

Breast Cancer in Saudi Females: Epidemiology, Survival and Quality of Life

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Abstract

Breast cancer (BC) is the leading cause of cancer-related mortality in Saudi Arabia. Its incidence continues to increase. Research into the epidemiology of BC, including its mortality, in the Saudi population is limited. This thesis investigated BC incidence and survival patterns in the Saudi female and evaluated its impact on their Health-Related Quality of Life.

Data on 27,664 women diagnosed with BC were obtained from the Saudi Cancer Registry from 1994 to 2018 and 3,408 females from the King Faisal Specialist Hospital and Research Centre (KFSH&RC) registry between 2008 and 2017. Age-specific and age-standardised incidence rates were calculated. The distribution of BC by age, stage, tumour grade and region were examined. BC incidence rates increased between 1994 and 2017 from 6.26 to 24.58 per 100,000 persons per year; the median age at diagnosis was 49 years; the most common type was infiltrating ductal carcinoma (78%). Grades II and III accounted for the majority of cases (70%), and regional BC accounted for 43%.

The 5-year overall survival rate calculated using Kaplan Meier was 73%. Older patients experienced lower survival rates (76.1%) than younger ones (79.7%), and advanced grades exhibited lower survival rates, with 68% for grade 4 compared to 88.6% for grade 1. Surgery is the cornerstone of therapeutic intervention, with a 5-year overall survival rate of 97%.

Quality of life was assessed in 275 females diagnosed with BC attending KFSH&RC using disease-specific tools (EORTC QLQ-C30 & BR23). The results showed low quality of life scores on QLQ-C30 (52 ± 25.7). The utility values obtained were mapped onto a generic measure (EQ-5D) to estimate health-related utility values.

This study demonstrated the importance of early detection of BC to improve survival and the importance of further research to better understand how to improve the quality of life in Saudi women diagnosed with BC.

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Abbreviations

AI	Aromatase Inhibitors
AIC	Akaike information criterion
AJCC	American joint committee on cancer
APC	Annual percent change
ASR	Age-standardised rate
ASMR	Age-standardised mortality rate
BC	Breast Cancer
BCT	Breast conserving therapy
BIC	Bayesian Information Criterion
BRCA	Breast cancer gene
CHEERS	The Consolidated Health Economic Evaluation Reporting Standards
CI	Confidence interval
CT	Computed Tomography
DCIS	Ductal carcinoma in situ
EORTC	European Organisation for research and Treatment of Cancer
EQ-5D	European Quality of Life 5 Dimensions
ER	Oestrogen receptor
FACT-B	Functional assessment of cancer therapy – breast
HDI	Human Development Index
HER-2	Human Epidermal growth factor Receptor 2
HR	Hazard ratio
HRQoL	Health-Related Quality of Life
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
IDC	Invasive ductal carcinoma
ILC	Invasive lobular carcinoma
IQR	Interquartile range
KSA	Kingdom of Saudi Arabia
KFSH&RC	King Faisal Specialist Hospital and Research Centre
MRI	Magnetic Resonance Imaging
NCCDPPH	National Centre for Chronic Disease Prevention and Health Promotion
NOS	Not otherwise specified
OR	Odd ratios
OS	Overall Survival
PIR	Proportional incidence ratio
PNU	Princess Nourah Bint Abdul Rahman University
PR	Progesterone receptor
QALY	Quality adjusted life years
QLQ-C30	Quality of Life Questionnaire – core 30
QLQ- BR23	Quality of Life Questionnaire – breast cancer 23
QoL	Quality of Life
RR	Relative Risk
SCR	Saudi Cancer Registry
SD	Standard deviation

SF-36	The short form 36 health survey questionnaire
SG	Standard gamble
SPSS	Statistical package for the social sciences
TNM	Tumour, node, metastasis
VAS	Visual- analogue scale
WHO	World Health Organization

Chapter 1 Introduction

1.1 Background of the study

Breast cancer (BC) is the most prevalent cancer among women. In 2022, it was diagnosed in 2.3 million women globally, and 666,000 deaths were estimated to be attributable to it (Ferlay, Ervik M, Lam F, et al., 2024a). BC is the leading cause of cancer-related mortality; this represents 15.5% of all female cancer deaths. In the Middle East and specifically the Kingdom of Saudi Arabia (KSA), BC is ranked as the leading cancer affecting females in terms of incidence. The incidence of BC among women is expected to continue to increase in KSA. In 2017, BC contributed 30.9 % of all cancers reported among females, up from 25 % in 2014 (AL Zomia et al., 2024). Data on BC mortality in KSA are lacking (Basudan, 2022).

The median age at diagnosis is lower in Saudi females; most studies found that the median age at diagnosis for BC females globally is 62 (Surveillance Research Program, 2024), but in Saudi females, the median age at diagnosis was younger (48 years) (Basudan, 2022). It has also been reported that BC is diagnosed at a later stage (Chaudhri et al., 2020).

This study focuses on the epidemiological aspects of BC in Saudi females, such as the incidence and the survival. BC has been increasing in KSA in recent years with different patterns than in other countries, where BC in Saudi females is diagnosed in younger ages and late stages. This variation in the pattern of BC diagnosis raises two issues. First, we need to have a clear insight into the characteristics of BC in Saudi females and its incidence patterns in relation to the age and stage of diagnosis and to establish whether these have changed over the years. It is essential to identify the trends in the age and stage of diagnosis because it helps to inform and optimise the screening programmes, helps healthcare providers improve access to treatment, and allows for the evaluation of progress in healthcare initiatives. Different characteristics of BC in Saudi females and incidence patterns are likely to affect treatment decisions, BC females' survival, and quality of life, which were explored in this study.

Studies on BC survival in KSA are limited. Only a few studies have analysed the survival of BC in Saudi females (Basudan, 2022; Abdulwassi et al., 2020; Al-Hamdan, 2014; Abu Zaid et

al., 2017). It is important that the survival pattern and its relationship with the BC risk factors and the effect of treatment modalities on survival are identified.

1.2 Aims and objectives of the study

This study aims to explore the characteristics of BC in Saudi females, the incidence patterns over the years between 1994 to 2017 and by age and stage at diagnosis, the management and survival patterns of BC, and the quality of life of Saudi females diagnosed with BC. In addition, the survey was used to find out the quality of life and the utility values of BC in Saudi females, which was found to be unavailable in the literature when conducting a systematic review to evaluate the use of hormonal therapy, specifically aromatase inhibitors (AI) versus tamoxifen in oestrogen receptor-positive BC females.

The initial direction of my research was to investigate cost-effectiveness of adjuvant endocrine therapy in estrogen receptor positive breast cancer and the plan was to conduct a systematic review, Economic Evaluation of Aromatase Inhibitors in Estrogen Receptor-Positive Breast Cancer Patients compared to Tamoxifen. After conducting the systematic review, I realized that performing the planned cost effectiveness analysis as part of my PhD would not be possible due to the lack of Saudi specific utility values and the update to the guidelines for BC treatment which changed from prescribing tamoxifen and aromatase inhibitors drugs as alternative to using aromatase inhibitors for postmenopausal women and using tamoxifen for premenopausal women. This meant the research question of comparing aromatase inhibitors with tamoxifen in early-stage BC was not reasonable and had no clinical relevance. For these reasons that objective of my PhD research has been revised.

The specific objectives for this PhD are:

1. To determine incidence patterns of Breast Cancer (BC) subtypes in Saudi Arabian females between 1994-2017 in:
 - a. Different age groups
 - b. Different Saudi regions
 - c. Cancer stages at diagnosis

2. To analyse BC survival rates in Saudi Arabian women by:
 - a. Age group
 - b. Genotype
 - c. Treatment modality
 - d. Cancer stage

To investigate changes in survival driven by risk factors.

3. To examine the treatment patterns in the management of BC by:
 - a. Age group
 - b. Molecular subtype
4. To determine Health-Related Quality of Life (HRQoL) in Saudi females:
 - a. To evaluate the impact of BC on HRQoL
 - b. To measure the quality of life in Saudi female BC patients in different age groups, disease stages and treatment modalities by using disease-specific tools (EORTC QLQ-C30 & BR23)
5. To measure health utility via mapping utility values obtained by disease-specific tools (EORTC QLQ-C30 & BR23) onto a generic measure (EQ-5D)

1.3 Breast cancer

1.3.1 Breast cancer definition & subtypes

BC is a disease in which there is uncontrollable growth of breast tissues forming tumours. The tumours are usually generated from the breast ducts or lobules. However, they can also spread to other tissues and parts of the body, which is called metastasising (Raymond W. Ruddon, 2007).

The most common cancer types are ductal carcinoma in situ, where the tumour is located in the duct and not spread to other tissues; Invasive ductal carcinoma, where the cancer cells begin in the duct tissues and then spread to other tissues; and invasive lobular carcinoma, where the cancer cells start in the lobules and spread to other tissues (Nascimento & Otoni, 2020).

BC is classified based on how the cells appear under the microscope, and there are three grades: grade 1, well-differentiated; grade 2, moderately differentiated; and grade 3, poorly differentiated. Cancer is also classified according to its size and spread using the TNM staging system. T refers to the size and extent of the tumour, N refers to the number of lymph nodes involved, and M refers to the spread or whether the cancer has metastasised. The TNM combinations are grouped into four stages: stages I and II are considered early-stage BC, and stages III and VI are considered advanced BC (Amin, 2017).

Breast cancer is often discovered by the patient and described as a painless lump or mass, or it is found during a routine physical examination or mammogram. The main signs or symptoms reported are a lump, a change in the size or shape of the breast, and changes in the skin of the breast, such as dimpling, nipple retraction, or discharge (Lina, 2021).

BC is diagnosed using clinical examination, imaging such as mammography, ultrasound, magnetic resonance imaging (MRI), computed tomography (CT), and the core needle biopsy. The needle biopsy is considered critical in confirming the diagnosis (Harbeck et al., 2019).

1.3.2 Epidemiology of BC

Morbidity

Globally, BC ranked as the second most common cancer in 2022 after trachea, bronchus and lung cancer. It is the first most frequently diagnosed cancer among women. In 2022, BC accounted for 11.5% of all cancers diagnosed worldwide in females, with 2.3 million cases diagnosed, contributing to 23.8% of all cancers diagnosed in females (World Cancer Research Fund International, 2023).

According to the world standard population using Segi's world population (Segi, 1960), the world's age-standardised incidence rate (ASR) of BC in females is 46.8 per 100,000. The ASR varied between regions, with the highest rate in France, with an ASR of 105.4 per 100,000; the US showed an ASR of 95.9 per 100,000 female population, and the UK showed an ASR of 94.0 per 100,000 women (Ferlay et al., 2024). In Saudi Arabia, the ASR was 28.4 per 100,000 Saudi female population (AL Zomia et al., 2024), which is much lower than in other countries mentioned.

Mortality

BC is considered the leading cause of cancer death in women worldwide, accounting for 15.4% of the total cancer deaths (Bray et al., 2024). Globally, BC caused 670,000 deaths in 2022, with an ASR of 12.7 per 100,000 (World Cancer Research Fund International, 2023). The average age-standardised mortality rate (ASMR) varies between countries, with higher rates in low and middle-income countries than in high-income countries (OECD/World Health Organization, 2020). The median age of death from BC was 70 years; most BC cases will die due to the metastasis of the disease to other organs such as lungs, bones, and brain (Department of Defense Breast Cancer Research Program, 2023).

In KSA, BC is considered the fourth leading cause of cancer-related deaths in both genders and ranked the first cancer-related death in females. The ASMR was 45 per 100,000 females (Ferlay, Ervik M, Lam F, et al., 2024a).

Survival

The 5-year survival rates of BC globally increased from 90.05% in 2000 to 93.19% in 2020 (Surveillance Research Program, 2023). The survival rate varies by stage at diagnosis. In the localised BC (early stage I and stage II), the 5-year relative BC survival was 99.6%, while in the regional BC (stage II and stage III), it was 86.7% and decreased to 31.9% in distant BC (stage IV).

In KSA, the 5-year observed survival increased from 66.4% in 1994-1999 to 72% in 2005-2009 (Aseafan et al., 2022). The survival was affected by the stage at diagnosis; cases with localised BC showed higher survival rates than those with regional and distant BC (Alotaibi et al., 2018).

1.3.3 BC risk factors

Studies indicate that the risk of BC arises from a combination of factors. Lifestyle-related BC risk factors include obesity, exercise, smoking, and diet (Łukasiewicz et al., 2021) , (Cohen et al., 2023). In contrast, some risk factors cannot be changed, such as gender, family history and genetic factors (Dadziak et al., 2023).

The relationship between diet and nutrition and cancer has been addressed in many studies. High meat consumption and a diet rich in fat may increase the risk of BC (Momenimovahed & Salehiniya, 2019). Obesity has a substantial effect on the occurrence of BC. Increased physical activity was associated with a reduction in developing BC. Exercising after diagnosis reduces BC's recurrence, mortality and morbidity (Momenimovahed & Salehiniya, 2019). The correlation between smoking and alcohol consumption with BC has been addressed. The more alcohol consumption, the greater the likelihood of developing BC (Boya Lu & Elango Natarajan, 2024). The risk of BC also increases in active smokers; studies have shown that there is a dose-response relationship between the number of years of smoking and the risk of developing BC (Momenimovahed & Salehiniya, 2019).

Gender is a significant risk factor for BC, as females are at higher risk of developing it than males. In fact, BC in males accounts for less than 1% of all BC cases (Momenimovahed & Salehiniya, 2019). Age is also considered a significant risk factor for BC. It has been shown that the risk of BC increases with age and reaches its maximum at menopause, then gradually decreases. Family history and genetic factors can play an essential role in the development of BC; genetic mutations, e.g., BRCA1 and BRCA2, are associated with a higher risk of BC by influencing reproductive factors (Poggi, 2024). Reproductive factors play a significant role in increasing the risk of BC; prolonged exposure to hormones such as oestrogen and progesterone can increase the risk of BC. Late age at menarche, early age at menopause, and breastfeeding, especially if women breastfeed for an extended period, are considered protective factors. Conversely, late age at first birth (later than 30) and nulliparity are considered risk factors (Poggi, 2024). The use of oral contraceptives was associated with an increased risk of BC, specifically ER-negative BC (Hurson et al., 2024); this risk increased as the age of the women increased.

Using hormonal therapy has been found to be associated with an increase in the risk of BC, especially ER-positive BC, which is related to the duration of use and the type of combination; using a combination of oestrogen and progesterone was associated with a higher risk than using only oestrogen therapy (Narod, 2011).

The following Directed Acyclic Graph (DAG) presents a conceptual framework that demonstrates how various determinants, such as age, obesity, physical inactivity, smoking, diet, gender, and family history, influence breast cancer incidence and survival. The diagram illustrates the interplay between these factors, demonstrating that many of them have direct impacts on all key outcomes. Figure 1.1.

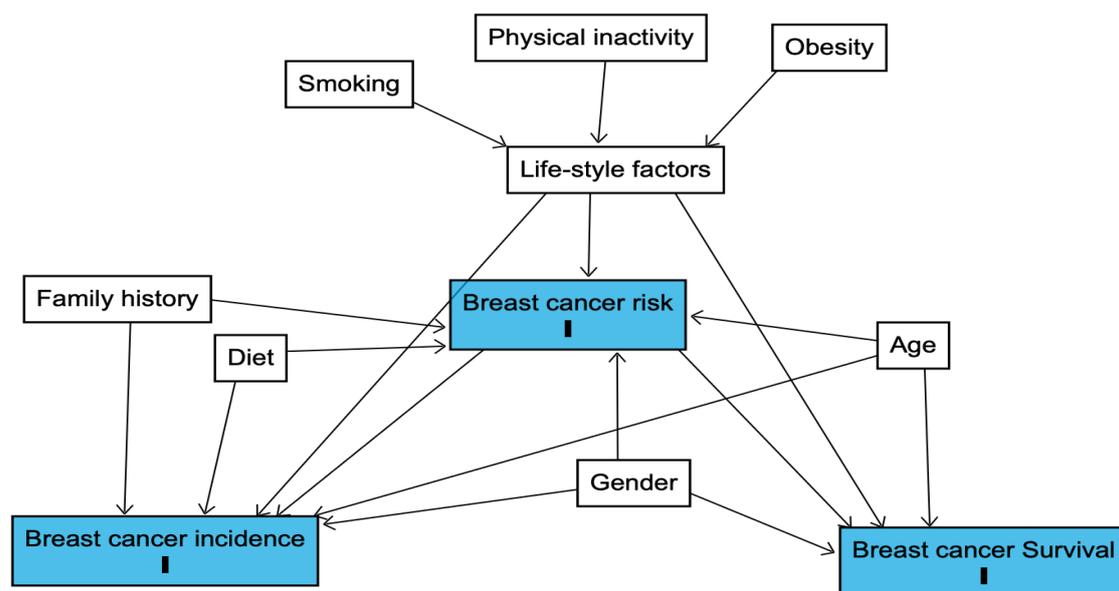


Figure 1.1. BC determinants and their influence on BC incidence and survival.

1.3.4 BC treatment

Breast cancer treatment encompasses a variety of approaches tailored to the individual patient. Treatment choice depends on several factors, including patient preference, type and stage of BC, and the patient's overall health (Rezaei, 2023). The treatments include surgery, chemotherapy, radiation, hormonal therapy and biological therapy (Wang & Wu, 2023).

Surgery:

Surgery is considered the cornerstone of treatment for most types of BC. There are two available surgical options: mastectomy, in which the whole breast tissue is removed and breast-conserving therapy, where the surgeons remove the tumour with the adjacent breast tissues (Golar et al., 2024). The choice of method depends on various factors, such as the patient's preference, age, and ability to comply with radiation after mastectomy. Surgery can be used alone or in combination with other modalities to treat early-stage, locally advanced, and some types of metastatic BC (Association of Breast Surgery et al., 2009).

Chemotherapy:

Chemotherapy is a systemic treatment for BC. It involves using anticancer medications (cytotoxic) to destroy cancer cells. It can be given orally or intravenously as a single drug or in combination. Chemotherapy can be used preoperatively (neoadjuvant) to shrink the tumour size and improve the surgical outcomes or after surgery (adjuvant) to eliminate any remaining cancer cells and reduce the risk of recurrence (Masood, 2016). Adjuvant chemotherapy is indicated for patients with positive axillary nodes or node-negative but with other risk factors such as diagnosed at age <35 years where the BC tends to be aggressive, HER-2 positive, and those with hormone receptor ER/PR negative. While neoadjuvant chemotherapy is used in advanced BC or early stages with large-size tumours (McDonald et al., 2016).

Radiation:

Radiation therapy involves using high-energy rays to target the tumour or the post-surgery tumour site specifically. Generally, all patients who underwent surgery required radiation. It is usually used after mastectomy or breast-conserving surgery to prevent recurrence (Polgár et al., 2022). However, there are some circumstances in which radiotherapy can be omitted, such as in patients over 70 years old, those with tumours smaller than 2 cm, negative lymph nodes, or cases with positive oestrogen receptors (McDonald et al., 2016).

Hormonal therapy (endocrine therapy):

Hormonal therapy is used for the treatment of hormone receptor-positive BC cases. Hormonal therapy works by either blocking the hormone receptors, such as tamoxifen or by lowering the oestrogen level in the body, such as aromatase inhibitors and ovarian suppression (Lindsay Morgan, 2023). The choice of hormonal therapy depends on the menopausal status of the patient, which should be assessed before the initiation of the treatment, as this determines the source of oestrogen, which can be either ovarian or adrenal. In premenopausal women, the ovaries produce high basal oestrogen levels in which antioestrogen therapy, e.g., tamoxifen, is compelling. Tamoxifen works by blocking the oestrogen receptors on BC cells, preventing oestrogen from stimulating their growth. In contrast, aromatase inhibitors work by blocking oestrogen production; they block the aromatase enzyme that converts androgen into oestrogen in postmenopausal women, so this approach is used in postmenopausal women with hormone receptor-positive BC (Drăgănescu & Carmocan, 2017).

Biological therapy:

Biological therapy, also called targeted therapy, works by targeting breast cancer cells to destroy them or slow their growth. It can be used as adjuvant or neoadjuvant therapy in any stage of BC (Foon, 1986). Several types of biological therapy exist, but monoclonal antibodies and small-molecule inhibitors are most commonly used. It is predominantly used in HER2-positive BC cases (Tinoco et al., 2013).

1.3.5 BC screening

Population screening aims to detect the disease in its early stages, during the asymptomatic phase, contributing to early intervention when the treatment is more likely to be effective (Harbeck et al., 2019). Early detection of BC significantly improves survival rates.

Many approaches to screening are taken, such as breast self-examination, where women examine their breasts for lumps or abnormalities; clinical breast examination, a physical examination performed by a health care professional; and mammography, an X-ray of the breast (Blamey, 2000). Mammography is the recommended primary screening modality (Ren et al., 2022).

Most guidelines recommend annual or biennial mammographic screening for the average-risk population aged 50-69 years and to start screening younger for high-risk groups (Ren et al., 2022). The Saudi guidelines recommended screening in women aged 40-49 every 1 to 2 years while for women aged 50-69 every 2 years (Omalkhair Abualkhair & Ahmad Saadeddin, 2014).

1.3.6 BC Quality of life

Quality of life (QoL) was defined by the World Health Organization (WHO) as “the individual’s perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns” (Turner et al., 2013). It is considered an important outcome measure for BC patients, contributing to improved

treatment. Given the increasing incidence of BC and early disease detection, which leads to prolonged survival, assessing quality of life is essential (Paraskevi, 2012).

QoL is multidimensional, including physical, mental and social functioning. The physical domain encompasses the subjective evaluation of an individual's health status and body functions, such as fatigue and pain. The cognitive domain includes the psychological impact of BC, including mental health issues like anxiety and depression, while social functioning examines how BC can affect social interactions and relationships (Gavric & Vukovic-Kostic, 2015).

Being diagnosed with BC can impact the patient's QoL. An individual diagnosed with BC often experiences a range of emotional responses, including depression and anxiety. These feelings occur as a result of uncertainty about treatment options and prognosis. Additionally, various treatments can negatively impact the QoL by introducing physical side effects. Patients may also experience fatigue, pain, and changes in body image, which affect their daily functioning and overall perception of life (Mokhtari-Hessari & Montazeri, 2020). It is essential to address the different aspects of QoL to develop effective treatment strategies. Improving QoL can lead to better health outcomes (Gavric & Vukovic-Kostic, 2015).

Many instruments have been developed to assess the QoL; they are standardised tools used to evaluate their overall well-being and functional status. They were classified into two main categories: generic and specific. Generic instruments are designed to assess the quality of life across various conditions, providing a broader overview, such as the SF-36 (Short Form 36) (Ware Jr., 1999) and EQ-5D (European Quality of Life 5 Dimensions) (Rabin & de Charro, 2001). Specific tools are tailored to evaluate the QoL in particular health conditions, such as EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire- Core 30) (Sprangers & Bonnetain, 2014) and FACT (Functional Assessment of Cancer Therapy) (Bonomi et al., 1996).

1.4 Thesis structure

The thesis comprises eight chapters. The first chapter focuses on an introduction to BC and its epidemiology, as well as the study's aims and objectives. The second chapter provides a

literature review on BC in Saudi Arabia. Chapter three provides a detailed overview of the data sources used in this study and the data collection process. Chapter four examines the incidence of BC in Saudi females in population- and hospital-based studies. Trends in incidence rates by age group and by BC stage and grade are presented in this chapter.

The fifth chapter focuses on the treatment of BC and analyses the trends in treatment modalities based on hospital data. Further, the systematic review of using aromatase inhibitors in ER+ve BC is presented in this chapter, along with the distribution of BC treatment modalities by molecular subtype and age group.

In the two following chapters, the focus was on the prognosis of BC. The prognosis for BC consists of two aspects: survival and quality of life. Chapter six presents the survival analysis of BC among Saudi females by different age groups, BC stages and grades. Chapter seven includes the QoL of BC females, examining the effects of the disease on various aspects of their lives, using generic and specific tools, and then discussing the mapping methods used to estimate the health utility. In the last chapter, conclusions and recommendations are presented.

Chapter 2 Literature Review

2.1 Introduction

Breast cancer is one of the most frequently diagnosed cancers worldwide, and it is the most frequently diagnosed cancer in females. In 2022, an estimated 2.3 million new female BC cases were diagnosed globally, which accounts for 23.8% of all female cancers (Ferlay, Ervik M, & Lam F, 2024). This percentage is higher in the Kingdom of Saudi Arabia (KSA), where the number of new female cases diagnosed with BC was 3777, which accounts for 28.3% of the total female cancer cases (Bray et al., 2024). It is essential to understand the epidemiology, survival rates, and quality of life (QoL) of Saudi females diagnosed with breast cancer to develop effective prevention, detection, and treatment strategies and to improve patient outcomes.

This literature review summarises the available evidence on global trends in BC incidence and survival and what is known about QoL in women living with BC, as well as literature specific to KSA and the Middle East on these topics.

2.2 Epidemiology of breast cancer

2.2.1 Incidence

The incidence rate of BC has increased over the years. In 10 years, the age-standardised incidence rate (ASR) for BC globally rose from 43.1 per 100,000 in 2012 to 46.8 per 100,000 in 2022 (Ferlay et al., 2024).

Studies show that BC incidence is strongly related to the Human Development Index (HDI). The HDI is a statistical tool used to evaluate a country's development in three dimensions: health, education and standard of living. It provides a single value ranging from zero to one, with higher values indicating greater levels of development (Alamoudi & Bafail, 2023). It has been shown that countries with the highest HDI have a higher incidence of BC with four-fold variation worldwide; the incidence ranges from an ASIR of 94.2 per 100,000 in Australia and New Zealand to 25.9 per 100,000 in South-Central Asia (Huang et al., 2021). A study conducted in 2015 to assess the correlation between HDI and ASIR in Asian countries showed that there was a moderate positive correlation ($r = 0.56$) between the ASR of BC and HDI, indicating that the

higher HDI levels are associated with an increased incidence of BC, and this relationship was statistically significant (Ghoncheh et al., 2015). According to the Human Development Report 2019, KSA is considered one of the countries with a very high HDI with a score of 0.875 (Pedro Conceição, 2023); this fact suggests that the incidence of BC in KSA will increase in the future.

This increase in incidence in developed countries may be explained by the increased prevalence of established risk factors for BC in these countries, such as physical inactivity and obesity, and by improved healthcare services, including routine screening for BC, resulting in higher rates of BC detection (Momenimovahed & Salehiniya, 2019b). A study conducted in the USA compared the incidence rate before and after the introduction of mammography screening, and it showed that the absolute change in the incidence of BC among women aged 40 or older after the introduction of mammography was 122 cases per 100,000 (Bleyer & Welch, 2012).

In Gulf countries, including KSA, the incidence of BC has increased consistently over time. However, there are distinct characteristics of diagnoses in this region. It has been reported that BC is often diagnosed at a more advanced stage and a higher grade, as well as being more frequently diagnosed in younger age groups (Al-Shamsi et al., 2023). However, there is heterogeneity in BC incidence between countries within the Gulf region. In 2020, the ASR per 100,000 for the six Gulf countries ranged from as high as 85.5 in the United Arab Emirates to 28.8 in KSA (Al-Shamsi et al., 2023). BC incidence trends in KSA showed a consistent increase over the years (1990-2021); the ASR increased from 15.4 per 100,000 in 1990 to 46.0 in 2021 and is projected to continue rising, with a forecasted rate of 49.6 in 2026, according to a recent study (AL Zomia et al., 2024). The authors speculate that this is due to the implementation of programmes specific for screening and effective therapeutic strategies and due to the improvement in access to healthcare services.

2.2.2 Age at diagnosis

Incidence of BC is strongly related to age; incidence increases with age, and the highest incidence rates have been observed in older females, with a median age at diagnosis for women in the UK and USA of 62 years (Cancer Research UK, 2024; Surveillance Research Program, 2023). However, a recent study suggests that this trend has changed. The study

evaluates global incidence trends of BC among females by age and region. The incidence tends to be higher in younger females (aged <50 years) in twelve countries, including Japan, Germany, Slovakia, New Zealand and China (Huang et al., 2021). According to the authors, the specific reason for this shift is unknown. It could be related to various factors, including obesity, which has increased among younger groups due to lifestyle changes. This younger population tends to be less active and has experienced changes in their dietary habits. Another study conducted in Brazil observed the same trend of increasing incidence of BC in younger females (< 40 years), and the mean age at diagnosis was 52.3. (Orlandini et al., 2021)

The literature on age at diagnosis of breast cancer in Saudi females generally reports the median age or menopausal status of the population at diagnosis. Most studies found that a high proportion of cases are diagnosed at younger ages compared to Western countries, with many diagnosed under the age of 50 (Alabdulkarim et al., 2018; al-Idrissi et al., 1992; Ezzat et al., 1999a). In a study conducted at King Faisal Specialist Hospital in Riyadh, which treated patients from all age groups, 315 patients with BC were identified. The median age at diagnosis was 46 years, and almost two-thirds of patients (64%) were younger than 50 (Ezzat et al., 1999). Another study conducted in AL-Khobar, KSA and including 130 women with invasive BC, reported that the median age at diagnosis was 40 years, with 16% younger than 30 years and 37% older than 50 years at diagnosis (al-Idrissi et al., 1992). Both studies collected data during the same period between 1981 and 1990/1 but in two different regions, the central and the eastern regions of KSA, these two regions in addition to Makkah region are the areas with the highest incidence rates of BC among all regions. A study aimed to investigate the demographic characteristics of patients with operative BC was conducted in King Saud University Medical City, Riyadh, with 224 patients who underwent surgery for BC and found that the mean age at diagnosis was 48.8 (Alabdulkarim et al., 2018); this was consistent with the results of other studies (Saggu et al., 2015; Alghamdi et al., 2013), which suggest that the median age at diagnosis was younger than 50 years.

In contrast, more recent research from KSA shows a shift toward an increase in the incidence rate in women over 50 years. A study reported that BC incidence gradually increased with advancing age, with the highest incidence rate being among those aged 60 years and above (ALZomia et al., 2024), and the results of their study are consistent with the highest incidence of BC in older ages reported globally. In addition, a recent study found that the

average age at diagnosis differed by the type of cancer. The median age at diagnosis was 56 years for invasive cancer and 51 years for in situ (Asiri et al., 2020). In a retrospective descriptive study conducted in a tertiary care centre in Riyadh, the median age at diagnosis was reported to be 50.1 (Omer et al., 2024); another study found that the median age increased from 48 in 2001 to 51 by the end of the study period, which was 2017 (Basudan, 2022). The results of these studies suggests that the median age at diagnosis in KSA is tending to increase toward the median age at diagnosis globally. The possible explanation for this change is the shift in the population's age distribution over time as the population ages (Omer et al., 2024). While ASR corrects for population age structure when comparing incidence rates, they do not directly reflect changes in median age. Therefore, the observed changes in the median age at diagnosis might partially result from demographic shifts in the population. A study on the age structure in KSA from 2012 to 2022 revealed that in 2022, about 25.95% of the population was aged between 0 and 14, 71.2% were between 15 and 64, and 2.81% were 65 years and older. In comparison, in 2012, 28.6% of the population was 0 to 14 years old, 69.2% were between 15 and 64 years old, and 2.17% were 65 and above (O'Neill, 2024).

2.2.3 The stage at diagnosis

Identification of the stage of breast cancer at diagnosis is considered necessary in determining the prognosis of the disease and its treatment plan. Globally, it was found that in high-income countries, most female BC patients were diagnosed early at localised stages I and II (85%) (Bryan et al., 2018), in contrast to low- and middle-income countries, where BC was diagnosed at advanced stages in the majority of cases (Youlden et al., 2014).

The distribution of BC cases by stage at diagnosis varies significantly between regions worldwide, with higher proportions of metastatic BC and unknown stage observed in low-income countries, low socioeconomic status, and older age groups (Benitez Fuentes et al., 2024). This may be attributed to BC screening guidelines, which typically do not recommend screening for women over 75 due to the unclear benefit of screening in this age group. The majority of BC cases were diagnosed in the early stages (grades I and II) in high-income countries such as Canada and in middle-income countries such as Hungary, where early-stage diagnoses accounted for 81.7% and 52.7%, respectively (Bryan et al., 2018; Tittmann et al., 2024).

