms (20). The study comprised a convenience sample of 129 African American women between the ages of 30 and 84 who self-reported identifying a breast symptom within the previous 12 months prior to receiving a breast cancer diagnosis. Most women put off seeking medical attention for more than three months. There were no correlations discovered between the time to seek medical attention and spirituality, religion, or fatalism. Compared to women

who sought care within three months of noticing their symptom, those who postponed seeking medical attention for more than three months were more likely to come with breast cancer at a later stage. Breast cancer stage at diagnosis and time to seek medical attention were found to be significantly correlated; the longer the delay, the more advanced the stage of breast cancer ($P = 0.01$).

The stage of breast cancer and the delay of symptom presentation for medical diagnosis were significantly positively correlated, according to logistic regression ($OR = 6.37$, $95\% CI = 2.84-14.30$).

In order to assess the impact of emergency admission and delays on prognosis, Redondo et al. conducted a research on 411 patients with histologically confirmed breast cancer who were treated at the Costa del Sol Hospital in Marbella, Spain between January 1, 1996, and December 31, 2001 (21). Three components were identified for oral delay. Primary care and patient delays were defined as the time between the onset of symptoms and the initial hospital visit; diagnostic delays were defined as the time between the initial hospital visit and the final histopathologic diagnosis; and treatment delays were defined as the time between the diagnosis and the initial treatment. In those orders, the median delay times were 87, 11, and 36 days. Advanced stages were linked to patient and primary care delays of more than six months, even though these tumors had pathological features that indicated a favorable prognosis, such as non-ductal type and positive estrogen and progesterone receptor status. On the other hand, a diagnostic delay of less than 30 days was substantially linked to larger tumors, lymph node metastases, and ductal type ($P < 0.05$), as well as to poorly differentiated tumors and a negative progesterone receptor status. The presence of signs or symptoms other than a lump, ductal type, and negative hormone receptor status were all strongly correlated with treatment delays of less than 30 days ($P < 0.05$).

Between 1984 and 2007, Elzawawy et al. conducted a number of investigations in Port Said, Egypt, examining the pathological tumor size and the delay in seeking medical advice (22). Both the number of advanced cases and the number of delays decreased over time.

A retrospective cohort research was carried out by Elmore et al. on 400 female patients with breast cancer who were diagnosed between 1985 and 1993 and were monitored until June 20, 2001 (23). Women who finished their evaluation within 30 days had a significantly higher chance of being diagnosed with local disease (83%) among the 117 women with

patient-detected breast cancer than those who took longer than 30 days, who were more likely to be diagnosed with regional disease (36%, $P < 0.05$). Compared to women who had an examination within 30 days, those who took more than 30 days had a considerably higher chance of dying or experiencing a recurrence of breast cancer (24 versus 8%; $P < 0.05$).

A population-based study of 287 women with newly diagnosed invasive symptomatic breast cancer, aged 18 to 80, looked at patient delay (the interval between the onset of symptoms and the first doctor's visit) and its effect on disease stage (24). Among patients with symptoms, the median patient delay was 16 days, and 18% of all patients with breast cancer experienced a patient delay of more than three months. When stratified by tumor differentiation, the data showed a varied relationship between patient delay and stage at breast cancer diagnosis. The proportion of late-stage breast cancer did not change as patient delay increased for women with well-differentiated tumors ($P_{\text{trend}} = 0.83$); however, for women with poorly differentiated tumors, there was a monotonic trend between the length of patient delay and late-stage diagnosis ($P_{\text{trend}} = 0.03$).

185 cancer patients who visited a breast unit were interviewed two months after diagnosis in order to investigate the degree and factors influencing patient and general practitioner delays in the presentation of breast cancer (9). 19% of patients had a presentation delay of 12 weeks or longer to the general practitioner, which was associated with a clinical tumor size of ≥ 4 cm ($P = 0.0002$) and a greater frequency of both locally progressed and metastatic disease ($P = 0.01$).

A case-control study of patients with breast cancer was carried out by Lannin et al. at the University Medical Center of Eastern Carolina between 1985 and 1992 (25). There were 414 community-matched controls and 540 cases in total. Delaying medical care due to financial constraints was found to be a predictor of advanced breast cancer stage (OR = 1.6, 95% CI = 1.1–2.5).

1.5. Studies of Survival and Delay

Using the California Cancer Registry database, a retrospective case-only analysis assessed treatment delay (the number of weeks between the date of diagnosis and the date of decisive therapy) in 8,860 instances of breast cancer in adolescents and young adults diagnosed between 1997 and 2006 (26). Women who had surgery and experienced a

treatment delay of more than 6 weeks had an 80% 5-year survival rate, while those who experienced a treatment delay of less than 2 weeks had a 90% 5-year survival rate ($P = 0.005$). Longer treatment delays were a significant risk factor for shorter survival in multivariate analysis. Increased treatment delay had a larger detrimental impact on survival for African American women, women with public or no insurance, and women from lower socioeconomic backgrounds.

In order to investigate the effects of a lengthy interval between a biopsy-confirmed breast cancer diagnosis and the start of treatment on survival, McLaughlin et al. performed a retrospective analysis of 1,786 low-income, adult female North Carolina Medicaid enrollees who were diagnosed with breast cancer between January 1, 2000, and December 31, 2002, in the associated North Carolina Central Cancer Registry-Medicaid Claims database (27). 22 days was the median delay. Intervals between diagnosis and first treatment ≥ 60 days were linked to significantly worse breast cancer-specific survival among late-stage patients ($HR = 1.85$, $95\% CI = 1.04\text{--}3.27$; $P = 0.04$), but adjusted Cox proportional hazards regression showed that the delay interval had no effect on survival among those diagnosed at an early stage.

The period in days between the date of the initial diagnosis of breast cancer metastasis (the date of the first metastatic biopsy or CT scan) and the date of the start of the first treatment was used to define treatment delay in a study of 553 patients with metastases from breast cancer in Pittsburgh (28). Negative survival outcomes were linked to treatment delays of more than 12 weeks.

In a comprehensive, multidisciplinary breast oncology program in two hospital systems, Brazda et al. retrospectively reviewed patients receiving therapy for breast cancer from August 2005 to December 2008 (29).

The investigators divided patients into groups according to intervals to treatment of <90 and >90 days because prior research had shown decreased survival with delays >90 days; however, there was no discernible difference in survival between these two groups.

In order to evaluate the disparities in the factors linked to breast cancer mortality between African-American and European-American women, Smith et al. studied 314 participants in South Carolina's Breast and Cervical Early Detection Program between 1996 and 2004 (30). Three delay intervals were examined in the study: total delay, treatment delay,

and diagnostic delay. The time between the date of the pathologic diagnosis of breast cancer during that screening cycle and the date of the initial screening examination (clinical breast exam or mammography) that revealed an abnormality was known as the diagnostic delay. The amount of time that passed between the pathological diagnosis of breast cancer and the start of the initial treatment was known as the "treatment delay." Using Cox Proportional Hazards models, there was no discernible correlation between the delay intervals and the probability of death.

Women with stage I/II breast cancer diagnosed between January 1, 1996, and December 31, 2001, who received adjuvant chemotherapy, were the subjects of a study by Hershman et al. in the Henry Ford Health System tumor registry (31). For every patient, the observed/expected ratio of treatment duration and completed chemotherapy cycles was computed. Sixty percent of the 344 patients who received the anticipated number of cycles had delays, although this did not lower survival. Only 17% of the patients experienced delays longer than two weeks, the authors noted, raising the possibility that either the delays were not severe enough to impact survival or that the study lacked the necessary power to identify their effects.

In order to determine if delays by clinicians in ordinary practice for diagnosis affect survival, Sainsbury et al. performed a retrospective examination of breast cancer patients registered in the Yorkshire Cancer Registry (32). Data for 36,222 breast cancer patients between 1976 and 1995 were accessible. Patients were divided into four groups based on how long it took them to receive therapy after being referred by their family physician: less than 30 days, 30–59 days, 60–89 days, and 90 days or more. While the median delay from family physician referral to hospital visits decreased marginally from 10 to 12 days during the same period, the median delay between the first hospital visits and treatment virtually doubled from 7 to 13 days. Patients with shorter wait times (less than 30 days) between referral to a family physician and treatment fared worse than those with longer waiting times ($P < 0.001$).

Patients' and doctors' delays were randomly classified as short (0–14 days), intermediate (15–60 days), and long (>60 days) in a research study including 7,608 patients with primary breast cancer (33). When compared to a short patient's delay, a lengthy patient's delay was linked to a worse outcome; however, the opposite was true for doctor's delays, as patients with long doctor's delays had better prognoses than those with short doctor's delays.

Furthermore, the predictive value of delay on mortality rose by 13% for a short doctor's delay compared to a longer one and by 24% for a long patient's delay compared to a shorter one when age was considered. According to the authors, the doctor's delayed findings show that physicians can differentiate between more and less dangerous cancers.

A study by Richards et al. examined 2,964 women who visited Guy's Hospital in London between 1975 and 1990 with breast cancer in any stage (8). Before their initial hospital visit, 32% of the women had symptoms for at least 12 weeks. Compared to 10% of women with delays of less than 12 weeks, 32% of these women had locally progressed or metastatic illness. The survival rates of women who experienced delays of 12–26 weeks were considerably lower than those of women who experienced delays of less than 12 weeks. Longer delays were linked to more advanced stages, which is why multivariate analysis showed that delays had a negative effect on survival. However, within disease stages, this negative influence vanished.

2. LITERATURE REVIEW

The bulk of deaths from breast cancer take place in developing nations (34). Lack of access to early medical assistance is the fundamental reason why developing countries have not seen the mortality reductions seen in rich countries over the past few decades (35). Compared to high-income nations, the majority of cancer cases in low- and middle-income countries (LMC) are discovered later in life (36).

It is widely believed that the population's lack of knowledge and the inadequate coverage of screening programs are to blame for this delayed diagnosis. On the other hand, there are surprisingly few studies on the causes of women in developing nations delaying getting treatment for breast cancer.

This study aims to identify research gaps for LMC by organizing, summarizing, and critically evaluating the available data on women with breast cancer who delay receiving medical attention.

A study of the literature was done on research on breast cancer delay that were published in publications in either English or Spanish between 1950 and 2008. The following terms were searched for in both English and Spanish using the PubMed and Scielo electronic databases: breast cancer delay, delay and breast carcinoma, delay and breast neoplasms, breast cancer experience, breast cancer, and help-seeking behavior. To locate further studies, references from pertinent papers were also consulted. Since the factors causing delay vary throughout cancer types, only literature on delay for breast cancer was included, and not for other malignancies (37, 38).

This review includes a summary of data from 96 investigations. A selection of studies was examined to address goals. The findings are divided into six sections, each of which relates to one of the following goals: I) comprehend the history of the advice to "do not delay when you discover breast cancer signs or symptoms"; II) go over the various definitions and categories of delay that have been applied; III) assess the current body of knowledge regarding the effect of delay on prognosis; IV) pinpoint delay-related factors and the most pertinent methodological aspects of studies that have examined them; V) Evaluate the information on delays that is now available critically; as a result, VI) determine what more

research is needed in LMC on this subject, with a particular emphasis on NW Syria. The source and enduring nature of the advice to "do not delay"

Even if prompt treatment for breast cancer is now proven by science to be essential for survival (7), this knowledge was already "public domain" for about a century prior to the discovery of the evidence. Women have been advised to get medical help as soon as they notice any lump or alteration in their breasts since the turn of the 20th century (39).

Surgeons widely believed that surgery could "cure" patients if it was performed "in time" when William Halsted invented the "radical mastectomy" surgical method in the late 19th century (39).

"A cure for breast cancer is not only possible, but, if operated upon early, quite probable," stated Halsted in his own words (40). For more than seven decades,

2.1. Breast Cancer Postponement

Categorization and definition A total delay in cancer treatment is any period greater than three months from the time a patient first notices symptoms to the start of medical intervention. Extended postponements are linked to a lower chance of survival.

According to eight studies conducted in various nations, the overall delay in breast cancer cases ranges from 17% (24) in a population sample from the German Saarland region to up to 42.5% (41) in a regional hospital sample from Tehran, Iran. Usually, patient and provider delays are separated into the total delay.

a) Delayed patient

Pack and Gallo conducted the first investigation on cancer delay in 1938, describing the two forms of delays. "Three months or more elapsed time between discovery of symptoms and a visit to a physician" (42) was the definition given for "undue patient delay.

"Thirteen Surprisingly, most patient delay studies have maintained this initial criterion for the past 70 years, despite the fact that the time barrier was set at random.

b) The delay of the provider

A protracted interval between the first medical consultation and the start of conclusive therapy is referred to as a "provider delay." It goes by the names "system" and "doctor delay." A month is "enough time for the physician to take appropriate action," according to Pack and Gallo. Thirteen This was also decided upon arbitrarily. The diversity in the time used to characterize provider delay has been higher than that of patient delay, even though other researchers have employed it.

Some writers have further separated provider delays into two categories: treatment delays, which are the intervals between the start of therapy and the diagnosis of cancer, and the period between the first clinical consultation and the diagnosis (43, 44). It has less frequently been separated into two categories: hospital delay, or the interval between a referral and the start of final cancer treatment, and referral or general practitioner delay, or the period between a primary care visit and a hospital referral (32, 45).

2.2. The Prognosis is Affected by Breast Cancer Latency

In this part, we make the case that the advancement of the disease makes waiting worse for survival. The study's findings about the relationship between delay and the most significant known prognostic variables are examined.

a) Effect of breast cancer postponement on longevity

For a minimum of a century, this correlation was presumed, until it was verified in 1999.8 (7)

Previously, conflicting results were obtained from several investigations. Diverse sample characteristics (i.e., patients in all clinical stages or only patients with operable cancer), variations in the delay interval under study (patient, diagnosis, treatment, provider, total delay, or different combinations), and variations in the time periods used to define delay (e.g., 1, 2, 3, 6 months, etc.) can all contribute to discrepancies in study conclusions.

Studies that discovered an inverse relationship between survival durations and delay generally defined delay by taking into account the amount of time that passed between the

discovery of symptoms and the initial consultation: either patient delay, total delay of (46), (33), or hybrids of patient delay and provider delay subtypes (8, 47).

Only women with treatable malignancies were included in the studies where no correlation could be identified (12, 48). As evidenced by the discussion that follows, delay appears to impact survival via accelerating the growth of cancer.

Therefore, one possible explanation for the poor results of these investigations could be because, as other research have demonstrated, the length of symptoms has no effect on survival for patients within the same clinical stage (8, 49,50).

There has been greater debate over the relationship between provider delay and survival. Several writers have found no correlation. Others have discovered a negative correlation between survival time and diagnosis delay (32,33,46).

Moreover, some researchers have discovered a clear correlation that may appear counterintuitive: the longer the survival, the longer the provider delay (33). This has been defined as the ability of medical professionals to recognize instances that are more advanced and likely have a shorter survival period, and to initiate therapy more quickly.

Research supporting this claim have shown that early clinical stage (51) and tiny tumors (33,52) are linked to delays, most likely because early disease diagnosis is more difficult for doctors to make.

Richards and associates made a significant contribution in 1999 to elucidating the contentious correlation between survival and total delay. Their meta-analysis of observational studies from 1907 to 1996 showed that women who start treatment later than three months after symptom onset have a shorter survival time than women who postpone treatment for longer than three months (7).

Although this study has many limitations, it represents the strongest evidence to date. The inclusion of studies utilizing varying operational definitions of delay and survival measures was mandatory. However, the authors attempted to create a more valid comparison by categorizing the studies into three groups based on the type of survival measure employed.

Another drawback, as the authors acknowledge, was that only a few of the studies included considered the possible confounding effect of "Leadtime bias" regarding the

relationship between delay and survival. When survival is solely assessed from the moment of diagnosis rather than the onset of symptoms, lead-time bias may arise.

Survival time is predicted to decrease as the amount of time that passes between the onset of symptoms and the confirmation of the diagnosis increases.

Consequently, this lead-time effect may be responsible for the effect of delay on survival if surviving time is calculated from diagnostic confirmation.

Patients who had delays longer than six months were not included in the meta-analysis, and comparisons were limited to patients who had delays between three and six months and those who had delays shorter than three months in order to minimize this bias (7).

The authors of the original research attempted to account for this bias in subsequent studies by measuring survival based on both diagnosis confirmation and symptom discovery. They discovered a strong correlation between delay and both survival metrics (8).

Clinicians may view these data with caution because breast cancer can spread quickly during the illness.³⁴ Recent research has demonstrated that ductal carcinoma in situ cells are capable of metastasizing (53).

This may lead one to question the true significance of a three- to six-month break in the disease's clinical phase. Although there is a good chance that delays of three to six months will not alter a patient's five-year survival for many, research indicates that delays of this length increase the likelihood of clinical progression, which has been demonstrated to have a deleterious effect on survival (50, 54).

Despite the unpredictable heterogeneity of breast cancer's natural history (55, 56), the majority of studies have demonstrated a decrease in mortality with an earlier diagnosis (57).

Thus, efforts should be directed toward an early and appropriate diagnosis and course of therapy if this condition cannot be prevented.

b) Effect of postponement of breast cancer on clinical stage

According to most of the research, women are more likely to receive an advanced stage diagnosis the longer they wait (Table 2.1.) (58).

Table 2.1. Studies of breast cancer delay and its effect on prognostic factors

Ref.	Year	Country	Delay Type	Operational definitions of delay	DV	N	Patient characteristics	A
(30)	1957	USA	TD	Symptom discovery to beginning of treatment. TD (Months: <2, 2-6, >6)	N	1281	BC patients who had radical mastectomy	X
(20)	1962	USA	PD	Symptom discovery to 1 st medical consultation. PD (<6 d, <28 d, <6 m, <12 m)	OS	3623	Patients with different cancers (644 BC) CS	√(D)
			DD	1 st medical consultation to diagnosis confirmation. (<6 d, <28 d; <6 m)	OS			√(D)
								√(I)
(31)	1975	USA	PD	Symptom discovery to 1 st medical consultation. (Months: <1, 1-3, >3)	OS	237	BC patients who had radical mastectomy	X
			SD	1 st medical consultation to beginning of treatment. (Months: <1, >1)				X
(48)	1977	USA	TD	Symptom discovery to beginning of treatment. TD Months: 1.1-3, 3.1-9,	T	1539	BC patients with operable disease (stages I & II)	√(D)
(28)	1980	Canada	PD + DD	Symptom discovery to diagnosis confirmation. PD + DD Months: 2-11, 12)	CS	1591	BC patients diagnosed in 1945, 1950, 1955, 1960, 1965, 1970, 1975	√(D)
					OS			√(I)
(21)	1983	USA	PD	Symptom discovery to 1 st medical consultation. (Months: <3, 3-11, ≥12)	OS	1497	BC patients treated at 1 (1976-1977) & 15 NY hospitals (1975-1979)	√(I)
(71)	1983	USA	PD + RD	Symptom discovery to arrival at hospital. (Months: <1, 1 to <3, 3 to <6, ≥6)	T	569	BC patients treated at 1 hospital (1967-1978)	X
(29)	1983	USA	PD + RD	Symptom discovery to arrival at hospital. (Quantitative variable: months)	OS	185	BC patients treated at 1 hospital between 1957 and 1965.	√(I)
(51)	1983	USA	DD	Normal interpretation of mammogram to cancer biopsy.	N	165	Women with breast lumps & normal mammogram	√(D)
(22)	1984	Israel	PD	Patient perception of delay between symptom discovery and diagnosis (yes/no)	CS	2299	Patients with different types of cancer (412 BC)	√(D)
(25)	1985	USA	TD	Symptom discovery to beginning of treatment. (Months: <3, 3-6, >6)	OS	685	BC patients treated at one hospital between 1962 and 1969	√(I)
(23)	1985	USA	PD	Symptom discovery to 1 st medical consultation. (Months: 3-6, ≥7)	OS	4518	BC patients treated at MD Anderson Center (1949-1968)	√(I)
(40)	1986	Italy	PD + DD		CS	1110	BC patients seen at 63 Italian public hospitals (1983-1984)	√(D)
					T			√(D)
					N			√(D)
(26)	1990	Italy	TD	Symptom discovery to beginning of treatment. (Days: <30, 31-90, 91-180, 181-365, >365.)	OS	189	BC patients treated at two hospitals in Rome between (1982-1988)	√(I)
(42)	1990	USA	PD+DD	Symptom discovery to diagnosis confirmation. (Weeks: 0-2, 3-12, >12)	CS	1055	Cancer patients, residents of New Mexico, ≥65 years old (1984-1986)	√(D)
					T			X
(24)	1994	Denmark	PD	Symptom discovery to 1 st medical consultation. (>60 days)	OS	7608	BC patients registered at the Danish BC Cooperative Group between 1977 & 1982	√(I)
			SD	1 st medical consultation to surgery. (>60 days)	T			√(D)
					N			√(D)
								X
(41)	1998	UK	PD	Symptom discovery to 1 st medical consultation. (≥12 weeks)	CS	185	BC patients with symptoms, treated at one hospital (1992 & 1994)	√(D)
(27)	1999	UK	TD	Symptom discovery to beginning of treatment. (Weeks: <12, 12-26, >12)	T	2964	BC patients treated at one hospital between 1975 & 1990	√(D)
					CS			√(D)
(15)	1999	USA	DD	1 st medical consultation to diagnosis confirmation. (Months: <3, ≥3)	OS	606	BC patients who received medical attention at one of the authors' office	√(I)
					CS			X
					T			X
(19)	1999	UK	TD	Patient referral to beginning of treatment. (Days: <30, 30-59, 60-89, >90)	OS	36222	BC patients identified at Yorkshire Cancer Registry (1976 -1995)	X
(8)	1999	UK	TD	Symptom discovery to beginning of treatment. (Months: <3, ≥3)	CS	87	Studies published between 1907 & 1996 (87 studies, 101,954 patients)	√(D)
(45)	2001	Germany	PD+DD	Symptom discovery to diagnosis confirmation. (Months: 0-1, 1-3, >3)	OS	380	Residents of Saarland region, with BC diagnosed by any means	√(I)
(11)	2002	Germany	PD	Symptom discovery to 1 st medical consultation. (Months: 1-3, >3)	CS	280	Residents of the Saarland region, diagnosed with symptomatic BC	X
(49)	2002	Canada	DD	Abnormal mammogram to cancer diagnosis confirmation. (Weeks: ≤4, 4-12, >12 to 20, >20 to 52, >52 to 104, >104)	T	4465	BC patients diagnosed within three years of abnormal mammogram in five Canada provinces	√(D)
					N			√(D)
(43)	2003	Iran	PD	Symptom discovery to 1 st medical consultation. (Months: ≤3, >3)	CS	190	BC patients that received medical attention at 2 hospitals in Tehran	√(D)
(44)	2006	USA	DD	1 st medical consultation to diagnosis confirmation. (Quantitative variable: months)	CS	40	BC patients seen at 1 hospital (1995 – 2005), with diagnosis delay of more than three months	X
					T			X
					N			X
(39)	2006	UK	PD	Symptom discovery to 1 st medical consultation. (Weeks: <12, ≥12)	CS	69	BC patients ≥65 years, diagnosed at two London hospitals (2002 - 2003)	√(D)

Unger-Saldaña K & Infante-Castañeda C, 2008. Abbreviations. TD= total delay, PD= patient delay, SD= system delay or provider delay, DD= diagnosis delay, RD= referral delay, TD= treatment delay, d= days, w= weeks, m= months, DV= Dependent variables, OS= overall survival, CS= clinical stage, T= tumor size, N= lymph node involvement, BC= Breast Cancer, A= Association: I= inverse association, D= direct association

This link has been repeatedly verified by studies that have taken into account patient delay or overall delay as independent variables (using the most widely used operational definitions) (40, 49,50,59-62).

The London group's 8 metanalysis also turned up 13 published research that supports this same conclusion. There aren't many research that refute the association between delay and clinical stage (8,47,63).

In one such study, the diagnostic delay was defined using an overly generous time criterion (more than three months between the patient's initial visit with the doctor and the confirmation of the diagnosis) (60). Notably, the authors altered their own patient records, seriously jeopardizing the validity of the findings. A relatively small sample of women with delay was included in another study where no correlation between doctor delay and clinical stage (62) was observed, making it difficult to compare the results with those of women without delay.

Another study that looked at patients diagnosed with breast cancer using any method (mammography screening, clinical breast examination, or patient symptom discovery) found no correlation between patient delay and clinical stage. 45 When examining just women who were symptomatic, the same authors found a positive correlation between patient delay and clinical stage in a later paper. The most plausible explanation for the relationship between delay and survival in light of this evidence is that delay effects disease progression, which in turn affects survival, especially since clinical stage has been shown to affect survival (38, 49, 50, 60, 64).

According to data from other studies, the correlation between delay and survival vanishes when clinical stage is taken into account, lending credence to this theory (8,49, 50).

c) Breast cancer delay's effect on tumor size

One of the most significant prognostic indicators for breast cancer is the size of the tumor (38).

It is the predictive factor that has been most consistently linked to delay after clinical stage (24,45,66-71). The tumor size at diagnosis increases with duration of delay. This is yet another sign of the impact of delay on the cause of the illness.

d) Effect of delayed breast cancer on involvement of lymph nodes

Involvement of local lymph nodes is another significant breast cancer prognostic factor. According to certain authors, there is a strong correlation between regional lymph node involvement and total delay (33, 65).

Two of the studies that examined patient delay discovered a strong correlation, but someone else did not (66).

In the latter, individuals with little to no involvement of lymph nodes were restricted to those in clinical stages I and II. There is no connection between lymph node involvement and provider delay. But in one study that tracked the amount of time between an abnormal mammography and the confirmation of a breast cancer diagnosis, and in another that examined the amount of time between a normal mammogram interpretation for a clinically noticeable breast lump and a diagnostic biopsy, a correlation was discovered (67).

e) Effect of delayed breast cancer diagnosis on life quality

Delays in treating breast cancer are linked to shorter survival times. Delay carries a higher chance of requiring more aggressive therapies since the patient is more likely to appear with big tumors and regional lymph node involvement, the longer the delay. Therefore, a woman's likelihood of needing a mastectomy rather than conservative surgery as well as more toxic or prolonged adjuvant treatment increases with the length of time she delays (68).

It has also been demonstrated that patients with advanced illness experience significant psychological morbidity (69). The patient's quality of life is significantly affected by both factors.

2.3. Delays in Breast Cancer-Related Factors

Various causes have been identified in connection with delays experienced by patients and providers. This section covers the key variables that have been investigated in connection with provider and patient delays, as well as the methodological aspects of this research.

a) Patient delay-related factors

As can be shown in Table 2.3., the patient's advanced age and single marital status were the only sociodemographic characteristics that appeared to be highly associated with patient delay up to 1999, according to the systematic review conducted by Ramirez et al.(54).

Subsequent research has, however, continued to produce inconsistent findings (25, 72-75).

Regarding the impact of presenting breast symptoms other than a lump and the patient's initial assessment of her symptoms as "not serious," there appears to be agreement (59, 73,76-80). While inconclusive, poor educational attainment and ethnicity other than non-Hispanic white (in nations where the majority population is Caucasian) appear to be significant variables (6).

Studies reveal that Hispanic and African American patients have shorter survival times than white American patients (23,46,60), and that their breast cancer diagnoses occur at later clinical stages (82-85). It hasn't been conclusively shown that socioeconomic status (SES) and delay are related. However, given the various methods used to measure this variable vary throughout studies, it cannot be completely ruled out.

Given that SES is a "powerful determinant of possessing particular health-enhancing resources," it is most likely connected to delay. A low SES is probably linked to many of the factors that have been linked to delays, such as being a member of an ethnic minority, having less education, living in a rural area, not having health insurance, having access issues to treatment, and engaging in activities that conflict with seeking medical assistance.

Notably, most quantitative research have not supported the inverse relationship between cancer-related information and delay, even though some studies have shown this to exist (6, 25,41,72,73).

When laypeople and health professionals are compared, there are no discernible delays (74).

It has also been shown that there is no correlation between practice and knowledge for other disease behaviors (75).

Numerous qualitative research have revealed that a patient's awareness of other cancer patients is a significant factor affecting their decision to seek help (76). However, the findings of quantitative studies regarding this association have generated controversy (41, 59).

Again, there is a lack of consistency in the operationalization and measurement of this variable across research, which makes drawing conclusions challenging (6). Fear merits specific attention among the psychological variables that have been examined in connection with delay. Research indicates that fear has a curvilinear relationship with patient delay; it can either cause or expedite the need for medical intervention (73,77). It is still unclear what processes lead a particular fearful patient to behave in a particular way.

Furthermore, disparities exist in the instruments used to measure various types of worries, making cross-study comparisons more challenging. The role of several pertinent factors found in qualitative studies, such as fatalism, denial, rationalization/suppression (78) embarrassment of being examined by a doctor (77), and risk perception, has not been adequately measured in high-quality quantitative studies, according to our analysis (79). It is noteworthy to emphasize that most women believe they have a low personal risk of developing breast cancer, according to studies on the subject. This finding may have a significant impact on early detection strategies and the timing of seeking medical attention for breast symptoms (80).

And lastly, we found a dearth of research on the function of social networks, and social support in the delay of breast cancer.

b) Elements associated with provider latency

Provider delay factors are presented in Table 2.4. When comparing Tables 2.3 and 2.4, it is evident that much less research has been done on this kind of delay than on patient delay. This, in our opinion, reflects two trends:

- 1) The medical model has historically attributed health problems and lack of medical attention to the affected individuals, thus blaming the "victim" (81) which causes social problems to be reduced to individual behaviors without consideration of the influence exerted by the socio-structural factors and inequity that lead to a differential distribution of disease.
- 2) The second factor is the minimization of socio-medical and health services research that competes with the overwhelming advances in biomedical knowledge and technology, availability of healthcare services and standard of care.

Patient characteristics are again among the most researched factors in relation to provider delay: low socioeconomic status, being African or Hispanic in countries where the majority of the population is Caucasian (82); young age and having breast symptoms other than a tumor (83), both of which make the physician's diagnosis more difficult (84), over young age and presenting symptoms distinct from a breast lump, there appears to be agreement; nevertheless, there is ongoing debate over the relationship between provider delay and SES and ethnicity. To determine how they intervene with prompt medical attention through the availability, accessibility, and acceptability of health services, they have both been inadequately quantified (85).