Although there is considerable literature about BC subtypes in KSA, research focusing on BC stages remains limited. Existing studies indicate that BC in Saudi females is often diagnosed at a late stage, which poses significant challenges for treatment (Chaudhri et al., 2020; Alabdulkarim et al., 2018; Elkum et al., 2007; Ibrahim et al., 1998). A study conducted on 292 patients at King Fahd Hospital in 1998 found that 46% of BC cases were diagnosed at stage III or IV, with only 9% diagnosed at stage I and 30% at stage II. However, this study had some limitations; it covered the eastern province of KSA only, and the authors noted that staging procedures were not consistent over the study period which was between 1985 and 1995 (Ibrahim et al., 1998). Another study reported that there was a significantly higher incidence of grade III tumours in younger patients (aged less than 40 years) compared to older patients (aged 40 years and over) (Elkum et al., 2007). This study reviewed the data of 867 females with stage I-III BC who had definitive surgery at KFSH&RC from 1986 to 2002. Although these studies are somewhat dated, their findings remain consistent with recent research. A study performed on 224 patients between 2005 and 2012 who underwent surgery at King Saud University Medical City in Riyadh reported that very few patients presented with early-stage disease (12%) (Alabdulkarim et al., 2018), and another study reported that one-third of BC cases were diagnosed in the late stages of the disease based on SCR data from 2001 to 2014 (Chaudhri et al., 2020). Another study used the SCR data reports from 2004 to 2016 and found an increase in the localised BC cases accompanied by a slight decrease in regional BC cases, which has been observed and reported as statistically significant. The authors noted that this result was an essential part of their analysis and suggested that this was related to the introduction of a screening programme in 2010 established by the Ministry of Health that leads to early diagnosis (Albeshan & Alashban, 2021).

Previous studies indicated that BC was diagnosed at advanced stages in Saudi females. However, recent research demonstrates a change, with BC being diagnosed at early stages (Albeshan & Alashban, 2021). Since KSA is considered a high-income country, the recent results align with the global findings of BC being diagnosed in the early stages in high-income countries. However, more research using recent data is required to confirm these findings.

2.2.4 Risk factors

Multiple risk factors are associated with breast cancer. Some risk factors cannot be changed encompass age, gender, family history, and genetic factors. While others can be changed which include dietary factors, hormonal therapy, alcohol consumption, obesity, and physical inactivity.

Although a review study reported that no risk factors were identified in 70% of BC patients, some risk factors can be associated with the development of BC (Kamińska et al., 2015). The increase in BC incidence observed implicates the necessity of identifying the risk factors related to the occurrence of the disease, such as age, family history of cancers, and environmental factors.

Age is one of the critical risk factors for BC. According to the National Centre for Chronic Disease Prevention and Health Promotion (NCCDPHP) (National Center for Chronic Disease Prevention and Health Promotion, 2024), the risk of BC increases as age increases, particularly after the age of 50, until menopause, when the rate of increase slows dramatically. While earlier studies in KSA indicated that BC was predominantly diagnosed in women under 50, as mentioned earlier, this trend has changed in recent studies where the median age at diagnosis increased to 51 by 2017 (Basudan, 2022), which aligns more closely with global patterns.

In addition to age, family history is considered one of the risk factors related to BC. BRCA1 and BRCA2 are among the most well-known genetic risk factors; mutations in these genes have been found to be associated with an increased risk of BC of 65% (Kamińska et al., 2015). It was reported that changes in BRCA1 and BRCA2 account for 5-10% of BC cases (Casaubon et al., 2023). Two studies documented an increased risk of BC associated with positive family history of BC from first-degree relatives, with a relative risk of 2 in the first study (Fraser & Shavlik, 1997) and about 25% of all BC cases found to be related to family history in first-degree relatives (Sun et al., 2017). Consistent with those results, the same percentage was detected in KSA, with about 26% of BC patients reporting a family history of first- or second-degree family history of BC (Omer et al., 2024). A systematic review and meta-analysis of studies from KSA related to the epidemiology of cancers reported that mutations in BRCA1 and BRCA2 increase the risk of development of BC (Alqahtani et al., 2020).

Reproductive factors, such as early menarche, late menopause, late age at first pregnancy, and low parity, are considered risk factors for BC (National Breast and Ovarian Cancer Centre, 2009). The relationship between oestrogen levels, whether endogenous or exogenous, and BC has been indicated and found to be associated with an increased incidence of BC due to more prolonged exposure to oestrogen activity. A review conducted by (Kamińska et al., 2015) discussed the risk factors of BC and concluded that each delay of menarche by two years was associated with a reduced risk of BC occurrence by 10% and each year of continuing menstruation increased the risk by 3%. In addition, it reported a protective effect of early pregnancy and prolonged breastfeeding; each year of breastfeeding is associated with a decrease in the risk of BC of 4.3%. Other literature supported the results of those studies, in addition to reporting that each additional birth reduces the risk of BC by 10% (Sun et al., 2017), while another study found that older age at first pregnancy was reported to increase the risk of BC with a relative risk (RR) of 1.43 (95%CI: 1.06, 1.93) (Fraser & Shavlik, 1997).

Studies on the association between reproductive factors and BC in KSA and Gulf countries are lacking (Ravichandran & Al-Zahrani, 2009). According to the results of one of the few studies conducted in Makkah, KSA, studying the determinants of BC in Saudi women, a case-control study included a total of 432 females with 214 Cases and 218 controls. It showed that early age at first menarche increases the risk of BC. (Alsolami et al., 2019). Another study also conducted in Makkah during the same period, 2017, included 135 postmenopausal women diagnosed with BC used as case management and 270 healthy women as control to predict the probability of developing cancer, it showed that multiple pregnancies played a protective role in BC (Babiker et al., 2020). In contrast, both studies found that breastfeeding did not have protective values for BC.

Exogenous oestrogen includes the administration of hormonal therapy and oral contraceptives; the relationship between oral contraceptives and the risk of BC is still controversial. Some studies have found that using oral contraceptives is associated with an increase in the risk of BC, while other studies did not support this finding (Marchbanks et al., 2002) . A meta-analysis study suggests that oral contraceptives did not increase the risk of BC; however, they found that BC increased when using contraceptives before a first full-term pregnancy or when used for longer than five years (Kanadys et al., 2021). In KSA, the literature showed that using hormonal oral contraceptives was found to increase the risk of BC in a case-

control study conducted from 2014 through 2016 in the Makkah region of KAS, including a total of 432 females with 214 cases and 218 control selected from the same region of cases and made up of hospital workers and patient's companion and friends (Alsolami et al., 2019). A systematic review highlighted the use of oral contraceptives as one of the highly recognised risk factors for BC (Alqahtani et al., 2020)

Regarding hormonal therapy, studies suggest that the risk of BC increased according to the duration of treatment; using hormonal therapy for five and ten years was associated with an increase in BC risk of 15% and 34%, respectively (Kamińska et al., 2015) which was supported by the results of another study (Fraser & Shavlik, 1997) that reported a significant increase in the relative risk of BC with exposure to hormonal replacement therapy. Aligned with these results, a case-control study conducted in three different hospitals in Jeddah on 151 cases and 166 controls found that there was an increased risk of BC when using exogenous oestrogen and progesterone (Al-Qutub et al., 2013). A strong relationship was found between using hormonal replacement therapy and the risk of BC, and it was reported as the strongest predictor among all risk factors investigated in that study, which were age, family history and postmenopausal (Ahmed et al., 2019).

Lifestyle factors, including dietary fat intake and physical inactivity, which may lead to obesity, can increase the incidence of BC (McTiernan, 2008). Regular physical activity was shown to have a protective effect on BC, although the mechanism by which it influences BC remains unclear but could be explained by reducing exposure to endogenous sex hormones. A prospective cohort study that was conducted on pre and postmenopausal women in UK Biobank showed a reduction in BC risk associated with greater physical activity. Knowing that high BMI is considered as risk factor for BC, the same results were obtained when adjusting for adiposity, the RR was 0.84 (95% CI 0.73, 0.96) in postmenopausal women and 0.79 in premenopausal women (95% CI 0.66, 0.95) (Guo et al., 2020). Another study reviewing the risk factors of BC suggested an increase in the risk of BC by 27% in women who exercised infrequently (Fraser & Shavlik, 1997), but this was inconsistent with the results of a study in KSA that reported a higher frequency of exercise among cases compared to controls with an odds ratio of 1.45 (95% CI 0.90, 2.35) however, the confidence interval includes one suggesting that this result is not statistically significant. The results cannot conclude that there is a true association between exercise and BC. (Al-Qutub et al., 2013).

Dietary fat intake was shown to increase the risk of BC; it was shown that an increase of 10% in processed food in the diet was associated with an 11% increase in BC (Łukasiewicz et al., 2021). However, vitamin D deficiency was found to increase the risk of BC, especially in postmenopausal women, by 45%, but the mechanism of action is not fully understood. (Mackey et al., 2023). Another study reported that Vitamin D intake reduced the relative risk of BC by 20%, and regular physical activity reduced the risk by 20-40% (Kamińska et al., 2015). Dietary fat intake is related to obesity and body mass index; a positive correlation was detected between body mass index and the risk of BC, which was significant in the obese group. A dose-response meta-analysis of prospective cohort studies showed that there was a 2% increase in the BC risk with every 5kg/m² increase in BMI (Liu et al., 2018). In a case-control study on Saudi female from Makkah region showed that a high BMI (>30 kg/m²) was associated with a fourfold increase in the risk of BC compared to normal-weight women (Alsolami et al., 2019). This result aligns with the findings from previous studies that suggest a strong relationship between BC and dietary fat intake. Despite the lack of Saudi literature investigating the relationship between dietary fat intake and the risk of BC (Almutlaq et al., 2017). One review study, reviewed studies that have established evidenced based BC risk factors and the published studies on BC risk factors in KSA, it found a strong positive association between the risk of BC and a diet high in fat (Alothaimeen et al., 2004).

2.2.5 Conclusion

Several studies have investigated the incidence pattern in the Saudi female population. However, the results of those studies had limitations. Most of the studies were descriptive in nature (Omer et al., 2024), limiting their ability to identify causality or any relationship between risk factors and incidence. Additionally, many were retrospective, leading to data incompleteness and potential bias, and were often conducted in a single region or centre, which limits their generalisability (Asiri et al., 2020). Another drawback is the reliance on a secondary dataset, which affects the accuracy, completeness of the data and lack of relevance (AL Zomia et al., 2024). Risk factors such as genetic factors, hormone use, and lifestyle should have been considered, as these significantly impacted the incidence and outcomes. In addition to all these limitations, most of the studies were conducted over short periods, less than ten years, limiting their ability to detect trends over time. One of the aims of this thesis is to gain

a clear insight into the epidemiology of BC in Saudi females, including patterns in incidence by age and stage of diagnosis, and to determine whether these have changed over the years.

2.3 Survival

2.3.1 Overall survival rates (OS)

It has previously been reported that there are geographical differences in BC survival, with longer survival documented in high-income countries compared to low and middle-income countries (Huang et al., 2021).

The 5-year OS rate for BC in the UK, reported by the NHS, was 85.9% from 2016 to 2020 (NHS England, 2023). This supports the findings that the 5-year relative survival rate was above 80% in some developed countries such as North America and Japan (Sun et al., 2017). The high survival rates in developed countries could be attributed to early detection using annual mammography and the availability of adequate medical resources and treatment compared to low-income countries.

Few studies on survival have been published in Gulf countries, but the available literature generally showed a high survival rate, such as the overall 5-year survival in Kuwait, which was 90.5% (Al-Shamsi et al., 2023).

The results from Saudi literature vary for several reasons, such as variation in age or stage at diagnosis or data obtained from different regions or single centres and not population-based studies; these factors result in different survival outcomes reported in the literature (Alabdulkarim et al., 2018) , (Al-Shamsi et al., 2023). A study conducted at KFSH&RC on data from 867 BC patients between 1968 and 2002 found that the 5- and 10-year disease-free survival rates were 82% and 66%, respectively (Elkum et al., 2007).

Another two studies reported different rates; a study reported a low 5-year survival rate in KSA at 72% (Al-Shamsi et al., 2023); the authors suggest that this low rate was likely related to advanced stages at diagnosis and low screening rates. A study conducted between 2005 and 2012 reported a higher rate with a 10-year OS of 87% (Alabdulkarim et al., 2018). Nevertheless,

this high rate could be due to the study's limitations as it included operable cases only, which means that stage IV cases are excluded, a small sample size of 224 patients and a single centre.

Regarding the survival rate trends over time, it has been shown that survival rates have improved over time and an increase in the 5-year OS globally has been documented (Tang et al., 2025). It was reported that the five-year survival increased by 5.39% from 2000-2004 to 2015-2019 in the UK (Barclay et al., 2023). In the Netherlands, there was an increase in 5-year relative survival from 76.8% to 91.0% between 1989 and 2016, related to the advances in therapeutic guidelines and personalised treatments based on tumour characteristics (van der Meer et al., 2021). The same pattern was observed in KSA, where the 5-year survival rate increased from 66.4% in 1994-1999 to 72% in 2005-2009 (Aseafan et al., 2022). A recent study conducted between 2009 and 2017 in a university hospital in Jeddah reported a higher 5-year OS rate of 89% (Abdulwassi et al., 2020).

2.3.2 Factors affecting survival

Survival from BC depends mainly on early detection and access to optimal treatment (Ghoncheh et al., 2016), which can improve survival and life expectancy. Predictors of poor survival include being diagnosed at late stages (III and IV), the number of positive lymph nodes, comorbidities, postmenopausal status, and a histologic grade III (AL Zomia et al., 2024). The majority of the available studies confirm that advanced stage, tumour size, and nodal status had a negative effect on OS and disease-free survival (Elkum et al., 2007).

Stage at diagnosis:

It has been reported that OS rate is higher if BC was diagnosed at the early stages (localised) than in the late stages (regional and distant). According to the United States Cancer Statistics, the 5-year relative survival for BC by stage at diagnosis was higher in localised BC (98%) followed by regional BC (85%), with the lowest survival rate detected with distant metastasis (30%) (Centers for Disease Control and Prevention, 2021). Similar findings were found in Europe, where the 5-year survival of the early or localised stage of BC was 96% compared to 38% of metastatic or advanced BC (OECD/European Union, 2020).

A study supports these findings in northeast Thailand, where the 5-year survival rate was 60% and 27% for the early and late stages, respectively (Poum et al., 2012). The same results were obtained in Uganda, with a 5-year survival of 74% for early disease and 39% for advanced BC (Gakwaya et al., 2008). Similar to the findings of these studies, in Saudi literature, a study consisting of 321 cases showed that localised or early BC cases had better survival (67.5%) than regional (55.6%) and distant metastasis (57.6%); however, the difference was not significant ($P = 0.15$), as mentioned by the authors who suggests the reason behind this could be due to misclassification of cases either due to inadequate diagnostic facilities or inaccuracies in registration (Ravichandran & Al-Hamdan, 2014). More specifically, a study conducted in KFSH&RC on stage III patients found only that stage IIIB patients showed poor survival compared to stage IIIA ($P=0.008$) (Ezzat et al., 1999). In line with these findings, another study conducted from 2004 to 2013 found that those with localised BC had better survival than regional and distant metastasis, which was statistically significant (Alotaibi et al., 2018).

Age at diagnosis:

Globally, studies regarding survival rates and the age at diagnosis are inconsistent. Some studies reported poor survival in older age groups, while others reported the opposite (Brandt et al., 2015). This inconsistency in the findings could be attributed to the difference in the definition of old groups versus young groups, as different cut offs are used, or because these studies were not population-based.

A study conducted in Brazil showed that younger patients (< 40 years) had lower survival rates because BC was diagnosed in late-stage and more aggressive subtypes tended to be diagnosed at younger ages (Orlandini et al., 2021). In contrast, another study in KSA reported that older groups had worse OS and disease-free survival than younger groups, but the study was limited to locally advanced BC patients (Trabulsi et al., 2021a). Another study that involved operable BC patients in KFSH&RC from 1986 to 2002 reported that young patients (≤ 40 years) with positive lymph nodes had a worse survival rate than patients above 40. (Elkum et al., 2007)

Breast cancer characteristics:

Breast cancer survival rate can be influenced by various tumour characteristics such as tumour size, nodal status, and hormonal receptor status, which have been shown to have a negative impact on BC survival. (Elkum et al., 2007).

When a high number of lymph nodes are involved, survival is negatively affected; as the number of lymph nodes involved increases by more than two, the relative survival decreases. However, this was related to the stage; it was significant only in the early stages and not in the late stages of BC. The authors mentioned that many studies were inconsistent with their results, and they did not observe any statistical significance after adjusting for age and stage (Fujimoto et al., 2019).

A study performed on patients who underwent axillary lymph node dissection in KSA failed to find an association between OS and the number of lymph nodes detected. Still, as the authors mentioned, this could be attributed to the small sample size, 217 patients, which may have lacked sufficient statistical power, and the short follow-up duration, 39.8 months (Ibrahim et al., 2010).

Regarding tumour characteristics in Saudi literature, in one study investigating the pattern of triple-positive breast cancer in the Saudi population, where the tumour has an overexpression of the human epidermal growth factor receptor 2 (HER2) pathway and is positive for ER and PR, an OS of 89.5% was reported (Alzahrani et al., 2019). Consistent with these findings, tumours with positive ER and PR receptors were associated with better OS than those with one or both receptors being negative (Trabulsi et al., 2021). A review that summarised the key studies of risk factors and prevention of BC noted that triple-negative breast cancer tends to have lower survival rates and poor prognosis (Sun et al., 2017) . Additionally, worse outcomes and short survival were linked to the overexpression of the HER-2/neu proto-oncogene, which was reported in 20-30% of invasive BC (Almutlaq et al., 2017).

2.3.3 Treatment modalities (surgery, chemotherapy, radiotherapy, hormonal therapy)

In recent years, BC treatment strategies have advanced. However, surgery, chemotherapy, radiation therapy, and hormonal therapy are still considered the main treatments and have been demonstrated to improve the survival rate (Ho et al., 2020).

Despite the different modalities available for BC treatment in KSA, only a few studies focus on outcomes associated with various treatment strategies. A study conducted between 1981 and 1991 on stage III patients in KFSH&RC stated that radiotherapy was the only adjuvant modality affecting survival favourably, but this study focused only on stage III BC, and the median age for the participants was 46, with 62% being premenopausal. Furthermore, only 28% of the tumours were hormone-positive, limiting the number of participants who would have received hormonal therapy (Ezzat et al., 1999). Inconsistent with this finding, two other studies failed to detect this effect, which could be attributed to the small sample size ($n = 153$) and the restriction of cases included to locally advanced BC in a study conducted between 2009 and 2017 (Trabulsi et al., 2021) while the other study conducted between 2001 and 2012 on 155 BC patients at King Fahad Medical City, Riyadh mentioned that this could be related to the infrequent utilisation of radiotherapy in their institution (Abu Zaid et al., 2017). In this study by Abu Zaid et al., the effect of the combination of surgery and radiotherapy on survival was better than the combination of surgery and chemotherapy, with a 3-year survival rate of 100% and 94.7%, respectively. This finding aligns with the results of another study conducted in Brazil, which found that surgery combined with radiotherapy significantly increased the 5-year survival rate (90.6%) compared to other treatments (37.5%) (Fujimoto et al., 2019).

The use of adjuvant chemotherapy had a favourable influence on OS. A retrospective study at King Fahad Hospital University on 292 BC females between 1985 and 1995 reported a favourable effect on both OS and progression-free survival (Ibrahim et al., 1998), while the other study conducted between 2009 and 2017 on stage I to III BC found that adjuvant chemotherapy was associated with better disease-free survival (Abdulwassi et al., 2020). Regarding neoadjuvant chemotherapy, Ezzat et al. reported a deleterious effect on survival, and this could be due to the advanced stage of the disease of the included patients and the small number of patients receiving it in their study ($n = 33$ vs. $n = 221$) which may limit the statistical power and increase the potential for variability in results (Ezzat et al., 1999a), while in Ibrahim et al. study, this effect could not be ascertained due to their infrequent use. (Ibrahim et al., 1998)

Alabdulkarim and colleagues studied the association between survival and therapy received and showed a weak positive correlation between the number of neoadjuvant chemotherapy cycles and patient outcomes where the OS increased (Alabdulkarim et al., 2018). This correlation was more robust for stage III disease patients; in addition, younger age groups benefit more from neoadjuvant chemotherapy than older groups, but these findings are limited by the small study sample size (n = 80).

Concerning surgery, when comparing survival in patients who underwent radical mastectomy with patients who received breast-conserving treatment, the results showed no survival advantages of one over the other, and it was evidenced that breast-conserving treatment was as safe as modified radical mastectomy in terms of overall survival (Alnefaie et al., 2024). In another study, the hazard of death was higher in patients who underwent mastectomy compared to patients who underwent lumpectomy; this could be attributed to the aggressiveness of the disease as they included only localised advanced BC (stage III) patients in their study (Trabulsi et al., 2021).

In terms of targeted therapy, there is no consistent evidence across a range of studies to demonstrate an apparent beneficial effect of adjuvant tamoxifen on survival, with some studies reporting minor or no beneficial effects of tamoxifen on survival. This could be attributed to multiple reasons, including the predominancy of young premenopausal patients where the likelihood of positive hormone receptors is low (Ibrahim et al., 1998; Ezzat et al., 1999; Trabulsi et al., 2021); also the debatable effect of tamoxifen on stage III BC (Trabulsi et al., 2021; Ibrahim et al., 1998), or due to the small number of patients receiving tamoxifen in the study (n = 71) (Ezzat et al., 1999), or the recent introduction of anti-HER2 treatment in their institution as mentioned by the authors (Trabulsi et al., 2021).

2.3.4 Conclusion

In conclusion, there is limited literature on survival after a diagnosis of BC in KSA. The studies that have been conducted report that survival rates in Saudi females are considered high and improving with time. Studies consistently showed that advanced stages at diagnosis were associated with poor survival (Ravichandran & Al-Hamdan, 2014; Alotaibi et al., 2018). In contrast, the effect of age at diagnosis on the survival rate in KSA was inconsistent and needs further study.

Studies in the Saudi literature were limited (Al-Hamdan, 2014; AlJohani et al., 2016; Asefah et al., 2022; Trabulsi et al., 2021b), and the available studies had limitations; there is little published research on survival analysis conducted on the Saudi cancer registry data, and most of the data used in these studies were from a single centre or one region only, which limits the generalisability of these studies and affects the accuracy of the results. Moreover, the literature on BC survival by treatment modalities in KSA is still somewhat limited. While several studies compared different treatment modalities for various stages of the disease, many of these are either regional or focused on specific aspects of treatment (Trabulsi et al., 2021; Abu Zaid et al., 2017). To improve the survival rate, studies on the entire female Saudi population should be conducted to get an insight into the different factors that could affect survival and to improve treatment strategies.

2.4 Quality of life (QoL) in breast cancer patients

Literature focusing on the impact of BC on QoL, and the gaps in the available literature are summarised in this section.

To understand the QoL and the importance of calculating utility values, a brief introduction to pharmacoeconomic studies and the importance of the QoL of breast cancer in those studies is outlined. Pharmacoeconomic studies are concerned with comparing two or more pharmaceutical products or services with respect to their costs and consequences (Tonin et al., 2021a). Several different approaches can be taken when conducting this type of study, which include cost-benefit, cost-effectiveness, and cost-utility analysis, all of which measure the cost in monetary units. These approaches differ in how they evaluate outcomes. In cost-benefit analysis, outcomes are quantified in monetary units, while natural units such as lives saved or disease prevented are measured in cost-effectiveness analysis, and Quality Adjusted Life Years (QALYs) are measured in cost-utility analysis. In pharmacoeconomic oncology studies, cost-utility analysis is preferred over cost-benefit analysis and cost-effectiveness analysis because it combines both the quantity (duration of survival) and QoL of patients, which are essential dimensions of the health benefits of different treatments (Tonin et al., 2021).

To calculate QALYs, the outcome of interest in cost-utility analysis, years of life lived are multiplied by a measure of Health-Related QoL (HRQoL). HRQoL is defined as "the impact of a

disease and its treatment on a person's perception of his or her ability to lead a full and productive life" (Ward, 1999). It is measured by assigning a health state utility value on a 0-1 scale, where one represents full health, and zero represents death (Moini et al., 2020). Breast cancer can negatively affect HRQoL due to the disease process itself or its treatment, as patients undergo several rounds of treatments with side effects (Heidary et al., 2023).

The main approaches to measure HRQoL are utility/preference-based measures, psychometric-based measures, and, less commonly, the Patient Generated Index (Whitehead & Ali, 2010). In utility/ preference-based measures, the participants are provided with descriptions of different health states and asked to express their preferences using various tools, time trade-off, standard gamble (SG), or visual analogue scale (VAS) approaches (Martin et al., 2000). In time trade-off, respondents will choose between living in the assessed health state for a given period and living in perfect health for a shorter period. In VAS, the respondent will be presented with a scale from 0 to 100, where 0 represents immediate death, and 100 represents perfect health. SG assesses the amount of risk the respondent is willing to accept in order to live in the best health state for a given period of time. These methods were considered too complex, difficult to comprehend, and time-consuming to use in the current study (Whitehead & Ali, 2010). Its difficulty lies in both the cognitive load it places on participants and the time-consuming nature of the procedure, making it less suitable to be used.

In contrast, Patient Generated Index is a personalised measure used to estimate the impact of a disease state on QoL. It allows respondents to identify and weight the areas of life that are important to them and affect their lives. The Patient Generated Index gives values that are not subject to a ceiling effect and allows respondents to self-report and prioritise the most important areas for their QoL. If used in cancer patients, Patient Generated Index is considered a cancer-specific quality-of-life measure (Aburub et al., 2016). In addition to the benefits of the Patient Generated Index, some drawbacks include it being time-consuming and lacking structure for free answer forms. However, due to their added benefits, it is possible to use them in addition to other HRQoL tools as complementary rather than as a replacement (Tang et al., 2014). Studies have showed that Patient Generated Index provides information not captured by other methods, which is suitable for within-person and within-condition comparisons (Mayo et al., 2017).

In psychometric-based measures, unobservable QoL domains like psychological functioning and emotions are measured by a group of questions. These measures are multidimensional and composed of physical functioning, psychological well-being, social and role functioning, and health perceptions. They are available in generic and disease-specific measures (Lam, 2010).

Generic instruments measure general health, such as the 5-dimensional EuroQol (EQ- 5D) and the 36-item Short Form Survey (SF-36). They can be used in different disease states and provide a single value that can be used in calculating QALYs. Disease-specific measures, such as the European Organisation for Research and Treatment of Cancer QoL Questionnaire Core 30 (EORTC QLQ- C30) or the Functional Assessment of Cancer Therapy- Breast (FACT-B), also exist (Patrick & Deyo, 1989). These are designed to collect patient's perceptions about specific domains of health that are affected by a particular disease and produce several numerical values for different domains (Lin et al., 2013).

Generic tools are more comprehensive but don't provide information on symptoms specific to the condition being studied, and this impacts their ability to detect differences between individuals. Disease-specific instruments focus on particular health problems and are considered more sensitive to clinically important differences (Longworth & Rowen, 2011). Therefore, disease-specific tools are preferred over generic ones; however, they provide multiple values corresponding to different dimensions of the patient's QoL and not a single value that can be used to compare various treatment options and calculate QALYs. The solution to this problem is mapping the values of disease-specific measures onto generic preference-based instruments using the regression technique (Longworth & Rowen, 2013).

Mapping or crosswalk is the development and application of models and algorithms used to predict health-related utility values based on data obtained from other health outcome measures. It involves three stages. First, an estimation dataset that contains both the source and the preference-based measures is obtained. Second, these data are mapped onto either index score or dimension responses using regression methods. Third, the utility scores for the targeted measure are estimated by applying the regression results (Longworth & Rowen, 2011).

In KSA, according to Althemery et al., the use of EQ-5D in clinical studies is limited. In a systematic review conducted between 2015 and 2020, only 13 articles were identified, and none used EQ-5D in cancer (Althemery, 2021). Most studies used EORTC-QLQ C30 or SF-36 to evaluate Saudi cancer patients' QoL. This means that specific measures have been more commonly used than generic ones. However, the responses from specific measures cannot be used in health economic studies unless they are transferred to generic preference-based measures to allow the calculation of utility values and QALYs.

Al-Jazairi et al. considered "*the lack of quality data for outcome measurement in the Saudi population, and the inapplicability of the available pharmacoeconomic evidence due to the differences in healthcare provisions*" as a challenge for the Saudi Arabian adaptation of the pharmacoeconomic concept (Al-Jazairi et al., 2011). According to the recommendations, Al Ageel et al. state that extrapolating international pharmacoeconomic results to the Saudi context is unacceptable, and decision-makers need to assess whether those results apply to the Saudi setting (AL Aqeel & Al-Sultan, 2012).

Lack of utility values is a barrier to conducting health economic research; mapping from disease-specific measures to generic instruments is the only solution when utility data are unavailable through direct methods. HRQoL is essential for physicians and policymakers and identifying factors that affect HRQoL is crucial to assisting in BC females' patient-care decisions (Longworth & Rowen, 2013). Before this study, no studies had been performed to estimate the health utility values in breast cancer Saudi females. Only one KSA study was identified that measured the health utility in cancer patients using the Time Trade-Off method. The results from this study could not be generalised to Saudi women with BC or used here in this study because most of the participants were male (75%), none of the cancer cases were breast cancer, and all participants were in the late stages of cancer (Iskedjian et al., 2020). Furthermore, no study has compared HRQoL among breast cancer females in different age groups or different treatment modalities.

The validity and reliability of the EORTC QLQ tools in Arabic speakers have been tested previously and it has been found that the Arabic versions of EORTC QLQ-C30 and BR23 are valid and reliable (Awad et al., 2008). Another study conducted in Bahrain found that both

tools are reliable and valid but with some modifications (Jassim & Alansari, 2020). The reliability was tested by measuring the internal consistency using Cronbach's alpha, where a value above 0.70 indicates acceptable reliability. The validity was tested by using known-group comparisons, where the questionnaire accuracy was tested to reflect differences in groups of patients who are expected to differ in their quality of life.

Few studies in KSA assessed the QoL of Saudi female breast cancer patients (Nageeti et al., 2019; Ahmed et al., 2018); further studies in this area are recommended.

2.4.1 Impact of BC on QoL

Studies on the QoL of BC in Saudi females are relatively limited; the earliest study in 2016 showed poor overall QoL 31.2, as measured by the validated measure tool, EORTC QLQ-C30, where the QoL is scored from 0 to 100, and the lower score reflects worse QoL (Almutairi et al., 2016). However, this low global health score was reported to increase to 72 in the latest studies (Abu-Helalah et al., 2022). This improvement in the QoL scores could be attributed to improved access to healthcare or advancement in treatment.

In 2019, two studies showed that global health was moderate, with scores of 64 (Nageeti et al., 2019) and 67.5 (Imran et al., 2019), but they showed variation in the scores of other domains; one study found that social functioning scored the lower value, while the other showed that physical functioning scored the lower score.

In a recent study conducted in 2022, the scores were higher, with an overall global health of 72.7; the worst score was for the physical domain, and the highest was for social functioning (Abu-Helalah et al., 2022). This study recruited participants from three regions along KSA with a sample size of 246 BC females, which is a strength over all other studies that recruited patients from one area only or a single centre. Those findings were contradicted by the results of one of the latest studies, which found that women with BC demonstrated poor HRQoL with a general health score of 55.41, and the lower values reported were for the role (48.6) and physical (50.1) functioning. Still, those results could be because they used a different tool, the SF-36 (Al-Karni et al., 2024).

The poor QoL reported in one study (Almutairi et al., 2016) was associated with worse symptoms, with insomnia, dyspnea and appetite loss scoring the highest. On the QLQ-C30 symptom scale, the two studies conducted in 2019 showed similar results; the worst symptoms in both were fatigue, pain and insomnia (Nageeti et al., 2019; Imran et al., 2019). At the same time, appetite loss and constipation were also reported to be high (Imran et al., 2019). In another study (Abu-Helalah et al., 2022), the worst scores were for fatigue and pain.

On the breast module, the QLQ-BR23, the worst scores on the functional scale varied between the studies. Two studies reported sexual functioning as the worst symptom (Abu-Helalah et al., 2022; Nageeti et al., 2019), while other studies reported future perspective (Almutairi et al., 2016) and body image (Imran et al., 2019) as the worst symptoms. On the symptom scales, the most distressing symptom was hair loss (Imran et al., 2019; Nageeti et al., 2019; Abu-Helalah et al., 2022). Worldwide, a systematic review reported that body image was the worst symptom (Javan Biparva et al., 2022). The overall QoL scores in KSA were similar to the global results, ranging between 64.2% and 67.5%.