Table 2.2. Factors related to patient delay in seeking medical attention for breast cancer

Factors	Qualitative studies	Quantitative studies	
		Association	No association
<i>Socio-demographic factors</i>			
Marital status: single		(5) (11) (12) (28) (43) (54)(§) (56)	(4) (7) (110) (32) (41) (50) (57) (60) (111) (112) (113)
Advanced age		(11) (24) (32) (54)(§) (68) (114)	(5) (7) (28) (41) (55) (57) (58) (60) (111) (110) (115)
Residence in rural areas		(12) (116)	(32)
African or Hispanic ethnicity (in countries where the major- ity of the population is non-Hispanic white)		(5) (23) (62) (63) (110) (54, 113)(‡)	(4) (29) (60) (57)
Low education		(12) (43) (54)(‡) (110) (115)	(4) (7) (50) (55) (58)
Low socioeconomic level	(98)	(7) (12) (60) (62) (68) (113) (116)	(4) (5) (28) (54) (55) (57) (111) (110) (115)
Accessibility barriers	(67) (77)	(111)	(4) (55)
Lack of health insurance		(58) (111)	(4) (110)
Activities that compete with health problem (e.g.: labor, vacations, caring for an ill family member or for young children,household activities, etc.)	(6) (59) (66) (67) (75) (77) (82) (98)	(112) (113)	(115)
Adversity / life crisis in last year			(50) (112) (117)
<i>Knowledge and beliefs</i>			
Lack of cancer knowledge	(66) (67) (69) (79)	(12) (61) (68) (65)	(4) (54) (55) (70) (71) (112) (116)
Previous experiences with family members or friends that had cancer	(6) (59) (66) (67) (74) (75) (76)	(12) (43) (68)	(41) (54) (57) (115)
<i>Psychological factors</i>			
Fatalism	(66) (67) (81) (80) (82)	(61) (111) (112)	
Denial	(66) (67) (81) (80) (118)	(68) (112)	(54) (119)
Rationalization / suppression	(66) (67) (79) (80)	(68) (116)	
Anxiety / cancer worry		(115)	(54) (110) (116)
Fear of cancer confirmation	(59) (66) (67) (69) (74) (77) (78)	(57) (111) (112)	(41)
Fear of mastectomy	(66) (67) (76) (78)	(68) (81) (111) (112) (113)	(115)
Fear of adverse effects on relationships with partner (inter- ference with sexuality, partner's abandonment)	(67) (78) (82)		
Fear of treatment's adverse effects	(59) (75) (76)	(39) (111)	(115)
Fear or lack of trust in doctors and hospitals in general	(66) (67) (82)	(68) (112)	
Embarrassment of being examined by a doctor	(59) (66) (67) (78) (82)	(68) (111) (112)	
Low risk perception of cancer	(79) (82) (83)	(61)	(39)
<i>Characteristics of symptoms / signs</i>			
Breast symptoms other than a lump	(59) (75)	(18) (21) (39) (41) (57) (113)	(32) (115) (116)
Absence of pain	(59)	(68)	(115)
Initial interpretation of symptoms as "not serious"	(59) (66) (69) (74) (75) (78) (79) (83)	(11) (54)(‡) (57) (68) (111) (112) (113) (115)	
<i>Social network and social support</i>			
Not talking to anyone about symptoms	(6) (78)	(39) (41) (54)(‡) (116)	(58) (115)
Lack of social support			(4) (54) (58)
<i>Health service utilization habits</i>			
No breast cancer screening habits	(67) (81)	(32) (46) (50) (113) (120)	(41) (54) (55)
Past experiences of health service utilization for other health problems		(4) (11) (12) (39) (111) (113) (115) (116)	(54)
Lack of a regular physician	(98)	(11) (12) (111) (110)	
Use of alternative medicine	(78) (81) (82)	(68) (113)	

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References highlighted in bold indicate meta-analysis studies when placed in the Quantitative studies columns and meta-synthesis when placed under Qualitative studies. References in italics are reviews without meta-analysis. Remaining references correspond to original research studies

‡ Moderate evidence according to Ramírez et al's meta-analysis (data are suggestive of an effect, with at least two studies in support of the direction of the effect, but conclusions could be affected by a new study with a large sample)

Strong evidence (a substantially greater proportion of studies point to one direction than one would expect to happen by chance) However, the way these variables have been conceived places the burden of delay on the patient as an individual rather than addressing the considerably more complicated issue of comprehending the ways in which health institutions discriminate against the poor and members of minority groups.

Even though health services are thought to be significant players in the study of delay, the few studies that deal with provider delay reduce the issue to estimating delay times and determining who was at fault—doctors are typically held accountable if the patient isn't at fault (86).

This is mirrored in the most frequently studied residual variables related to provider delay (Table 2.4), medical errors, which can take the form of false negative interpretations of mammography or biopsy, or the primary care physician's failure to suspect cancer at the initial visit (87). There is essentially no research done on the actual issues with health care quality and accessibility at the level of the health system, which can affect things like delayed medical attention for breast cancer (88).

Table 2.3. Factors related to provider delay in medical attention for breast cancer

	Qualitative studies		Quantitative studies
Factors	Association		No association
Patient and symptom characteristics			
Patient's young age	(5) (16) (19) (24) (32) (51) (54) ^(S)	(87) (88) (121) (89) (113)	(7) (15) (57) (90)
Patient's African or Hispanic ethnicity (in countries where the majority of the population is non-Hispanic white)	(14) (17) (54) ^(‡)		(15) (57) (121) (89)
Low socioeconomic level	(5) (90)		(57) (87)
Breast signs or symptoms other than a lump	(18) (41) (54) ^(§)	(87) (88) (121) (89) (113)	
Early clinical stage or small tumor size	(24) (32) (33)		
Quality of health services			
Medical errors in diagnosis	(6) (67)	(14) (15) (18) (51) (56) (88) (90) (89) (92) (91) (112) (113)	(54)
Administrative barriers to health care	(97)	(89) (112)	
Far distance from residence to cancer centers			(87)

Unger-Saldaña K & Infante-Castañeda C, 2008

* References highlighted in bold indicate meta-analysis studies when placed in the Quantitative studies columns and meta-synthesis when placed under Qualitative studies. References in italics are reviews *without* meta-analysis. Remaining references correspond to original research studies

‡ Moderate evidence according to Ramírez et al's meta-analysis (data are suggestive of an effect, with at least 2 studies in support of the direction of the effect, but conclusions could be affected by a new study with a large sample)

§ Strong evidence (a substantially greater proportion of studies point to one direction than one would expect to happen by chance)

c) Study methodological aspects on delay-related factors

Understanding the elements that have been researched in relation to breast cancer delay aids in understanding the design of the delay study.

However, research methodologies and tactics also play a crucial role in the advancement of scientific understanding. Therefore, to gain a more thorough understanding of past accomplishments and obstacles to be addressed in future study, it is also vital to investigate the methodological evolution of research studies on delay.

The overall features of the studies that examined the variables indicated in Tables 2.3 and 2.4 are shown in Table 4.1. As is evident, most research employs quantitative techniques that are not particularly useful for gaining a thorough grasp of the underlying causes of women's delays in seeking medical assistance as well as the barriers to health services they face.

The following problems with quantitative studies caught our attention:

- 1) There is a dearth of population-based research, which explains why there is a dearth of data on breast cancer patients who never seek medical attention from health services.
- 2) All studies are retrospective, which entails certain limitations because it is unethical to conduct prospective studies on delays.

Recall bias is the most often noted issue in delay research; women may report incorrect dates and delay times due to poor memory.

However, research has indicated that women typically do remember the onset of their symptoms rather clearly (89). Retrospective studies are also limited by the possibility that patients underreported their experimentation in an attempt to give the interviewer "an adequate answer".

- 3) Self-administered questionnaires were used in some studies, which has the drawback of lower participation rates, particularly when sent by mail, and the possibility of selection bias (90).

Compared to those who do not bother to answer the questionnaire, participants in this kind of survey are typically more concerned in their own health, a feature that is likely linked to prompt medical care seeking.

- 4) The quality of information obtained from clinical records and population registries is limited, and only data that is currently available may be utilized. Moreover, it has been demonstrated that delays that are computed using data from medical records are overestimated (89).
- 5) A recurrent issue across most studies is the lack of validation of tools used to evaluate delay.
- 6) There are significant differences in the operational definitions employed (Table 4.1), which makes it difficult to compare the results and conduct meta-analyses that would enable more reliable conclusions about the association between delay and other factors.

The most prevalent shortcoming found in the evaluated qualitative studies was the lack of theoretical analysis. Most of them are just descriptive. However, there is intriguing research that employs various hypotheses to try and understand the rationale behind women's refusals to seek medical care.

The majority of them employ psychological ideas, such as psychoanalysis (78). The theories of Leventhal's self-regulation, fear and danger control, Ajzen's planned behavior, Gollwitzer's intention implementation theory, reference group behavior, Merton & Kitt's theory of behavior, Anderson & Cacioppo's theory of total patient delay (91), and heuristic analysis (80).

The health belief model by Beck and Rosenstock (73), Bourdieu's social capital theory, and anthropological theories about meaning formation by Taylor, Lipowski, and Kleinman are a few of the social theories that have been applied (92).

Table 2.4. Characteristics of studies that analyze factors in relation to breast cancer delay

Ref	Year	Country	Dependent variables	Source of information	n	Patients	Data analysis ^a
(111)	1950	USA	PD=symptom discovery to 1 st consultation. (>3m)	Semistructured interviews	329	Random sample of people with cancer symptoms seen at one hospital	Bivariate analysis.
(80)	1951	USA	PD=Patient postpones medical consultation. (NS)	In depth interviews	NS	Cancer patients referred for psychiatry consultation in one hospital.	Defensive maneuver theory
(70)	1953	USA	PD=symptom discovery to 1 st consultation. (>3m)	Medical records	229	Doctors with cancer seen at one hospital. (Compared with 2000 lay patients)*9 doctors with BC	Bivariate analysis
(68)	1954	USA	PD=Delay caused by the patient. (NS)	Semistructured interviews + personality tests	100	Random sample of cancer patients attended at one hospital (50 with Delay and 50 without Delay)	Bivariate analysis
(66)	1955	UK	PD=symptom discovery to 1 st consultation. (≥3m)	Interviews + IQ instrument	314	Cancer patients (breast, cervix, oral cavity or skin) attended at one hospital	Descriptive
(116)	1957	USA	PD=symptom discovery to 1 st consultation. (≥3m)	Interviews	727	People with potential cancer symptoms seen at NY clinics	Bivariate & stratified analysis.
(60)	1959	USA	PD=symptom discovery to 1 st consultation. (>1m)	Medical records	633	BC treated at 1 hospital (1943-1951)	Bivariate analysis
(67)	1964	USA	PD=symptom discovery to 1 st consultation. (>2m)	Interviews	150	♀ with breast symptoms referred to one hospital	Psycho-analytic theory
(115)	1968	UK	PD=symptom discovery to 1 st consultation. (>1m)	Structured interviews + self-administered questionnaires	83	hospitalized for operation of breast tumors (benign or malignant)	Bivariate analysis
(112)	1974	UK	PD=symptom discovery to 1 st consultation. (>3m)	Psychiatric interviews + psychological tests	160	hospitalized for breast lump biopsy; (69 cancers; 91 benign)	Bivariate analysis
(28)	1980	Canada	Delay=symptom discovery to BC final diagnosis. (>1m)	Medical records	1591	BC patients diagnosed in 1945, 1950, 1955, 1960, 1965, 1970 & 1975	Bivariate analysis
(120)	1981	USA	DD=symptom discovery to 1 st consultation. (>2 to <6, >6m)	Structured interviews	2092	BC diagnosed in 14 hospitals of Georgia (1975-1979)	Bivariate analysis
(18)	1981	UK	PD=symptom discovery to 1 st consultation. (<1w, <3m, <6m) GPD=1 st consultation to treatment referral. (<2w, <3m) HD=referral to treatment. (NS)	Structured interviews + Medical records	145	BC diagnosed in four public hospitals of New South Wales & New Mexico ≥	Bivariate analysis
(71)	1983	USA	Delay=symptom discovery to arrival at 3 rd level hospital. (1 to <3, 3 to <6, ≥6m)	Medical records	569	BC operated at one hospital (1967-1978). *27/569 health professionals	Bivariate analysis
(21)	1983	USA	PD=symptom discovery to 1 st medical consultation. (≥3m)	Structured interviews + Medical records	664	BC patients seen in 15 Brooklyn hospitals (1975-1979)	Bivariate analysis
(29)	1983	USA	TD=symptom discovery to arrival at hospital. (Quantitative variable: months)	Structured interviews + Medical records	185	BC admitted to a hospital between 1957 & 1965. (29/185 African-American)	Bivariate analysis
(51)	1983	USA	DD=normal mammogram to BC biopsy. (NS)	Medical records	165	s+ with palpable breast masses & normal mammograms	Bivariate analysis
(119)	1984	UK	Delay=symptom discovery to 1 st consultation. (1 to <5w, 5 to <12w, >12w to <6m, >6m)	Structured interviews + psychological tests	24	Hospitalized BC who had breast surgery.	Bivariate analysis
(23)	1985	USA	PD=symptom discovery to 1 st consultation. (3-6m, ≥7m)	Medical records	4518	BC treated at MD Anderson Cancer Center (1949-1968)	Bivariate analysis
(46)	1988	USA	PD=symptom discovery to 1 st consultation. (>2m)	Structured interviews + Medical records	2083	BC diagnosed at 14 hospitals of Georgia	Bivariate analysis.
(4)	1988	USA	PD=symptom discovery to 1 st consultation. (3 to 12, >12w)	Structured interviews	800	65 old residents with cancer (1984-1986). *194 BC cases	Bivariate analysis.
(63)	1992	USA	Symptom duration=symptom discovery to 1 st consultation. (Quantitative variable: days)	Structured interviews + Medical records	735	BC residents of Atlanta, New Orleans & San Francisco (1985-86) (Afro-Americans & whites matched by age and geographic area)	Multivariate analysis
(62)	1992	USA	DD=symptom discovery to final BC diagnosis.	Cancer registry of Los Angeles	23567	BC Los Angeles residents (1977-1985)	Multivariate analysis
(113)	1993	USA	PD=symptom discovery to 1 st consultation. (≥3m) SD=1 st beginning consultation to treatment. (>1m)	Literature review	101	Delay studies published in English between 1975 and 1993	Critical review
(110)	1993	USA	PD=symptom discovery to 1 st consultation. (Quantitative variable: days)	Semistructured interviews + psychological tests	106	with self-discovered breast symptoms referred to two teaching hospitals	Multivariate analysis
(24)	1994	Denmark	PD=symptom discovery to 1 st consultation. (>60d) DD=1 st medical consultation to surgery or biopsy. (>60d)	National database - (DBCG) Danish BC Cooperative Group	7608	BC patients registered in the DBCG between 1977 and 1982	Multivariate analysis
(121)	1995	USA	SD=1 st medical consultation to BC final diagnosis. (Quantitative variable: days)	Structured interviews + Medical records (NCI Black/white Cancer Survival Study)	996	Cohort of African-American and white BC patients residents of Atlanta, New Orleans and San Francisco (1985-1986). *519 African-Americans & 477 white Americans	Multivariate analysis
(77)	1995	USA	Delay=symptom discovery to 1 st contact with health services - personal or by phone. (>3m)	In depth interviews	138	♀ with self-discovered breast symptoms referred to two teaching hospitals	Content analysis
(89)	1996	USA	SD=1 st medical consultation to final BC diagnosis. (>4m)	Structured interviews + Medical records (NCI Black/white Cancer Survival Study)	367	Cohort of African-American and white BC patients residents of Atlanta, New Orleans and San Francisco, who experienced system delay (1985-1986)	Bivariate analysis
(118)	1997	USA	PD=symptom discovery to 1 st consultation. (>3m)	Cases descriptions	5	Cancer patients with psychiatric problems & delay or nonadherence	Psychiatric description

Table 2.4 (continue). Characteristics of studies that analyze factors in relation to breast cancer delay

Ref	Year	Country	Dependent variables	Source of information	n	Patients	Data analysis ²
(114)	1998	UK	Concealed cancer = patient with breast lump that doesn't seek medical help. (≤ 6 m)	Medical records	170	BC between 1988 and 1992 in one general hospital	Bivariate analysis
(41)	1998	UK	PD = symptom discovery and 1 st consultation (≥ 3 m) GPD = failure to refer patient to a 3 rd level hospital after 1 st visit.	Semistructured interviews	185	Two series: 1) Cohort of BC aged <60 (141); 2) Case control: patients aged ≥ 60 , inoperable cancers matched with operable tumors	Multivariate analysis
(78)	1998	USA	Women's opinions about actions they would take if they discovered a breast symptom.	Focus groups	80	Voluntary with no cancer recruited in community organizations other than health care services.	Narrative analysis
(61)	1998	USA	Advanced BC clinical stage = patients with BC stages III & IV.	Structured interviews + Medical records	954	Cases: 540 BC diagnosed at one hospital (1985–1992). Controls: 414 matched by age, race & residence.	Multivariate analysis
(54)	1999	UK	PD = symptom discovery and 1 st consultation. (≥ 3 m) SD = 1 st medical consultation to treatment. (≥ 3 m)	Critical and systematic review of the literature	23	Cohort or case-control studies, published after 1960, with samples of only patients with BC, with validated measure of the involved factor, & that described a discrete interval of delay (23 out of 101 original studies)	No meta-analysis. Strength of evidence estimated for each factor.
(19)	1999	UK	SD = 1 st medical consultation to treatment. (30–59, 60–89, >90 d)	Yorkshire Cancer Registry	3622	BC patients diagnosed between 1976 and 1995	Multivariate analysis
(15)	1999	USA	DD = 1 st consultation to BC final diagnosis. (≥ 3 m)	Medical records	606	BC patients seen at the office of one of the authors	Bivariate analysis
(117)	2000	UK	PD = symptom discovery to 1 st consultation. (≥ 12 w)	Semistructured interviews + adverse life events & psychiatric tests	185	2 series: 1) Cohort of BC aged <60 (141); 2) Case control: patients aged ≥ 60 , inoperable cancers matched with operable tumors	Bivariate analysis
(14)	2000	USA	Diagnosis interval = abnormal mammogram to BC diagnosis. (>60 d) Treatment interval = final diagnosis to treatment. (>30 d)	National Breast and Cervical Cancer Early Detection Program (NBCCEDP)	1659	NBCCEDP participants with BC detected through screening mammography or clinical breast examination	Bivariate analysis
(82)	2000	USA	Women's opinions about actions they would take if they discovered a breast symptom.	Focus groups	45	Voluntary Chinese-American with no cancer recruited in community organizations (no health services).	Content analysis
(88)	2000	UK	HD = 1 st consultation to BC diagnosis. (QV: m)	Medical records	1004	BC in one hospital between 1988 and 1997	Bivariate analysis
(57)	2000	UK	PD = symptom discovery to 1 st consultation. (QV: d) SD = 1 st medical consultation to 1 st consultation with specialist. (QV: d)	Semistructured interviews + Medical records	692	with breast symptoms referred to one hospital between 1996 and 1997	Multivariate analysis
(56)	2000	Thailand	PD = symptom discovery to 1 st consultation. (QV: w) SD = 1 st medical consultation to hospital admission. (QV: w)	Structured interviews + Medical records	94	BC patients treated at the only university hospital in the Southern Region of Thailand	Multivariate analysis
(75)	2001	UK	Women's narratives about their experiences from symptom discovery to treatment.	Semistructured interviews	46	BC diagnosed at one hospital in previous two months	Framework method of analysis.
(69)	2001	Netherlands	Women's experiences from symptom discovery to seeking for medical attention.	In-depth interviews	23	Patients with self-discovered cancer symptoms (breast, melanoma, colon and testicular)	Andersen's PD theory
(79)	2001	Netherlands	Women's experiences from symptom discovery to seeking for medical attention.	In-depth interviews	33	23 patients with self-discovered cancer symptoms & 10 General Practitioners	Content analysis
(32)	2001	Italy	PD = symptom discovery to 1 st consultation. (≥ 1 , ≥ 3 m) DD = 1 st consultation to hospital admission. (≥ 1 , ≥ 3 m)	Semistructured questionnaires	644	with operable BC, operated at the National Cancer Institute of Naples	Multivariate analysis
(11)	2002	Germany	PD = symptom discovery to 1 st consultation. (1–3, ≥ 3 m)	VERDI study database + Structured interviews	380	Saarland region residents, with symptomatic BC (1996–1998)	Multivariate analysis
(122)	2002	USA	Self-reported likelihood of patient delay = probability of patient delay for BC symptoms.	Self-administered questionnaires	699	Voluntary without cancer recruited in community organizations other than health care services	Multivariate analysis
(91)	2002	USA	DD = physician action that completed an episode of care without diagnosing cancer of which there was a sign.	Medical records of patients seen by 1 surgeon (one of the authors)	454	BC patients referred to a single surgeon (between 1992 and 1999) (454 cancers in 436 patients)	Multivariate analysis
(123)	2003	Germany	SD = 1 st consultation to treatment. (1–3, ≥ 3 m)	VERDI study database + Structured interviews	380	Saarland region residents, with symptomatic BC (1996–1998)	Multivariate analysis

Table 2.4 (continue). Characteristics of studies that analyze factors in relation to breast cancer delay

Ref	Year	Country	Dependent variables	Source of information	n	Patients	Data analysis ^a
(65)	2003	Netherlands	Intention to seek medical attention for cancer symptoms.	Postal self-administered questionnaires		Convenience sample: controls of a longitudinal study of asymptomatic Dutch adults – recruited in 1999	Multivariate analysis
(74)	2003	Hong Kong	Illness experience of BC women from symptom discovery to recovery.	Semistructured interviews	17	Chinese & treated for non-metastatic BC in one public breast medical center	Phenomenological analysis
(6)	2003	UK	PD=symptom discovery to 1 st consultation.	Semistructured interviews + focus groups	33	Cancer patients diagnosed in previous two years	Content analysis
(43)	2003	Iran	PD=symptom discovery to 1 st consultation. (>12 w)	Structured interviews + Medical records	190	BC treated at two hospitals in Tehran	Multivariate analysis
(55)	2003	Mexico	Early Clinical Stage: women with BC stage I. SD=1 st consultation to beginning of treatment. (>3m)	Structured interviews	40	BC treated at breast clinic. Cases: stage I patients (10); Controls: stage II, III & IV patients (30)	Multivariate analysis
(16)	2004	UK	DD=1 st medical consultation to final BC diagnosis. (>2m)	Medical records	72	BC with diagnosis delay seen at one hospital (1988-1999)	Bivariate analysis
(92)	2004	Netherlands	DD=abnormal screening mammography to final BC diagnosis. (>3m)	Medical records	770	BC diagnosed after abnormal screening mammogram at two units of national screening program	Bivariate analysis
(17)	2004	USA	SD=1 st medical consultation to treatment.	Structured interviews + Medical records	831	BC, residents of Atlanta. (251 African-Americans & 580 whites)	Multivariate analysis
(87)	2004	UK	SD=1 st medical consultation to treatment.	Medical records	1097	BC identified through Scottish Cancer Registry (1997-1998)	Multivariate analysis
(50)	2004	Norway	PD=Definition not specified. (>1 m)	Semistructured interviews + psychological tests	96	BC stages I & II treated at one hospital	Multivariate analysis
(12)	2005	Iran	PD=symptom discovery to 1 st consultation. (>1m)	Structured interviews	200	BC with stage I, II, or IV seen at referral hospital of Tehran.	Bivariate analysis
(83)	2005	USA	Medical seeking behavior of women who experienced breast symptoms.	In-depth interviews	11	with previous experiences of breast symptoms	Heuristic analysis
(81)	2005	USA	Locally advanced BC=clinical stages II and IV at arrival to 3rd level hospital.	Semistructured interviews + psychological tests	35	BC seen at university hospital. (11 early stage & 11 late stage); & 13 patients' husbands	Descriptive analysis
(5)	2005	UK	PD=Definition not specified	Self-administered postal questionnaires	65192	Cancer patients (data extracted from 1999-2000 National Survey of NHS Patients)	Multivariate analysis
(59)	2005	UK	Cancer patients' experiences from symptom discovery to 1 st medical consultation.	Meta-synthesis	32	Qualitative studies related to cancer help seeking experience, published in English between 1985 & 2004	Meta-synthesis
(97)	2006	Canada	Patient perception of impeding and facilitating events in cancer care continuum.	Structured questionnaire + semistructured interview	120	♀ with BC receiving adjuvant radiotherapy between 2002 & 2003 at a university hospital	Content analysis. Andersen's PD theory
(39)	2006	UK	PD=symptom discovery to 1 st medical consultation. (>12 w)	Semistructured interviews	69	Consecutive series of 100 ^{266 cases} with BC diagnosed between 2002 and 2003 in two London hospitals	Quantitative/Qual: framework method
(76)	2006	USA	PD=symptom discovery to 1 st medical consultation. (>3m)	In-depth interviews	28	Voluntary ♀ with breast symptoms recruited in community organizations other than healthcare services	Heuristic analysis
(98)	2007	Canada	Women's descriptions of pathways from detection of breast abnormality to treatment.	Semistructured interviews	35	♀ recently operated for symptomatic BC	Critical ethnography
(90)	2007	Canada	DD=1 st diagnostic procedure to final BC diagnosis. (>5w)	Structured interviews + Medical records	696	with BC stages I, II and III who were receiving treatment	Multivariate analysis
(58)	2007	Colombia	Advanced BC=clinical stages III and IV at diagnosis.	Semistructured interviews + self-administered questionnaires	102	Cases: advanced BC. Controls: early BC (stage I & II)	Multivariate analysis
(7)	2008	Denmark	PD=symptom discovery to 1 st consultation. DD=1 st medical consultation to 1 st procedure of diagnosis. SD=1 st procedure of diagnosis to beginning of treatment.	Self-administered postal questionnaires + medical care events & Patients (socioeconomic data)	1892	Cancer patients residents of Aarhus County, identified through County Health Service Registry (2004-2005) (291 BC cases)	Multivariate analysis
(33)	2008	Spain	Interval from diagnosis to treatment = F ¹ diagnostic test to beginning of treatment.	Medical records	1023	Cancer patients diagnosed in 22 public hospitals of Barcelona (266 BC cases)	Multivariate analysis

2.4. Future Research Directions in Poor Nations

Since the 1990s, breast cancer mortality rates have been gradually declining in Europe and the United States of America by 1% to 2% annually. This decline has been mostly ascribed to advancements in systemic therapy and screening mammography (93). On the other hand, breast cancer death rates have not changed in nations with inadequate resources (94). The general public's ignorance of breast cancer, socioeconomic and cultural barriers, organizational issues with the health service, resource limitations, and low-quality health services are often utilized by individuals with low socioeconomic status (SES) who lack formal employment, financial stability, and health insurance are some of the obstacles to improving medical care for breast cancer in developing nations.

Increased public awareness of the issue, political will, and scientific study have probably all contributed to improvements in breast cancer mortality rates in developed nations. A health system ultimately consists of the several social subsystems that interact to form it, rather than just the Ministry of Health or the individual medical services provided (95).

The focus of breast cancer policies and initiatives in many LMCs, including most Latin American nations, is currently on screening mammography (96), even if the question of whether this procedure is "more good than harm" is still up for debate (97).

In addition, the establishment of a nationwide screening program entails not only the purchase of mammography equipment but also its fair distribution, training, and assignment of technical staff for its use and interpretation. It seems unjustified to spend so much money on a screening test, the effectiveness of which is still debatable in terms of its influence on mortality, in nations where there is still a dearth of easily accessible, high-quality breast cancer healthcare services. Prioritizing the development of mammography screening programs should be done in order to create and implement suitable treatment guidelines and to make diagnostic and treatment services accessible (96,98).

3. METHODOLOGY

3.1. Study design

We conducted a retrospective Cross-sectional study using oncology center data from the Idleb central hospital database.

In addition to designing questionnaires for patients about the most important reasons for the delay in reaching a diagnosis of cancer and then the delay in starting chemotherapy.

3.1.1. Construction of the questionnaire

The questionnaire was built to assess time from the first identification of a breast problem that could be cancer to arrival at a cancer hospital, and possible associated factors with delayed beginning of treatment.

The questionnaire was assembled with consideration for previous research results from a review of the literature and qualitative interviews of patients with breast cancer symptoms.

The questionnaire was designed for application through face-to-face interviews due to the difficulties associated with self-administered research instruments in northwest Syria among people with little formal education, like our study participants.

Development and validation of a questionnaire to assess delay in treatment for breast cancer _ BMC Cancer _ Full Text.pdf

3.2. Study population

The population in northwest Syria out of regimen control is about 4.4 million people according to the HNAP (Humanitarian Needs Assessment Programme) estimation of April 2022.

The women are about 51% of the population.

The age of women in the study is older than 15 of age.

The percentage of women older than 15 years old age is about 26.02% according to the HNAP (Humanitarian Needs Assessment Programme) estimation of April 2022.

So, the study population is about 1,144,880.

3.3. Sample size calculation

The oncology center in Idleb central hospital is the only center for cancer patient in northwest Syria, so the sample size is all women with breast cancer who treated in the center between January 2021 to the end of December 2021.

3.4. Sample selection

All women with breast cancer who present to the oncology center and start the treatment between January 2021 and December 2021.

3.5. Study location

Northwest Syria.