2.4.2 Factors influencing QoL

Demographic factors (age, marital status, education level):

Regarding factors that affect BC QoL, better QoL in the Saudi female population was associated with younger age, higher education level, unmarried status, employed status, physical activity, and longer disease duration (Al-Karni et al., 2024).

Most studies reported a better QoL for younger ages (Abu-Helalah et al., 2022; Al-Karni et al., 2024; Imran et al., 2019). Specifically, older ages had poor physical functioning (Alzahrani et al., 2019) and worse emotional function scores (Nageeti et al., 2019). It was also reported that age at diagnosis is a significant predictor of a patient's future perspective (Almutairi et al., 2016).

A meta-analysis study affirmed a significant relationship between age and the QoL. However, in contrast to the results found in the Saudi literature, studies confirm that any increase in age will lead to improvement in the QoL, such as the systematic review and meta-analysis on BC women worldwide (Javan Biparva et al., 2022) and another study conducted in

the UK on a total of 4451 BC patients (Hopwood et al., 2007). These results also aligned with a study conducted in 2022, which aimed to describe the relationship between QoL in women diagnosed with BC and their age (Alvarez-Pardo et al., 2022). It was found that older age is associated with better social and sexual functioning, and older people were less concerned about their future compared to younger ages.

Regarding quality of life by marital status, the association between marital status and the QoL varies according to different studies. Married women reported low QoL scores (Abu-Helalah et al., 2022), while other studies found that single and married women had higher social well-being scores than widowed and divorced women (Alzahrani et al., 2019). Another study reported marital status as a significant predictor of financial difficulty scores (Almutairi et al., 2016).

Disease-related factors (stage, treatment type):

Stage of BC at diagnosis has been reported to be a significant predictor of QoL. Advanced stages were associated with lower global QoL scores and functional scores. Staging was also substantial in the scales of body image, breast symptoms, arm symptoms, and being upset by hair loss.(Almutairi et al., 2016). In contrast, another study found that staging was not a significant predictor (Imran et al., 2019). One study conducted in the Asia-Pacific region found that staging did not significantly affect general QoL (Youlden et al., 2014).

Patients who underwent any of the BC cancer treatment modalities, including surgery, chemotherapy, radiation and hormonal, reported fatigue and poor sleep quality (Alsharif et al., 2022). Radiotherapy was associated with poor sleep quality, which was related significantly to depression, anxiety, stress, and hot flashes (Elamin et al., 2024).

Patients who underwent radiation and immune therapy had higher scores for the spiritual well-being subscale, indicating better spiritual well-being (Alzahrani et al., 2019). While endocrine therapy was not associated with any effect on the QoL (Hopwood et al., 2007). About 87% of patients who underwent mastectomy reported being satisfied after surgery, but a different tool was used, as the authors developed the tool used to measure their satisfaction (Barkar et al., 2023).

Patients using chemotherapy in a study conducted in Jeddah, KSA reported experiencing nausea (78.6%) and vomiting (35.7%) and reported moderate to extreme impact on their QoL, with 70.4% with nausea and 62.9% with vomiting (Ilyas et al., 2020). A study conducted on BC and colon cancer patients to measure the QoL after receiving the first cycle of chemotherapy showed that patients reported better overall global health status before taking their first cycle compared to after, and they experienced worse symptoms after taking the first cycle of chemotherapy (Zamel et al., 2021).

Global studies showed that patients who received chemotherapy had lower global health scores, which could be because of the therapy's side effects that negatively affect the QoL, but higher scores were reported in functional scales than those who received other treatment modalities (Youlden et al., 2014). Another study reported a negatively significant impact of chemotherapy on multiple domains, including the global health scores (Battisti et al., 2021). BC patients diagnosed with lymphedema showed low scores on QLQ-C30, which means that comorbidities negatively affect the QoL (Tamam et al., 2021).

Employment status

Regarding employment status, there were significant associations between employment and physical and emotional functioning (Almutairi et al., 2016); employed had higher psychological well-being scores than women who were not (Alzahrani et al., 2019). These results are consistent with those from other worldwide studies: Females with secure jobs had better scores in overall QoL (Youlden et al., 2014).

In conclusion, the QoL of BC reported in the literature varies between the studies but has tended to increase in recent years (Tamam et al., 2021; Fetaini et al., 2020; Nageeti et al., 2019; Ahmed et al., 2018a). This variation could be linked to the small sample size used in most studies and to using data or recruiting participants from one region or a single centre, considering the population variation in different areas of KSA, which may not reflect the whole population and could affect the results. Despite the growing burden of BC in KSA, there is a lack of country-specific health utility values to assess the QoL and cost-effectiveness studies, which highlight the need for research to provide health utility values for BC in KSA to inform health decision making.

2.5 Conclusion

This literature review has demonstrated the need for further work to explore the epidemiology of breast cancer in women living in KSA and of survival in this population. It also revealed a lack of existing literature to inform health economic evaluations of competing treatments for BC in this setting. Few studies have reported consistent results concerning the incidence or survival of BC in Saudi females. This could be due to the limited number of patients in most studies and regional differences when comparing results of studies conducted in different regions, which show different incidence rates according to the recent cancer registry report. In addition, some studies were limited to specific types of BC tumours, which cannot be generalised; other studies were limited to particular patient characteristics, for example, patients who had undergone surgery, have taken chemotherapy or have different characteristics. These findings and limitations necessitate conducting a new study which covers all the regions of KSA, including all female BC cases in KSA and includes data on treatment strategies to gain more insight into the epidemiological pattern of BC in Saudi females, which will affect clinical practice and guide in treatment selection.

The same applies to quality-of-life studies. Few studies in Saudi literature cover this area. Studies on predictors of QoL of BC in Saudi females are scarce, and even the results of those studies are conflicted, which necessitates further studies that evaluate the QoL in Saudi females and investigate the predictors that significantly affect the domains of QoL.

Chapter 3 Data Sources and Collection

This chapter gives an overview of the primary data sources used in the study and how the data were obtained. To achieve the aims and objectives of this study, two different kinds of data were collected: (i) retrospectively collected data necessary for the epidemiological analysis of BC incidence and survival, and (ii) data pertaining to health-related quality of life, which were collected through the administration of questionnaires. In the following sections, the data sources used are described.

3.1 Data Sources

Data were obtained from three different sources:

- The Saudi Health Council: Saudi Cancer registry, data collected from 1994 to 2017.
- King Faisal Specialist Hospital & Research Centre (KFSH&RC):
 - The hospital's cancer and tumour registries contained data from 2008 to 2017.
 - The oncology clinics: survey was collected from January 2023 to September 2023.
- The Saudi General Authority for Statistics provided data on the total female Saudi population from 1999 to 2000 and from 2004 to 2017, which includes the total population in Saudi Arabia classified by region, age, nationality, and sex. The data for the years 2001 to 2003 were unavailable.

Ethical approval for this study was obtained from both Newcastle University in October 2019 and updated in June 2022 (Ref: 16453/2018) and KFSH&RC in February 2021 (RAC # 2201268). The ethical approval was updated in June 2022 after including the health-related quality of life study (Ref: 23508/2022).

3.1.1 Saudi Cancer Registry (SCR)

The Saudi Cancer Registry is a population-based registry, and the first national registry established in Saudi Arabia. It was founded in 1992 by a resolution of the Minister of Health to determine the population-based incidence of cancer in Saudi Arabia. Initially, its administrative office was located at KFSH&RC in Riyadh. However, in 2014, it was transferred under the authority of the Saudi Health Council, specifically under the Department of National

Registries within the National Centre for Health Information. It is funded by the Ministry of Finance of Saudi Arabia (Saudi Health Council, 2024).

The initial cancer cases were recorded in the registry in January 1994. The registry is responsible for recording cancer data from all hospitals in the Kingdom of Saudi Arabia (KSA) based on clinical and/or histopathological diagnosis through five regional offices. The primary site and morphology of malignancies are coded according to the International Classification of Diseases for Oncology 3rd Edition (ICD-O-3), published by the World Health Organization (WHO) in 2000 (Constance et al., 2000).

Registrars actively collect cases from a total of 295 hospitals and histopathology laboratories. Additionally, the SCR directly receives notifications from hospital-based registries since cancer has been officially designated a mandatory notifiable disease by royal decree.

The main office in Riyadh supervises the regional offices to ensure the accuracy and quality of data collected from each region. This includes site verification, morphology, staging information, case linkage, and data consolidation.

The SCR aims to define cancer incidence, prevalence, and trends in Saudi Arabia. This initiative supports clinical and epidemiological research and promotes the evaluation process of relevant national programmes and activities. Moreover, it aims to enhance service planning and provision by providing valuable insights and information.

3.1.2 King Faisal Specialist Hospital and Research Centre (KFSH&RC) in Riyadh: Cancer registry and oncology clinics

KFSH&RC is a tertiary referral hospital where patients from all Saudi regions are referred for cancer treatment. This hospital is known for its notable oncology service, making it the leading cancer control centre in both the country and the Gulf region. KFSH&RC holds a pioneering position in the Middle East, particularly in the fields of kidney and bone marrow transplantation, oncology, orthopaedics and cardiovascular surgery. Moreover, it has the largest cancer facility in the Gulf region, providing high-quality surgery, chemotherapy, radiation, and palliative care. In terms of cancer treatment, it provides treatment to approximately 30% of the country's overall cancers and 70% of paediatric cancers.

The cancer registry at KFSH&RC maintains a comprehensive database of all patients referred to the hospital since 1975. The registry is primarily staffed with tumour registrars who assist in managing the database in the aspects of case ascertainment, abstracting, follow-up, and statistical analyses. The basic source document is the patient's medical record, from which relevant information is extracted for use in the Registry. Oncology clinics at KFSH&RC run on four consecutive days each week, from Monday to Thursday; those clinics receive approximately 300 patients weekly.

3.1.3 The Saudi General Authority for Statistics

Data for the Saudi population were needed to calculate the crude and age-standardised BC incidence rates in this study. Upon request from the Saudi General Authority for statistics, data on the total female Saudi population from 1999 to 2000 and from 2004 to 2017 were provided. This includes the total population in Saudi Arabia classified by region, age, nationality, and sex. Despite the enquiries for data from 1994 to 2017, data from 1994 to 1998 and from 2001 to 2003 were unavailable in their records.

To estimate the total female population for these years, the population size from two points during the period with known populations was used, and it was assumed that the increase in population size was constant between the two points. The average annual growth rate between 2004-2010 and 2011-2017 was calculated and found to be 1.98% and 1.93%, respectively, which shows a 0.05% difference in the growth rate between the two periods. This means that using the population size from two points during this period to estimate the total female population is justified (Rowntree, 1962).

Steps to estimate the total female population for the years from 1994 to 1998 and from 2001 to 2003:

- 1- Two years with known population sizes, 2000 and 2004, were chosen because these four-year intervals fall between the two unknown periods.
- 2- The average annual growth rate is calculated by dividing the difference in the total female population for these two years by the time interval of four $(8,198,409 - 7,788,754)/4 = 102,414$.

3- The average annual growth rate, along with the population for the known years, were used to estimate the total population for the unknown years.

- For years before 2000:

female population in 2000 - (average annual growth rate* time interval)

- For years after 2000:

female population in 2000 + (average annual growth rate* time interval)

The female population in each age group in the years from 1999 to 2003 needed to be estimated by following the steps below:

First, the age distribution was calculated and compared for the years 2004, 2010, 2011 and 2017, the years with known age group population (Table 3.1). The results showed that the percent of the distribution of different age groups is nearly the same for all other years; the Chi-square test showed $P= 0.9$; this makes it possible to use the common age distribution to estimate the population in different age groups for years before 2004 (Rowntree, 1962).

Age group	2004	2010	2011	2017
0-9	1,726,726 (21.06%)	1,943,254 (21.11%)	1,963,853 (21.10%)	2,110,181 (21.05%)
10-19	1,486,432 (18.13%)	1,670,516 (18.14%)	1,688,615 (18.14%)	1,816,961 (18.13%)
20-29	1,573,906 (19.20%)	1,771,088 (19.23%)	1,789,894 (19.23%)	1,923,475 (19.19%)
30-39	1,326,366 (16.18%)	1,485,253 (16.13%)	1,502,248 (16.14%)	1,622,277 (16.19%)
40-49	941,609 (11.49%)	1,057,215 (11.48%)	1,068,838 (11.48%)	1,151,198 (11.49%)
50-59	596,443 (7.28%)	669,527 (7.27%)	676,910 (7.27%)	729,216 (7.28%)
60-69	320,244 (3.91%)	358,083 (3.89%)	362,269 (3.89%)	391,787 (3.91%)
70-79	151,844 (1.85%)	168,637 (1.831%)	170,802 (1.84%)	185,972 (1.86%)
80+	74,839 (0.91%)	83,125 (0.90%)	84,191 (0.90%)	91,644 (0.91%)
Total	8,198,409 (100%)	9,206,698 (100%)	9,307,620 (100%)	10,022,711 (100%)

Table 3.1. Population number and percentage by age group for 2004, 2010, 2011, and 2017.

The estimated population for age groups for years before 2004 are illustrated in Table 3.2 below.

Age group	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003
0-9	1,456,614	1,478,223	1,499,833	1,521,442	1,543,051	1,564,660	1,643,427	1,665,036	1,686,645	1,708,255
10-19	1,251,584	1,270,151	1,288,719	1,307,286	1,325,854	1,344,422	1,412,101	1,430,669	1,449,236	1,467,804
20-29	1,325,450	1,345,113	1,364,777	1,384,440	1,404,104	1,423,767	1,495,440	1,515,104	1,534,768	1,554,431
30-39	1,115,587	1,132,137	1,148,687	1,165,237	1,181,787	1,198,337	1,258,662	1,275,212	1,291,762	1,308,312
40-49	792,508	804,266	816,023	827,780	839,537	851,294	894,149	905,906	917,663	929,420
50-59	501,876	509,322	516,767	524,213	531,658	539,104	566,242	573,688	581,133	588,579
60-69	268,542	272,526	276,509	280,493	284,477	288,461	320,983	306,966	310,950	314,934
70-79	127,022	128,907	130,791	132,676	134,560	136,444	143,313	145,197	147,082	148,966
80+	62,131	63,052	63,974	64,896	65,817	66,739	70,099	71,021	71,942	72,864

Table 3.2. Population in each age group from the year 1994 to 2004

3.2 Inclusion Criteria

The purpose of the epidemiological study conducted as part of this PhD was to determine the incidence pattern of BC subtypes in Saudi women and the survival of BC by age, stage at diagnosis, tumour grade, and region in KSA; therefore, cases were selected for inclusion in the analysis if they met the following inclusion criteria:

Patients with the following criteria were included in the retrospective epidemiological study:

- Female Saudi nationality: The Saudi population consists of more than 30% expatriates. To study the epidemiology of BC in the Saudi population, non-Saudi nationals living in KSA were excluded due to the different ethnic groups and specific patient characteristics that could affect the study results.
- Diagnosed between 1994 and 2017: The study time frame was set between 1994 and 2017; the aim was to collect comprehensive data from the first year the Saudi cancer registry started to record cases till the latest annual report published by the SCR when data were collected, which was for the year 2017.

Patients with the following criteria were included in the health-related quality of life questionnaires:

- Saudi female BC patients from all age groups and different disease stages who had been treated at KFSH&RC for at least six months with different treatment modalities and were able to provide informed consent and fill out the questionnaire.
- Participants were excluded from the study if they were terminally ill or in severe pain, patients with psychiatric or mental disease or refused to participate.

3.3 Data collection

Data from the SCR and hospital registries were received in Excel and then transferred to Stata software for analysis.

3.3.1 Saudi Cancer Registry Data

Data on 39,281 patients diagnosed with BC between 1987 and 2017 were obtained from the SCR after submitting a request and completing their standard form asking for data for BC patients until 2017 on the following variables: age, gender, nationality, diagnosis date, stage at diagnosis, grade, last contact date, vital status at last contact, laterality, cause of death using the following link <https://datarequest.nhic.gov.sa/Request/Create>.

This study is specific to BC in females; therefore, 253 cases of men were excluded, leaving 39,027 cases. After examining the final data, the date of diagnosis for included cases ranged from 1987 to 2017, as shown in Figure 3.1. However, no cases were recorded in the years before 1994, except for one case recorded in each of the following years: 1987, 1988, 1991, and 1993. This means data for these years is incomplete, so they have been excluded; non-Saudi nationals living in KSA were also excluded following the inclusion criteria for this study.

After excluding cases that did not meet the inclusion criteria for this study within Stata, the remaining cases were inspected by ID number to check for record duplication. This reduced the total number of cases to 27,664 remaining. Then, the time from the date of diagnosis to the last contact was calculated. If this resulted in a negative number, it would mean the date of last contact was recorded as preceding the date of diagnosis, and 100 negative values were found. This indicates an error with the date of last contact. These cases were excluded from the survival analysis but retained in the incidence calculations. After excluding these 100 cases, 27,546 were available for the survival analysis.

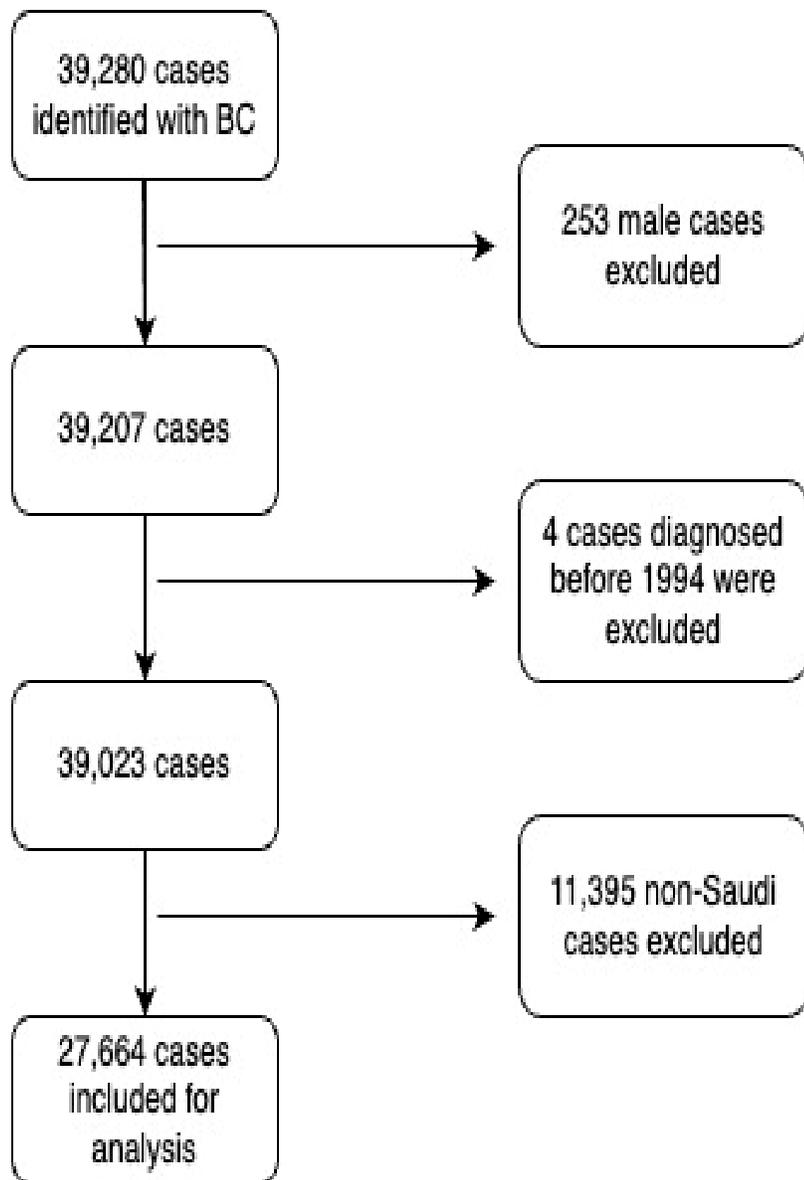


Figure 3.1. Flow chart of the cancer registry cases included in the study from 1994 to 2017.

Data for these cases were available on the variables listed in the table below.

Variables included in the dataset requested to SCR
Individual characteristics
Age at diagnosis
Region (Asir, Baha, Eastern, Hail, Jazan, Jouf, Madinah, Makkah, Najran, Northern, Qassim, Riyadh, Tabuk)
Marital status (divorced, married, single, widowed)
Tumour characteristics
Date of diagnosis
Morphology (Infiltrating duct carcinoma, NOS, Inflammatory carcinoma, Ductal Carcinoma in situ, Lobular carcinoma, NOS, Metaplastic carcinoma, NOS)
Grade (I, II, III, IV)
Laterality
Metastasis
Mortality
Date of last contact
Vital status
Cause of death (where appropriate)

Table 3.3. Variables included in the dataset provided by SCR from 1994 to 2017.

3.3.2 Breast cancer registry at KFSH&RC

A request was submitted to the hospital's breast cancer registry through the Biostatistics, Epidemiology Department. The data requested were for female BC patients during the period from 2008 to 2017. Data for a total of 3176 records of breast cancer cases for the period between 2008 and 2016 were obtained, with the variables listed in Table 3.4 below.

Variables included in the dataset requested to BC registry at KFSH&RC
Individual characteristics
Gender (male, female)
Date of birth
Nationality (Saudi, Non-Saudi)
Referral region (central, eastern, western, southern, northern)
Age at diagnosis/ menarche/ first pregnancy/ menopause
Menopausal status (pre-, peri-, post)
Pregnant at diagnosis
Family history of cancer (No family history of cancer, Immediate (mother, sister, daughter), Distant, Immediate & distant)
History of oral contraceptives/ hormonal therapy
Tumour characteristics
Date of diagnosis/ method of diagnosis
Signs & symptoms
Laterality
Clinical tumor stage
Histopathologic type / grade (Non- invasive, Invasive Ductal Carcinoma, Invasive Lobular Carcinoma, Carcinoma NOS)
Site of metastasis
Hormonal receptor status, Her2/ neu receptor status, Ki-67 labelling index

Treatment related variables
Type of management
Modalities of treatment (chemotherapy, biological, radiotherapy, surgery, hormonal)
Follow up
Date of clinical response
Date of follow up visit
Mode of follow up
Recurrence (site, date, treatment)
Progression
Date of progression
Site of progression
Method of diagnosis
Death
Status of last contact
Date of death
Cause of death

Table 3.4: Variables included in the dataset provided by the BC registry at KFSH&RC from 2008 to 2017.

From the 3176 cases obtained, Saudi female cases diagnosed between 2008 and 2017 were identified by excluding 26 male cases, 161 who were not a Saudi national, 35 cases diagnosed before 2008, and 3 after 2018. The remaining cases were inspected for duplication; 25 duplicate observations were detected and deleted, leaving 2926 cases for analysis.

3.3.3 Tumour Registry at KFSH&RC

As data on breast cancer patients for the year 2017 were not yet available in the breast cancer registry held at KFSH&RC, they offered to provide the data requested for this year from the KFSH&RC tumour registry in the hospital, meaning that variables availability was different than data obtained from the breast cancer registry and the information was not as extensive as the database. Information about the menopausal status, BC stage and grade, and treatment modalities were unavailable in the tumour registry.

Data for 538 breast cancer patients were obtained from the tumour registry on the variables listed in the following table:

Variables included in the dataset requested to tumour registry at KFSH&RC
Individual characteristics
Marital status
Family history of any cancer Histology/ behavior
Age at diagnosis
Tumour characteristics
Site (primary)
Laterality
Grade /differentiation
Summary stage
Death/ Recurrence
Date recurrence
Date last patient contact or death

Table 3.5. Variables included in the dataset provided by the tumour registry at KFSH&RC for 2017.

The KFSH&RC breast cancer registry and tumour registry data were cleaned by merging the two datasets into one file, excluding male cases and cases diagnosed before 2008 and after 2017, and inspecting the ID number for duplicates. The final number of cases was 2926 from the hospital BC registry and 482 from the hospital tumour registry, giving a total of 3408.

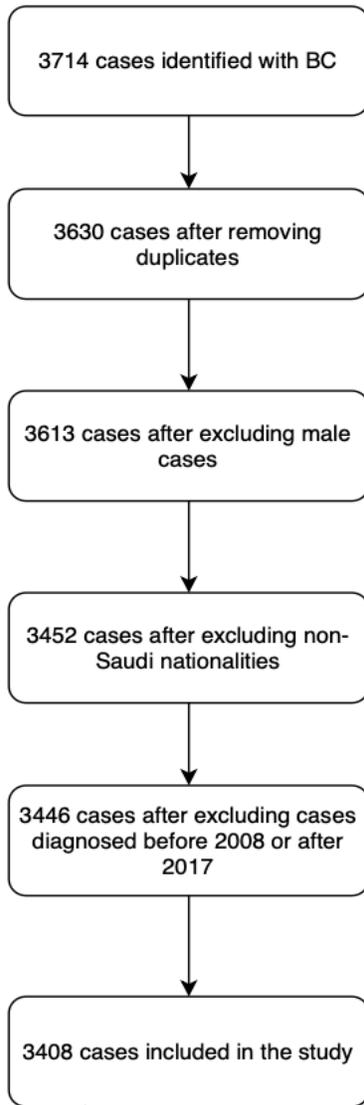


Figure 3.2. Flow chart of the hospital cases included in the study from 2006 to 2017.

Completeness of data:

For the Saudi cancer registry data, complete data were available for all variables except for the date of last contact, for which five cases had missing data. Stata software was used to check for the missing variables.

For hospital registry data, the variables collected were more extensive than those collected from the national registry, containing more details on the patient's demographics and tumour characteristics. However, the completeness of the data was low in some variables, as indicated in Table 3.6.

Variable	Completeness	Date
Individual characteristics		
Age at diagnosis	100%	2008- 2017
Marital status	99.4%	2008- 2017
Family history of cancer	86.3%	2008- 2017
Menopausal status	96.6%	2008- 2016
Region	99%	2008- 2017
Tumour characteristics		
Year of diagnosis	100 %	2008- 2017
Hormone receptor status	94.9 %	2008- 2016
Her2/neu receptor status	98.7 %	2008- 2016
Ki-67 proliferation	39.9 %	2008- 2016
Histological type	98.2 %	2008- 2016
histopathological grade	81.5 %	2008- 2016
Clinical tumour stage	96.6 %	2008- 2016

Table 3.6. The date of availability and percent of completeness of different variables in KFSH&RC.

The number of cases included from each data source after applying the inclusion criteria is presented in Table 3.7.

Data Source	Dates	Number
SCR	1994-2017	27,664
Hospital BCR	2008-2016	2892
Hospital Tumor registry	2017	538

Table 3.7. Number of BC cases in different data sources.

3.3.4 Oncology clinics

Data for the QoL survey were collected starting from January 2023 and up to four months or until we reached the target sample size (278 patients), whichever came first.

An electronic version of the questionnaire with a bar code and a printed hard copy were prepared and distributed to the nurses in the screening rooms; each patient who passed the screening was asked to fill out the forms using any method they preferred.

3.4 Conclusion

The data sources were identified to provide the best possible data to address the objectives of the current study. Using the national registry data allowed for calculating the incidence and generalising the results because it is population-based data, while using the hospital-based data allowed for more specific details within the Saudi population that are not available or routinely collected in the national registry, such as the treatment modalities, the family history, and oestrogen receptor status to be considered.

Selecting the same hospital to collect the data used in assessing health-related quality of life presented the advantage of ensuring data consistency. Furthermore, having access to the patient's medical records helped reduce data incompleteness, such as missing data on the date of diagnosis or type or stage of BC. However, obtaining data from one hospital, despite the fact that it is a referral hospital, will limit the generalisability of the study results, and the limitations were considered in the discussion.

Chapter 4 Incidence of BC in Saudi females (Population-based and Hospital-based study)

4.1 Introduction

Incidence is the measure of the probability of occurrence of new cases or events over a specified period for the population at risk for that event. The measure of incidence can be calculated for a whole population, such as the crude incidence rates that are general measures which provide an overall picture of disease occurrence in the population, or it can be calculated for a specific sub-group as age-specific incidence rate, which provides more detailed information on how disease incidence varies by different age groups within a population and take account of these differences. The age-standardised incidence rate is another measure used to control for age as a confounding variable (Isable, 1999), it is used to take account of different age structures in populations and to enable comparisons to be made between rates of disease between populations(Ahmad & Pinto, 2001).

In this study, data were obtained from the Saudi cancer registry and the KFSH&RC registry to calculate the incidence and trends in incidence by different factors (age at diagnosis, BC stage, type, and region). Throughout this thesis, these data will be referred to as SCR (Saudi cancer registry) data and hospital (KFSH&RC registry) data. Chapter 3 provided more details on the two sources.

4.2 Methodology

This is an observational retrospective study of Saudi females with BC. This section presents the methods used to analyse the data from both registries.

4.2.1 Descriptive statistics

Data were summarised using descriptive statistics (frequency, percentage, mean, median) to provide basic information about the dataset's variables. The available variables were classified into numerical (Quantitative) variables and categorical (Qualitative) variables.

The quantitative variable, age at diagnosis, is recorded in both registries as a continuous variable. It was tested for normality graphically by Q-Q plot and numerically by the Kolmogorov-Smirnov test and

found to be not normally distributed ($P = 0.0001$). Therefore, it was summarised using the median and interquartile range (IQR).

In contrast, categorical (Qualitative) variables: the date of diagnosis, marital status, family history, menopausal status, region, age group, and tumour characteristics (type, stage, hormone receptor status, Her2/neu receptor Status, Ki-index labelling), were described in terms of frequencies and percentages.

Details of variables available in both registries

Variables that are available in both registries are listed below:

- Year of diagnosis with BC:

SCR data cases were classified according to the year of diagnosis over 24 years, starting from 1994 to 2017.

On the other hand, the hospital registry data was classified into ten years, from 2008 to 2017; the selection of this specific time frame was based on the availability of hospital data, with the most recent data available in the hospital's registry when the request was made in 2021 were for the year 2017. A ten-year duration was chosen to capture a more comprehensive view of trends in BC incidence, and fluctuation in the annual rates could be explored; a shorter period could lead to misleading results.

- Age at diagnosis: the data on age are recorded as a continuous variable. In this study, the distribution of BC cases was analysed based on age at diagnosis; to facilitate the analysis, age in both registries was classified into eight groups. This includes a group for individuals below 20 years, followed by six ten-year interval groups (20-29, 30-39, 40-49, 50-59, 60-69, 70-79), and a final group for individuals above 80.

- Marital status: to investigate the impact of marital status on the stage of BC at diagnosis, marital status in both registries was grouped into four categories: Single, married, divorced, and widowed.

- Region: Saudi Arabia includes 13 administrative provinces (Asir, Baha, Eastern, Hail, Jazan, Jouf, Madinah, Makkah, Najran, Northern, Qassim, Riyadh, Tabuk) spread over five regions (central, eastern, western, northern, and southern) shown in the map below (Figure 4.1). The eastern region is the largest, with an area of 672,522 km², while Makkah has the greatest population of 8,557,766. Riyadh region's population is 8,216,284, and the eastern region's population is 4,900,325. The three areas account for 68% of the total population. The 13 administrative categorisations were used in the SCR data, which is more detailed than the five regions classification used in the hospital files.