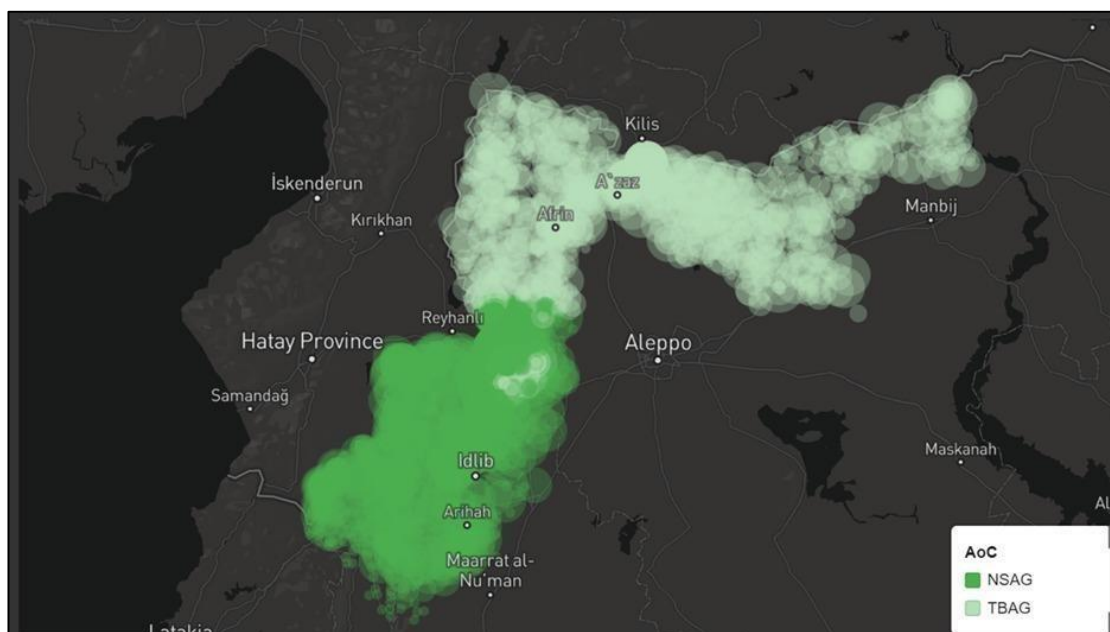


Figure 3.1. Map of Northwest Syria, Humanitarian Needs Assessment Programme 2022

The population in northwestern Syria is about 4 million people, most of them live below the poverty line, and many of them are displaced due to the war from different regions

of Syria, where they live in temporary homes or in tents, and a few of them live in their homes.

The health system in northwest Syria is completely dependent on the support of non-governmental organizations and the United Nations, and the support gradually decreases every year for many reasons, and therefore the distribution of hospitals and health centers varies from one region to another according to the support provided.

The government supervising health differs in different regions because of the difference in control. This creates a broken and weak health system in northwestern Syria, where most hospitals and health centers focus on gynecological and pediatric diseases in addition to trauma.

Most of the deaths in northwest Syria are caused by injuries and heart diseases. The cancer comes in third place.

There is one oncology center in northwest Syria that focuses on treating the most common tumors in the region: breast, colon, Hodgkin's, non-Hodgkin's, testicular, and ovarian cancers.

The most important problem for breast cancer in the northwest Syria is that patient come to the oncology center late, in advanced stages.

3.6. Data Collection Tool

- Data in the Oncology Center
- Questionnaires that are conducted with patients

3.7. Data Collection Process

- Retrospective data analysis.
- Complementary data collection through focused interviews.

3.8. Data Collection Period

- If the retrospective data analysis is achieving the objective of the study, then this phase is expected to take one month
- four more months may be required for the questionnaire.

3.9. Inclusion Criteria

- The patients included in this study were women who were referred or come to the Breast Tumors Department of the Idleb Central Hospital with a probable breast cancer diagnosis, and then the diagnosis was confirmed.

3.10. Exclusion Criteria

- if they had received previous cancer treatment for the current breast cancer.
- if they had a personal history of cancer.
- if they were unable to participate in the interview (because of impaired hearing, inability to communicate in Arabic, or mental disability).
- patients who died.
- if they had a history of a benign breast condition that had been under medical surveillance.
- if the patient did not recall one or more of the relevant dates.

3.11. Study Variables and Definition

- The conceptual and operational definitions of the time intervals agree with many studies of breast cancer delay and recent recommendations of a consensus.
- The variables that will be calculated are:
- ***First compliant date:*** The date of the first clinical sign the patient had before seeing the doctor.
- ***First doctor seen:*** The date of the first visit to the doctor (general practitioner - gynecologist - general surgery - oncologist) after the appearance of clinical signs.
- ***First oncologist seen:*** The date of the first visit to the oncologist.
- ***First chemotherapy treatment:*** the first dose of chemotherapy

- **Total interval:** the time from identification of the problem (symptoms) to the beginning of cancer treatment.
- **patient interval:** the time from identification of the problem to the first medical consultation.
- **provider interval:** the time from the first presentation (first medical consultation) to the beginning of cancer treatment.
- **Age:** the age of the patient when they referred to the oncology center.
- **Education:** whether the patient studied for more or less 8 years.
- **Stage of cancer** depends on the TNM stage.
- **Marital status:** if the patient is married, divorced, or single when they referred to the oncology center.
- **Availability of an early detection center for cancer:** Availability of a center for early detection of cancer no more than 10 km away from the place of residence of the patient at the time of the onset of symptoms.
- **Breastfeeding:** yes or no at the onset of symptoms.
- **Pregnant:** yes or no at the onset of symptoms.
- **displacement situation:** whether the patient is displaced away from her home or not.
- **Morphophilia:** kind of breast cancer depends on the pathology report.
- **Hormonal receptors:** depends on the IHC for the biopsy.
- **Last seen status:** if the patient is alive or died.
- **Lateralization:** if the cancer is in the right or left breast.

3.12. Data Analysis Plan

- Entered the data into an excel database.
- exported to a statistical analyzing app (SPSS).
- Face to face questionnaire.

3.13. Ethical Approval

- Ethical approval from the Idleb central hospital where the oncology center is in.
- Ethical approval from the Ankara Yildirim Bayazit university.
- Ethical approval from the patients who will participate in the questionnaire.

3.14. Problem Statement

The most important problem for breast cancer in the northwest Syria is that patient come to the oncology center late, in advanced stages. Delay diagnosis led to advanced stage and that cause a lot of death due to breast cancer.

3.15. Study Benefit

The benefit of the study lies in shedding light on:

1. The risks of late detection of breast cancer.
2. Importance of early detection of detectable cancers.
3. Trying to find out the reasons behind this.
4. give some advice and solutions to reduce this delay.

3.16. The Study's Objectives

3.16.1. General Objectives

- Evaluate the delays in breast cancer diagnosis in northwest Syria and identify the factors contributing to the associated negative outcomes.

3.16.2. Specific Objectives

1. Assess the financial, social and emotional support impact on seeking cancer medical care.
2. Examine the proficiency of the existing referral medical system in the NW Syria, and its impact on the patient's outcome.
3. Explore the degree of community awareness of the national screening program and medical care access.

3.17. Hypothesis

The Delayed diagnosis of breast cancer in the NW Syria can leads to disease advanced stages due to the lack of organized medical apparatus and the social, economic and logistic reasons.

4. RESULTS

During the study time-period 89 individuals presented to the oncologist for breast cancer treatment. The majority of which were women 98.9% (n=88/89). The majority 78.7% (n=70/89) of the study participants experienced delay (i.e., defined as treatment started 3 months or greater). The average age for the study cohort was 48 years, and the average age did not differ between those who experienced delay (mean age= 48.5 +/- standard deviation 10.0) as compared to those without delay (mean age= 47.9 +/- standard deviation 11.5; p value = 0.850).

Descriptive statistics and Chi-Square independence test results for the variables used in this study are presented in the Tables (4.2 to 4.7). There was no difference between the two groups no delay versus delay in terms of the method of diagnosis symptoms (94.7% versus 94.3%), mammogram (0% versus 1.4%) and self-screening (5.3% versus 4.3%), p=1.000, see table 4.2). There were significant differences between the two groups in terms of initial presentation. The participants with no delay were more likely to have a breast lump (78.9% compared to those with delay (30.0%), while those with delay were more likely to have a mass in the axilla (44.3%) versus (5.3%, p<0.001, see table 4.2). There were significant differences in the self-reported reasons for the delay. The patients without delay were more likely to report denial (21.1% versus 15.7%), while those with delay were more likely to report a lack of serious symptoms (34.3% versus 21.1%) and misdiagnosis (18.6% versus 5.3%; p=0.040, see Table 4.2).

Table 4.1. Clinical Presentation and Initial Symptoms

	No Delay (N=19)		Delay (N=70)		p-value
	N	%	N	%	
Method of diagnosis					
Symptoms	18	94.7	66	94.3	1.000
Mammogram	0	0.0	1	1.4	
Self-Screening	1	5.3	3	4.3	
Initial presentation					
Breast Features Changes	2	10.5	8	11.4	<0.001
Breast Lump	15	78.9	21	30.0	
Breast Pain	1	5.3	4	5.7	
Mass In The Axilla	1	5.3	31	44.3	
Nipple Discharges	0	0.0	6	8.6	
Healthcare reasons					
Family Advisement	4	21.1	11	15.7	0.816
Limited Daily Activities	0	0.0	1	1.4	
Decline Answer	0	0.0	1	1.4	
Presenting Symptoms	1	5.3	8	11.4	
Worsening Symptoms	14	73.7	49	70.0	
Seek medical management					
Delav	8	42.1	46	65.7	0.108

Immediately	4	21.1	6	8.6
Soon	7	36.8	18	25.7

Table 4.1. (continue). Clinical Presentation and Initial Symptoms

	No Delay (N=19)		Delay (N=70)		p-value
	N	%	N	%	
Reason for delay					
Denial	4	21.1	11	15.7	0.040
Family/Social Concerns	1	5.3	6	8.6	
Healthcare Accessibility	1	5.3	0	0.0	
Lack Of Serious Symptoms	4	21.1	24	34.3	
Misdiagnosis	1	5.3	13	18.6	
Negligent	2	10.5	11	15.7	
Other	6	31.6	5	7.1	

There were also significant differences between the two groups in terms of the specialty of the first encounter. Those with no delay were more likely to have been seen by a gynecologist (36.8% versus 24.3%) or oncologist (21.1% versus 1.4%), while those with delay were more likely to have been seen by a surgeon (61.4% versus 36.8%, $p=0.010$, see table 4.3). There were also several significant differences in terms of the time it took from symptom onset until the participant talked with someone. The participants with no delay usually talked with someone within one week (73.7% versus 40.0%). Participants with delay usually waited more than a month to talk with someone (32.9% versus 15.8%, $p=0.042$, see Table 4.4). Although not significant, participants with delay reported that the person that they talked to advised them to see a doctor (87.1% versus 68.4%, $p=0.069$, see Table 4.4).

Table 4.2. Sociodemographic Factors and Healthcare Pathways

	No Delay (n=19)		Delay (n=70)		p-value
	N	%	N	%	
Source of referral					
Breast screening center	0	0.0	2	2.9	0.518
general surgery	13	68.4	32	45.7	
gynecology	0	0.0	4	5.7	
primary health care	1	5.3	4	5.7	
private center	5	26.3	28	40.0	
Specialty of first encounter					
GP	1	5.3	3	4.3	0.010
Gynecologist	7	36.8	17	24.3	
Midwife	0	0.0	6	8.6	
Oncologist	4	21.1	1	1.4	
Surgeon	7	36.8	43	61.4	
Initial diagnosis					
benign tumor	1	5.3	10	14.3	0.768
cancer	4	21.1	11	15.7	
other	3	15.8	10	14.3	
suspicion of cancer	11	57.9	39	55.7	
NSAIDs/Antibiotics	6	31.6	24	34.3	1.000
First encounter biopsy	15	78.9	49	70.0	0.570
Herbal/alternative medicine	2	10.5	15	21.4	0.347

Help with daily activities	18	94.7	67	95.7	1.000
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Table 4.3. Financial and Emotional Support

	No Delay (N=19)		Delay (N=70)		p-value	
	N	%	N	%		
First person talked to						
brother/sister	4	21.1	4	5.7	0.302	
friend	1	5.3	4	5.7		
husband	10	52.6	35	50.0		
mother	1	5.3	3	4.3		
other	1	5.3	6	8.6		
son/daughter	2	10.5	18	25.7		
Time from symptom to talk to someone						
about a month	0	0.0	11	15.7	0.042	*
immediately	2	10.5	8	11.4		
less than one week	14	73.7	28	40.0		
more than a month	3	15.8	23	32.9		
Did this person advise						
you to see a doctor	13	68.4	61	87.1	0.069	x
The person who advised you to see a doctor for the first time						
No answer	0	0.0	1	1.4	0.237	
brother/sister	4	21.1	3	4.3		
friend	2	10.5	11	15.7		
husband	5	26.3	25	35.7		
mother	1	5.3	2	2.9		
other	5	26.3	13	18.6		
son/daughter	2	10.5	15	21.4		

There were no differences between the two groups in terms of who paid for the visit, which was about evenly divided between family and husband ~40%, see Table 4.5. In addition, there were no differences in terms of who helped with the healthcare providers. For both groups it was generally the husband, brother/sister or son/daughter. See Table 4.5. Likewise, there were no differences between the two groups in terms of who provided emotional and psychological support, see Table 4.5. There were no significant differences between the two groups in terms of screening (pap smear or mammogram), cancer testing or staging, see Table 4.6.

Table 4.4. Financial and Emotional Support

	No Delay N=19		Delay N=70		p-value
	N	%	N	%	
Who Paid					
borrow/debt	3	15.8	8	11.4	0.874
family	8	42.1	30	42.9	
husband	8	42.1	32	45.7	
Healthcare provider					
brother/sister	5	26.3	11	15.7	0.285
husband	9	47.4	37	52.9	
mother	1	5.3	0	0.0	
other	0	0.0	4	5.7	
son/daughter	4	21.1	18	25.7	
Emotional/psychological support					
brother/sister	4	21.1	4	5.7	0.373
friend	0	0.0	2	2.9	
husband	9	47.4	31	44.3	

mother	1	5.3	3	4.3
other	1	5.3	7	10.0
son/daughter	4	21.1	23	32.9

For the overall cohort the median time to oncologist was 4.1 months (Median) with the 25th and 75th percentiles (inter quartile range IQR) being 3.0 and 7.2 months, see Table 4.7 After the participants had been divided into the two groups (no delay < 3 months and delay ≥ 3 months), the median time to oncologist for the no delay group was 2.3 months with a IQR of 2.1 and 2.9 months, respectively. The median time to oncologist for the delay group was 5.0 months with an IQR of 3.7 and 8.6 months, respectively.

Table 4.5. Impact of Delays on Disease Progression

	No Delay N=19		Delay N=70		p-value
	N	%	N	%	
Pap smear	2	10.5	5	7.1	0.638
Familiar with mammogram	4	21.1	21	30.0	0.570
Previous mammogram	1	5.3	4	5.7	1.000
Family history of breast cancer	6	31.6	20	28.6	0.783
Histology	19	100.0	70	100.0	1.000
AJCC(TNM)	19	100.0	70	100.0	1.000
Staging					
II	13	68.4	40	57.1	0.751
III	6	31.6	28	40.0	
IV	0	0.0	2	2.9	
Lateralization					
left	8	42.1	37	52.9	0.447
right	11	57.9	33	47.1	
HR+HER2-	8	42.1	38	54.3	0.440
HR-HER2+	3	15.8	16	22.9	0.753
HR-HER2-	7	36.8	14	20.0	0.138
HR+HER2+	1	5.3	2	2.9	0.518

Kaplan-Meier curves were used to measure and demonstrate the timeline for the two groups in terms of time to first oncologist visit and time between first oncologist visit to chemo treatment. The average time (i.e., when 50% of the cohort had received an oncologist visit or in other words, the point where half of the participants in the group had received a visit) was 2.4 months for the no delay group compared to the 7.3 months for the delay group, $p < 0.001$, see Figure 4.2. There was no difference between the two groups in terms of the time from the first oncologist visit to the time that chemo was started (no delay 0.93 months and delay 0.92 months, $p = 0.756$, see Figure 4.2).