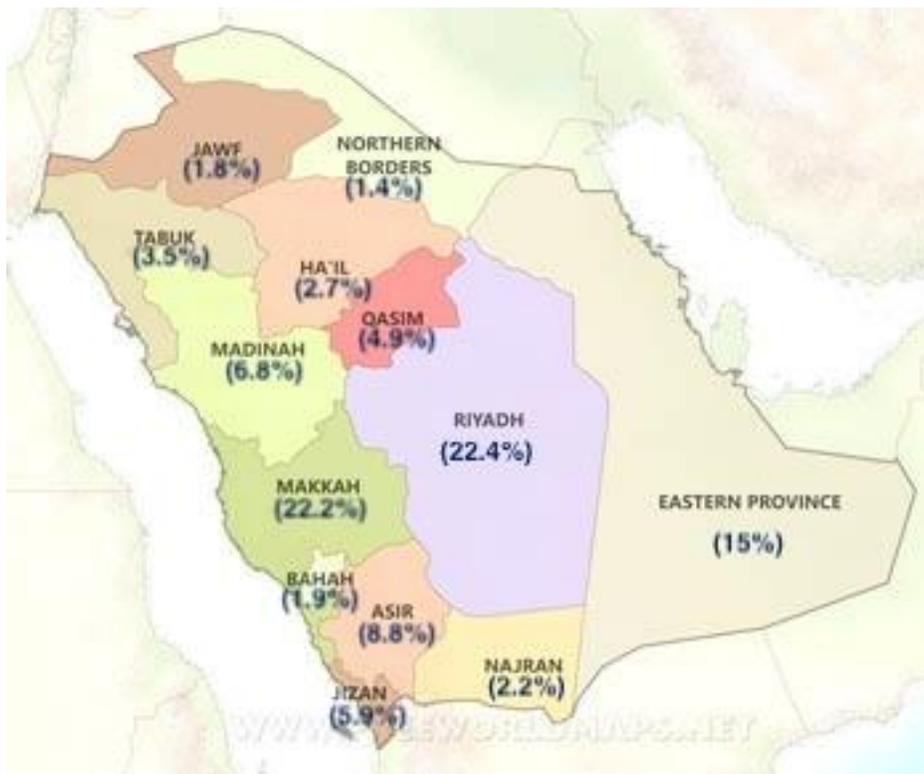


Figure 4.1. The distribution of Saudi females (%) in different regions of KSA.

- Tumour characteristics:

- Type: In the SCR, breast cancer was classified morphologically into six categories: infiltrating ductal carcinoma, inflammatory carcinoma, Ductal Carcinoma in situ, Lobular carcinoma not otherwise specified (NOS), Metaplastic carcinoma NOS, and other, encompassing any variant not previously mentioned.

BC classification was different in the hospital registry. It was classified into five categories: non-invasive, invasive ductal carcinoma (IDC), invasive ductal with ductal carcinoma in situ, infiltrating lobular carcinoma (ILC), and carcinoma NOS. Morphological type analysis did not include data from 2017 because they were unavailable in the hospital tumour registry (Nascimento & Otoni, 2020b).

- Stage: BC was classified in terms of stage in the SCR based on the extent of spread beyond the tumour site into in-situ, localised if there is no sign that cancer has spread outside of the breast, regional if cancer has spread to nearby structures, and distant if cancer has spread to distant parts of the body (Nci & Seer, 2018).

In the hospital data, BC was staged by the TNM system (Tumour, Node, Metastasis) according to AJCC (American Joint Committee on Cancer) TNM Staging (Amin, 2017). T describes the extent of the primary tumour, N describes whether the tumour has spread to the lymph nodes, and M describes whether the cancer has spread to other body parts. Six stages were identified: stage 0 (non-invasive, in-situ), in which the disease is present only in the ducts or lobules of breast tissue and does not spread to the surrounding tissues of the breast; stage I, stage II, stage III, stage IV, and unstageable (Table 4.1).

Combined TNM staging	T Category	N Category	M Category
Stage 0	Tiny clusters of cancer cells in a breast duct	None	None
Stage I	Tumour < 2 cm	N0	None
Stage IIA	Tumour < 2 cm Tumour >2 cm <5 cm	N1 N0	None
Stage IIB	Tumour >2 cm <5 cm Tumour >5 cm	N1 N0	None
Stage IIIA	Tumour > 5 cm Tumour >5 cm	N2 N1 or N2	None
Stage IIIB	Tumour spreads to the skin and/ or the chest wall	N0- N2	None
Stage IV	Any size	Any involvement	Detectable

Table 4.1. Combined TNM staging classification.

Note: N0= no spread to lymph nodes, N1= cancer spread to 1 to 3 axillary lymph nodes, N2= cancer spread to 4 to 9 axillary lymph nodes.

As noted in Chapter 3, the data collected by the SCR and hospital registries were inconsistent, meaning that specific data were available in one registry but absent in the other. The variables, according to their respective sources, are listed below.

a. Details on available variables for the SCR:

- In SCR, BC is also classified by grade into grade 1 (well-differentiated), grade 2 (moderately differentiated), grade 3 (poorly differentiated), and grade IV.

- Topography: topographic diagnosis determines the anatomical position of the tumour; the topography is classified according to quadrant position. The quadrant started from the nipple, the quadrant over the left and right (upper inner-outer), and the quadrant below the left and right (inferior inner-outer).

- Laterality: describes which side of a paired organ is the origin of the primary cancer. It is classified into Right, left, bilateral, not paired, paired site late, and not paired (unknown).

- Diagnostic procedure: Breast cancer diagnosis was confirmed either clinically, by cytology/haematological, by death certificate, histology, medical imaging, or other (surgery, autopsy, laboratory test).

b. Details on available variables for the hospital's registry:

- A family history of cancers was considered a risk factor for BC. To investigate the relationship between family history and BC subtypes, it was categorised into four groups: cases with no family history of cancers, immediate if the family history of cancers is among their first-degree relatives, distant if the affected relatives are beyond the first-degree, and both immediate and distant in cases who have a family history of cancers among both their immediate and distant family members.

- Menopausal status is an important risk factor for BC; it was categorisation into premenopausal, peri-menopausal, and postmenopausal.
- Receptor status provides essential information for treatment planning and prognosis of BC. It was categorisation into four categories:
 - Oestrogen receptor (ER) positive and progesterone receptor (PR) positive
 - ER positive and PR negative
 - ER negative and PR positive
 - ER negative and PR negative.

A patient's expression of these markers not only affects their prognosis but might also influence the choice of hormone therapy and chemotherapy.

- Her2/neu (human epidermal growth factor receptor 2) receptor status is essential in determining the treatment options for BC; it was described as negative, positive, or equivocal; cases with positive Her2/neu receptors are associated with poor prognosis.
- The Ki-67 proliferation index is an excellent marker for providing information about the proliferation of cancerous cells, particularly in the case of breast cancer. The proliferative activities determined by Ki-67 reflect the aggressiveness of cancer, the response to treatment, and the recurrence time (Inwald et al., 2013). It was categorised into <10%, 10-15%, and > 15%.

Data Completeness:

An essential element of data analysis is ensuring all the data are complete, as missing or incomplete data may lead to inaccurate results. Complete data denotes that all variables were available for all cases; completeness of data is discussed in Chapter 3 (section 3.4).

For the SCR registry, the data were available for all variables. The assessment of data completeness for the hospital's registry using Stata software revealed that the percentage of missing data was below 10% in all variables except for Ki-67 proliferation. Data were found to be missing completely at random (MCAR) when checked using Stata software. This meant that complete case analysis was the appropriate method to handle missing data, in which analysis is restricted to patients with complete data, and

patients with missing data are excluded from the analysis (Mack et al., 2018). The exception to this was Ki-67 proliferation, for which 60% of the data were missing; this variable was consequently excluded from the analysis.

4.2.2 Incidence Calculations

Saudi Cancer Registry data

Crude incidence rate:

To calculate the crude incidence rate of BC, the number of new BC cases in a defined population over a given period is divided by the total person-time at risk during that period. In this study, the BC crude incidence rate was calculated using the total number of BC Saudi females diagnosed from 1994 to 2017 obtained from the SCR as the numerator and data on the total female Saudi population provided by The Saudi General Authority for statistics as the denominator as noted previously in Chapter 3. The crude incidence rate was calculated by dividing the number of new breast cancer cases from 1994 to 2017 by the total number of the Saudi female population during the same period.

Incidence rates by year of diagnosis were also calculated by dividing the number of new BC cases each year by the total number of Saudi females in that year. The 95% confidence interval around the incidence rate using normal approximation to Poisson distribution was calculated by the following formula:

$$X_u = (1000/n) (x + 1.96) \quad X_l = (1000/n) (x - 1.96)$$

Where X= the number of cases, n= denominator of the rate (total number of Saudi female population), X_u =the upper bound of the confidence interval, X_l = the lower bound of the confidence interval.

Age-specific and age-standardised incidence rate (ASR):

Age is a significant determinant of breast cancer incidence. Age-specific and age-standardised incidence rates were calculated to eliminate the effect of different age distributions on the incidence rates and to enable comparison between the Saudi populations and other populations with different age structures.

Age-specific incidence rates are defined as the number of new breast cancer cases of a given age group presenting during a given year per 100,000 of the average female population of that age. Eight

age groups from age below 20, followed by ten-year intervals from 20-29 up to individuals aged 80 and above, were calculated for the purpose of this study. The average female population for different age groups for each year was obtained from the Saudi General Authority for statistics upon request.

Incidence rates were age-standardised using 10-year categories (0-9, 10-19 years, *etc.*), with the final category being ages 80+ years; the world standard population weight for the age group 80+ years was calculated by summing the weights for the age groups 80-84 and 85+. ASR for BC from 1994 to 2017 was calculated using the direct method, and the World Standard Population (Ahmad & Pinto, 2001) using Stata software. ASR was calculated by multiplying each age-specific rate by the age-specific weight and summing the products expressed per 100,000 population.

Temporal trends in BC incidence using Joinpoint regression analysis:

Breast cancer crude incidence rates by year of diagnosis and ASR by year of diagnosis were analysed using the Joinpoint Regression Programme (National Cancer Institute, 2020). Joinpoint regression was used to explore temporal trends and investigate trends in breast cancer incidence based on age group, tumour-specific factors, and geography. It was also used to determine if those changes are statistically significant and estimate the magnitude of any change.

In the Joinpoint regression programme, a segmented regression model fits a series of straight-line segments to the data; each segment represents a different trend. Then, the optimal number of Joinpoints that best fit the data is determined based on Bayesian Information Criterion (BIC). The number of join points was obtained using a permutation test via Monte Carlo resampling; the significance level was set at $P < 0.05$ (Kim et al., 2009).

KFSH&RC Registry Data

Proportional incidence (%) (crude relative frequency):

To calculate a disease incidence rate, it is necessary to have information on the population size from which cases arise. This information was unavailable because the actual population at risk for the hospital is unknown. In such situations, when an accurate denominator is unavailable, the proportional incidence measure can be calculated as an alternative to the incidence rate (Isabel, 1999). The proportional incidence is calculated by dividing the number of female BC cases in the hospital during a specified period by the number of all female cancer cases in the same hospital during the same time period.

Therefore, this study estimated the proportional incidence of breast cancer based on the number of female cases recorded in the hospital tumour registry from 2008 to 2017 (Isabel, 1999). The total number of female hospital cancer cases, including those of all age groups, was obtained from the tumour registry annual report of the oncology centre research unit at KFSH&RC from 2008 to 2017.

Proportional incidence ratio (PIR):

PIR is the ratio between the total observed number of BC cases and the number expected if the cases occurred according to a standard relative frequency.

The observed cases are the number of female BC cases diagnosed in the hospital; the expected cases are calculated by multiplying the number of female total cancer cases diagnosed in the hospital by the corresponding proportions in the standard proportions. The standard proportions are calculated by dividing the number of female BC cases by the number of all female cancers in the SCR (Jensen et al., 1991).

Age-standardised cancer ratio :

Age is a significant risk factor for breast cancer, and age standardisation is necessary when comparing different populations with different age structures or in analysing time trends in incidence. The age-standardised cancer ratio is a direct method of standardisation. It is the average of the age-specific relative frequencies weighted by a standard distribution of the age at which cancer occurs.

To calculate the age-standardised cancer ratio for each year, the age-specific rate is calculated by dividing the number of BC cases in each age group by the corresponding number of all female cancer cases diagnosed in the hospital for that age group. All age groups were included in the analysis, following the methodology outlined by the Agency for Research on Cancer (IRAC), as described in the WHO publication. Then, each age-specific rate is multiplied by the corresponding population proportion in the standard population and summed to get the age-standardised cancer ratio (Jensen et al., 1991).

In the absence of a standard population for any other relevant country, the standard proportion used was obtained by dividing the number of all female Saudi cancer cases diagnosed in Saudi Arabia in each age group by the total number of all cancers in all age groups in 2013, 2013 was chosen because it is the middle year in the data set.

4.2.3 BC Incidence trends for SCR data by different variables

4.2.3.1 BC distribution by age at diagnosis

Age is an important factor in the incidence of BC, so it is essential to examine the incidence trends of BC distribution by age at diagnosis and whether it is affected over time. Temporal trends in age-standardised incidence rate (ASR) per 100,000 for BC within the study period by different age groups, eight groups from age below 20, followed by ten-year intervals from 20-29 up to

individuals aged 80 and above, were analysed using Joinpoint analysis for trend examination and the annual percent changes were reported (APC). Using the age-specific incidence provides a clearer understanding of the trends of BC incidence rates by removing the confounding effect of age.

The APC represents the rate of change in ASR per year over a given time period. It detects the points in time when the trend direction changes significantly. The APC was estimated by fitting log scale linear trends for the ASR using the year of diagnosis as the independent variable. A two-sided t-test was used to test whether the APC was statistically different from zero ($P < 0.05$); a negative APC describes a decreasing trend, and a positive APC describes an increasing trend. 95% Confidence intervals for each APC were computed.

4.2.3.2 BC distribution by stage at diagnosis

For SCR data, stages were classified into in-situ, localised, regional, distant metastasis, and unknown stages. To calculate the incidence and trend by stage, In-situ (3 cases) and the cases with the unknown stage (2804 cases), which account for 10% of the cases, were excluded.

The trends of BC incidence by stage at diagnosis were analysed using Joinpoint regression analysis software, and the APC were examined for trend changes from 1994 to 2017.

4.2.3.3 BC distribution by tumour grade

For SCR data, a Joinpoint analysis for age-standardised incidence rate by tumour grade was conducted during the period from 1994 to 2017. Grades were classified into five categories: G I well differentiated, G II moderately differentiated, G III poorly differentiated, G IV undifferentiated, and unknown grade.

4.2.3.4 BC distribution by region

For SCR data, the age-adjusted incidence rate was calculated by dividing the number of female cases in each age group in a specific region by the total number of females in the corresponding age group in that region.

To determine the age-adjusted incidence rate by region from 1994 to 2017, the total number of females in each age group for each region must be known. However, data on the size of the female population by region in Saudi Arabia from 1994 to 2003 were unavailable. To address this, the approach utilised was to compute the percentage of the female distribution by age category in each region using the years with available data. Subsequently, this percentage was used to estimate the number of female populations in each age category in each region for the years with unavailable data (Table 4.3) (Rowntree, 1962).

First, the distribution of Saudi females in each region was estimated from the years with a known population in each region by dividing the number of female populations in each region by the total female population in Saudi Arabia and multiplying by 100.

Second, these percentages in Table 4.2 were used to estimate the number of females in each region in the years with an unknown female population from the total population. (e.g., Asir female population accounts for 8.83% of the total population: $(6,901,314 * 8.83) * 100 = 609,386$).

After calculating the age-adjusted incidence rate by region, trends were analysed using Joinpoint analysis software to examine the annual percentage change (APC) for the specified period (Table 4.3).

The estimation of female population distribution in each region is listed in the table below (Table 4.2):

Region	%
Asir	8.83%
Baha	1.98%,
Eastern	15%,
Hail	2.71%
Jazan	5.96%
Jouf	1.86%
Madinah	6.84%
Riyadh	22.4%
Tabuk	3.5%
Northern	1.44%
Qassim	4.97%
Makkah	22.23%
Najran	2.17%

Table 4.2. The estimated percentage of female population distribution in each region.

Year	Asir	Baha	Eastern	Hail	Jazan	Jouf	Madinah	Makkah	Najran	Northern	Qassim	Riyadh	Tabuk	Population
1994	609,386	136,646	1,035,197	187,025	411,318	128,364	472,049	1,534,162	187,206	99,379	342,995	1,545,894	241,546	6,901,314
1995	618,426	138,673	1,050,554	189,800	417,420	130,269	479,053	1,556,922	151,980	100,853	348,084	1,568,828	245,129	7,003,697
1996	627,467	140,700	1,065,912	192,575	423,522	132,173	486,056	1,579,682	154,202	102,328	353,172	1,591,762	248,713	7,106,080
1997	636,507	142,728	1,081,269	195,349	429,624	134,077	493,059	1,602,441	156,424	103,802	358,261	1,614,696	252,296	7,208,463
1998	645,548	144,755	1,096,627	198,124	435,726	135,981	500,062	1,625,201	158,645	105,276	363,349	1,637,629	255,880	7,310,845
1999	654,588	146,782	1,111,984	200,899	441,829	137,886	507,065	1,647,961	160,867	106,750	368,437	1,660,563	259,463	7,413,228
2000	689,130	154,527	1,170,662	211,500	465,143	145,162	533,822	1,734,922	169,356	112,383	387,880	1,748,189	273,155	7,804,416
2001	696,581	156,198	1,183,320	213,786	470,172	146,731	539,594	1,753,680	171,187	113,599	392,073	1,767,091	276,108	7,888,799
2002	705,621	156,198	1,198,677	216,561	476,274	148,636	546,597	1,776,440	173,409	115,073	397,161	1,790,025	279,691	7,991,181
2003	714,662	160,253	1,214,035	219,336	482,376	150,540	553,600	1,799,200	175,630	116,547	402,250	1,812,959	283,274	8,093,565

Table 4.3. The female population estimation in each region from year 1994 to 2003.

4.2.4 The association of BC risk factors with tumour molecular subtype (hormone receptor status) and stage at diagnosis for hospital data only

The Breast cancer risk factors variables collected in this study include age at diagnosis, family history, age at menopause, age at menarche, age at first pregnancy, using oral contraceptive methods and postmenopausal hormone therapy. Using hormonal therapy or oral contraceptives, is known to be associated with an increased risk of developing BC. BC risk increased in older age at diagnosis, having a positive family history of cancer, early age at menarche (period starts before the age of 12), late age at menopause (after 55), late age at first pregnancy (Momenimovahed & Salehiniya, 2019).

Risk factors were described by frequency and percentage. Before statistical analysis, they were classified as follows: age at menarche (< 12 vs. \geq 12), OC/ hormonal therapy (no, yes), age at diagnosis (< 50 vs. \geq 50), family history of cancer (no, yes), age at first pregnancy (\leq 30, >30).

The association of BC risk factors with tumour molecular subtype (hormone receptor status) was assessed by estimating the risk ratio (RR) and the 95% confidence intervals (CIs) using multinomial logistic regression methods. A logistic regression model was constructed with the tumour molecular subtype as the dependent variable and each risk factor as an independent variable. A forward selection was employed to identify significant predictors in the model; risk factors were added to the model based on their statistical significance ($P < 0.05$). This approach was used because it included only significant variables making the resulting model easier to interpret. In the last model, tumour molecular subtype, age at menarche, age at first pregnancy, age at diagnosis, family history of cancer, and history of OC/ hormonal therapy were all included in the model.

The stage at diagnosis was categorised into early stage, which includes stages I and II, and late stage, which includes stages III and IV. The association between the stage at diagnosis and various risk factors was assessed using a chi-square test. The risk factors considered included

age at diagnosis, family history, age at menarche, age at first pregnancy, and the use of oral contraceptives or hormonal therapy. All the analyses were conducted using Stata software.

4.2.5 Clinical response (recurrence/ progression) for hospital data and the association of recurrence with BC risk factors

Recurrence is an important outcome of BC to consider; after treatment, some residual tumour cells are detected but remain dormant for years before they resume their growth, resulting in tumour recurrence after time, which usually occur within the first few years after treatment.

Recurrence could be either locoregional or distant metastasis. The risk of recurrence is associated with many factors, such as tumour characteristics, age at diagnosis, lifestyle factors, and reproductive factors. Negative oestrogen, progesterone receptors, and high grade are associated with a high risk of recurrence (Lafourcade et al., 2018).

This study reports recurrence frequency and percentage. Logistic regression was used to calculate the odds ratios as an estimate of the association between recurrence and age at diagnosis. Age was set as the independent variable, and patients were grouped into two categories: those younger than 50 years and those aged 50 years and older. Binary logistic regression was used to test the association between the risk factors (receptor status and tumour stage) and breast cancer recurrence while controlling for age at diagnosis as a confounding factor. Recurrence was set as a dependent factor, and the tumour stage classified as stages I, II, III and IV was set as an independent variable in one model, and the tumour characteristics were classified into four groups (ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-) and set as an independent variable in the second model.

4.3 Results

This section presents the epidemiological study's results, including both the SCR data and the KFSH&RC data.

4.3.1 Descriptive statistics

Saudi Cancer Registry Data

Over the period 1994 to 2017, the mean annual number of breast cancer cases diagnosed was 1,153 (27,664 cases/ 24 years), and the mean annual number of breast cancer deaths was 139 (3340 deaths/ 24 years) (Table 4.6).

Individual characteristics:

Age at diagnosis:

The majority of cases were diagnosed in women aged 40-49 years, and about 52% of the patients were under the age of 50 years at the time of diagnosis (Table 4.4).

Age Group	#	(%)
< 20	29	0.10
20-29	1,122	4.06
30-39	5,121	18.51
40-49	8,415	30.42
50-59	6,733	24.34
60-69	3,778	13.66
70-79	1,784	6.45
80-89	555	2.01
≥ 90	119	0.43
Unknown	8	0.03
Total	27,664	100.00

Table 4.4. Frequency and percent of BC cases by age groups.

Age at diagnosis was not normally distributed based on a Q-Q plot, which shows a deviation from the straight line. Numerically using the Kolmogorov-Smirnov test, $P = 0.0001$ indicates that the age at diagnosis departs from a normal distribution.

The median age at diagnosis was 49 years ($Q1 = 40$, $Q3 = 58$), and the IQR was 18, which means that the age values for the middle 50% of the dataset range from 40 to 57 years. A Kruskal-Wallis test was conducted to determine if the age at diagnosis differed across the years; it showed a statistically significant difference between 1994 and 2017 ($P = 0.0001$).

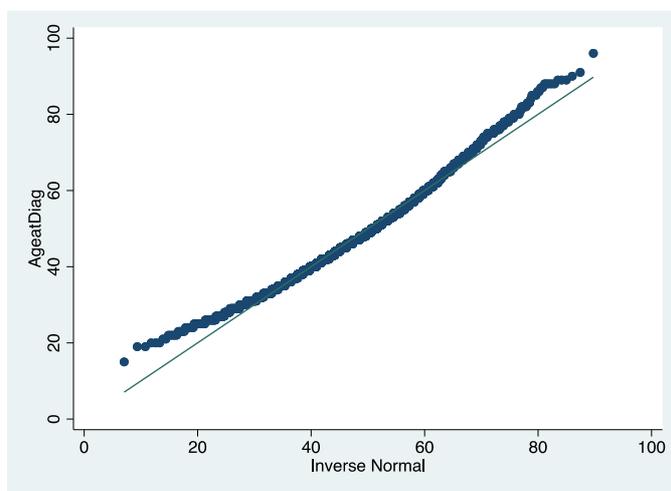


Figure 4.2. Q-Q plot for age at diagnosis with BC.

Marital status:

Married women accounted for 73% of female breast cancer patients (Table 4.5).

Marital status	n	(%)
Divorced	526	1.90
Married	20,363	73.61
Single	1,377	4.98
Unknown	3,728	13.48
Widowed	1,670	6.04
Total	27,664	100.00

Table 4.5. Marital status of BC cases: frequency and percentage.

Year of diagnosis	Cases n (%)	Median age at diagnosis	Breast Cancer Death (%)
1994	432 (1.56)	47.5	50 (1.49)
1995	436 (1.58)	46	51(1.52)
1996	466 (1.68)	46	77 (2.31)
1997	469 (1.70)	46	76 (2.27)
1998	519 (1.88)	45	128 (3.83)
1999	519 (1.88)	47	103 (3.08)
2000	605 (2.19)	47	139 (4.16)
2001	573 (2.07)	46	121 (3.62)
2002	676 (2.44)	46	171 (5.12)
2003	725 (2.62)	47	188 (5.62)
2004	824 (2.98)	47	191 (5.72)
2005	966 (3.49)	46	159 (4.76)
2006	1,003 (3.63)	47	139 (4.16)
2007	1,197 (4.33)	47	184 (5.51)
2008	1,235 (4.46)	47	182 (5.45)
2009	1,381 (4.99)	48	190 (5.68)
2010	1,638 (5.92)	49	171 (5.12)
2011	1,715 (6.20)	48	198 (5.92)
2012	1,630 (5.89)	49	144 (4.31)
2013	2,009 (7.26)	49	142 (4.25)
2014	1,919 (6.94)	50	151 (4.52)
2015	1,963 (7.10)	50	133 (3.98)
2016	2,300 (8.31)	50	119 (3.56)
2017	2,464 (8.91)	51	133 (3.98)
Total	27,664 (100)	-	3,340 (100)

Table 4.6. Female Saudi BC cases diagnosed and deaths between 1994 and 2017.

Note: % represents the percent of the total number of cases in a specific year.

Region:

Cases are registered in the Saudi cancer registry even if they travelled and got treatment outside KSA, they will be recorded in the region where they live in KSA. More than 70% of the cases were diagnosed in Makkah, Riyadh, and the Eastern region. (Table 4.7)

Region	n	(%)
Asir	1,208	4.37
Baha	301	1.09
Eastern	6,000	21.69
Hail	550	1.99
Jazan	632	2.28
Jouf	389	1.41
Madinah	1,460	5.28
Makkah	7,296	26.37
Najran	246	0.89
Northern	224	0.81
Qassim	1,340	4.84
Riyadh	7,254	26.22
Tabuk	599	2.17
Unknown	165	0.60
Total	27,664	100.00

Table 4.7. BC cases distribution by region: frequency and percent.

Tumour characteristics:

Distribution by stage, grade and morphology:

Histologically, infiltrating ductal carcinoma is the most common type of BC among Saudi females, accounting for 77.8% of cases (Table 4.8). Grades II and III account for most stages at diagnosis (38% and 32%, respectively), together accounting for more than 90% of all diagnoses in cases where Grade was recorded at diagnosis (Table 4.9).

Morphology	n	(%)
Infiltrating duct carcinoma, NOS	21,536	77.85
Inflammatory carcinoma	35	0.13
Ductal Carcinoma in situ	74	0.27
Lobular carcinoma, NOS	1,565	5.66
Metaplastic carcinoma, NOS	116	0.42
Other	4338	15.68
Total	27,664	100.00

Table 4.8. BC cases by tumour morphology: frequency and percentage. NOS: not otherwise specified.

Grade	n	(%)
Grade 1 (Well differentiated)	1,802	6.51
Grade 2 (Mod differentiated)	10,585	38.26
Grade 3 (Poor differentiated)	8,927	32.27
Grade 4 (Undifferentiated Anaplastic)	281	1.02
Unknown	6,068	21.93
Total	27,664	100.00

Table 4.9. BC cases by grade at diagnosis: frequency and percentage.

By laterality, the disease occurred with a similar frequency on the right and left side of the breast, with a small proportion of cases involving both breasts or having unknown laterality. (Table 4.10)

Laterality	n	(%)
Bilateral Involve	354	1.28
Left	13,324	48.16
Not paired (Unknown)	38	0.14
Paired site, late	1,288	4.66
Right	12,660	45.76
Total	27,664	100.00

Table 4.10 BC distribution by laterality: frequency and percentage.

By topography, Table 4.11 shows that most breast cancer cases (42%) were in the breast with no specific position, and 21% of the tumours were in the upper-outer quadrant of the breast.

Topography	n	(%)
C50.0 Nipple	378	1.37
C50.1 Central portion of the breast	1,039	3.76
C50.2 Upper-inner quadrant of the breast	1,629	5.89
C50.3 Lower-inner quadrant of the breast	913	3.30
C50.4 Upper-outer quadrant of the breast	5,889	21.29
C50.5 Lower-outer quadrant of the breast	1,193	4.31
C50.6 Axillary tail of breast	194	0.70
C50.8 Over lesion of breast	4,757	17.20
C50.9 Breast, NOS	11,668	42.18
C51.9 Vulva, NOS	1	0.00
C80.9 Unknown primary site	3	0.01
Total	27,664	100.00

Table 4.11 BC cases by topography: frequency and percentage.

By stage at diagnosis:

Regional and localised stages account for 42% and 31% of the cases, respectively.

Stage at diagnosis	n	(%)
In situ (stage I)	3	0.01
Localised (stage II)	8,696	31.43
Regional (stage III)	11,786	42.61
Distant Metastasis (stage IV)	4,375	15.81
Unknown	2,804	10.14
Total	27,664	100.00

Table 4.12. BC distribution by stage at diagnosis: frequency and percentage.

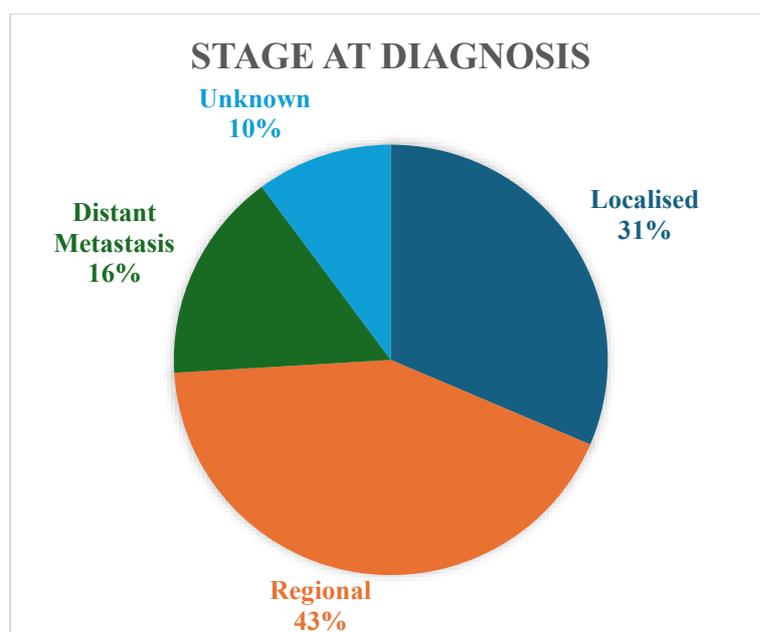


Figure 4.3 BC distribution by stage at diagnosis.

Diagnostic procedure:

Breast cancer was mainly diagnosed by histology of primary tumours in 90% of diagnosed cases.

Diagnostic procedure	n	(%)
Clinical	36	0.13
Cytology/Haematological	1,645	5.95
DCO (Death Certificate Only)	200	0.72
Histology	25,663	92.77
Medical Imaging (Xray, US)	35	0.13
Other (Surgery, autopsy, Laboratory test)	4	0.01
Unknown	81	0.29
Total	27,664	100.00

Table 4.13 BC diagnostic procedure: frequency and percentage.

The KFSH&RC data:

The mean number of patients diagnosed with BC annually over the ten-year period in KFSH&RC is 342, with a total of 3408 BC cases between 2008 and 2017 (Table 4.14). Patients diagnosed with BC mostly complained of lumps (48% of the cases), and about 42% complained of lumps with other symptoms like skin changes, pain, discharge, ulceration, nipple retraction, and axillary mass. The technique used for diagnosis was core biopsy in 62% of the cases.

Year of diagnosis	n	%
2008	281	8.25
2009	289	8.48
2010	333	9.77
2011	318	9.33
2012	333	9.77
2013	298	8.74
2014	365	10.71
2015	347	10.18
2016	362	10.62
2017	482	14.14
Total	3,408	100.00

Table 4.14: Distribution of BC female cases diagnosed from 2008 to 2017 at KFSH&RC.

Age at diagnosis was tested for normality and found to be not normally distributed ($P = 0.0001$); the median age at diagnosis was 47 years (Q1= 40, Q3= 56, IQR=16), of which most cases were diagnosed before age 50 (57%). By subdividing the patients according to the year of diagnosis subgroups, there was no significant difference in the age distribution at diagnosis across the years using the Kruskal-Wallis test ($P = 0.15$), and the median ranges between 46 and 49 from 2008 to 2017. (Table 4.15)

Year of diagnosis	Median age at diagnosis (IQR)
2008	46 (14)
2009	46 (15)
2010	47 (15)
2011	47.5 (15)
2012	47 (16)
2013	49 (17)
2014	47 (16)
2015	48 (16)
2016	48.5 (14)
2017	48.5 (17)

Table 4.15: Median age at diagnosis in years from 2008 to 2017 at KFSH&RC. IQR: Interquartile range.