Table 4.6. Overall Time to Event

Time reported in months		Time to				From diagnosis	From oncologist
		doctor	diagnosis	oncologist	chemo	to oncologist	to chemo
Overall	N	89	89	89	89	89	89
	Mean	5.1	6.0	6.2	7.1	0.2	0.9

Median		3.1	4.0	4.1	5.1	0.2	0.9
Std. Deviation		5.2	5.1	5.1	5.1	0.2	0.4
Percentiles	25	2.1	2.9	3.0	4.2	0.1	0.7
	75	6.0	6.6	7.2	7.9	0.3	1.2

Table 4.7. No Delay versus Delay Time to Event

Time reported in months		Time to				From diagnosis	From oncologist
		doctor	diagnosis	oncologist	chemo	to oncologist	to chemo
No Delay	N	19	19	19	19	19	19
	Mean	2.0	2.2	2.4	3.4	0.2	0.9
	Median	1.3	2.1	2.3	3.5	0.2	0.8
	Std. Deviation	2.6	0.5	0.5	0.7	0.2	0.4
	Percentiles	25	1.1	1.9	2.1	0.1	0.7
	75	2.1	2.8	2.9	3.8	0.4	1.3
Delay	N	70	70	70	70	70	70
	Mean	6.0	7.0	7.2	8.2	0.3	0.9
	Median	3.7	4.7	5.0	5.8	0.2	0.9
	Std. Deviation	5.4	5.3	5.3	5.4	0.2	0.4
	Percentiles	25	2.6	3.4	3.7	0.1	0.7
	75	6.9	8.3	8.6	9.1	0.3	1.2

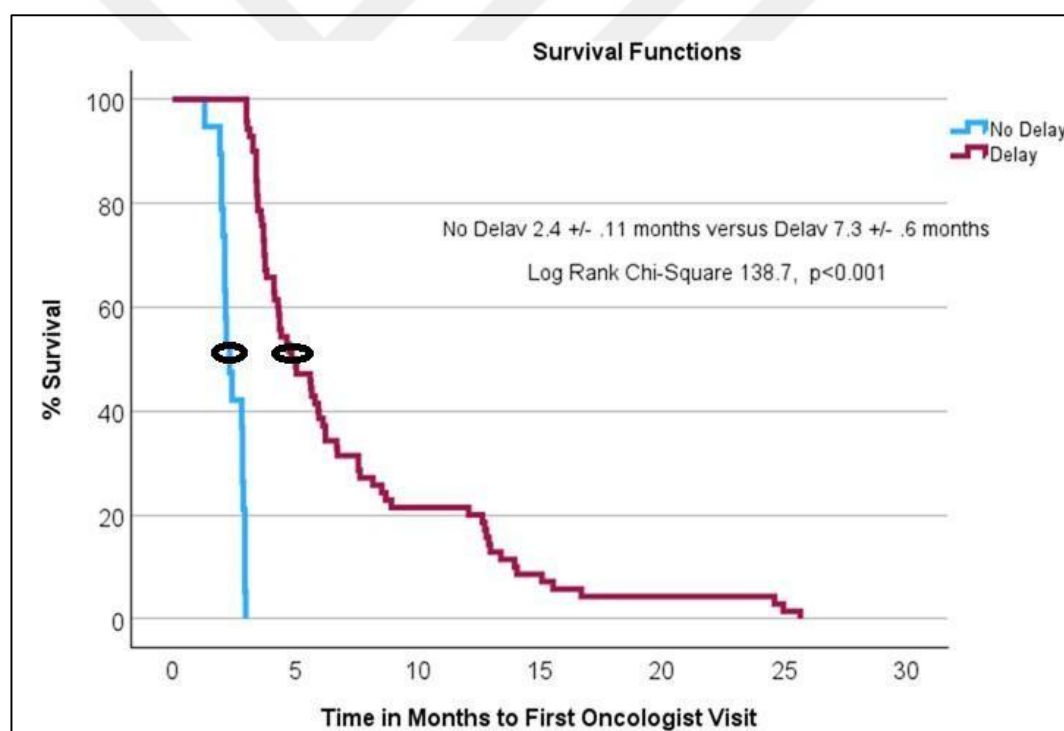


Figure 4.1. Time to First Oncologist Visit (50% Survival)

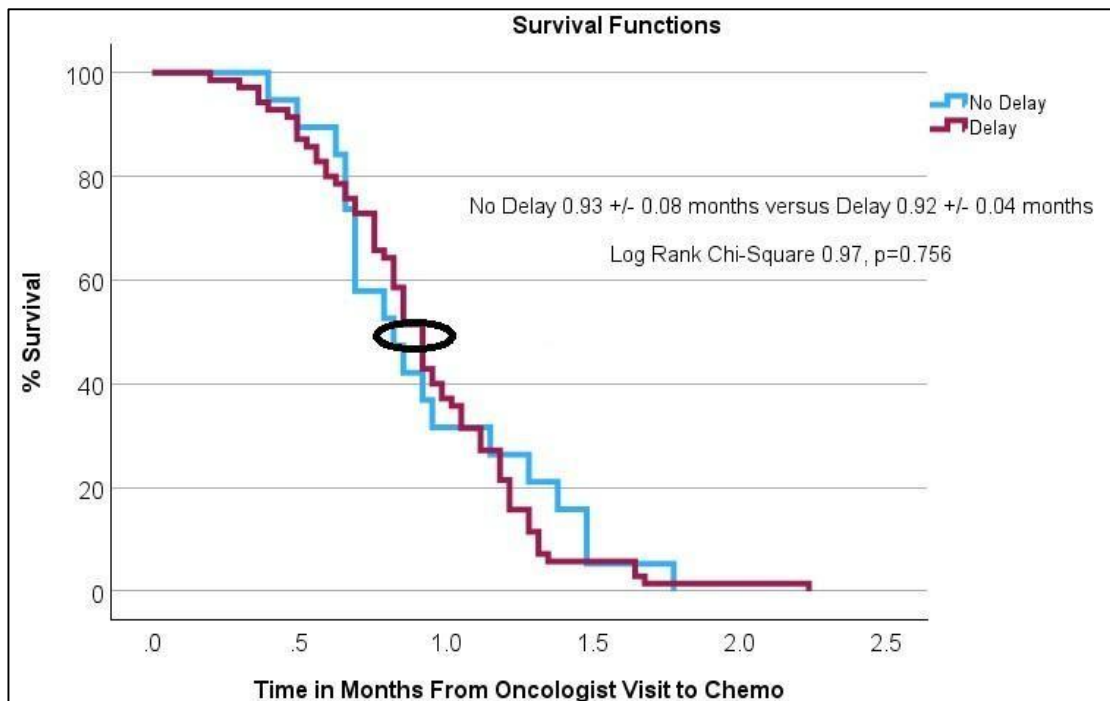


Figure 4.2. Time from Oncologist Visit to Chemo (50% Survival)

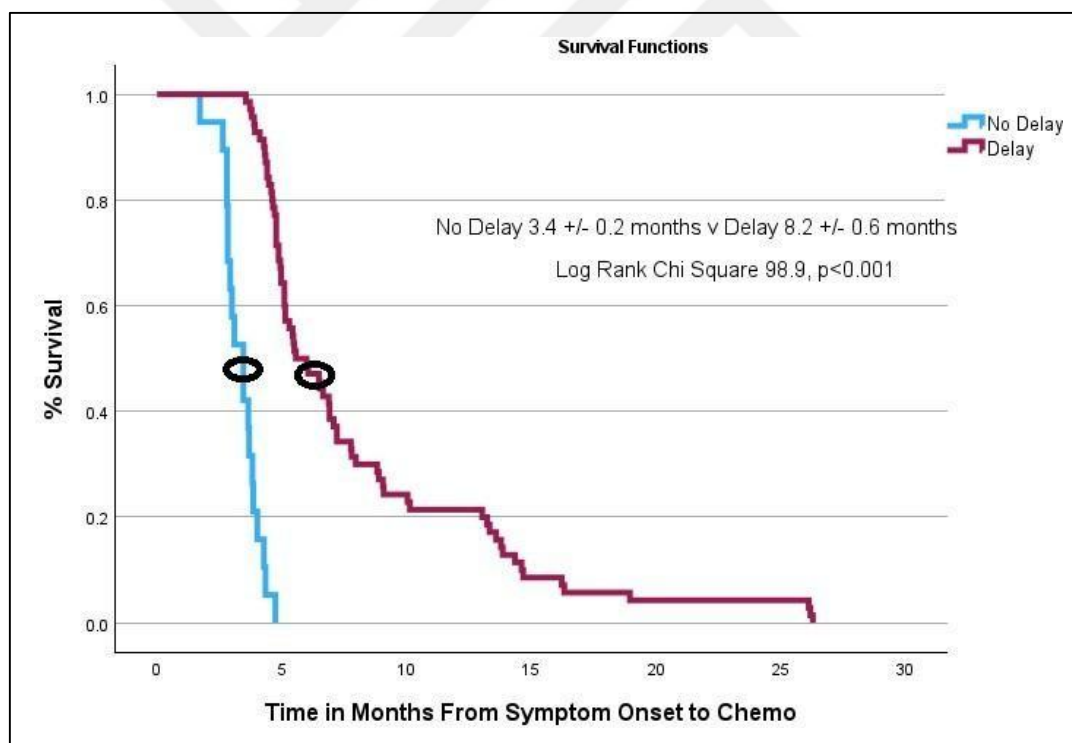


Figure 4.3. Time from Symptom Onset to Chemo (50% Survival)

5. DISCUSSION

Also compared to a previous similar study conducted in Damascus Hanafi et al. (2023) (99), both studies agree on the occurrence of a delay in diagnosis of more than 3 months, but the essential difference with my study is that the most important reasons for the delay in diagnosis in my study are negligence and not the difficulty of reaching specialized centers. Also, my study highlights the most important symptoms that patients reviewed upon diagnosis, while this was not mentioned in the other study. Also, there is also a link in my study with hormonal receptors and their effect on poor prognosis, but there is no link in the other study.

My study found that financial barriers were a significant cause of delays, with many patients relying on family members, particularly husbands, for emotional and financial support. Borrowing money for treatment was more common in rural areas, where economic hardships are more pronounced.

Whereas Hanafi et al (99) did not explicitly discuss financial support but mentioned the economic strain on the healthcare system and its impact on patient care. The cost of private diagnostics and treatment options was noted as a barrier for many patients.

The analysis reveals a profound disparity in the timelines for treatment initiation between the "No Delay" and "Delay" groups, with significant implications for patient outcomes. The median time from diagnosis to chemotherapy initiation was 2.8 months in the "No Delay" group, compared to 8.3 months in the "Delay" group (Table 4.3). This delay represents a critical barrier to effective cancer management, as prolonged timelines increase the likelihood of disease progression to advanced stages. Notably, the data indicates that delays are not isolated to patient behavior but are embedded within systemic deficiencies.

Our study goes along with the study conducted in Damascus Hanafi et al. (99). Both studies agree on the occurrence of a delay in diagnosis of more than 3 months, but the essential difference with my study is that the most important reasons for the delay in diagnosis in my study are negligence and not the difficulty of reaching specialized centers. Also, my study highlights the most important symptoms that patients reviewed upon diagnosis, while this was not mentioned in the other study. Also, there is also a link in my

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Whereas Hanafi et al. (99) did not explicitly discuss financial support but mentioned the economic strain on the healthcare system and its impact on patient care. The cost of private diagnostics and treatment options was noted as a barrier for many patients.

Furthermore our study highlight that the patients in the "Delay" group experienced longer intervals from diagnosis to oncologist consultation (7). This cascade of delays suggests challenges in healthcare system capacity, including limited specialist availability, scheduling inefficiencies, and potential resource shortages. These factors compound the burden on patients, who may already face personal, financial, and logistical barriers to timely care. Addressing these systemic issues are essential to reduce treatment delays and improve medical outcomes.

Nore over the delayed initiation of chemotherapy in the "Delay" group (8.3 months) compared to the "No Delay" group (2,8 months) is consistent with findings from studies in Sudan and Ethiopia, where similar delays were linked to limited healthcare infrastructure and specialist availability. In Ethiopia, delays of up to nine months were attributed to systemic deficiency and scheduling challenges (100). Compared to a high-income society, such as the United Kingdom, where structured care pathways have reduced median treatment delays to under two months (101). These stark contrasts highlight the disparity in healthcare systems between resource-rich and resource-poor settings, emphasizing the urgent need for systemic improvements in low- and middle-income countries LMICs.

In our cohort patients accessed care varied significantly between the two groups, as shown in Table 2.3 General surgery self-referrals were the primary choice for the "No Delay" group (68.4%), indicating the need for structured referral networks in the played a crucial role in expediting access to the prober specialized care. Conversely, 40% of the referrals in the "Delay" group originated from private centers, reflecting even worth patient outcomes.

The role of specialty in the first healthcare encounter was another significant factor ($p = 0.010$). Surgeons were the predominant first contact for the "No Delay" group (36.8%), while a higher proportion of the "Delay" group (61.4%) encountered surgeons after prolonged intervals. This finding implies that patients in the "Delay" group have presented with more advanced or complex cases. This necessitates the need for medical system where the patients presented to a trained family doctor or general practitioner, rather than the patient can go directly to self-determined specialist, that can cause more delay for the diagnosis.

The higher reliance on private centers (40%) in the "Delay" group mirrors findings from studies in India and Nigeria, where patients bypass public facilities due to perceived inefficiencies (102, 103). In contrast, European healthcare systems, maintain robust public referral networks that minimize delays (104). The significant role of surgeons as the initial encounter specialty in the "No Delay" group (36.8%) aligns with findings in UK, where surgical referrals accounted for quicker diagnostic timelines (105). This comparison underscores the need for well-integrated public healthcare systems to ensure equitable access to timely care.

We examine the initial symptoms and presentations of patients in both groups. The "No Delay" group predominantly presented breast lumps (78.9%), a hallmark early symptom of breast cancer, whereas the "Delay" group had a higher prevalence of axillary masses (44.3%). The significant association between advanced symptoms and delayed care ($p < 0.001$) indicates that patients who delay seeking medical attention are more likely to present with advanced disease.

Additionally, a higher percentage of patients in the "Delay" group reported worsening symptoms as their primary motivator for seeking care (70% compared to 73.7% in the "No Delay" group). This reactive approach highlights a critical gap in awareness and education about breast cancer, as patients may not recognize or prioritize symptoms until they become severe. Proactive educational interventions emphasizing early symptom recognition and the benefits of prompt care could significantly reduce delays and improve outcomes.

The predominance of advanced symptoms, such as axillary masses (44.3%) in the "Delay" group, reflects findings in Rwanda and Bangladesh, where delayed care correlated with late-stage presentations (106, 107). Studies in high-income countries, such as England,

report earlier-stage presentations due to widespread screening and public awareness initiatives (108). This discrepancy emphasizes the role of early detection programs and the need for public health education in LMICs to reduce advanced disease presentations.

The financial and emotional support systems for patients were heavily reliant on family members, particularly spouses, as shown in Table 4.1. Husbands were the predominant source of emotional and financial support in both groups (47.4% in the "No Delay" group and 52.9% in the "Delay" group). This finding underscores the cultural reliance on familial support networks in navigating healthcare.