After categorising the age at diagnosis into nine groups with 10-year intervals, it was found that three age groups, 30-59, account for about 79% of the cases diagnosed with BC. About 34% of cases were diagnosed in women aged 40-49, followed by 50-59, which accounts for 25% of the cases. The age group 30-39 accounts for about 20% of the cases diagnosed with BC during the study period.

Concerning marital status, results indicate that 77% of the cases were married. Furthermore, approximately 68% of the cases exhibited no familial history of cancer. With respect to the menopausal status, about 57% of diagnosed cases were in a premenopausal state. Additionally, more than half of the patients, specifically 59%, were referred from the central region where the hospital is located. The data about menopausal status were excluded for 2017 because they were unavailable as explained previously in Chapter 3. (Table 4.16)

Age at diagnosis	n	%
< 20	3	0.09
20-29	134	3.93
30-39	667	19.57
40-49	1150	33.74
50-59	866	25.41
60-69	403	11.83
70-79	146	4.28
> 80	39	1.15
Total	3,408	100.00
Marital Status	n	%
Single	199	5.85
Married	2,627	77.24
Divorced	175	5.15
Widowed	387	11.38
Unknown	20	0.59
Total	3,408	100.00
Family history	n	%
No family history of cancer	2330	68.36
Immediate (mother, sister, daughter)	362	10.62
Distant	195	5.72
Immediate & distant	55	1.47
NA	466	13.67
Total	3408	100
Menopausal status	n	%
Pre	1,606	54.88
Peri	92	3.14
Post	1,128	38.55
NA	100	3.42
Total	2,926	100.00

Region	n	%
Central	2,004	58.88
Eastern	254	7.45
Western	161	4.72
Southern	440	12.91
Northern	465	13.64
Outside KSA	17	0.50
NA	67	1.97
Total	3408	100

Table 4.16: Characteristics of BC cases at KFSH&RC. NA: not available

Hormone receptors subtypes and Her2/neu receptor Status:

Oestrogen and progesterone hormones were both positive in 55% of the cases. Specifically, oestrogen was identified as positive in 65% of the cases. Almost two-thirds of the cases (64%) were negative for Her2/neu receptor. (Table 4.17)

Hormone receptors subtypes	n	%
ER (+ve)/ PR (+ve)	1,621	55.40
ER (+ve) /PR (-ve)	280	9.57
ER (-ve)/PR (+ve)	19	0.65
ER (-ve)/PR (- ve)	858	29.32
Not known	148	5.06
Total	2,926	100.00
Her2/neu receptor Status	n	%
Negative	1,911	56.07
Positive	823	24.15
Equivocal	55	1.61
Not known	619	18.16
Total	3408	100.00

Table 4.17: BC cases by Hormone receptors subtypes & Her2/neu receptor Status at KFSH&RC.

Note: ER: oestrogen receptor, PR: Progesterone receptor, Her2/neu: human epidermal growth factor receptor 2.

Tumour characteristics (type and stage):

Among the BC cases, invasive ductal carcinoma is the most prevalent histological subtype in 65% of the cases. Invasive ductal carcinoma with DCIS accounts for about 20%, while the remaining histological types account for 15% of the cases (Table 4.18). The bar graph below was used to visually represent how the distribution of BC histological types has changed over the span of ten years. (Figure 4.4)

It was observed that the proportion of non-invasive carcinoma remains relatively low (11.62%), but there was a decrease in 2016, where it accounts for a lower proportion than in previous years (6.9%). IDC consistently makes up the highest proportion across all years,

ranging from 50% to 60%. IDC with DCIS had a relatively low proportion over the years with no statistically significant spikes. The proportions of invasive lobular carcinoma remain low throughout the period, representing a small fraction of overall BC cases.

Histological type	n	%
Non- invasive	247	11.62
Invasive Ductal Carcinoma	1,644	77.33
Invasive Ductal Carcinoma with DCIS %	116	5.46
Invasive Lobular Carcinoma	6	0.28
Carcinoma NOS	8	0.38
Other	84	3.95
Unknown	21	0.99
Total	2126	100.00

Table 4.18: Histological type of BC cases from 2008 to 2016 at KFSH&RC.

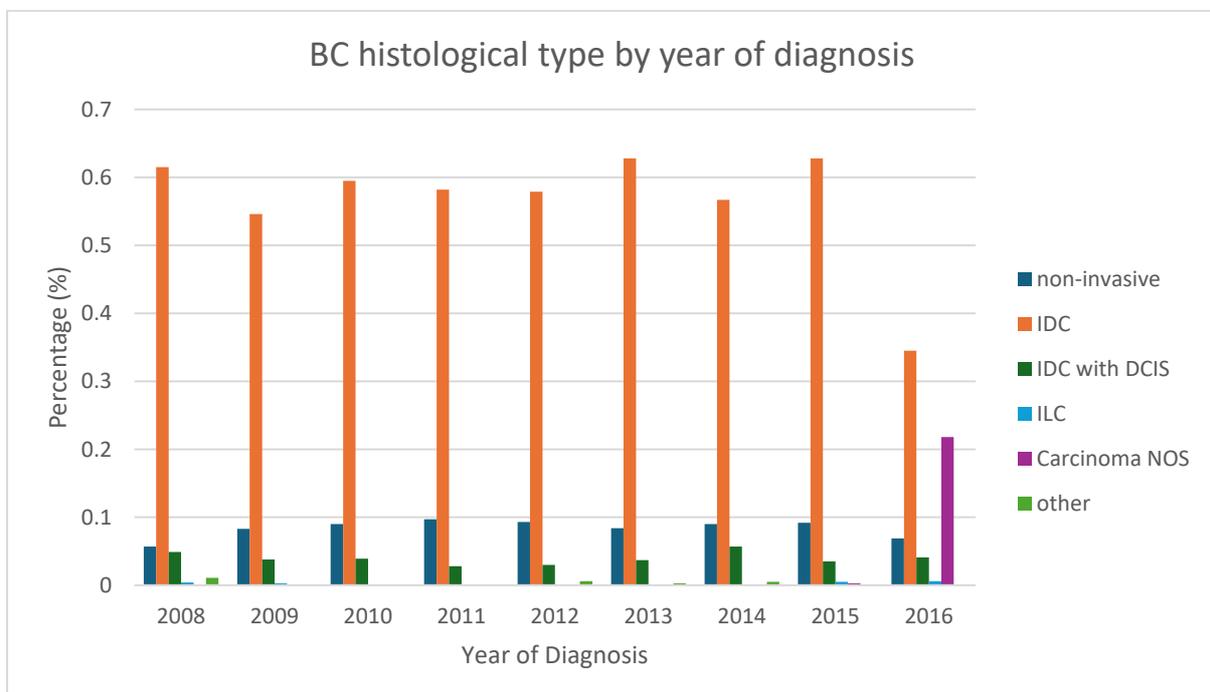


Figure 4.4. BC histological subtypes by year of diagnosis from 2008 to 2016 at KFSH&RC.

Clinical Tumour Stage:

When categorising the clinical tumour stage by year of diagnosis, it was observed that T2 was the most diagnosed stage across all years, representing 32% of all cases. However, this pattern shifted in 2009 and 2012, where T2 and T4 were the most diagnosed stages. The variation observed in the tumour stage across different years is likely not due to random chance but reflects an actual pattern ($P < 0.05$).

Regarding the axillary lymph node type, N1 accounted for 39% of the cases, followed by N0 type. Concerning distant metastasis, approximately two-thirds of cases were with M0 metastasis type. Furthermore, when considering the site of metastasis, the majority of cases (58%) involved bone, while 15% affected the liver and 20% affected the lungs.

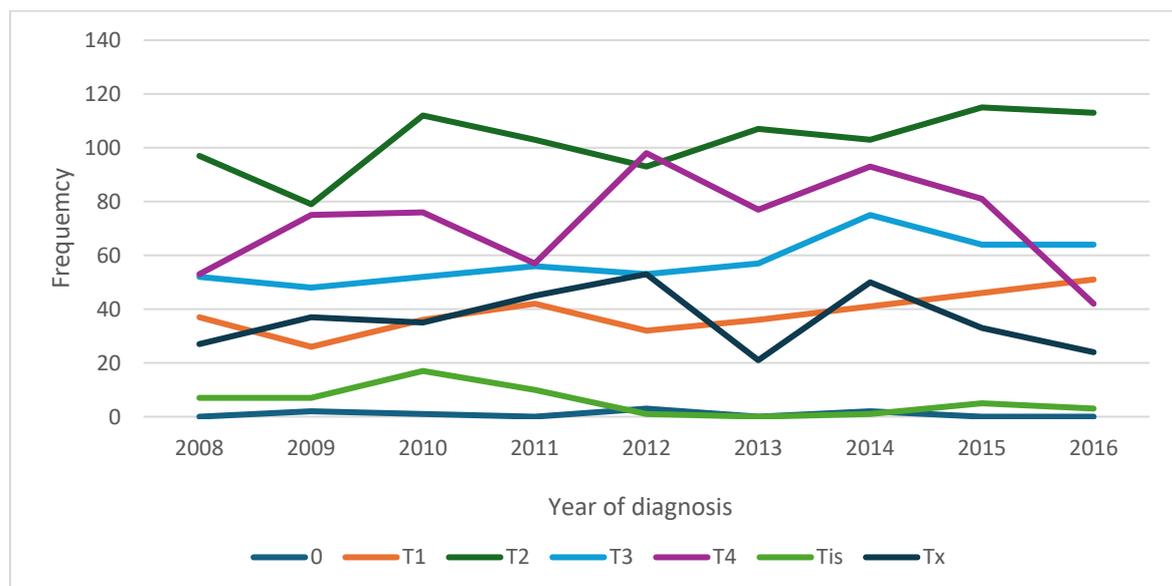


Figure 4.5: Clinical tumour stage by year of diagnosis at KFSH&RC.

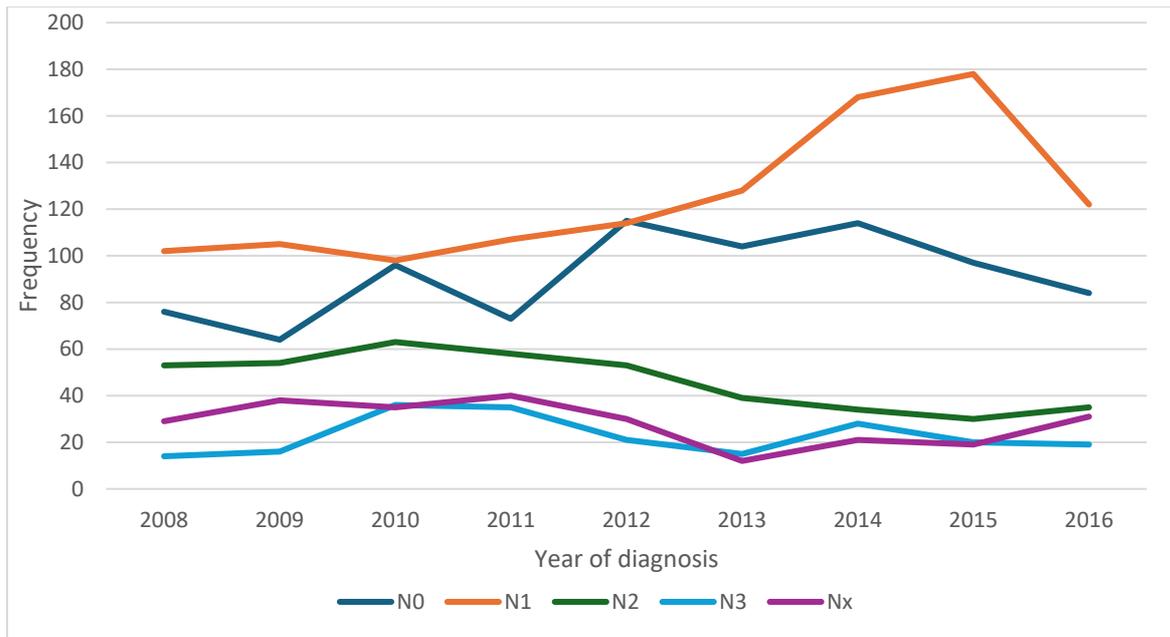


Figure 4.6: Clinical axillary lymph node by year of diagnosis at KFSH&RC.

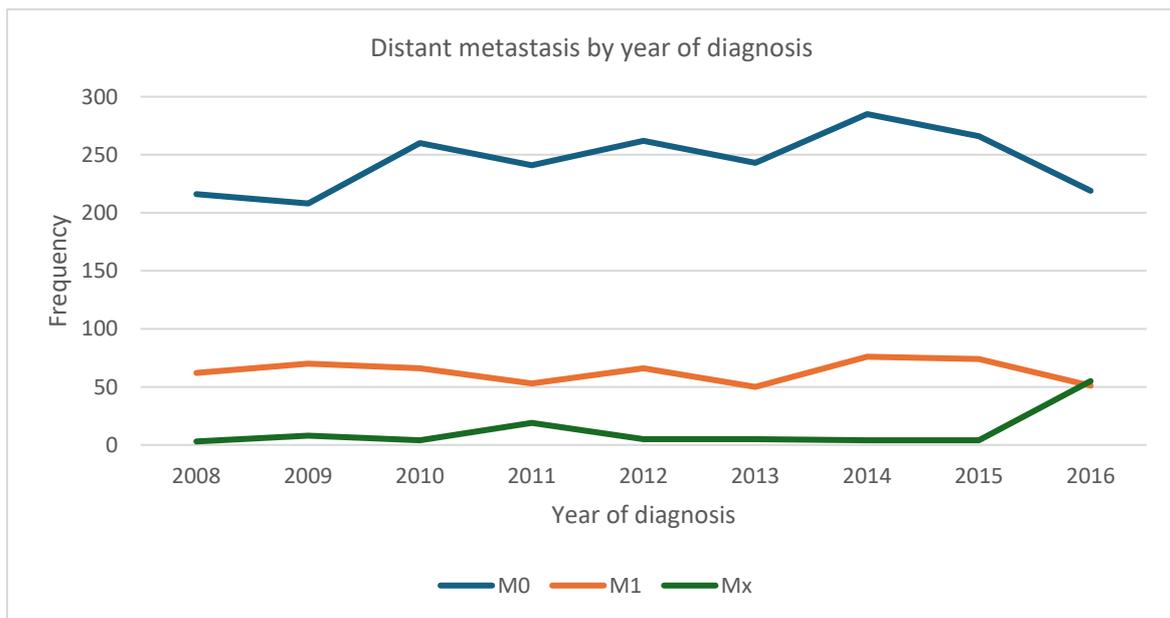


Figure 4.7: Distant metastasis by year of diagnosis at KFSH&RC.

Clinical Stage Combined TNM:

In the context of combined clinical staging, a substantial number of cases fall into either stages II or III, which account for about 31% and 30% of the cases, respectively. This shows that many diagnoses occur at intermediate to advanced stages. Furthermore, stage IV accounts for 19% of the cases.

Figure 4.8 was created to visually demonstrate the distribution of BC cases based on the clinical stage in relation to the year of diagnosis. It showed an increase in diagnosing early stages (stages I and II).

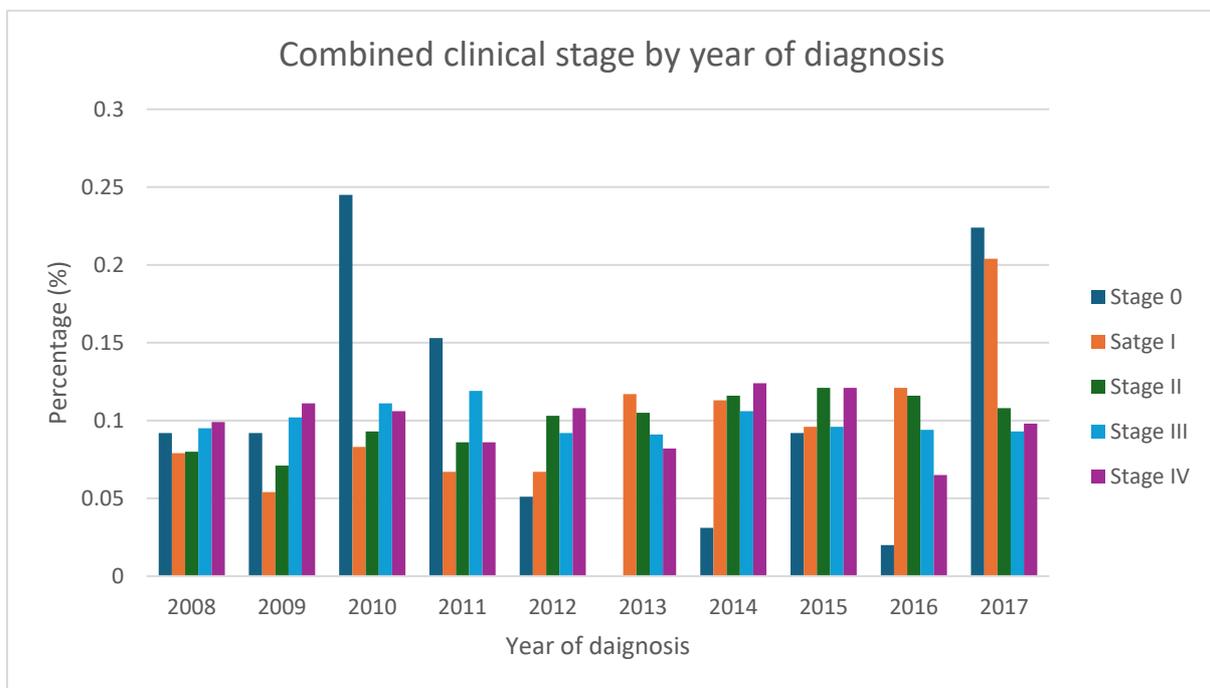


Figure 4.8: BC Combined clinical stage by year of diagnosis at KFSH&RC.

Clinical stage	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	Total (%)
0	9	9	24	15	5	0	3	9	2	22	98 (3.02)
I	19	13	20	16	16	28	27	23	29	49	240 (7.40)
IIA	44	36	52	43	61	53	55	65	53	59	521 (16.06)
IIB	38	37	43	45	44	54	64	59	66	51	501 (15.44)
IIIA	56	48	47	57	32	41	51	51	53	39	475 (14.64)
IIIB	36	51	61	59	57	47	52	42	38	51	494 (15.22)
IV	61	68	65	53	66	50	76	74	40	60	613 (18.89)
Unstageable	12	15	20	29	52	25	37	22	6	85	303 (9.34)
Total	275	277	332	317	333	298	365	345	287	416	3,245 (100)

Table 4.19: Distribution of clinical stage combined by year of diagnosis at KFSH&RC.

4.3.2 Incidence of BC

SCR data:

Crude incidence rate:

In this study, out of the total population of 203,310,878 women, 27,664 were diagnosed with BC and recorded in the SCR within the study period of 24 years between 1994 and 2017. This corresponds to a crude incidence rate of 13.6 per 100,000 women per year.

Incidence trends analysis over time:

BC crude incidence rate in Saudi females increased during the period from 1994 to 2017 from 6.26 to 24.58 per 100,000 persons per year (Table 4.21). Joinpoint analysis of incidence identified two Joinpoints with three-line segments joined at the Joinpoints of 2001 and 2010. The crude incidence rate significantly increased over the period from 1994 to 2001 by an annual percent change (APC) of 3.2% (95% CI 1.3, 5) and thereafter also increased significantly from 2001 to 2010 with APC of 9.4% (95% CI 11, 12.9) and from 2010 to 2017 with APC 4.8% (95% CI 2.9, 6.7) (Figure 4.9).

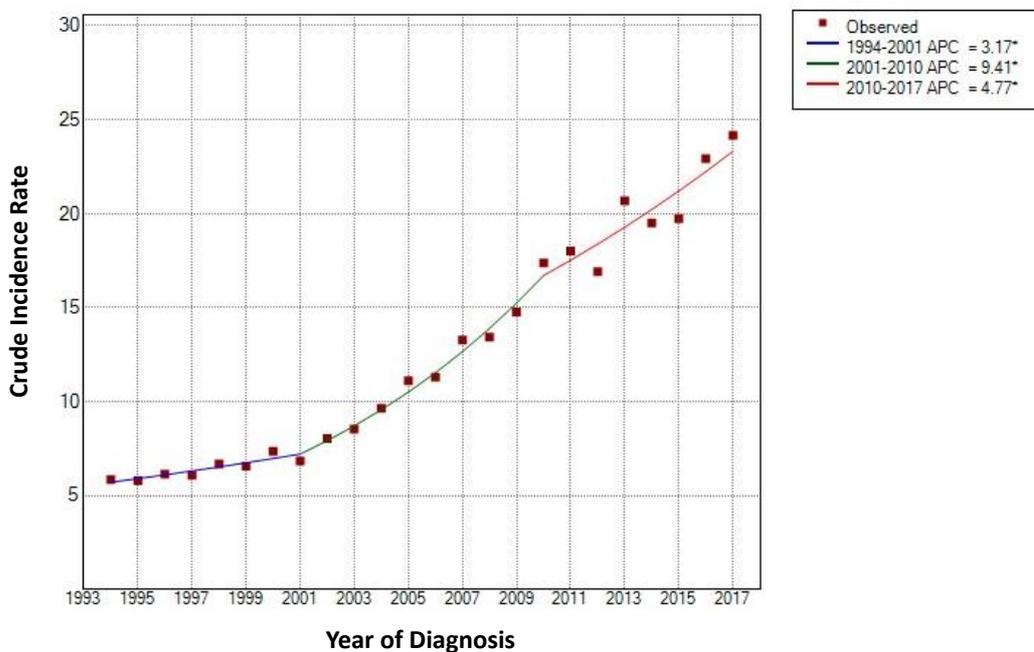


Figure 4.9 Joinpoint analysis for a crude incidence rate of BC in Saudi females, 1994-2017.

Age-specific and age-standardised incidence rate (ASR):

The age-specific incidence rate between 1994-2017 for each age group was calculated. The age-standardised incidence rate (ASR) for Saudi females between 1994-2017 was 15.70 per 100,000 population (Table 4.20).

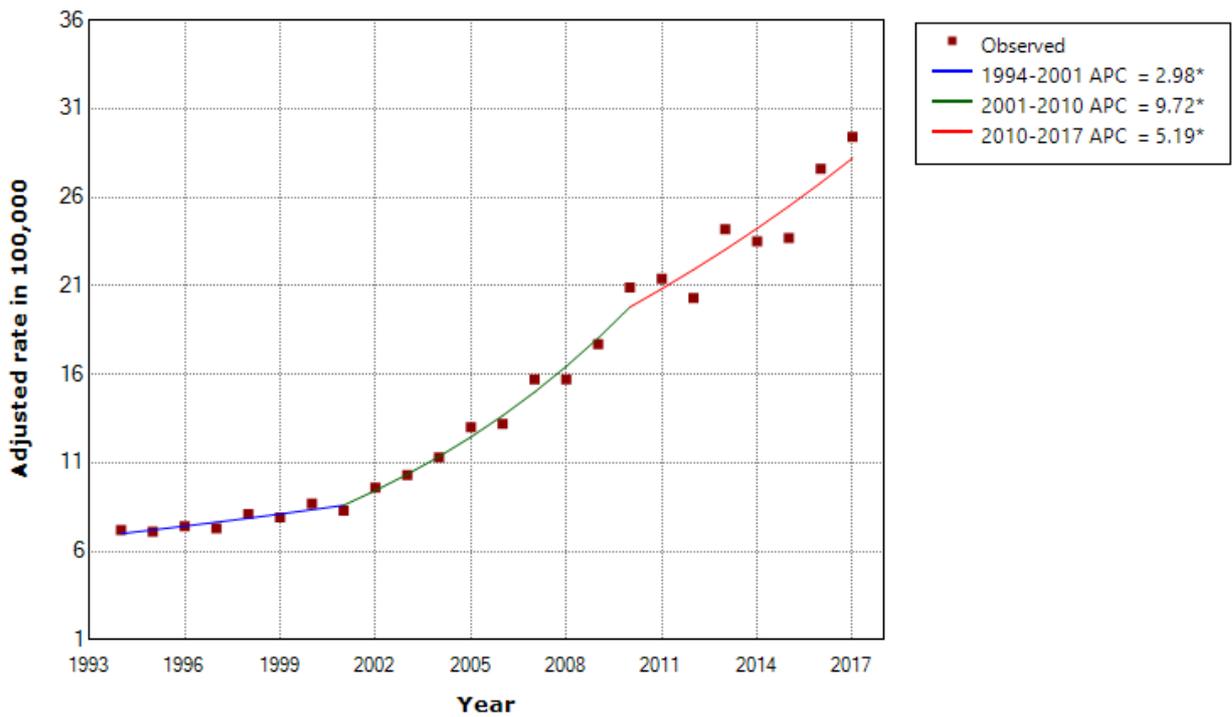
Age group	BC cases (d)	Female population (n)	Age-specific Incidence rate / 100,000 (a)	Age distribution of standard population (b)	a * b
10-19	29	36,865,540	0.08	0.18	0.01
20-29	1,122	39,044,959	2.87	0.16	0.46
30-39	5,121	32,844,781	15.59	0.12	1.87
40-49	8,415	23,346,215	36.04	0.12	4.32
50-59	6,733	14,786,350	45.54	0.09	4.09
60-69	3,778	7,942,367	47.57	0.07	3.33
70-79	1,784	3,750,122	47.57	0.03	1.43
≥80	674	1,843,210	36.57	0.005	0.18
All ages	27,656				ASR= 15.70

Table 4.20 BC age-specific rate per 100,000 by different age groups and ASR for BC between 1994-2017

ASR by year of diagnosis:

Age-standardised rates were calculated for each year and tested for trends by Joinpoint analysis. Using Joinpoint analysis, the trend showed a significant increase at two Joinpoints with three segments. The age-standardised incidence rate significantly increased from 1994 to 2001 by an annual percent change (APC) of 2.98% (95% CI 1.2, 4.8) and thereafter also increased significantly from 2001 to 2010 with an APC of 9.72% (95% CI 8.2, 11.3) and from 2010 to 2017 with an APC of 5.19% (95% CI 3.4, 7.0) (Figure 4.10).

All: 2 Joinpoints



* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level
Final Selected Model: 2 Joinpoints.

Figure 4.10 Joinpoint analysis for age adjusted incidence rate of BC in Saudi females, 1994-2017, SCR data.

Year of diagnosis	#	Population	The crude rate in 100,000	ASR in 100,000 (95% CI)
1994	432	6,903,384	6.3	7.2 (6.5, 7.9)
1995	436	7,005,798	6.2	7.1 (6.4, 7.8)
1996	466	7,108,212	6.6	7.4 (6.7, 8.1)
1997	469	7,210,626	6.5	7.3 (6.6, 7.9)
1998	519	7,313,040	7.1	8.1 (7.3, 8.8)
1999	519	7,415,454	7.0	7.9 (7.2, 8.6)
2000	605	7,788,754	7.8	8.7 (8.0, 9.5)
2001	573	7,891,168	7.3	8.3 (7.5, 9.0)
2002	676	7,993,582	8.5	9.6 (8.8, 10.3)
2003	725	8,095,996	9.0	10.3 (9.5, 11.0)
2004	824	8,198,409	10.1	11.3 (10.5, 12.1)
2005	966	8,379,069	11.5	13.0 (12.2, 13.9)
2006	1,003	8,560,590	11.7	13.2 (12.3, 14.0)
2007	1,197	8,742,073	13.7	15.7 (14.8, 16.7)
2008	1,235	8,920,708	13.8	15.7 (14.8, 16.7)
2009	1,381	9,090,699	15.2	17.7 (16.8, 18.7)
2010	1,638	9,206,698	17.8	20.9 (19.8, 21.9)
2011	1,715	9,307,620	18.4	21.4 (20.4, 22.5)
2012	1,630	9,405,130	17.3	20.3 (19.3, 21.3)
2013	2,009	9,522,889	20.5	24.2 (23.1, 25.3)
2014	1,919	9,635,942	19.9	23.5 (22.4, 24.6)
2015	1,963	9,742,108	20.1	23.7 (22.6, 24.7)
2016	2,300	9,850,218	23.3	27.6 (26.4, 28.8)
2017	2,464	10,022,711	24.6	29.4 (28.2, 30.6)
Total	27,664	203,310,878		

Table 4.21. BC incidence data in the period of 1994 to 2017. crude rate, ASR per 100,000, and 95% confidence interval

KFSH&RC data:

Proportional incidence %:

The total number of cancer cases among the female population recorded in the hospital registry between 2008 and 2017 was 13,839, with 3408 of those being female patients diagnosed with breast cancer during the previously mentioned time frame. The Proportional incidence was calculated to be 24.63% by means of the expression $((3408/ 13,839) *100)$.

Year of diagnosis	#	Population	Proportional Incidence (%)
2008	281	1,251	22.5%
2009	289	1,195	24.2%
2010	333	1,182	28.2%
2011	318	1,328	23.9%
2012	333	1,295	25.7%
2013	298	1,333	22.4%
2014	365	1,438	25.4%
2015	347	1,536	22.6%
2016	362	1,634	22.2%
2017	482	1,646	29.3%
Total	3408	13,839	24.63%

Table 4.22: Proportional Incidence % of BC in Saudi females at KFSH&RC between 2008 and 2017.

Note: #: number of breast cancer cases in the hospital, population: all female cancer cases in the hospital.

The proportional incidence has been relatively stable over the years. The Joinpoint analysis shows no significant change ($P = 0.72$), with an annual percentage change (APC) of 0.43 (95% CI -2.19, 3.12) CI, indicating a constant trend from 2008 to 2017.

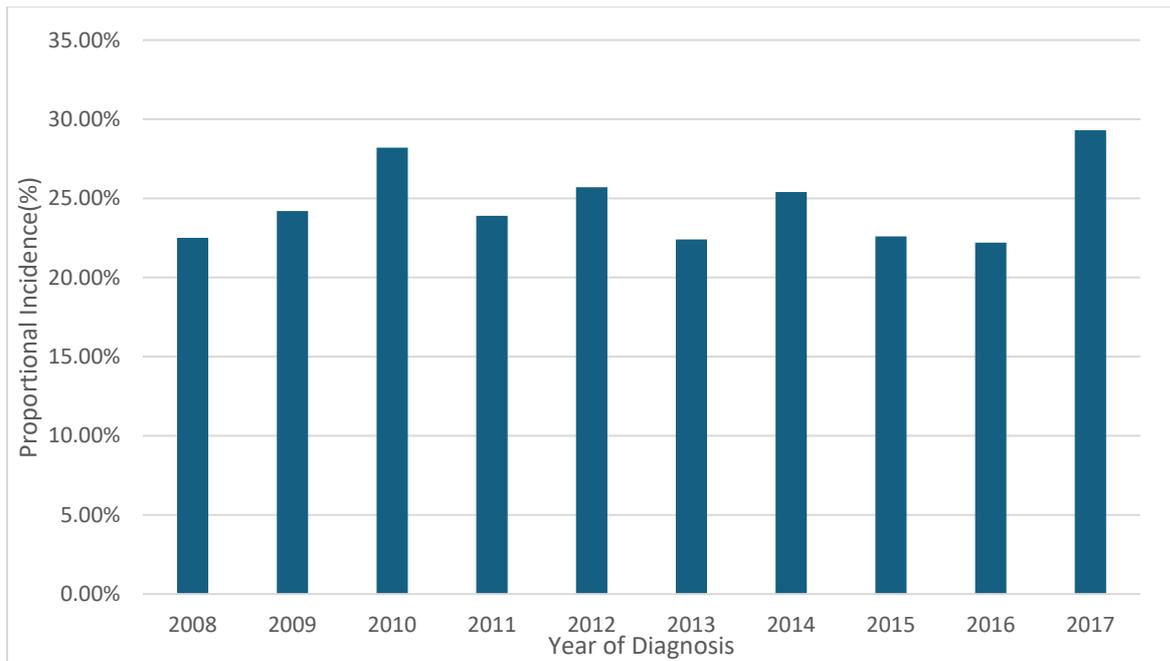


Figure 4.11: Proportional incidence % of BC between 2008 and 2017 at KFSH&RC.