Financial barriers emerged as a significant challenge, with 15.8% of the "No Delay" group and 11.4% of the "Delay" group reporting the need to borrow money for treatment. This reliance on borrowing indicates that financial constraints may deter or delay patients from seeking timely care, particularly in resource-limited settings. Policies to address these barriers—such as financial subsidies, insurance coverage, or community-based funding initiatives—are crucial to ensuring equitable access to care.

The reliance on husbands for financial and emotional support (47.4% in "No Delay" and 52.9% in "Delay") is consistent with findings from India and Palestine, where familial and spousal support were critical determinants of healthcare access (109, 110). In contrast, studies from Australia indicate the availability of broader societal safety nets, such as government subsidies and support groups, which reduce dependency on individual family members (111). Borrowing money for treatment (15.8% in "No Delay") aligns with findings in Kenya, where out-of-pocket expenses often delayed treatment (112). This highlights the urgent need for financial aid programs in LMICs to alleviate economic barriers.

The limited awareness of breast cancer screening methods, particularly mammograms, were evident in both groups. Only 30% of the "Delay" group reported familiarity with mammograms, as shown in Table 4.2. Similarly, the uptake of preventive measures such as prior mammograms or Pap smears was notably low across both groups. These findings reflect broader systemic challenges in public health policies and preventive care delivery.

Cultural beliefs and misconceptions about breast cancer may further exacerbate this lack of awareness. Community-based education campaigns tailored to address these cultural and systemic barriers are essential. Mobile screening units and partnerships with community leaders could also help bridge the gap in access and awareness.

This limitation of familiarity with mammograms in the "Delay" group (30%) parallels findings from studies in rural Uganda and Nigeria, where awareness of breast cancer screening methods was below 25% (113, 114). In South Korea and Japan, public health campaigns have achieved over 80% awareness, demonstrating the success of targeted educational initiatives (115, 116). These disparities highlight the importance of culturally sensitive education campaigns to increase awareness and promote early detection in LMICs.

The cascading effects of delays on disease progression are evident in the staging data provided in Table 4.2. While most patients in both groups were diagnosed at stage II or III, a small proportion of the "Delay" group presented at stage IV (2.9%). Advanced-stage presentations are strongly associated with poorer prognosis and higher treatment costs, emphasizing the critical importance of early detection.

Table 4.3 further underscores the cumulative impact of delays on the entire treatment pathway, from diagnosis to chemotherapy initiation. Addressing these delays requires not only improving individual patient behaviors but also strengthening systemic factors such as referral networks, diagnostic capabilities, and resource allocation.

The higher incidence of advanced-stage disease in the "Delay" group (2.9% stage IV) is consistent with findings from sub-Saharan Africa and Pakistan, where delays were strongly associated with late-stage presentations (117,118). In contrast, early-stage diagnoses dominate in countries like Sweden, where national screening programs ensure early detection (119). The prolonged delays in LMICs, as observed in this study, highlight systemic barriers that must be addressed to improve early detection and survival rates.

Also compared to a previous similar study conducted in Damascus Hanafi et al. (99), both studies agree on the occurrence of a delay in diagnosis of more than 3 months, but the essential difference with my study is that the most important reasons for the delay in diagnosis in my study are negligence and not the difficulty of reaching specialized centers. Also, my study highlights the most important symptoms that patients reviewed upon diagnosis, while this was not mentioned in the other study. Also, there is also a link in my study with hormonal receptors and their effect on poor prognosis, but there is no link in the other study.

My study found that financial barriers were a significant cause of delays, with many patients relying on family members, particularly husbands, for emotional and financial

support. Borrowing money for treatment was more common in rural areas, where economic hardships are more pronounced.

Whereas Hanafi et al. (99) did not explicitly discuss financial support but mentioned the economic strain on the healthcare system and its impact on patient care. The cost of private diagnostics and treatment options was noted as a barrier for many patients.

5.1. Strengths and Limitations

5.1.1. Strengths of the Thesis

1. Focus on a Unique Context:

The study addresses breast cancer diagnosis delays in Northwest Syria, a conflict-affected and resource-limited region. This provides valuable insights into challenges faced in similar low-resource settings, filling a significant gap in literature.

2. Comprehensive Analysis:

By examining both patient- and system-related factors, the thesis offers a holistic understanding of the barriers to timely diagnosis and their impact on breast cancer outcomes.

3. Relevance to Public Health:

The findings directly contribute to improving public health strategies by identifying actionable areas for intervention, including awareness, infrastructure, and policy changes.

4. Evidence-Based Approach:

The thesis integrates findings from primary data and an extensive review of literature, ensuring that the conclusions and recommendations are well-supported by evidence.

5. Practical Recommendations:

The study goes beyond identifying problems by providing clear, feasible recommendations tailored to the socio-cultural and healthcare context of Northwest Syria.

6. Ethical Considerations:

Ethical approval and adherence to research protocols reflect the study's commitment to integrity and respect for participants' rights.

5.1.2. Limitations of the Thesis

1. Sample Size and Representativeness:

The sample size may be limited, and participants may not fully represent the diversity of the population in Northwest Syria. This could affect the generalizability of the findings.

2. Self-Reported Data:

Reliance on self-reported data introduces the risk of bias recalling, as participants may inaccurately remember timelines or details related to symptom onset and healthcare-seeking behavior.

3. Cross-Sectional Design:

The study's cross-sectional nature limits its ability to establish causal relationships between identified factors and diagnostic delays.

4. Context-Specific Findings:

While the findings are highly relevant to Northwest Syria, they may not fully apply to other regions with different healthcare systems, socio-cultural dynamics, or conflict levels.

5. Data Collection Constraints:

Conducting research in a conflict-affected region poses challenges, such as limited access to certain areas and potential disruptions during data collection, which could influence the comprehensiveness of the findings.

6. CONCLUSION AND RECOMMENDATION

6.1. Conclusion

Breast cancer remains a significant public health concern globally, and its impact is particularly severe in low-resource settings like Northwest Syria. This study has investigated the factors influencing the delayed diagnosis of breast cancer and their associated negative outcomes. By exploring both patient- and system-related delays, the research has provided valuable insights into the barriers that hinder early diagnosis and treatment.

The findings of this study highlight that delayed diagnosis of breast cancer is multifaceted, involving a combination of individual, cultural, and systemic factors. Patient-related delays were largely attributed to a lack of awareness regarding breast cancer symptoms, fear of diagnosis, stigma, and misinterpretation of symptoms as non-serious. On the other hand, systemic delays were linked to inefficiencies within the healthcare infrastructure, including limited access to diagnostic facilities, prolonged wait times for appointments, and inadequate training of healthcare personnel.

This delay in diagnosis has been shown to significantly impact prognosis. Women who experience longer diagnostic delays are more likely to present with advanced-stage disease, leading to poorer treatment outcomes and lower survival rates. The study underscores the urgency of addressing these delays to improve breast cancer outcomes in Northwest Syria, where healthcare resources are scarce, and cultural barriers further exacerbate the issue.

This research contributes to the growing body of literature on breast cancer in low- and middle-income countries (LMICs) by focusing on a conflict-affected region. The findings underscore the interplay between socio-cultural factors and systemic inefficiencies in delaying diagnosis. In doing so, the study fills a critical gap in understanding how resource-constrained settings uniquely shape breast cancer outcomes.

Moreover, the study's findings hold broader implications for public health initiatives, not only in Syria but also in other LMICs facing similar challenges. It emphasizes the need for targeted interventions that prioritize awareness, early detection, and the strengthening of healthcare systems to reduce diagnostic delays and improve survival rates for breast cancer patients.

While this study has provided valuable insights, certain limitations must be acknowledged. First, the sample size may not fully represent all breast cancer patients in Northwest Syria due to logistical constraints and the ongoing conflict. Second, the reliance on self-reported data introduces the possibility of recall bias, particularly when patients are asked to report timelines for symptom onset and healthcare visits. Additionally, the study's findings may not be generalizable to other regions with differing healthcare structures and cultural contexts.

Future research should aim to address these limitations by incorporating larger, more diverse samples and utilizing longitudinal designs to better understand the progression from symptom onset to diagnosis. Comparative studies between regions with varying levels of healthcare accessibility would also be valuable in identifying context-specific interventions.

Ultimately, reducing diagnostic delays requires a multi-pronged approach that combines public education, healthcare system improvements, and policy advocacy. By prioritizing early detection and treatment, significant progress can be made in reducing breast cancer mortality and improving the quality of life for patients in resource-limited settings.

This thesis serves as a foundation for further research and action to address breast cancer in Northwest Syria. The findings and recommendations provide a roadmap for stakeholders seeking to make a meaningful impact in the fight against this devastating disease.

6.2. Recommendation

Addressing the delayed diagnosis of breast cancer in Northwest Syria requires targeted and practical solutions that account for the unique challenges faced by the region. Based on the findings of this study, the following recommendations are proposed to mitigate diagnostic delays and improve outcomes for breast cancer patients:

1. Enhancing Public Awareness and Education

Educational initiatives should focus on increasing awareness about breast cancer symptoms, risk factors, and the importance of early diagnosis. This can be achieved through:

Community-Based Campaigns: Engage local leaders, religious figures, and community influencers to promote early detection messages. Campaigns should be tailored to cultural norms and delivered in local dialects to maximize reach.

Health Literacy Programs: Offer workshops in schools, workplaces, and community centers to educate women and their families about breast cancer and the necessity of seeking timely medical attention.

Utilizing Media and Technology: Leverage radio, television, and social media platforms to disseminate educational content. Mobile health apps can also provide reminders for self-examinations and healthcare check-ups.

2. Strengthening Healthcare Systems

To reduce delays caused by systemic inefficiencies, it is crucial to invest in and optimize healthcare infrastructure and services. Key steps include:

Capacity Building: Train healthcare workers, including general practitioners and nurses, to recognize early symptoms of breast cancer and provide appropriate referrals. Training programs should include cultural competency to improve patient-provider interactions.

Infrastructure Improvement: Increase the number of diagnostic facilities, such as mammography units and pathology labs, in underserved areas. Mobile diagnostic units could provide services in remote regions.

Streamlined Referral Systems: Establish clear referral pathways to ensure that patients suspected of having breast cancer are diagnosed and treated promptly. This includes setting up dedicated breast cancer clinics within regional hospitals.

Improving Access: Subsidize transportation costs and provide mobile healthcare services to ensure women in rural and conflict-affected areas can access diagnostic and treatment facilities.

3. Policy and Advocacy

Policy interventions are essential to create a sustainable framework for addressing delayed diagnoses. Policymakers and stakeholders should:

Allocate Resources: Increase funding for cancer-related healthcare services, focusing on early detection and treatment programs.

Develop National Guidelines: Establish and disseminate standardized guidelines for breast cancer diagnosis and treatment, emphasizing timelines and best practices.

Collaborate with International Organizations: Partner with global health organizations to secure technical and financial support for breast cancer programs. This can include training exchanges and equipment donations.

Implement Screening Programs: Launch population-based breast cancer screening initiatives, prioritizing high-risk groups and ensuring follow-up care for detected cases.

4. Addressing Cultural and Psychological Barriers

Cultural and psychological factors play a significant role in patient-related delays. Interventions should focus on:

Combating Stigma: Normalize discussions about breast health through community dialogue sessions and support groups. Highlight survivor stories to inspire others to seek care.

Providing Psychosocial Support: Establish counseling services within healthcare facilities to help women overcome fears of diagnosis and treatment. This includes addressing concerns about mastectomy, chemotherapy side effects, and perceived social consequences.

Empowering Women: Encourage women to prioritize their health through education and support. Family-centered interventions can also foster supportive environments for women to seek timely care.

5. Promoting Research and Data Collection

Ongoing research is critical to understanding and addressing the challenges of breast cancer diagnosis and treatment in Northwest Syria. Efforts should include:

Longitudinal Studies: Conduct follow-up research to evaluate the long-term outcomes of interventions aimed at reducing diagnostic delays.

Community-Based Research: Engage local communities in research to identify region-specific barriers and facilitators to early detection.

Data Monitoring Systems: Develop a centralized cancer registry to track incidence rates, diagnostic timelines, and treatment outcomes. This data will guide future public health strategies.

6. Leveraging Technology and Innovation

Technology can play a pivotal role in addressing diagnostic delays and expanding access to care. Recommendations include:

Telemedicine Services: Implement teleconsultation platforms to connect patients in remote areas with oncologists and specialists.

Mobile Diagnostic Units: Deploy mobile units equipped with mammography and ultrasound machines to provide on-site diagnostic services in underserved regions.

Digital Awareness Tools: Use apps and SMS services to remind women about regular breast self-examinations and schedule medical check-ups.

7. Encouraging Multisectoral Collaboration

Efforts to address diagnostic delays must involve a wide range of stakeholders, including healthcare providers, policymakers, NGOs, and community leaders. Recommended actions include:

Public-Private Partnerships: Encourage collaboration between government bodies and private organizations to expand access to diagnostic and treatment services.

NGO Involvement: Partner with local and international non-governmental organizations to implement awareness campaigns and fund infrastructure improvements.

Community Engagement: Involve community members in the design and implementation of interventions to ensure cultural relevance and acceptability.

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8. APPENDICES

Appendix 1. Informed Consent and Questionnaire (EN)

CONSENT FORM

PLEASE ALLOW ENOUGH TIME TO READ THIS DOCUMENT CAREFULLY

You are invited to participate in the research study 'Delay diagnosis of Breast Cancer in the North West Syria: Influencing Factors and Associated Negative Outcomes' by Jamil Debel. You have to know how and why this research will be conducted. For this reason, it is very important to read and understand this form. If you do not understand things that are not obvious to you, or if you want more information, please do ask for further clarification.

Participation in this study is entirely **voluntary**. You **do not have to participate** in this study and if you participate, you have the right to **discontinue** at any time. **Your positive response to the study will be interpreted as you consent to participate in the study.** Do not feel oppressed or manipulated by anyone while answering the questions in the forms provided to you. The information obtained from these forms will be used purely for research purposes.

1. Information About the Research Study:

- Purpose of the Study:** The purpose of this study is to investigate the relationship between delayed diagnosis and worse stages of the breast cancer in the conflict area, in addition to, exploring the reasons for these prolonged intervals between the onset of clinical symptoms in patients and establishment of a diagnosis in northwest Syria.
- Content of the Study:** The study will be cross-sectional including all women who were diagnosed with breast cancer in the oncology center in Central Idleb hospital between 1 January 2021 and 31 December 2021.
- Type of Research:** () Scientific Research Study (✓) Thesis Study
Estimated Time for the Study: 12 months
- Expected Number of Participants / Volunteers to the study:** about 180
Location (s) of the Research: Syria – Idleb – Oncology unit in Idleb central hospital

2. Consent to Participate in the Study:

I fully understand the scope and purpose of the study and the volunteer responsibilities by reading the information above that should be given to the participants before participating/volunteering in the study. **Written and oral explanations about the study were made by the researcher named below, I had the opportunity to ask questions and discuss and got satisfactory answers. The potential risks and benefits of the study have been explained to me verbally as well.** I understand that I have the right to discontinue the study at any time without mentioning any reasons and that I will not encounter any negativity when I leave this study.

I agree to participate in the study voluntarily under the conditions explained to me, without any pressure or force.

Participant's (with your own handwriting)

Name-Surname:

Signature:

(If any) For those in custody or tutelage,

Parent/s or Vassin/s (with your own handwriting)

Adi-Soyadi:

Signature: **P.S.:** This form is arranged in two copies. One of these copies is given to the volunteer by signature, and the other is kept by the researcher.

Researcher's:

Name-Surname: Jamil Debel

Signature:

Appendix 2. AYBU Ethical Approval

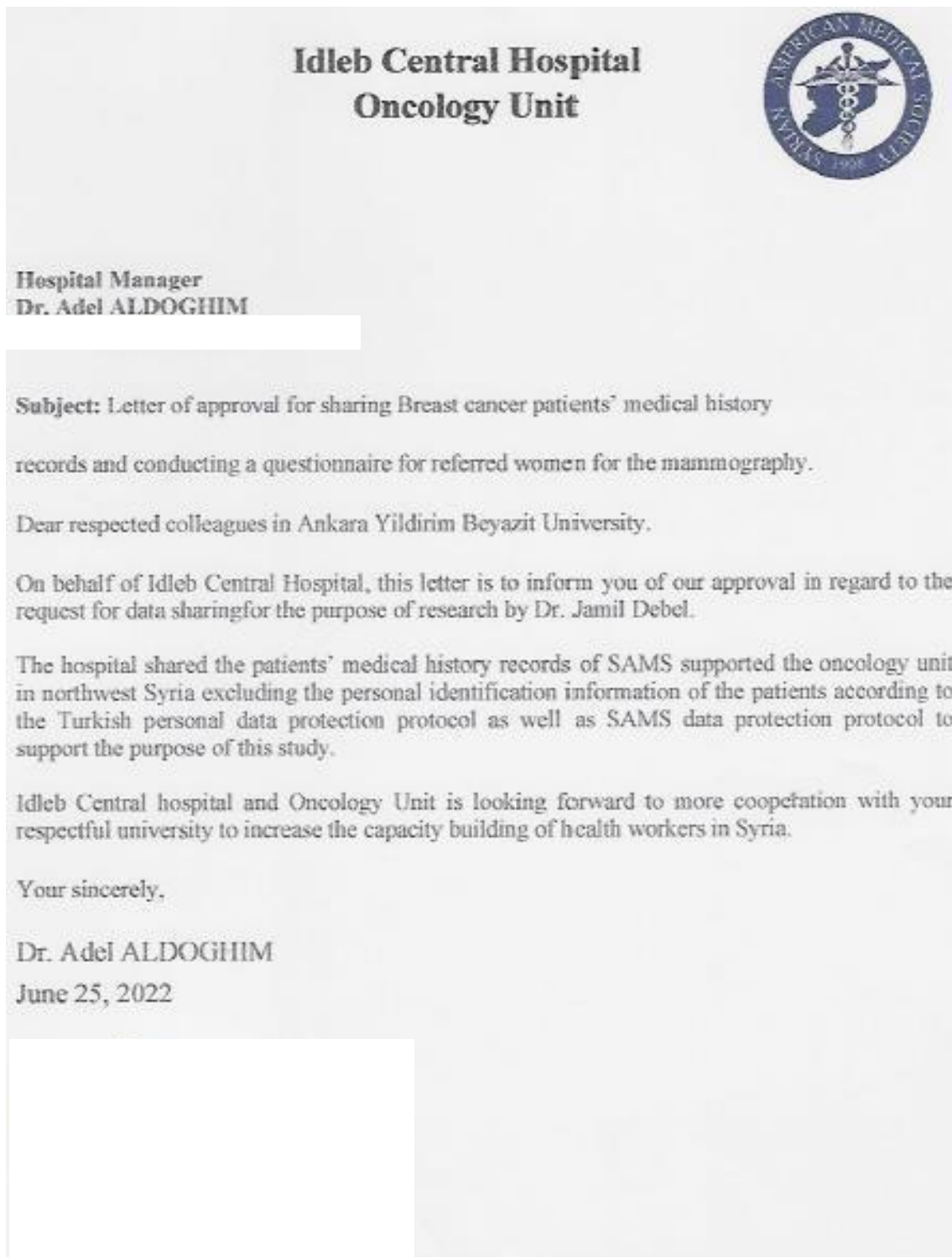


ANKARA YILDIRIM BEYAZIT UNIVERSITY (AYBU) HEALTH SCIENCE ETHICS COMMITTEE RESEARCH PROJECT APPROVAL FORM



THE TITLE OF THE RESEARCH PROJECT					
Delayed diagnosis of Breast Cancer in North West Syria: Influencing Factors and Associated Negative Outcomes					
RESEARCHER/S*					
	Title	Name-Surname	Position	Phone	e-mail
1**	Student	Jamil Debel	AYBÜ, Tıp Fak. Halk Sağlığı AD.		
2	Prof.Dr.	Salih Mollahaliloğlu	AYBÜ, Tıp Fak. Halk Sağlığı AD.		
3					
4					
The researcher's affiliation with AYBU***: Student *The academic advisor's signature is not required for the research studies under the supervision of an advisor. ** The name of the person who applies directly to the ethics committee should be listed first. *** In this section, at least one of the researcher/s must be clearly related to AYBU. The AYBU Health Science Ethics Committee reviews only the applications of employees or students in our university.					
THE RESEARCH PERIOD					
Start Date*: 15-08-2022			End Date: 15-11-2022		
* In this section, the start and the end of the data collection process should be given. The date of data collection can not begin before the approval of the Ethics Committee. Therefore, it is recommended to apply at least 1 month before the start of the project.					
THE TYPE OF RESEARCH					
☐	Academic Staff Research				
☐	Doctoral Thesis				
☒	Master's Thesis				
☐	Other _____ (Please specify)				
RESEARCH SUPPORT / GRANT					
☒	No				
	Yes				
		University			
		TUBITAK			
		International			
		Other (please specify)			

Appendix 3. Organization Ethical Approval



Appendix 4. Questionnaire

ARABIC

تأخير تشخيص سرطان الثدي في شمال غرب سوريا: العوامل المؤثرة والنتائج السلبية المرتبطة بها			
استبيان			
1. العرض الأول الذي حدده المريض			
2. تفسيرات المريض الأولية للأعراض			
القلق الأولي		الجدية المتصورة	
اهمال		التفسير الأولي للسرطان	
3. أعراض سرطان الثدي الموجودة عند الوصول إلى مستشفى السرطان			
قرحة الثدي		اعتلال العقد اللمفية	
حكة الثدي		ألم الثدي	
تكبير الثدي		ألم في الذراع	
تغييرات في شكل الثدي		تنمل الثدي و / أو الذراع المماثلة	
إفرازات الحلمة		تغييرات مميزة الثدي	
4. الأعراض الأكثر إثارة للقلق للمريض			
5. سبب طلب المريض للرعاية الطبية (ظهور الأعراض / استمرار الأعراض / تفاقم الأعراض)			
6. تصور المريض للتأخير			
إدراك تأخر مقدم الخدمة		إدراك تأخر المريض	
7. الأسباب المتصورة للمريض لتأخير المريض			
الإهمال / الإهمال		اعتقدت أن الأعراض ستزول بمفردها	
خوف		لم أكن أعرف أين تطلب الرعاية	
أخرى (اذكرهم)		تعذر الوصول	
8. العوائق المتصورة للمريض التي تسببت في تأخير مقدم الخدمة			
نقص الموارد المالية		نقص المعلومات عن الخدمات الصحية	
صعوبة التغيب عن العمل		خوف	
أوقات الانتظار الطويلة للمواعيد الطبية		الأخطاء المتصورة في تشخيص الأطباء الأوائل الذين تمت استشارتهم	
اضطرت إلى اقتراض المال للحصول على الرعاية الطبية		اضطرت إلى رعاية الشباب أو كبار السن أو الأقارب المرضى	
نقص خدمات الرعاية الصحية في منطقتهم		التشريد	
أخرى (اذكرهم)		مصدر تمويل لدفع تكاليف الرعاية الصحية	

9. الاستفادة من الخدمات الصحية	
أول خدمة صحية مستخدمة (عامة، خاصة، أخرى)	تم استشارة الموجات فوق الصوتية للثدي من قبل الطبيب الأول
عدد مقدمي الرعاية الصحية المختلفين الذين تمت استشارتهم	طلب خزعة من قبل الطبيب المستشار أولا
الانطباع التشخيصي للطبيب الأول الذي تمت استشارته	الخدمة الصحية للإحالة إلى المستشفى
تصوير الثدي بالأشعة السينية بطلب من أول طبيب استشاري	الخزعة التي يتم إجراؤها قبل الوصول إلى المستشفى
10. الدعم الاجتماعي والطبي لطلب الرعاية الطبية	
الدعم الآلي	الجنس والقرباة للشخص الأكثر دعما
العلاقة مع شخص يعمل في القطاع الطبي	هل قدم هذا الشخص دعما طبيا لتسريع التشخيص؟
توصيات لاستشارة الطبيب	من قدم هذه النصيحة؟
الدعم المالي	هل حصلت على دعم مالي لإجراء فحوصات طبية للوصول إلى التشخيص؟
ما هو تخصص أول طبيب قمت بزيارته بعد ظهور الأعراض؟	جنس الطبيب الأول الذي زارته
11. الوقت بين تحديد المشكلة والمرة الأولى للتحدث إلى شخص ما عنها	
12. استخدام الطب البديل	
13. المعرفة المتعلقة بالسرطان	
معرفة شخص مصاب بالسرطان	سمعت عن تصوير الثدي بالأشعة السينية
معرفة فائدة التصوير الشعاعي للثدي	معرفة العمر الموصى به للفحص الأول للتصوير الشعاعي للثدي
14. ممارسات فحص السرطان	
مسحة عنق الرحم الأخيرة	فحص الثدي السريري قبل مشكلة الثدي الحالية
تصوير الثدي بالأشعة السينية قبل مشكلة الثدي الحالية	ممارسة الفحص الذاتي للثدي
15. التمرور	
اكتشاف الأعراض	الاستشارة الطبية الأولى

CURRICULUM VITAE

JAMIL ALI DEBEL

Hematology/Oncology Specialist | Public Health Professional | Researcher

SUMMARY/ OBJECTIVES

Experienced healthcare physician specializing in Hematology and Oncology. Dedicated medical professional with a strong background in both clinical practice and public health.

Driven to bridge clinical oncology advancements with comprehensive public health strategies, aiming to improve the Syrian Health Systems in the Rebuilding Era.

EXPERIENCE

- **Oncology Coordinator, Syrian American Medical Society (SAMS), February 2025 – Present, Syria**
- **Founder and CEO, Syrian National Advisory Committee for Hematology and Oncology, January 2025 – Present, Syria**
- Providing comprehensive medical care and treatment to patients, resulting in improvement in patient health outcomes.
- Focuses on advancing cancer care and treatment within the country.
- Improving oncology infrastructure, enhancing access to quality cancer treatments, and possibly fostering research initiatives tailored to Syria's unique healthcare challenges.
- Given the context of Syria's prolonged conflict and strained healthcare system, managed strengthening oncology services to address the rising burden of cancer.
- Training healthcare professionals in specialized care, and advocating for resources to support patients' in a resource-limited environment.

- **Director, Mohammed Bin Zayed Hospital for Hem/Onc, December 2024 – Present, Aleppo Syria**

- Providing comprehensive medical care and treatment to patients, resulting in improvement in patient health outcomes.
- Ensures that the department delivers state-of-the-art care for patients with blood disorders and cancers.

This involves supervising a team of hematologists, oncologists, nurses, and support staff, as well as setting standards for treatments like chemotherapy, immunotherapy, and bone marrow transplants.

- **Administrative Leadership:** manage budgets, staffing, and resources, ensuring the department runs smoothly. This includes negotiating with hospital administration for funding, equipment (e.g., advanced imaging or infusion centers), and hiring specialists to address patient needs.
- **Education and Training:** oversee fellowship programs, training the next generation of Hem/Onc specialists. Develop curricula, mentor fellows, and ensure compliance with accreditation bodies.

- Research Advocacy: A key part of the role is fostering a research environment. This could mean securing grants, collaborating with institutions or overseeing clinical trials for novel therapies—critical in a field where treatments evolve rapidly.
 - Patient-Centered Care: advocate for multidisciplinary care, coordinating with surgeons, radiologists, and palliative care teams to provide holistic treatment plans, especially for complex cases like late-stage cancers or rare hematologic conditions.
- **Head of Hem/Onc Department || Hematologist and Oncologist, Idlib Central Hospital, 2022 – Present, Idlib, Syria**
 - Provided comprehensive medical care and treatment to patients, resulting in improvement in patient health outcomes.
 - Diagnosed and treated a wide range of medical conditions, reducing misdiagnosis rates.
 - Conducted thorough patient examinations and developed personalized treatment plans, increasing patient satisfaction.
 - Collaborated with a multidisciplinary healthcare team to ensure integrated care, enhancing care coordination.
 - Managed emergency cases efficiently, decreasing emergency response time.
 - Educated patients and communities on health prevention and management, raising public health awareness.
 - **Medical Officer, UDER, February 2022 – Present, Idlib, Syria**
 - Collaborated with local healthcare providers to identify and address community health needs, resulting improvement in health service utilization.
 - Created educational materials and resources, enhancing accessibility and understanding of health information.
 - Educated patients and communities on health prevention and management, raising public health awareness.
 - Documented patient information accurately, improving medical record-keeping accuracy.
 - Participated in public health campaigns and outreach programs, increasing community health service utilization.
 - **Health Coordinator, World Vision International, July 2019 - September 2021**
 - **Idlib, Syria**
 - **Health Coordinator, Syria Relief organization, April 2017 - December 2018**
 - **Idlib, Syria**
 - **Field Medical Officer, International Medical Corps, March 2015 – March 2017, Idlib, Syria**
 - Coordinated health programs and initiatives, increasing community health service coverage.
 - Developed and implemented health policies and procedures, ensuring compliance and improving operational efficiency.
 - Monitored and evaluated health program outcomes, leading to improvement in program effectiveness.
 - Collaborated with local and international partners to secure funding and resources, increasing budget allocation.
 - Facilitated community outreach and education campaigns, raising public health awareness.
 - Managed health data and reporting, improving data accuracy and reporting efficiency.

EDUCATION

- Master's Degree master of **Global Health and Health Policy**, *Ankara Yeldirim Bayazit University*.

Turkey, 2021 - 2025

- Resident Doctor, SAMS Fellowship Program for Hem/Onc, **Idlib, Syria**
- Master of Hematology **2020**
- Master of Oncology **2023**
- Resident Doctor, Aleppo University Hospital, **Aleppo, Syria, 2011 - 2013**
- Doctor of Medicine (M.D.), University of Aleppo, **Aleppo, Syria, 2011 (79.51%)**

SKILLS

• Academic Medical Research	• Training and Capacity Building
• Health Policy Development	• Public speaking & Presentational Skills
• Project Management	• Direct Patient Care
• Educational Leadership	• Business Networking
• Data Reporting	• Analytical Thinking
• Epidemiological Analysis	• Humanitarian work and responses

PUBLICATIONS

<https://www.linkedin.com/in/jamil-debel-m-d-mph-3bb0a588>

<https://orcid.org/0000-0002-5051-1197>

LANGUAGES

Native Language

Arabic

First Foreign Language

English

Excellent Proficiency (C1)

Debel, Jamil, 2025