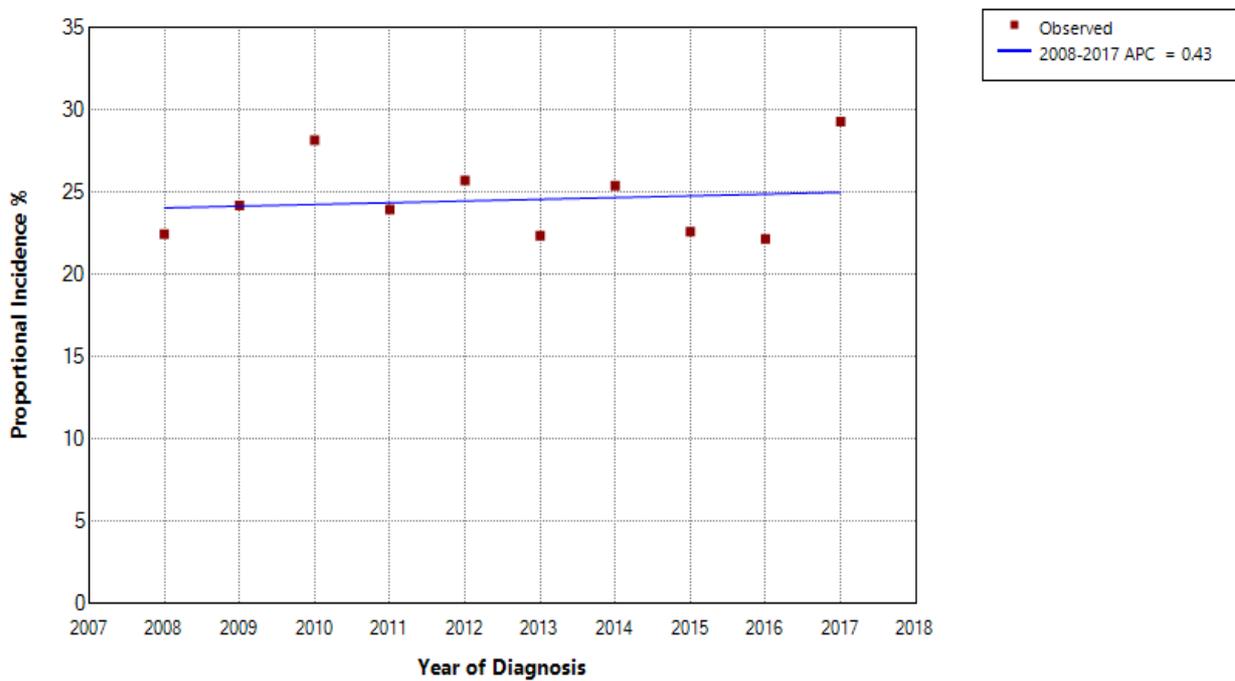


Figure 4.12: Joinpoint regression analysis for Proportional Incidence from 2008 to 2017 at KFSH&RC.

Proportional incidence ratio PIR:

The ratio was calculated for each year by using the Saudi population obtained from the SCR as a standard. The standard proportion was calculated by dividing the number of female BC cases in a specified year by the number of females of all cancers in the registry for the corresponding year.

The PIR was calculated by dividing the number of BC cases diagnosed in the hospital in a specific year by the expected number of BC cases in the hospital in the specified year. The expected number is calculated by multiplying the number of all cancers in the hospital by the standard proportion.

Year	Saudi population			Hospital			PIR=(x/E) *100
	BC (a)	All cancers (b)	Proportion (a/b)	BC (x)	All cancers (y)	Expected E=(y*(a/b))	
2008	1,235	4,710	0.262	281	1,261	330.4	85.1%
2009	1,381	5,349	0.258	289	1,195	308.3	93.7%
2010	1,638	5,506	0.297	333	1,182	351.1	94.8%
2011	1,715	6,097	0.281	318	1,337	375.7	84.6%
2012	1,630	5,967	0.273	333	1,295	353.5	94.2%
2013	2,009	6,364	0.316	298	1,334	421.5	70.7%
2014	1,919	6,364	0.302	365	1,438	434.3	84%
2015	1,963	6,584	0.298	347	1,536	457.7	75.8%
2016	2,300	7,358	0.313	362	1,634	511.4	70.8%
2017	2,464	7,975	0.309	482	1,646	508.6	94.8%
Total	18,254	6,274		3,408	13,858		

Table 4.23. The proportional incidence ratio of BC in Saudi females at KFSH&RC between 2008-2017.

Proportional incidence ratio trend analysis over time:

The PIR was calculated for each year and analysed for trends using Joinpoint regression analysis. The trend showed a non-significant decrease in the PIR with an APC of -1.5 (95%CI - 4.9, 1.9), indicating that the observed decrease occurred due to chance, and the PIR was stable.

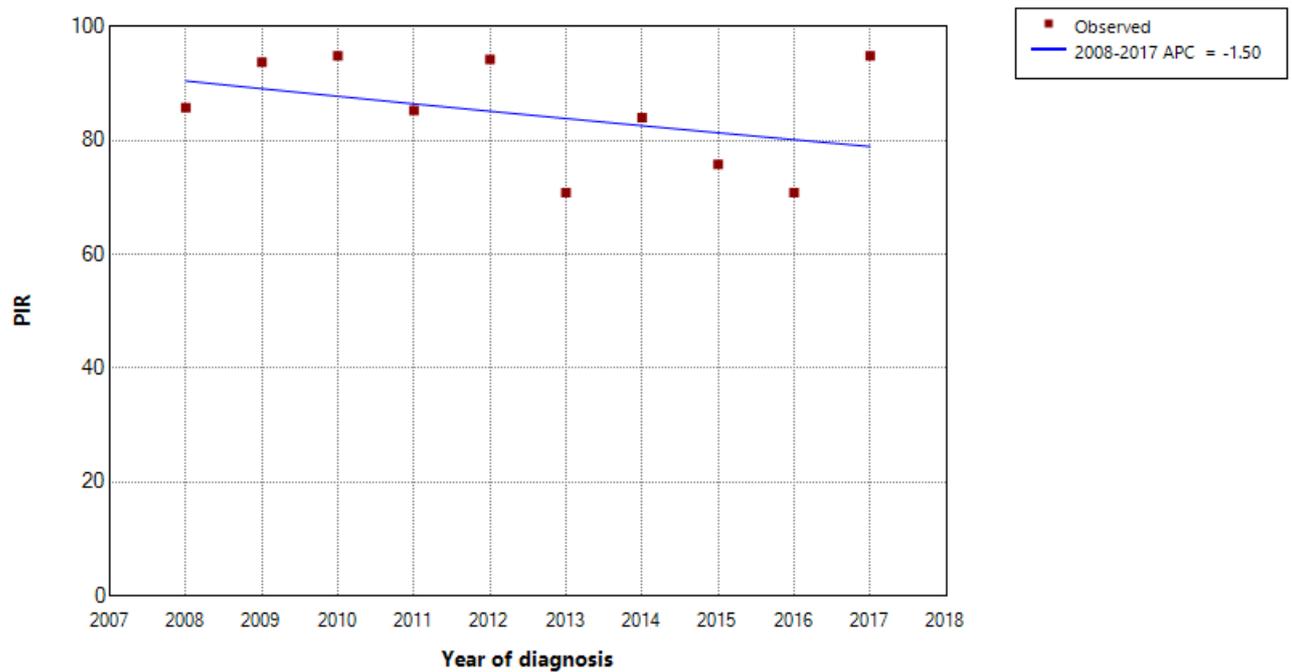


Figure 4.13. Joinpoint regression analysis for proportional incidence ratio (PIR) of BC at KFSH&RC from 2008 to 2017.

Age-standardised cancer ratio

It was found that age-standardised cancer ratio between 2008 and 2017 was 24.99%

Age at diagnosis	(n)	All cancers	n / all cancers	St. Prop. %	(n/all) *St. Prop
0-9	0	810	0	3.36	0
10-19	3	749	0.004	3.35	0.013
20-29	134	1237	0.108	6.10	0.659
30-39	667	2145	0.312	12.46	3.888
40-49	1150	2957	0.389	19.94	7.757
50-59	866	2798	0.310	22.85	7.084
60-69	403	1882	0.214	16.34	3.497
70-79	146	958	0.152	6.69	1.017
80+	39	322	0.121	8.89	1.076
Total	3,408	13858	1.608	100	ASCAR= 24.99

Table 4.24: Age Standardised cancer ratio for BC in Saudi females at KFSH&RC between 2008 and 2017.

Note: Standard proportion: Saudi population. n= number of cases, St. Prop. = standard proportion, ASCAR= age-standardised cancer ratio.

The age-standardised cancer ratio for each year was calculated in the table below:

Year of diagnosis	ASCAR
2008	23.13
2009	24.72
2010	28.83
2011	24.02
2012	27.07
2013	22.66
2014	25.58
2015	22.84
2016	22.25
2017	29.48

Table 4.25. The age-standardised cancer ratio (ASCAR) for BC at KFSH&RC by year of diagnosis from 2008 to 2017.

Temporal trends in age-standardised cancer ratio using Joinpoint regression analysis:

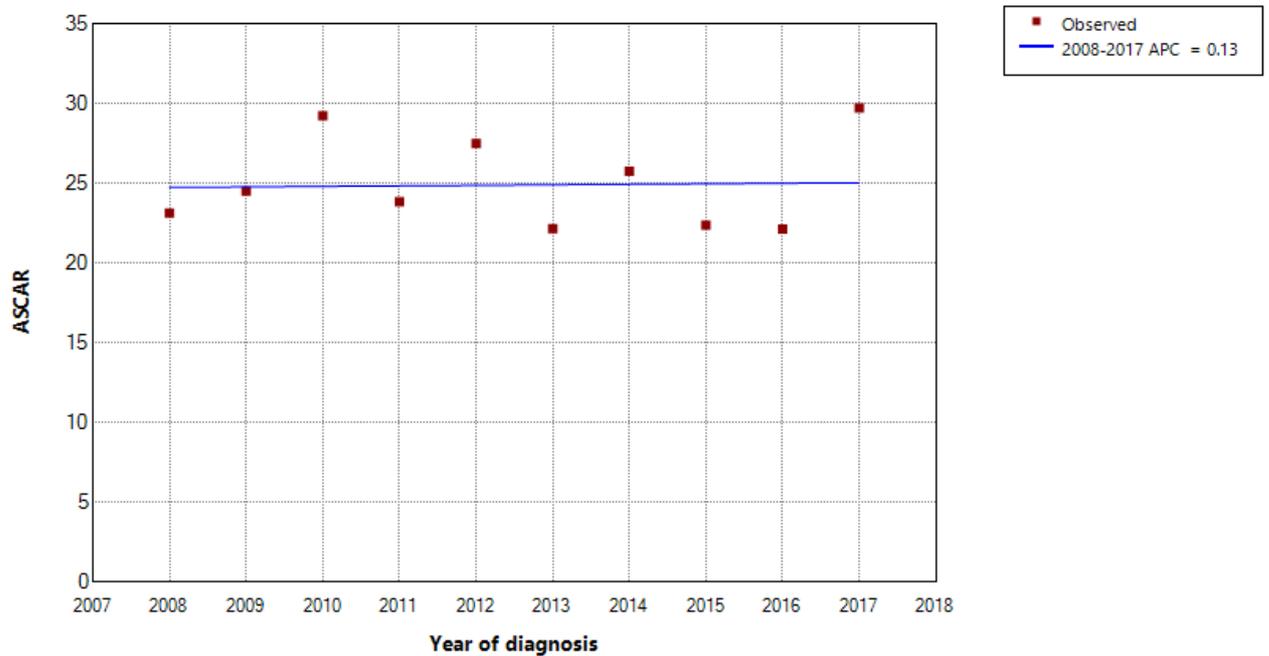


Figure 4.14. Joinpoint regression analysis for ASCAR of BC at KFSH&RC from 2008 to 2017. ASCAR: age-standardised cancer ratio

The age-standardised cancer ratio was calculated for each year from 2008 to 2017 and analysed for trends. The trend analysis showed a non-significant increase from 2008 to 2015 with an APC of 0.13 (95% CI -4.39, 4.77), indicating that there was no increase or decrease and the age-standardised cancer ratio was stable.

4.3.3 BC Incidence trends for SCR data by different variables

4.3.3.1 Distribution by age at diagnosis

The trend of age-specific incidence rate for the seven age groups were analysed using Joinpoint regression analysis. Women aged 40–49 had the highest overall breast cancer age-specific incidence rates from 2001- 2007. A significant increase in breast cancer incidence was evident among women in all age groups, with the highest APC of 13.2% noted among women aged 40 to 49 years for the period from 2001 to 2007 (Table 4.26).

Age group	Years	APC (95% CI)	P-Value
20-29	1994 – 2017	2.1 (0.8, 3.3)	0.002
30-39	1994 – 2017	4.7 (4.1, 5.3)	0.00001
40-49	1994 – 2001	5.0 (2.6, 7.4)	0.00001
	2001- 2007	13.2 (9.0, 17.6)	0.00001
	2007- 2017	4.0 (2.7, 5.4)	0.00001
50-59	1994- 2001	2.2 (-1.2, 5.7)	0.193
	2001– 2017	10.9 (9.8, 11.9)	0.00001
60-69	1994 – 2000	1.2 (-3.6, 6.2)	0.062
	2000- 2017	7.8 (6.7, 8.8)	0.00001
70-79	1994 – 1997	-5.0 (-18.4, 10.7)	0.49
	1997- 2017	9.0 (8.1, 10.0)	0.00001
80+	1994 – 2017	6.6 (4.9, 8.2)	0.00001

Table 4.26 Joinpoint analysis of BC between 1994 and 2017 by different age groups

Figure 4.15 and Figure 4.16 illustrate age-standardised incidence rates per 100,000 for BC, 1994-2017, for all age groups.

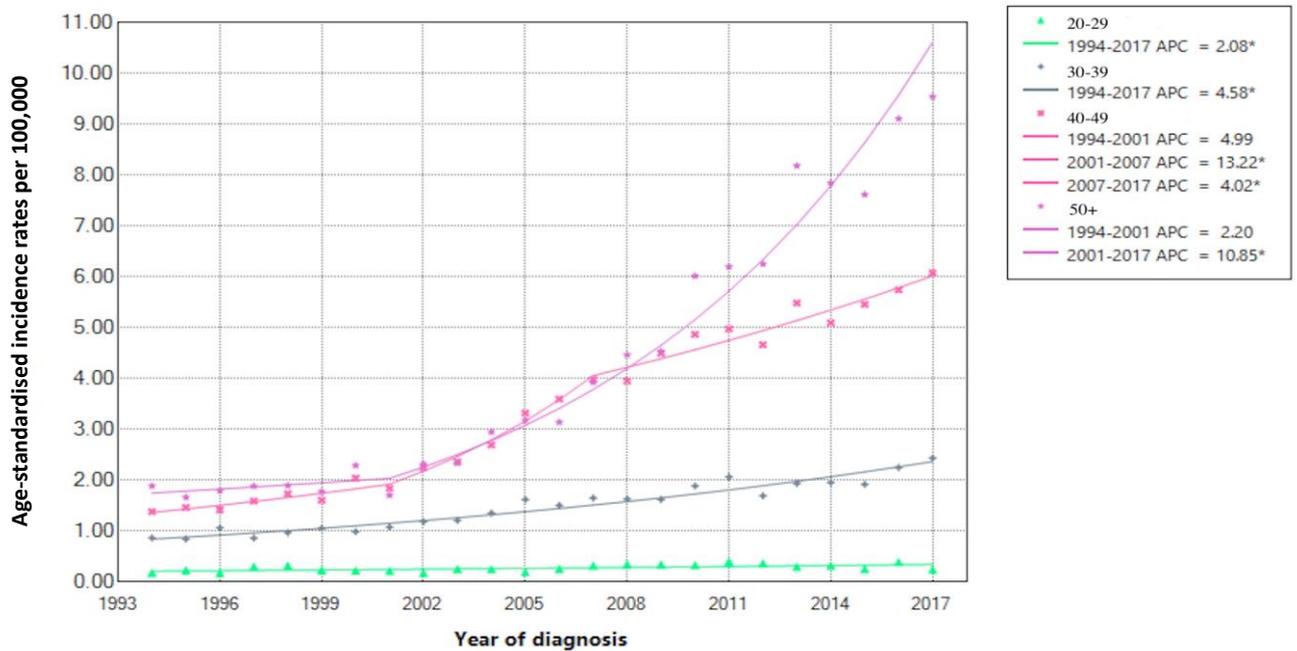


Figure 4.15 Joinpoint analysis for an ASR of BC by diagnostic year from 1994-2017 for different age groups.

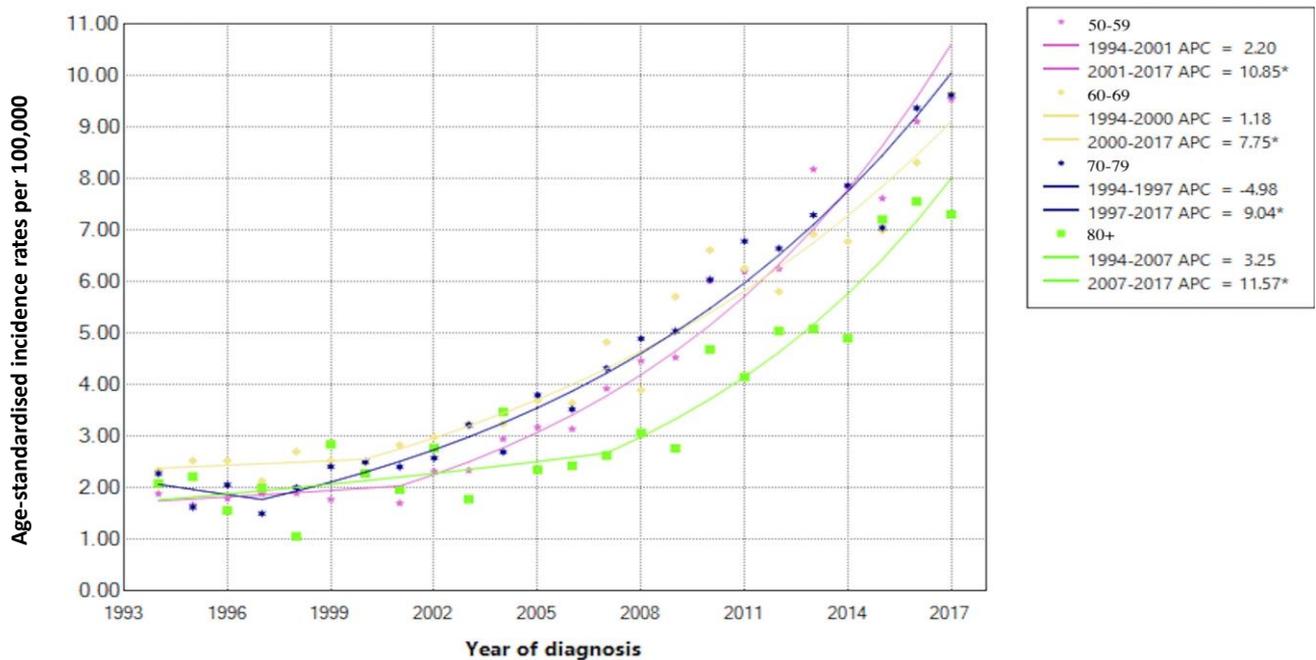


Figure 4.16 Joinpoint analysis for an ASR of BC by diagnostic year from 1994-2017 for different age groups.

4.3.3.2 Distribution by stage at diagnosis

Regional BC was the most common type in Saudi females (Table 4.12). To calculate the crude incidence and trend by stage, the in-situ cases (3 cases) and the cases with an unknown stage (2804 cases) were excluded.

Joinpoint analysis of ASR by stage identified a non-significant decrease in localised (stage II) BC from 1994 to 1999, with an APC of 5.75% (95% CI -11.7, 0.5), followed by a significant increase from 2000 to 2017, with an APC of 11.82% (95% CI 10.8, 12.9) (Figure 4.17).

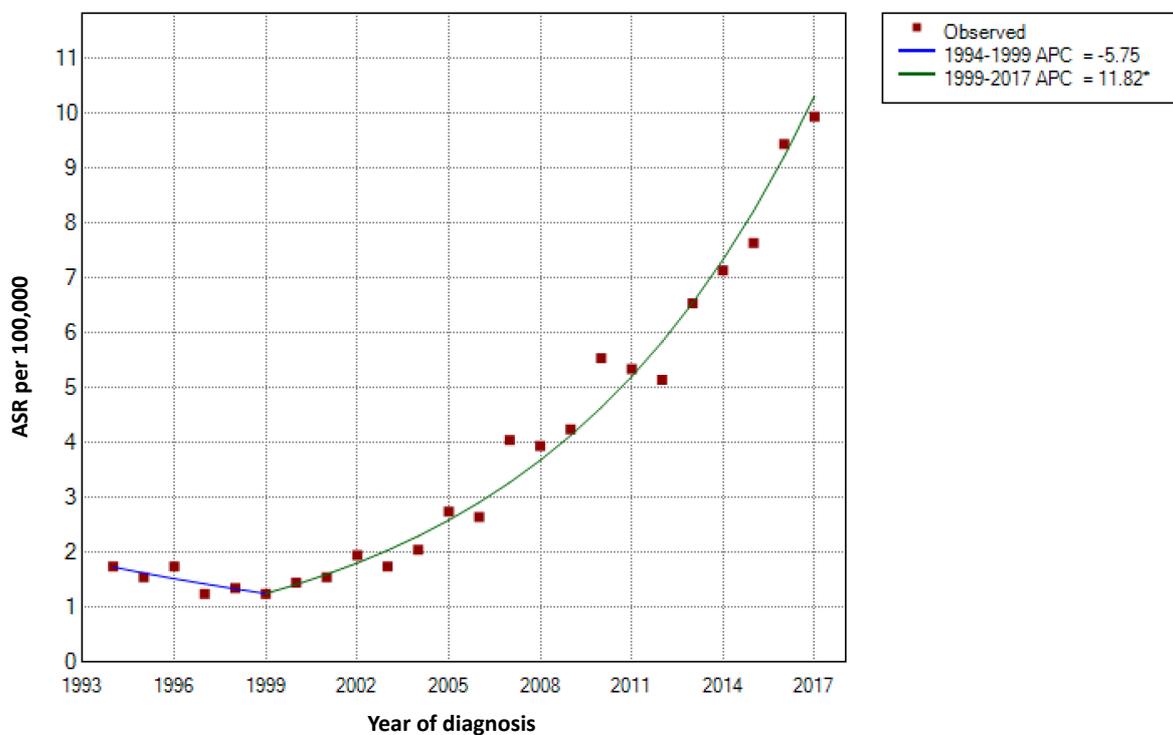


Figure 4.17 Joinpoint analysis for ASR per 100,000 BC for localised cases between 1994- 2017.

There is a statistically significant increase in regional BC (stage III) between 1994 and 1998 at APC of 16.7 (95% CI 9.6, 24.3) and a significant increase in the period from 1998 to 2017 at APC 5.94 (95% CI 5.3, 6.6) (Figure 4.18).

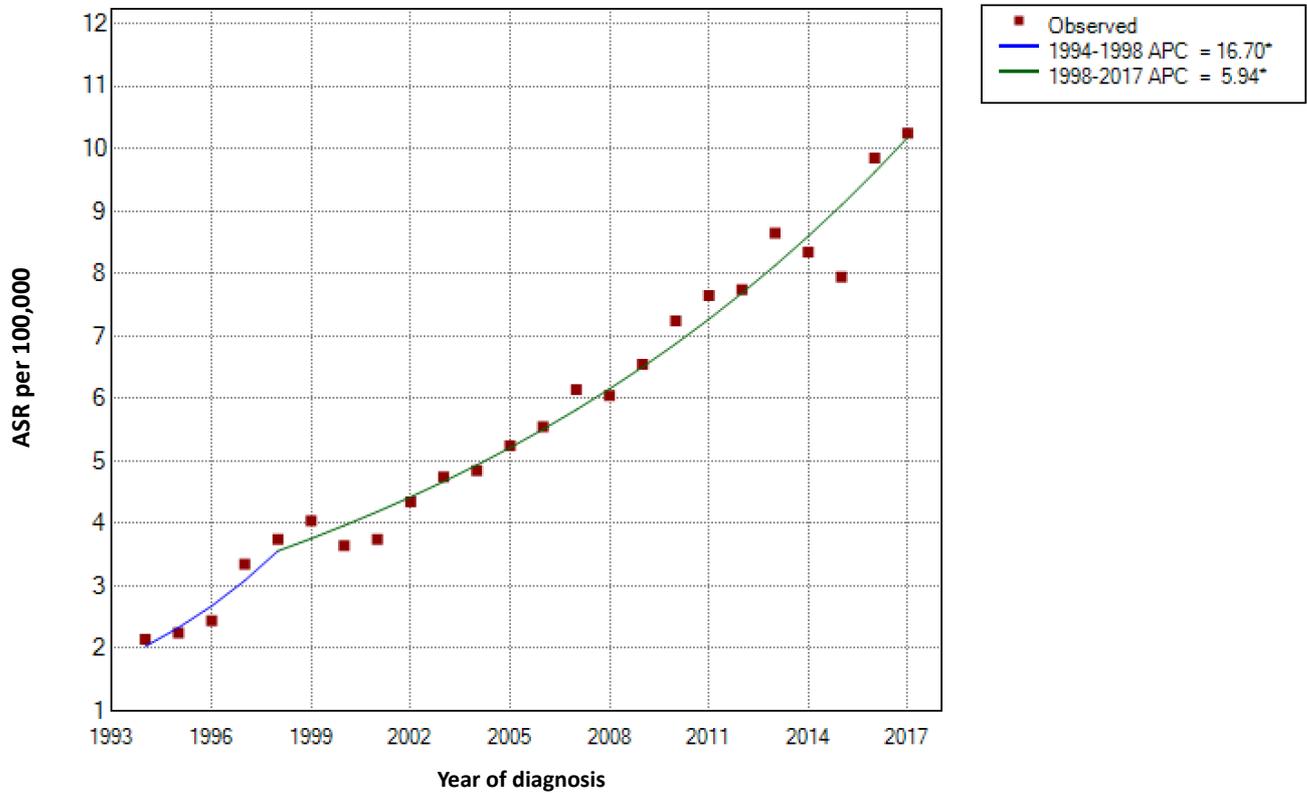


Figure 4.18 Joinpoint analysis ASR per 100,000 BC for regional cases between 1994- 2017.

The trend showed to be levelling off; the decrease in distant metastasis (stage IV) was significant between 1994 and 1999 at APC -12.25% (95% CI -18.8, -5.2) and a significant increase during the periods 1999 to 2010 at an APC 11.29 (95% CI 8.3, 14.3) while the increase was non-significant from 2010 to 2017 at an APC 2.89 (95% CI -1.7, 7.7) Figure 4.19

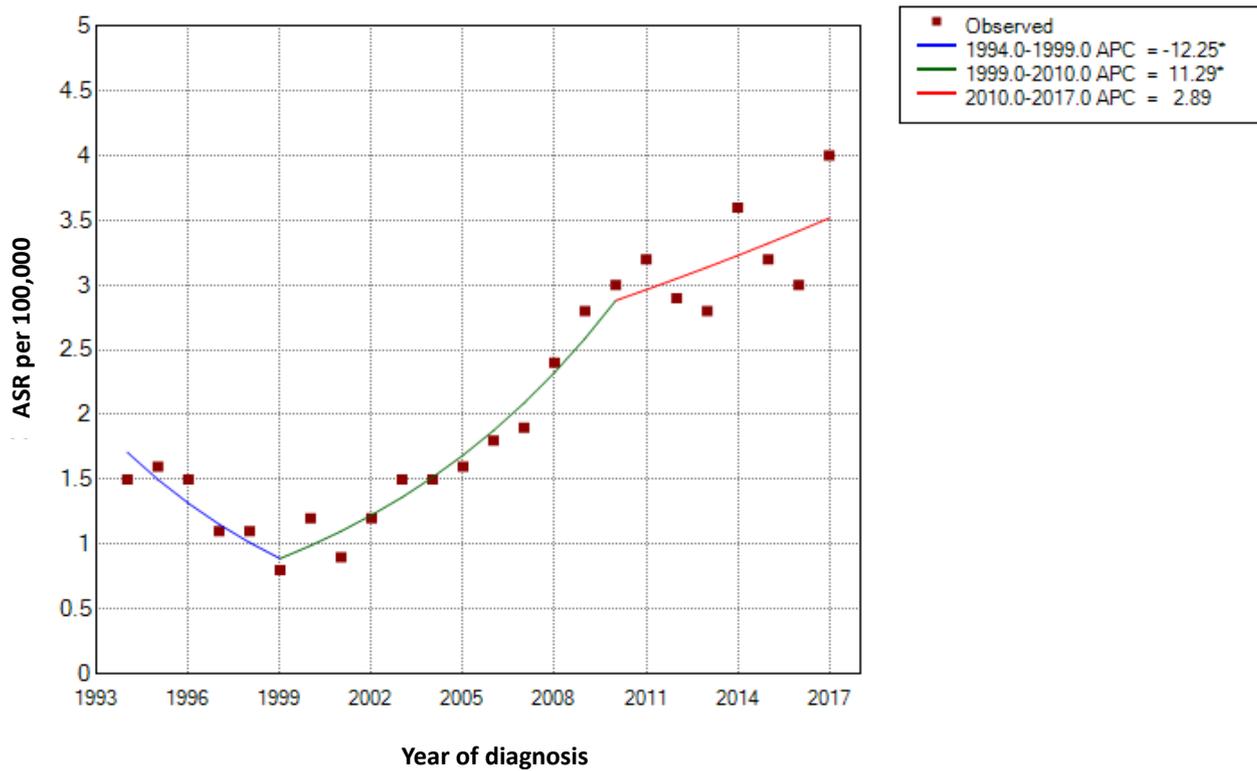


Figure 4.19 Joinpoint analysis for ASR per 100,000 BC for distant metastasis cases between 1994- 2017.

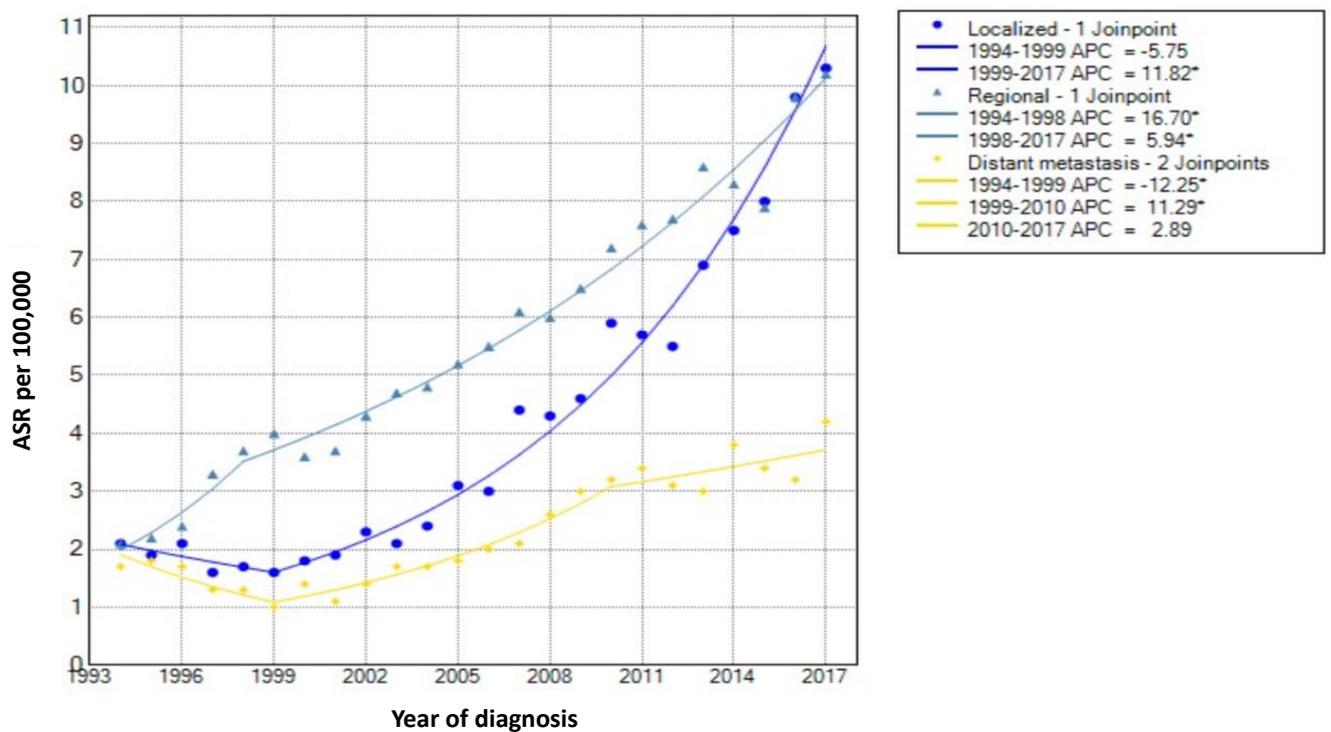


Figure 4.20 Joinpoint analysis ASR per 100,000 of BC by stage at diagnosis between 1994- 2017.

Year of Diagnosis	Localised ASR (95%CI)	Regional ASR (95%CI)	Distant Metastasis ASR (95%CI)
1994	1.9 (1.6, 2.3)	1.9 (1.6, 2.3)	1.5 (1.2, 1.8)
1995	1.7 (1.4, 2.0)	2.0 (1.6, 2.3)	1.6 (1.3, 1.9)
1996	1.9 (1.6, 2.2)	2.2 (1.9, 2.6)	1.5 (1.2, 1.8)
1997	1.4 (1.1, 1.7)	3.1 (2.7, 3.5)	1.1 (0.8, 1.3)
1998	1.5 (1.2, 1.8)	3.5 (3.1, 3.9)	1.1 (0.9, 1.4)
1999	1.4 (1.1, 1.6)	3.8 (3.3, 4.2)	0.8 (0.6, 1.1)
2000	1.6 (1.3, 1.9)	3.4 (2.9, 3.8)	1.2 (0.9, 1.5)
2001	1.7 (1.4, 2.0)	3.5 (3.1, 4.0)	0.9 (0.7, 1.1)
2002	2.1 (1.7, 2.4)	4.1 (3.7, 4.6)	1.2 (1.0, 1.5)
2003	1.9 (1.6, 2.2)	4.5 (4.0, 5.0)	1.5 (1.2, 1.8)
2004	2.2 (1.8, 2.5)	4.6 (4.2, 5.1)	1.5 (1.2, 1.8)
2005	2.9 (2.5, 3.3)	5.0 (4.5, 5.5)	1.6 (1.3, 1.9)
2006	2.8 (2.5, 3.2)	5.3 (4.8, 5.7)	1.8 (1.5, 2.1)
2007	4.2 (3.8, 4.6)	5.9 (5.4, 6.4)	1.9 (1.6, 2.2)
2008	4.1 (3.6, 4.5)	5.8 (5.2, 6.3)	2.4 (2.1, 2.7)
2009	4.4 (4.0, 4.9)	6.3 (5.8, 6.9)	2.8 (2.5, 3.2)
2010	5.7 (5.2, 6.2)	7.0 (6.4, 7.6)	3.0 (2.6, 3.4)
2011	5.5 (5.0, 6.0)	7.4 (6.9, 8.0)	3.2 (2.9, 3.6)
2012	5.3 (4.8, 5.8)	7.5 (6.9, 8.0)	2.9 (2.5, 3.3)
2013	6.7 (6.2, 7.3)	8.4 (7.8, 9.0)	2.8 (2.5, 3.2)
2014	7.3 (6.7, 7.8)	8.1 (7.5, 8.7)	3.6 (3.2, 4.0)
2015	7.8 (7.3, 8.4)	7.7 (7.1, 8.3)	3.2 (2.8, 3.5)
2016	9.6 (9.0, 10.3)	9.6 (8.9, 10.2)	3.0 (2.7, 3.4)
2017	10.1 (9.5, 10.8)	10.0 (9.4, 10.7)	4.0 (3.5, 4.4)

Table 4.27 ASR of BC per 100,000 and 95% CI by stage at diagnosis for the period between 1994 -2017

4.3.3.3 BC Distribution by Tumour Grade

In terms of grade at diagnosis, most cases were diagnosed in grades 2 and 3, and the difference in proportion diagnosed at each stage over time was significant ($P < 0.05$) (Table 4.9). The age-standardised incidence rate of BC for Grade 1 increased significantly from 1998 to 2017 (APC 13.7%, $P = 0.0001$, 95% CI 12, 15.6). For Grade 2, there was a steady increase, which was also significant between 1994 and 2017, with an APC of 9.16, $P = 0.0001$ (95% CI 8.6, 9.7). Rates for Grade 3 increased significantly from 1994 to 2017 with an APC of 8.5% (95% CI 7.8, 9.3, $P = 0.0001$) (Figure 4.21).

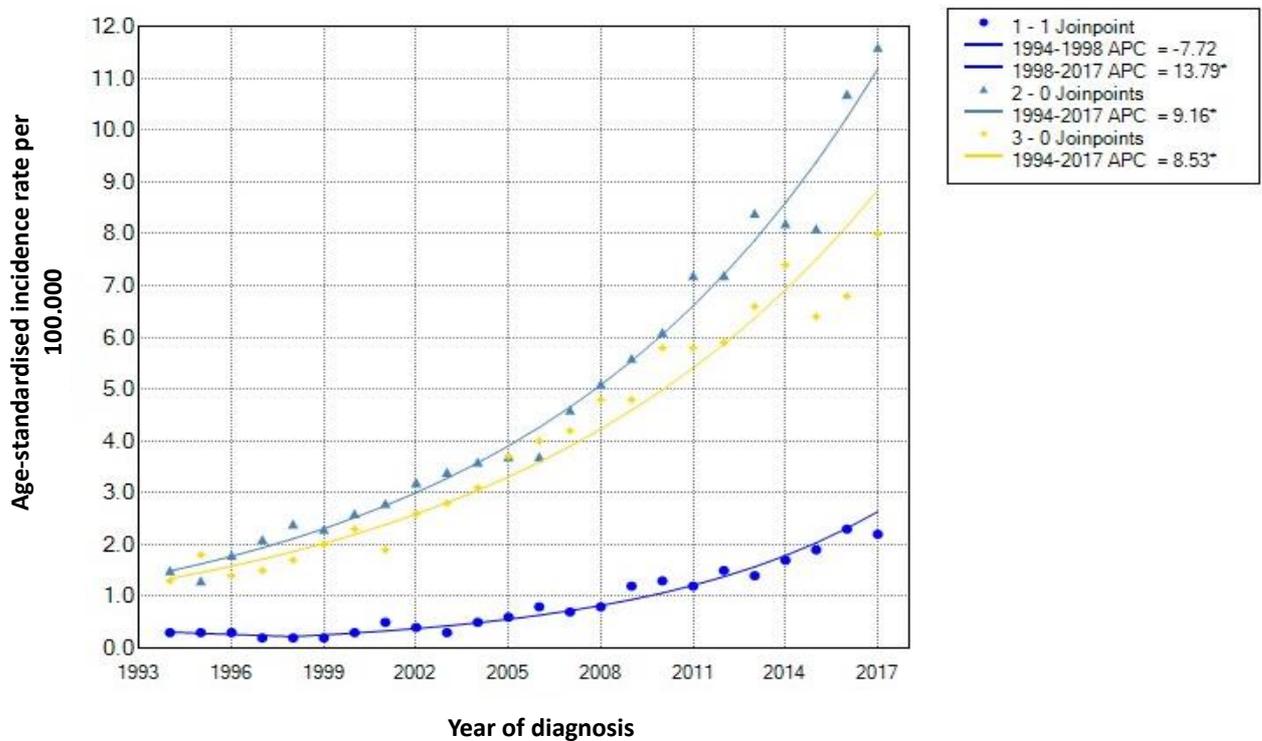


Figure 4.21 Joinpoint analysis for ASR per 100,000 of BC for all Grades between 1994- 2017.

The age-standardised incidence rate per 100,000 and 95% confidence interval are shown in the table below.

Year	Grade			
	1 (ASR, 95% CI)	2 (ASR, 95% CI)	3 (ASR, 95% CI)	4 (ASR, 95% CI)
1994	0.3 (0.2, 0.5)	1.5 (1.2, 1.8)	1.3 (1, 1.6)	0.0 (0, 0.1)
1995	0.3 (0.1, 0.4)	1.3 (1.0, 1.6)	1.8 (1.5, 2.1)	0.1 (0, 0.2)
1996	0.3 (0.2, 0.5)	1.8 (1.5, 2.1)	1.4 (1.2, 1.7)	0.1 (0, 0.1)
1997	0.2 (0.1, 0.3)	2.1 (1.8, 2.4)	1.5 (1.2, 1.8)	0.1 (0, 0.2)
1998	0.2 (0.1, 0.3)	2.4 (2.0, 2.7)	1.7 (1.4, 2.0)	0.1 (0, 0.2)
1999	0.2 (0.1, 0.3)	2.3 (2.0, 2.7)	2.0 (1.6, 2.3)	0.0 (0, 0.1)
2000	0.3 (0.2, 0.5)	2.6 (2.3, 3.0)	2.3 (1.9, 2.6)	0.1 (0, 0.1)
2001	0.5 (0.3, 0.7)	2.8 (2.4, 3.2)	1.9 (1.6, 2.2)	0.1 (0, 0.2)
2002	0.4 (0.2, 0.5)	3.2 (2.7, 3.6)	2.6 (2.3, 3.0)	0.1 (0, 0.2)
2003	0.3 (0.2, 0.5)	3.4 (3.0, 3.8)	2.8 (2.4, 3.1)	0.2 (0.1, 0.3)
2004	0.5 (0.3, 0.7)	3.6 (3.2, 4.0)	3.1 (2.7, 3.5)	0.2 (0.1, 0.3)
2005	0.6 (0.4, 0.7)	3.7 (3.3, 4.1)	3.7 (3.3, 4.1)	0.2 (0.0, 0.2)
2006	0.8 (0.6, 1.0)	3.7 (3.2, 4.1)	4.0 (3.6, 4.5)	0.2 (0.1, 0.3)
2007	0.7 (0.5, 0.8)	4.6 (4.2, 5.1)	4.2 (3.7, 4.6)	0.2 (0.1, 0.2)
2008	0.8 (0.6, 1.0)	5.1 (4.6, 5.6)	4.8 (4.3, 5.3)	0.1 (0, 0.2)
2009	1.2 (0.9, 1.4)	5.6 (5.1, 6.1)	4.8 (4.3, 5.2)	0.2 (0.1, 0.3)
2010	1.3 (1, 1.5)	6.1 (5.6, 6.6)	5.8 (5.3, 6.3)	0.2 (0.1, 0.3)
2011	1.2 (0.9, 1.4)	7.2 (6.7, 7.8)	5.8 (5.3, 6.3)	0.3 (0.2, 0.4)
2012	1.5 (1.2, 1.8)	7.2 (6.6, 7.7)	5.9 (5.4, 6.4)	0.2 (0.1, 0.3)
2013	1.4 (1.2, 1.7)	8.4 (7.8, 9)	6.6 (6.1, 7.1)	0.3 (0.1, 0.4)
2014	1.7 (1.4, 2)	8.2 (7.6, 8.8)	7.4 (6.8, 7.9)	0.1 (0, 0.1)
2015	1.9 (1.6, 2.2)	8.1 (7.5, 8.7)	6.4 (5.9, 6.9)	0.1 (0, 0.1)
2016	2.3 (2.0, 2.6)	10.7 (10.1, 11.4)	6.8 (6.3, 7.4)	0.1 (0, 0.2)
2017	2.2 (1.9, 2.5)	11.6 (10.9, 12.3)	8 (7.4, 8.5)	0.0 (0, 0.1)

Table 4.28 Age-standardised incidence rates per 100,000 of BC cases by grade at diagnosis between 1994-2017.

4.3.3.4 Distribution by Region

Riyadh and Makkah were the regions with the highest number of BC cases at 26%, followed by the Eastern region with about 22%. Those three regions account for about 74% of the cases, and the remaining ten regions account for about 26% of BC cases in Saudi Arabia.

The age-standardised incidence rate in 100,000 was calculated by region for the period from 1994-2017.

Region	Age standardised incidence rate (95% CI)
Asir	6.7 (6.3, 7.1)
Baha	6.8 (6.0, 7.6)
Eastern	19.8 (19.3, 20.4)
Hail	9.3 (8.5, 10.1)
Jazan	4.9 (4.5, 5.3)
Jouf	11.6 (10.3, 12.8)
Madinah	10.9 (10.3, 11.4)
Makkah	15.5 (15.2, 15.9)
Najran	5.6 (4.8, 6.3)
Northern	7.9 (6.8, 8.9)
Qassim	13 (12.3, 13.8)
Riyadh	16.7 (16.3, 17.1)
Tabuk	8.5 (7.7, 9.2)

Table 4.29 Age-standardised incidence rate of BC by different Saudi regions

Joinpoint analysis for all the regions is shown in the graphs below. The results were displayed in three graphs to make it easier to view.

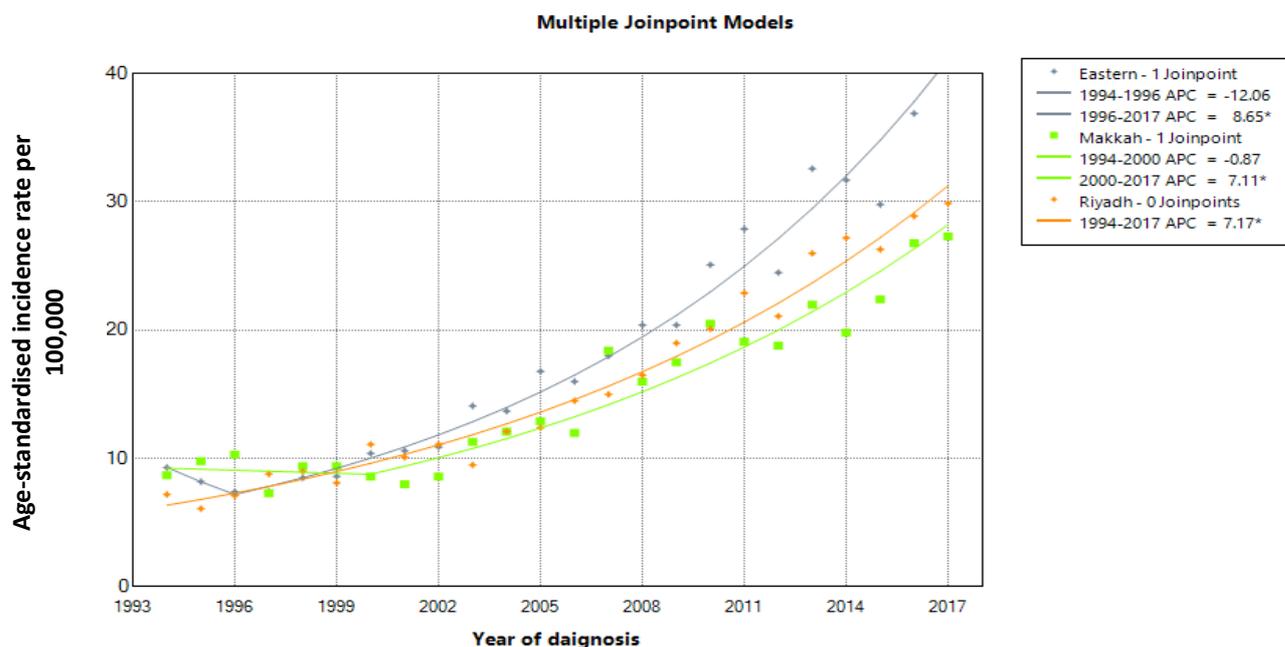


Figure 4.22 Joinpoint analysis for an ASR of BC by region for the following regions: Eastern, Makkah, and Riyadh from 1994-2017

In the eastern region, the APC in the incidence rate exhibited distinct patterns over two time periods. From 1994 to 1996, the APC was estimated at -12.1% (95% CI -29, 9.6), signifying a statistically non-significant decrease in the incidence rate, which could be very likely due to chance. In contrast, from 1996 to 2017, the APC demonstrated a notable and statistically significant increase (APC 8.6%; 95% CI 8, 9.3).

While in Riyadh, it shows a steady significant increase with an APC of 7.7% (95%CI 6.6,7.8). Makkah exhibited a pattern comparable to the eastern region; there was a non-significant decrease in the first period from 1994 to 2000 with an APC of -0.8 (95%CI -6.7, 5.3). This indicates that the rates were stable from 1994 to 2000, followed by a significant increase with an APC of 7.1 (95%CI 5.8, 8.5).

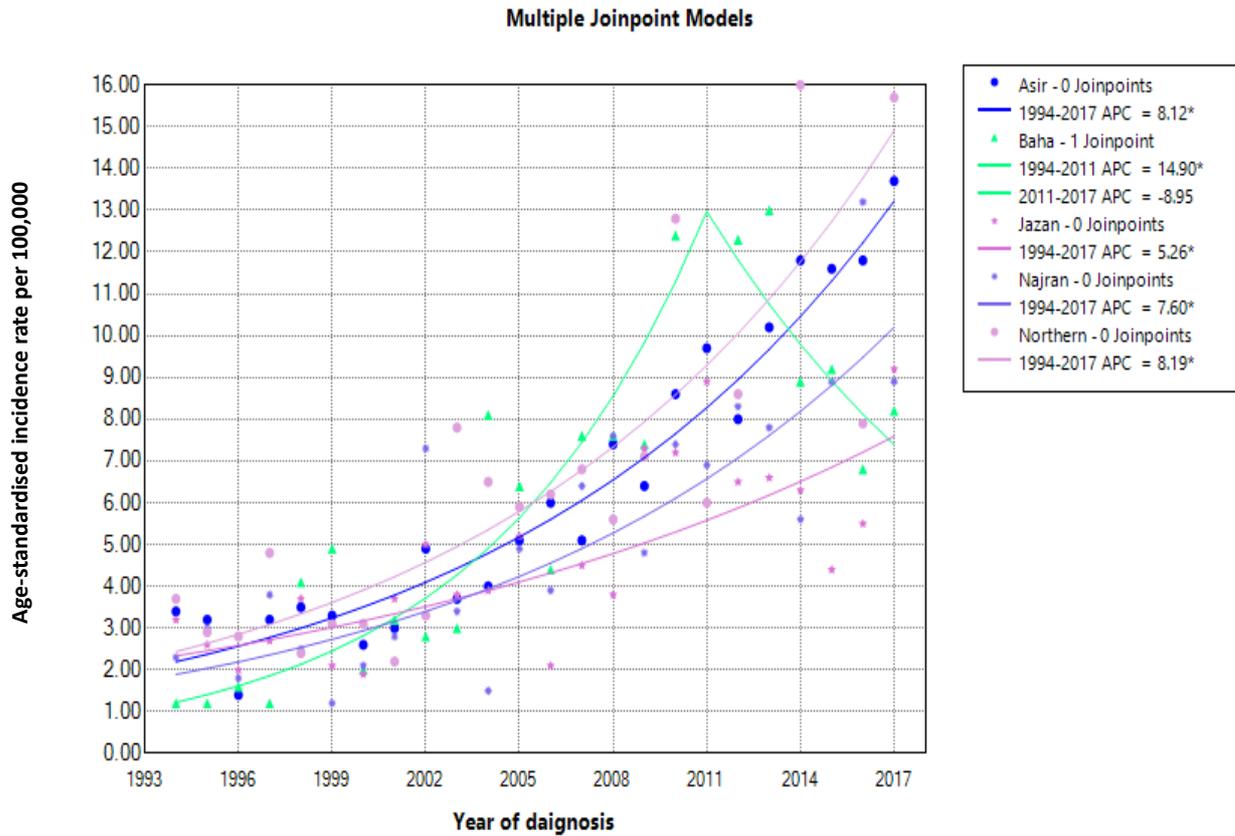


Figure 4.23 Joinpoint analysis for an ASR of BC for the following regions: Asir, Baha, Jazan, Najran, and Northern between 1994- 2017.

There was a steady increase in all the other regions, which was significant from 1994 to 2017, except for Asir, Baha, and Hail.

In Asir, there was a non-significant decrease in the period from 1994 to 1996 ($P = 0.2$), which means that the rates were stable, followed by a significant increase with an APC of 9.1 (95%CI 7.9, 10.3). In Baha, the results showed a statistically significant increase with an APC of 14.9 (95%CI 11.1, 18.8) from 1994 to 2011, followed by a non-significant decrease from 2011 to 2017 ($P = 0.24$).

Hail was the only region that showed two Joinpoints with three segments. First, there was a significant increase from 1994 to 1996 with an APC of 202.6 (95%CI 41.9, 545.2). Then, there was a non-significant decrease ($P = 0.52$) from 1996 to 1999, followed by a statistically significant increase from 1999 to 2017 with an APC of 9.8 (95%CI 7.1, 12.5).

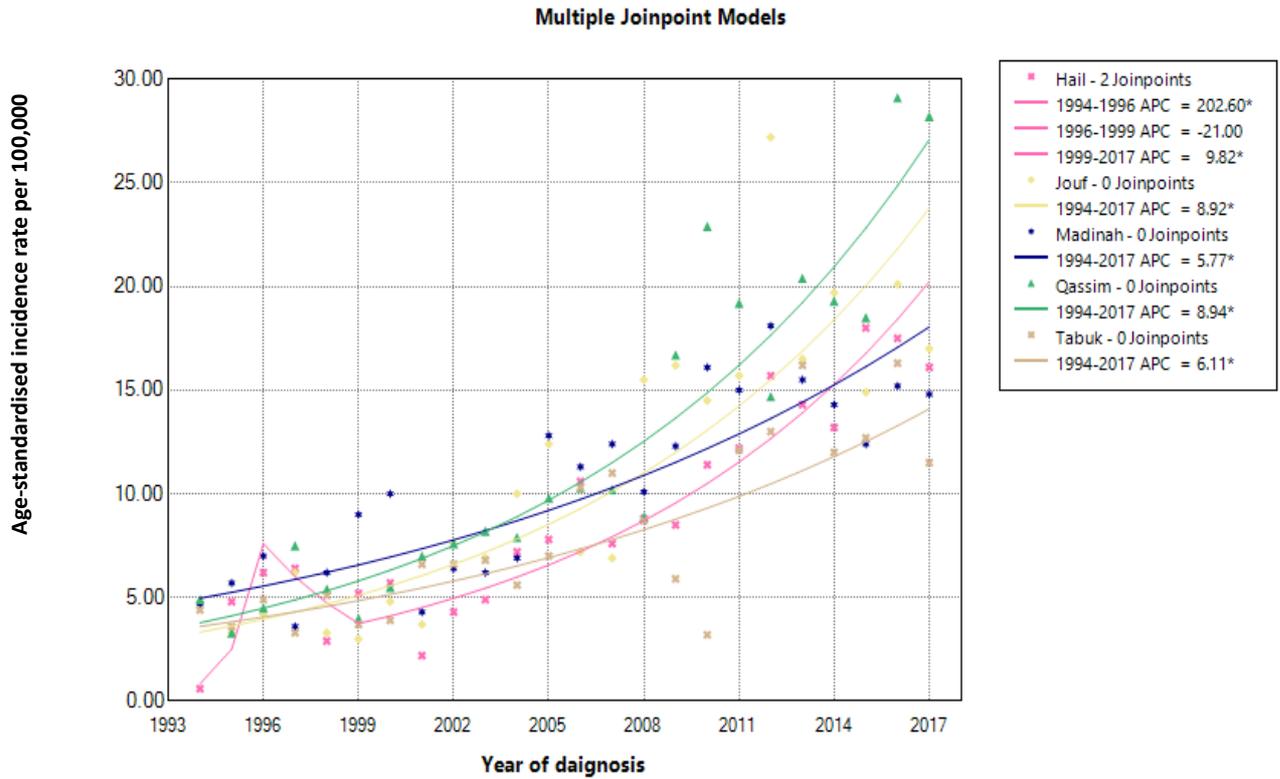


Figure 4.24 Joinpoint analysis for an ASR of BC for the following regions: Hail, Jouf, Madinah, Qassim and Tabuk between 1994-2017.

4.3.4 The association of BC risk factors with tumour molecular subtype (hormone receptor status) and stage at diagnosis for hospital data only

Risk factors:

Risk factors include a positive family history of cancers; about 67% of cases were without a family history of any cancer. On the other hand, within the cases with a positive family history of cancer, about 56% had a family history of breast cancer.

In 57% of the cases, the onset of menarche occurred between the ages of 12 and 15, whereas the age at menopause was not reported in 2761 cases, which is inadequate to establish any association between BC and the age of menopause. About 44% of the BC cases experienced their first pregnancy between the ages of 15 and 25 years. One of the risk factor included in this study is using hormonal therapy or oral contraceptives, and approximately 50% of the cases reported the use of oral contraceptives /hormonal therapy.

Risk category	n	%
Family history		
Positive	612	17.81
Negative	2,330	68.36
Using oral contraceptives or Hormonal therapy		
Positive	1,200	49.63
Negative	439	18.16
Not available	879	42.21
Total	2,418	100
Age at menarche		
< 12	173	5.97
12-13	876	30.25
14-15	778	26.87
16- 17	95	3.28
≥ 18	8	0.27
Not available	965	33.33
Total	2,895	100
Age at first pregnancy		
< 15	78	2.70
15- 20	797	27.58
21- 25	484	16.75
26- 30	283	9.79
>30	94	3.25
Not available	1,153	39.91
Total	2,889	100

Table 4.30: BC risk factors frequencies and percentages. OC: oral contraceptives

4.3.5 Association of breast cancer risk factors with tumour subtypes and stage at diagnosis

There was no difference in risk of developing BC among tumour subtypes and late age at menarche ($P = 0.7$) or early age at 1st pregnancy ($P = 0.06$); although the p-value approached significance, the results of the multinomial regression analysis indicated that the association was not statistically significant. Moreover, association with a family history of cancer did not differ significantly across molecular subtypes ($P = 0.6$).

On the other hand, cases using oral contraceptives or hormonal therapy were found to have a lower risk of negative receptors ER-/PR- (OR 0.69, 95% CI 0.54, 0.89; $P = 0.004$).

The cases with an age of ≥ 50 at diagnosis had a decreased risk of the ER-/PR- subtype (OR 0.56, 95% CI 0.47, 0.66; $P = 0.0001$). The odds ratios were estimated using a logistic regression model; the results are presented in Table 4.31 below.

	Relative Risk Ratio (CI 95%)	P value
Age at menarche (<12 vs. ≥ 12)		
ER+/ PR+	1 (referent)	
ER+/ PR-	0.97 (0.57, 1.7)	0.921
ER-/ PR+	0.46 (0.1, 2.2)	0.327
ER-/ PR-	0.88 (0.62, 1.2)	0.468
Oral contraceptives/ hormonal therapy (no, yes)		
ER+/ PR+	1 (referent)	
ER+/ PR-	0.746 (0.51, 1.1)	0.135
ER-/ PR+	0.457 (0.15, 1.41)	0.174
ER-/ PR-	0.695 (0.54, 0.89)	0.004
Age at diagnosis (< 50 vs ≥ 50)		
ER+/ PR+	1 (referent)	
ER+/ PR-	1.159 (0.89, 1.49)	0.252
ER-/ PR+	0.868 (0.34, 2.16)	0.762
ER-/ PR-	0.559 (0.47, 0.66)	0.0001
Family history (no, yes)		
ER+/ PR+	1 (referent)	
ER+/ PR-	1.174 (0.85, 1.6)	0.313
ER-/ PR+	0.795 (0.22, 2.80)	0.723
ER-/ PR-	0.964 (0.77, 1.19)	0.738
Age at 1 st pregnancy (≤ 30, >30)		
ER+/ PR+	1 (referent)	
ER+/ PR-	1.05 (0.71, 1.56)	0.803
ER-/ PR+	0.33 (0.04, 2.6)	0.299
ER-/ PR-	1.05 (0.82, 1.36)	0.666

Table 4.31. Association between risk factors and hormone receptor status. ER: oestrogen receptor, PR: progesterone receptor, CI: confidence interval, OC: oral contraceptive.

Regarding the stage at diagnosis, there was a significant association between stage at diagnosis and age at diagnosis ($P = 0.017$) and a significant association with family history ($P = 0.0001$). At the same time, there was no association between the stage and the age at menarche ($P = 0.716$), age at first pregnancy ($P = 0.461$), and using oral contraceptives or hormonal therapy ($P = 0.111$).

4.3.6 Clinical response (Recurrence/ progression) for hospital data only

After treatment, complete remission was achieved in 69% of the cases, while 22% of the cases showed disease progression. Most metastasis cases involved bone (48.6%), and the most frequently used technique for diagnosing recurrence and progression was a CT scan (72%).

Recurrence:

Recurrence after treatment was uncommon; only 15% of the cases experienced recurrence, 68% of them were systemic, and 40% of the local recurrences were in the chest wall. The relationship between the recurrence and the treatment modality used showed that the combination of Chemotherapy + Radiotherapy + Hormonal therapy was associated with the highest recurrence with 25%, followed by the combination of Chemotherapy + Surgery + Radiotherapy+ Hormonal therapy with about 21% of recurrence cases. In 36% of the recurrence cases, chemotherapy was used, and 19% used radiotherapy.

The association between recurrence and age at diagnosis tested by the logistic regression showed that younger ages (< 50) are associated with a lower risk of recurrence (OR 0.58, 95% CI 0.46, 0.74).

When controlling for age at diagnosis as a confounding variable and testing for the association between the recurrence and risk factors, cases with ER negative and PR positive were associated with high risk (OR 1.52, 95% CI 1.04, 2.23), while cases with negative oestrogen and progesterone receptors had a higher risk of recurrence (OR 2.3, 95% CI 1.79, 2.96).

In respect of recurrence and tumour stage, cases in stage II showed a high risk of recurrence (OR 2.28, 95% CI 1.15, 4.48), while cases in stage III showed a higher risk of recurrence (OR 6.67, 95% CI 3.44, 12.95), and cases in stage IV showed a lower risk of recurrence (OR 0.37, 95% CI 0.14, 0.96).

4.4 Discussion

The first objective of this study accomplished in this chapter using a retrospective, population-based, and hospital-based study was to describe the incidence of BC in Saudi females and the trends of incidence of BC in different age groups, BC subtypes, and Saudi regions.

Several key findings were observed in SCR data including 1) BC incidence increased more than fourfold from 6.4 cases per 10,000 women (432 cases) in 1994 to 26.4 cases per 100,000 women (2464 cases) in 2017, with the highest incidence noted among ages 40-49 from 1994 to 2017. 2) The median age at diagnosis was 49 years. 3) the most common type diagnosed was infiltrating ductal carcinoma (78%), with grades II and III accounting for a significant number of cases (70%) and regional BC accounting for 43% of the cases.

One of the major findings observed in this study is that over the entire study period, the crude incidence rate of BC increased fourfold between 1994 and 2017, with a 5% annual increase in the last seven years; this increase is consistent with the findings from existing literature in KSA and globally (AL Zomia et al., 2024; Ferlay, Ervik M, & Lam F, 2024). A study conducted in KSA showed that ASR increased from 15.4 per 100,000 in 1990 to 46.0 in 2021 and projected to continue increasing with a forecasted rate of 49.6 in 2026 (AL Zomia et al., 2024), which is consistent with the findings of the current study.

The apparent increase in BC incidence is likely multifactorial and might be attributed to a combination of factors such as improved awareness about BC in the community through educational campaigns encouraging women to seek medical advice, an increase in screening programmes started with non-governmental campaigns in 2007 (Abulkhair et al., 2010), followed by campaigns initiated by Saudi MOH in 2015 to increase awareness of early screening (Gosadi, 2019). It could also be due to improvements in healthcare access, which allow for more diagnoses.

In this study, the age-standardised incidence rate significantly increased from 1994 to 2001 by an APC of 2.98% and thereafter increased substantially from 2001 to 2010 with an APC of 9.72% and from 2010 to 2017 with an APC of 5.19%. Comparing this increase in ASR with the constant trend in proportional incidence reported from the hospital data during 2008 to 2017 suggests stable case distribution within the hospital settings or because more cases are being diagnosed outside the

hospital or better screening. The highest increase in ASR observed from 2001 to 2010 can't be explained by screening because the Ministry of Health initiated the screening programme in 2015. Another factor could be lifestyle changes, such as physical inactivity and a diet rich in fat and sugar, which may increase the risk of obesity (Alquaiz et al., 2021). A study conducted in KSA measured the physical activity of 161 participants who reported high levels of inactivity among Saudi females compared to international reports (Al-Eisa & Al-Sobayel, 2012). Additionally, Reproductive habits have shifted from early marriages and high parity (Ravichandran & Al-Zahrani, 2009) to delaying childbearing and having fewer children, which are considered risk factors for BC (Al-Khraif et al., 2020).

In comparison, the crude incidence rate was 13.6 per 100,000 population, and the age-standardised rate was 15.7 per 100,000, which is higher than the crude rate. This means that the standardised world population are, on average, older than the Saudi population.

Although the increase in the incidence rate was significant in Saudi females, it is still lower than in UK females. The ASR in the UK was 94.0 per 100,000 people in 2022, compared to ASR of 25.3 per 100,000 people in Saudi Arabia in the same year (Ferlay, Ervik M, & Lam F, 2024). This could be related to the differences in the age structure; KSA has a relatively younger population where youth and children represent more than two-thirds of the Saudi population, and the age group (15-34 years) has the highest percentage amongst all age groups (36.7%) (Statistical Analysis and Decision Support Center, 2020).

The second important finding is the early age at diagnosis. Aligning with previous studies, the median age at diagnosis was found to be lower (49 years) than the global findings; it was 49 years in the SCR data and 47 years which is slightly younger in the hospital data. About 55% of the cases were diagnosed between the ages 40-59, which is significantly younger than the median age of 62 reported in Western countries or the UK. Still, these populations are older than the Saudi population. The incidence trend by age at diagnosis was significantly increased in all age groups, but it increased most in the age group 40-49, with an APC of 13.2%, followed by age from 50-59. The years from 2001 to 2007 showed the highest increase for age from 40-59.

One of the most noteworthy findings in this study is that the highest incidence of BC was noted among those aged 40-49 years, which could be attributed to several factors. The relatively younger

population demographic in the region compared to Western countries mentioned previously may play a role.

Additionally, genetic differences or gene mutations could influence the earlier onset of BC; it was found that a larger proportion of young women with BC have pathogenic variants in cancer predisposition genes such as BRCA1/2 compared to late-onset BC (Zhu et al., 2023). Another study suggests that young women may be distinct with a unique underlying biology (Gabriel & Domchek, 2010). In Saudi women, BRCA1 and BRCA2 mutations are an essential factor in the aetiology of BC (Abulkhair, 2014); another substantial factor likely contributing to BC predisposition in the Saudi population is the disruption of DNA repair pathways (Alshammari, 2019).

The incidence trend by stage showed an increase in stage II with an APC of 11.8% from 1999 to 2017 APC of 13.7%. This increase in earlier-stage diagnosis may reflect improved awareness and screening efforts. However, there was also an increase in stage III with an APC of 5.9% from 1998-2017 and an increase in metastasis stage IV by an APC of 12% from 1994-1999 and 11.3% from 1999-2010. This suggests that while some progress has been made in identifying BC earlier, late-stage diagnosis remains prevalent.

The increase in the ASR was significant across all grades. These results are consistent with those from previous Saudi studies. Compared with Western countries, BC is highly diagnosed in the late stages in Saudi females. The high incidence of late-stage diagnosis raises significant concerns as it is associated with poorer survival. Several factors could contribute to this delay, which may reflect limitations in healthcare access, including inadequate screening programmes, especially for high-risk populations. Also, low or lack of awareness of BC symptoms could contribute to late presentation (Waheed et al., 2023).

Sociodemographic status impacts the timing of patient presentation for diagnosis; one of the significant factors is the educational level. Low education level was found to be associated with late-stage diagnosis, which could be due to the patient's ability to recognise the symptoms and seek care, in addition to their adherence to screening programmes (Alotaibi et al., 2019).

Studies have consistently found that early age at diagnosis was associated with aggressive disease and late stages at diagnosis. A review conducted in 2023 reported that BC in young women is

diagnosed in advanced stages and has more aggressive biological features (Zhu et al., 2023). Another study conducted in Argentina found that BC in young women (≤ 40 years of age) was associated with aggressive pathological features and locally advanced disease at the time of diagnosis (Fabiano et al., 2020). The same results were reported in a UK-based study between 2000 and 2008 (Azim & Partridge, 2014). Still, this study failed to find an association between age and stage at diagnosis, which could mean that the late stage is influenced by other factors such as genetics, lifestyle or socioeconomic factors such as educational level.

Factors such as cultural behaviour might contribute to differences in BC onset; even though screening in KSA is free, females of older ages are often hesitant to participate in the screening process because of the misunderstanding of the procedure, or they may be afraid of the results (Abdel-Aziz et al., 2017).

Regarding regions, the three Saudi regions that accounted for the highest percentage of cases (78%) were Makkah, Riyadh, and the Eastern region. These three regions collectively represent 68% of the total population, which may partially explain the higher incidence observed in these areas. In 2016, according to the Ministry of Health Statistics, there were four oncology centres located in these three areas in addition to Al-Qassim, enhancing access to specialised care. Additionally, maldistribution of healthcare services and facilities was reported, which delayed people living in remote areas and borders from seeking medical services (Almalki et al., 2011); Riyadh contains the largest proportion of hospitals (17.8%), followed by Makkah (14.3%), then the eastern region (12.4%), this may explain the high percentage of cases diagnosed in these three areas specifically. The availability of screening programmes could further contribute to the differences in BC among different regions.

Regarding hospital data, hormonal receptor status was shown to be ER+ve in 65% of the cases; this type of tumour is less aggressive, spreads slower compared to the negative tumours and responds to hormonal therapy with a lower risk of recurrence. Her2/neu receptor status was negative in 56% of the cases, which has a better prognosis than positive HER2/neu. There is no association between risk factors and BC except for using oral contraceptives or hormonal therapy in ER-ve/PR-ve receptor status.

Strengths and limitations of the study

This study was a population-based study using data from the SCR, setting it apart from incidence comparisons from previous KSA studies that were not population-based and depended on single-centre reports or studies that used the registry data but for a short period of time. It covers a period of 23 years, making it the longest study on Saudi females BC obtained from population-based data, including cases from all ages and stages. However, the data completeness and validity can't be fully assessed, which could impact the study's findings by introducing bias or uncertainty into the study's findings.

Missing or incomplete data may lead to underestimation or overestimation of incidence trends. Moreover, the SCR lacks comprehensive information on tumour markers, and in order to address this limitation, data on tumour markers was obtained from the hospital; however, the unavailability of tumour markers constrains the generalisability of the results. Variations in the quality of data between sources, such as hospital records versus registry data, could affect the consistency and reliability of the analysis. Furthermore, the study did not include data on certain risk factors, such as genetic factors, as these were not available in the registry, even though including these factors would provide valuable information about their role in BC incidence, stage, and age at diagnosis.

4.5 Conclusion

The incidence of BC in KSA has been increasing over the years, characterised by a unique prevalence among younger women and late-stage diagnoses. These findings underscore the importance of understanding demographic variations in BC incidence. Moreover, this study highlights significant trends and emphasises the urgent need to enhance awareness of BC symptoms, promote self-examination, and improve screening programme policies targeting high-risk populations. The absence of genetic factors in the analysis suggests a need for further research, including genetic aspects that could enrich the understanding of BC trends in KSA.

Chapter 5 Breast Cancer Management

5.1 Introduction

This chapter covers the management of BC in Saudi females based on the data obtained from the KFSH&RC registry. The third objective of this thesis was to explore the treatment patterns in the management of BC based on age group and molecular subtype. Considering that BC is typically diagnosed in most Western countries and the UK at an older mean age of 63 (Surveillance Research Program, 2024), compared to Saudi females who are diagnosed at an earlier mean age of 49 (Basudan, 2022), as discussed in Chapter 4, treatment options may vary according to age. For example, younger ages tend to undergo breast-conserving surgery rather than mastectomy in comparison to older ages (Rossi et al., 2019). Concerning radiation therapy, additional radiation was associated with reduced local recurrence in younger women. The beneficial effect of luteinising-hormone releasing hormone agonists after chemotherapy was detected in younger women but not in older premenopausal women (Ribnikar et al., 2015).

The fact that BC is diagnosed in younger women increases the likelihood that the tumours will be diagnosed in late, poorly differentiated and have greater rates of triple-negative and HER2-overexpressing tumours, which require different treatment plans (Anastasiadi et al., 2017). Despite all BC treatment modalities being used in practice in KSA, few comprehensive studies have focused on the pattern of BC treatment (Alnefaie et al., 2024; Abdulwassi et al., 2020; Abu Zaid et al., 2017; Trabulsi et al., 2021b; Ezzat et al., 1999a).

Multidisciplinary approaches are used in the management of breast cancer, including surgery, radiation, hormonal therapy, chemotherapy, and biological treatment (Moulder & Hortobagyi, 2008). The treatment strategies are tailored to individual patients based on several factors, which include tumour stage and characteristics, menopausal status, and patient preference (Sharma et al., 2010).

A primary breast tumour is usually treated with surgery, chemotherapy, and radiotherapy. Despite this, BC treatment usually involves multiple treatment methods. Women are treated differently based on their hormone receptor status and/ or HER2 status, as different subtypes of BC respond differently to treatment strategies (Trayes & Cokenakes, 2021).

The treatment plan depends on the stage of BC at diagnosis; the standard management is the surgery-based treatment with or without axillary node dissection in case of operable BC (stage I and II), whether breast-conserving surgery or total mastectomy. Neoadjuvant chemotherapy will be used in locally advanced BC (stage IV) and large tumours. Adjuvant chemotherapy, radiotherapy, endocrine therapy, and targeted therapy are administered after the surgery according to the patient's medical condition and tumour characteristics (Loibl et al., 2024).

This chapter used data from the KFSH&RC registry, including 2688 records of BC cases from 2008 to 2016, detailed in Chapter 3. It presented a descriptive analysis of the data on BC management and an analysis of the distribution of these modalities by molecular subtype and age group.

5.2 Methods

5.2.1 Descriptive statistics

Descriptive analysis was presented by the number and percentage of the type of management the hospital provides. For each treatment modality administered to BC patients in the hospital, descriptive statistics about the type of treatment were presented in terms of number and percentage.

5.2.2 Distribution of BC treatment modalities by molecular subtype and age group

In this study, the distribution of BC cases in relation to treatment strategies (surgery, chemotherapy, radiation, hormonal, biological) over time is first presented by ER status (ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-) and age group (<20, 20-29, 30-39, 40-49, 50-59, 60-69, 70-79, ≥80) as frequencies and percentage. Then, the Chi-Square test was used to assess whether there are significant associations between tumour subtype and the choice of treatment modality; a P -value < 0.05 was considered significant. Next, to further explore the relationship between treatment modalities, tumour subtype, and age group, a single logistic regression analysis was performed for each independent variable; the dependent variable was the treatment modality, and the independent variables included were the age group and the tumour subtype. Odds ratios (OR) with 95% confidence intervals were calculated using the logistic regression models to quantify the strength of the associations.

5.3 Results

5.3.1 Descriptive analysis

The total number of BC cases available for analysis in the KFSH&RC registry was 3408 females. The management of BC in the hospital revealed that a curative plan was applied in approximately 80% of the cases, whereas the remaining 20% were managed with palliative care. In the curative plan, a combination of different treatment strategies was used. As shown in Table 5.1, six patients did not receive any treatment, while the treatment modality for 849 patients was not specified or unknown. The remaining were 1563 cases with known treatment modalities.

Treatment modality	n	%
No treatment	6	0.25
Surgery	34	1.41
Surgery + Radiotherapy	23	0.95
Surgery + Radiotherapy+ Hormonal therapy	137	5.67
Surgery +Chemotherapy + Radiotherapy	172	7.11
Surgery +Chemotherapy + Radiotherapy + Hormonal therapy	320	13.23
Surgery +Chemotherapy + Hormonal therapy	129	5.33
Surgery + Hormonal therapy	115	4.76
Chemotherapy+ Surgery + Radiotherapy	244	10.09
Chemotherapy+ Surgery + Radiotherapy+ Hormonal therapy	367	15.18
Chemotherapy+ Surgery + Chemotherapy + Radiotherapy+ Hormonal therapy	20	0.83
Chemotherapy+ Radiotherapy+ Hormonal therapy	2	0.08
Others	846	34.99
Unknown	3	0.12
Total	2,418	100

Table 5.1. Treatment modalities provided at KFSH&RC.

By observing the distribution of cases with known treatment modalities by tumour subtype, it was found that radiotherapy was predominantly utilised in negative-receptor cases. In contrast, hormonal therapy was primarily used in positive-receptor cases. Among receptor-positive cases, treatment combinations frequently included hormonal therapy alongside surgery and/or chemotherapy. In contrast, receptor-negative cases more commonly involved radiotherapy and chemotherapy combinations, often without hormonal therapy.

Surgery:

Surgical intervention was undertaken in approximately 87% of the cases. Over half of these cases underwent a modified radical mastectomy. Furthermore, more than half of the cases involved axillary node dissection, with a range of 10 to 19 nodes being excised in 38% of the cases. Moreover, about 39% of these nodes were found to be negative.

Type of surgery	#	%
BCT (Breast conserving therapy)	471	29.36
Modified radical mastectomy	1102	49.02
Re-excision	20	0.88
Simple mastectomy	220	9.78
Skin sparing mastectomy	137	6.09
Palliative mastectomy	98	4.36
Unknown	9	0.40
Total	2,248	100

Table 5.2. Types of BC Surgery at KFSH&RC by number and percent.

Radiotherapy:

About 72% of the cases received radiotherapy; external 3D-CRT (conformal radiation therapy) was mainly used in 98% of the cases. Patients who received a boost dose were about 21% of the cases.

Type of radiotherapy	#	%
External 3D-CRT	1,506	98.69
External IMRT	11	0.72
Internal brachytherapy (intracavitary/ ballon catheter)	1	0.07
Internal brachytherapy interstitial (rows of bundles of catheters)	5	0.33
Intraoperative radiation therapy (IORT)	2	0.13
Total	1,525	100

Table 5.3. Types of radiotherapy at KFSH&RC by number and percentage.

Biological treatment (targeted therapy):

In most cases (approximately 74%), patients did not receive biological treatment. Among the 26% that did receive biological treatment, 26% used Herceptin.

Type of biological treatment	#	%
Herceptin	630	26.46
Avastin	7	0.29
Others	13	0.55
Tykerb (Lapatinib)	8	0.33
Unknown	1,824	72.37
Total	2382	100

Table 5.4. Types of biological treatment at KFSH&RC by number and percentage.

Chemotherapy, neoadjuvant & adjuvant:

Chemotherapy was administered in 73% of the cases. Neoadjuvant chemotherapies were used in 44% of the cases; however, in cases where neoadjuvant chemotherapy was used, FAC and Docetaxel (Taxotere) account for 32% of the neoadjuvant chemotherapy used. On the other hand, adjuvant chemotherapy was used in 36% of the cases. FEC is the most frequently used adjuvant chemotherapy, with approximately 45% of the cases, followed by AC (21%).

Type of Neoadjuvant chemotherapy	#	%
AC (Doxorubicin, Cyclophosphamide)	191	16.9
FAC (Fluorouracil, Adriamycin, Cytosol)	84	7.45
Taxol/ platinum	12	1.06
Taxotere/ platinum	58	5.15
FEC (Fluorouracil, Epirubicin hydrochloride, Cyclophosphamide)	452	40.12
Taxol	91	8.07
Docetaxel (Taxotere)	182	16.15
Unknown	57	5.06
Total	1,127	100
Type of Adjuvant chemotherapy		
AC	186	21.04
FAC	28	3.17
CMF	6	0.68
Others (not specified)	179	20.25
FEC	397	44.9
Taxol (Paclitaxel)	23	2.60
Docetaxel (Taxotere)	65	7.35
Total	884	100

Table 5.5. Types of Chemotherapy at KFSH&RC by number and percentage.

Hormonal therapy:

Hormonal therapy was used in 63% of the cases, with 74% of them using adjuvant hormonal therapy. Tamoxifen was used in 47% of the cases, while aromatase inhibitors were used in 22% of the cases.

Classification of hormonal therapy	#	%
Neoadjuvant	95	5.91
Adjuvant	1,191	74.07
Neoadjuvant + adjuvant	46	2.86
Palliative	254	15.80
Unknown	22	1.37
Total	1,608	100
Type of hormonal therapy		
Tamoxifen	1,064	46.83
Others	11	0.48
Aromatase inhibitors (Femara)	468	20.59
Aromatase inhibitors (Aromasin)	9	0.38
Aromatase inhibitor (Arimidex)	5	0.22
Unknown	715	31.46
Total	2,272	100

Table 5.6. Hormonal therapy at KFSH&RC by number and percentage.

The distribution of BC cases using hormonal therapy by receptor status showed that hormonal treatment was mainly used in oestrogen receptor-positive cases (73%).

Hormonal therapy	Receptor status				Total
	ER+/PR+	ER+/PR-	ER-/PR+	ER-/PR-	
Tamoxifen	764 (84.9%)	114 (12.7%)	4 (0.4%)	18 (2.0%)	900
Aromatase inhibitors	379 (81.5%)	79 (17.0%)	2 (0.4%)	5 (1.1%)	465
Tamoxifen then AI	116 (85.9%)	19 (14.1%)	0 (0%)	0 (0%)	135
AI then tamoxifen	8 (100%)	0 (0%)	0 (0%)	0 (0%)	8
Tamoxifen + other	18 (81.8%)	2 (9.1%)	0 (0%)	2 (9.1%)	22
AI + other	5 (100%)	0 (0%)	0 (0%)	0 (0%)	5
Not specified	74 (11.1%)	26 (3.9%)	7 (1.1%)	558 (83.9%)	665
Total	1,364 (62.0%)	240 (10.9%)	13 (0.59%)	583 (26.51%)	2,200

Table 5.7. Distribution of hormonal therapy by receptor status at KFSH&RC.

Distribution of hormonal therapy by menopausal status showed that tamoxifen was given mainly to premenopausal women (97%), while aromatase inhibitors were used in postmenopausal women (66.5%).

Hormonal Therapy	Menopausal status				Total
	Premenopausal	Perimenopausal	Postmenopausal	Unknown	
Tamoxifen	692 (76.4%)	35 (3.9%)	154 (17.0%)	25 (2.7%)	906
AI	23 (4.9%)	6 (1.3%)	434 (92.7%)	5 (1.1%)	468
Tamoxifen then AI	63 (46.7%)	4 (3.0%)	66 (48.9%)	2 (1.4%)	135
AI then tamoxifen	0 (0%)	0 (0%)	9 (100%)	0 (0%)	9
Tamoxifen + other	17 (73.9%)	2 (8.7%)	4 (17.4%)	0 (0%)	23
AI + other	1(20.0%)	2 (40.0%)	2 (40.0%)	0 (0%)	5
Not specified	457 (63.6%)	18 (2.5%)	232 (32.4%)	11 (1.5%)	718
Total	1,253 (55.2%)	67 (3.0%)	901 (40.0%)	43 (1.8%)	2,264

Table 5.8. Hormonal therapy by menopausal status at KFSH&RC.

5.3.2 Distribution of BC treatment modalities by molecular subtype based on the hospital data

Table 5.9 shows the variations in the distribution of BC in relation to treatment modality by the tumour subtypes as frequency and percentage. In addition, the table shows the results from a chi-square test and logistic regression analysis, which examines the association between treatment modalities and tumour subtypes.

Most patients who underwent surgery are classified as ER+/PR+ tumours (57%), followed by those in the ER-/PR- category (32%). Among those who did not receive surgery, ER+/PR+ is still the largest group (24%). The overall p -value ($P = 0.02$) suggests a statistically significant difference in surgery among molecular subtype groups compared to the reference group (ER+/PR+); specifically, the significant finding in the ER-/PR- category indicates that this group has 47% higher odds of undergoing surgery compared to the reference group (OR = 1.47, 95%CI 1.19, 1.94), this group are more likely to receive surgical intervention in their treatment plan.

The frequency of radiotherapy varies statistically significantly by tumour subtypes ($P = 0.04$). Specifically, patients classified as ER-/PR- have significantly higher odds of receiving radiotherapy compared to the reference group of ER+/PR+ with an OR of 1.32 (95% CI 1.07, 1.62). Additionally, patients classified as ER+/ER- also show increased odds of receiving radiotherapy with an OR of 1.28 (95% CI 0.94, 1.76). However, this increase was not statistically significant.

There was a statistically significant association between the use of chemotherapy and tumour subtype ($P = 0.001$). Logistic regression odds ratios and P - values showed that cases with ER+/PR- and ER-/PR- subtypes have a significantly higher likelihood of receiving chemotherapy than the reference group with OR = 1.78 (95% CI 1.29, 2.45) and OR = 3.48 (95% CI 2.7, 4.4), respectively. Indicating a 78% increased likelihood of receiving chemotherapy in ER+/PR-, while ER-/PR- cases showed a 248% increase in likelihood. Additionally, ER-/PR+ also exhibited higher odds of receiving chemotherapy with an OR of 1.39 compared to the reference group.

Regarding biological treatment, among patients with the ER+ subtype, 20% were using biological treatment compared to 80% who did not use biological treatment. The difference in the likelihood of receiving biological treatment among the groups was shown to be statistically significant with $P = 0.0001$. Notably, cases with ER-/PR+ had an OR of 2.01 (95% CI 0.8, 5.8), indicating that they were

more than twice as likely to receive biological treatment compared to the reference group, however, this increase was not statistically significant. Furthermore, patients with the ER-/PR- subtype showed an even stronger association with the use of biological treatment, with an OR of 3.09 (95% CI 2.5, 3.8).

Among patients receiving hormonal therapy, the majority were ER+/PR+ patients, comprising 84% of this group. In contrast, the group who did not receive hormonal treatment has a much larger proportion of ER-/PR- (82%). The results indicate that having one or more negative receptors was associated with a decreased likelihood of receiving hormonal treatment. Specifically, the odds ratio for receiving hormonal therapy was significantly reduced for ER-/PR+ (OR = 0.06; 95% CI 0.02,0.17), suggesting a 94% decreased likelihood compared to those with positive receptors. When both ER and PR receptors were negative, the odds ratio dropped further to 0.003 (95% CI 0.002, 0.005), indicating a 99.7% reduction in the likelihood of receiving hormonal therapy compared to cases with positive receptors.

5.3.3 Distribution of BC treatment modalities by age group based on the hospital data

The distribution of BC treatment strategies by age group is represented in Table 5.10. Regarding surgery, there was a statistically significant difference in the likelihood of receiving surgery across age groups ($P = 0.0001$). Patients aged 70-79 and ≥ 80 demonstrated significantly lower odds of undergoing surgery, with OR of 0.32 (95%CI 0.19, 0.52) and 0.27 (95%CI 0.12, 0.62), respectively, suggesting that they were less likely to receive surgical intervention compared to middle-aged groups.

With respect to radiotherapy, the youngest age group (< 20) and the oldest age group (≥ 80) exhibited the lowest percentages of receiving radiotherapy, at 0.11% and 0.6%, respectively. The analysis also revealed that older age groups (60-69, 70-79 and ≥ 80) showed significantly lower odds of receiving radiotherapy compared to individuals in younger age groups.

Regarding chemotherapy, the overall P -value indicates a statistically significant difference in the likelihood of receiving chemotherapy across the age groups. Specifically, patients aged 30-39 had a significant increase in the odds of receiving chemotherapy (OR = 1.39, 95% CI 1.02, 1.89), while older age groups had markedly lower odds of receiving chemotherapy.

In biological treatment, the highest percentage of biological therapy was observed in the 40-49 age group (36.6%), followed by the 30-39 age group (24.3%). The results suggest that the likelihood of receiving biological treatment for BC decreases with increasing age, with younger age groups (20-29) showing higher odds of receiving biological treatment (OR = 1.55, 95% CI 1.02, 2.37) compared to older age groups, who exhibit progressively lower odds.

The 40-49 age group has the highest percentage of individuals receiving hormonal therapy (34.4%), followed by the 30-39 age group (16.6%). The results indicate a significant decrease in the odds of receiving hormonal therapy in the 20-29 and 30-39 age groups compared to the reference group, with very high statistical significance ($P = 0.0001$). Notably, older age groups (60-69 and 70-79) showed an increased likelihood of receiving hormonal therapy with very high statistical significance.

Women in all age groups were more likely to undergo surgery, except for those aged 70 and older, where the use of hormonal therapy surpassed surgical intervention. Females under age 20 primarily received surgery and chemotherapy, while those aged 20 to age 59 were more likely to receive surgery, chemotherapy and hormonal therapy. In the 60-69 age group, there was a greater likelihood of receiving hormonal treatment alongside surgery, with a reduced likelihood of chemotherapy, radiation and biological treatments. Conversely, women aged 70 and older predominantly received hormonal therapy and surgery, with lower likelihoods of undergoing radiotherapy, biological treatment and chemotherapy.

5.4 Systematic review

Based on the results of this study, which found that 65% of Saudi female BC cases were hormone receptor-positive, this emphasises the importance of focusing on the treatment used in this case, which is hormonal therapy. Two different types of hormonal therapies are used mainly in hormone receptor-positive BC cases, and menopausal status primarily determines the choice of the type. In the case of premenopausal women, the drug of choice is tamoxifen, while in postmenopausal women, aromatase inhibitors are used.

This study found that treatment in KFSH&RC hospital followed the guidelines for using hormonal therapy in hormone receptor cases by menopausal status. It also found that treatment modalities

for hormone-positive cases include hormonal therapy, surgery, radiation, and chemotherapy. Tamoxifen was used in 97% of premenopausal cases, and aromatase inhibitors were used in 66% of postmenopausal cases.

In this study, a comprehensive systematic review was conducted to analyse the economic effectiveness of hormonal therapy in hormone receptor-positive BC. The subsection 5.7 is taken directly from the systematic review published in BMC Health Services Research 2023 (Althuwaibi et al., 2023).

5.5 Discussion

Breast cancer remains a significant health problem in KSA, emphasising the need for effective treatment modalities that align with local practices. BC exhibits distinct characteristics among Saudi females, particularly in terms of age and stage at diagnosis. This trend has significant implications for treatment strategies and health policies.

Findings indicate a predominance of surgical interventions (87%), followed by chemotherapy (73%) and radiation (72%). The use of hormonal therapy varies based on menopausal status and receptor status and is consistent with international treatment guidelines. Hormonal therapy was used in oestrogen receptor-positive cases (73%), and regarding menopausal status, Tamoxifen was primarily used in premenopausal women (97%), while AIs were used in postmenopausal women (66%).

The results of this study illustrate notable variations in BC treatment strategies across different age groups, highlighting the influence of age on decision-making and treatment preference. The data indicated that older ages were less likely to have chemotherapy and biological treatments but more likely to have hormonal therapy and surgery. This finding aligns with existing literature that suggests that the best local control for older women with BC is surgery. Still, in cases that are not eligible for surgery, such as comorbidities or risk of anaesthesia, hormonal therapy would be the best choice (Wyld et al., 2004).

Saudi females were diagnosed at younger median ages, less than 50 years, compared to Western countries, and it was found that treatments used in this age group were surgery, chemotherapy,

biological and radiotherapy. Aggressive treatments were used in younger patients, which could be potentially due to the higher likelihood of BC being diagnosed at more advanced stages in younger patients (Sariego, 2010).

This study showed that hormonal treatment was more common in the 40-49 age group, which is explained by the high percentage of hormone receptor-positive tumours, specifically in this age group, which are mainly treated with hormonal therapy. This finding is consistent with guidelines suggesting the use of hormonal therapy for hormone receptor-positive tumours (Waks & Winer, 2019).

The hormone receptor status plays a critical role in guiding treatment decisions for BC. In this study, most of the cases were found to have hormone receptor-positive tumours, which are most effectively treated with hormonal therapy. It was found that 97% of premenopausal women used tamoxifen, and 3% used AIs. While 23% of postmenopausal women used tamoxifen, and 66% used AIs. These findings align with the guidelines for using hormonal therapy in hormone receptor-positive BC, which recommends using tamoxifen in premenopausal cases and aromatase inhibitors in postmenopausal cases (Maughan et al., 2010). These results show that the practice in the hospital aligns with the recent guidelines.

The tumour subtypes ER-/PR- and ER+/PR- are associated with more aggressive disease characteristics (Nascimento & Otoni, 2020b). This may encourage clinicians to consider surgery, radiotherapy and chemotherapy more in these cases, as these tumours may not respond to hormonal therapies. Additionally, tumour subtype ER-/PR- is often linked to a higher risk of recurrence and poor prognosis (Sonnenblick et al., 2014); this may encourage healthcare providers to favour chemotherapy as a preventive measure against disease progression.

In contrast, hormonal therapies specifically target hormone-sensitive tumours. ER+/PR+ tumours are responsive to these therapies, leading to their predominance among patients receiving treatment. Clinical guidelines typically recommend hormonal therapy for patients with positive receptor status (Burguin et al., 2021). Consequently, patients with negative receptors are less likely to be considered for this type of treatment, which explains the low likelihood of receiving such therapies in these cases (Burguin et al., 2021).

While this study provides important insight into BC treatment strategies by age and receptor status, some limitations should be considered. The study was conducted based on data from a single hospital. Even though this hospital is a tertiary referral hospital and one of the largest oncology centres in KSA and the Middle East, the results cannot be generalised. By going back to Chapter 4 and analysing the regions from which cases were referred, it was found that more than 58% of the cases originated from the central region, where the hospital is located, this limits the generalisability of the results.

The study did not consider the confounding variables influencing the treatment decision, such as patient preference, comorbidities, and compliance. These factors can impact the treatment choice and affect the outcome. Another limitation is that this study was retrospective, which may introduce bias in the accuracy and completeness of data, such as misclassification of tumour stage or missing information on patient outcomes, which could affect the validity of the results.

Additionally, this study includes only 26% of patients who received targeted therapies for BC, reflecting the availability of these treatments during the study period. Given the rapid evolution of targeted therapies and the introduction of new drugs in recent years, this may influence the outcome and treatment decision.

Future studies should address these limitations by conducting a multi-site study with a larger sample size and from different regions in KSA to provide results that could be generalised in addition to including other confounding variables and the new therapies to provide a comprehensive view of treatment strategies.

5.6 Conclusion

This study highlights the significant impact of age and receptor status on treatment strategies for BC patients by demonstrating that patients aged 20 to 59 years are more likely to receive surgery, hormonal therapy and chemotherapy, patients with ER-/PR- has higher odds of undergoing surgery while ER+/PR+ are more likely to receive hormonal therapy. The findings reveal distinct patterns in the likelihood of receiving various treatments and underscore the necessity for personalised treatment plans that consider each patient's unique characteristics.

Treatment		Hormone receptor status				Total
		ER +ve / PR +ve (%)*	ER +ve / PR -ve (%)*	ER -ve / PR +ve (%)*	ER -ve / PR -ve (%)*	
Surgery	Yes	1245 (57.4%)	214 (9.9%)	13 (0.60%)	697 (32.1%)	2,169 (100%)
	No	208 (63.2%)	39 (11.9%)	3 (0.92%)	79 (24.0%)	329 (100%)
OR (95% CI) (P -value)	P = 0.02	1 (Reference)	0.92 (0.63, 1.3) (0.65)	0.72 (-0.20, 2.6) (0.62)	1.47 (1.19, 1.94) (0.006)	-
Radiotherapy	Yes	1,009 (56.6%)	186 (10.4%)	11 (0.62%)	578 (32.4%)	1,784 (100%)
	No	404 (62.9%)	58 (9.03%)	5 (0.78%)	175 (27.3%)	642 (100%)
OR (95% CI) (P -value)	P = 0.04	1 (Reference)	1.28 (0.94, 1.76) (0.12)	0.88 (0.30, 2.6) (0.82)	1.32 (1.07, 1.62) (0.007)	-
Chemotherapy	Yes	991 (52.2%)	204 (10.7%)	12 (0.63%)	693 (36.5%)	1,900 (100%)
	No	459	53	4	92	608

		(75.5%)	(8.7%)	(0.66%)	(15.3%)	(100%)
OR (95% CI) (P -value)	P = 0.0001	1 (Reference)	1.78 (1.29, 2.45) (0.001)	1.39 (0.44, 4.3) (0.57)	3.48 (2.7, 4.4) (0.0001)	-
Biological	Yes	258 (39.8%)	72 (11.1%)	5 (0.77%)	313 (48.3%)	648 (100%)
	No	1141 (64.1%)	181 (10.2%)	11 (0.62%)	448 (25.2%)	1,781 (100%)
OR (95% CI) (P -value)	P = 0.0001	1 (Reference)	1.76 (1.3, 2.4) (0.0001)	2.01 (0.8, 5.8) (0.12)	3.09 (2.5, 3.8) (0.0001)	-
Hormonal	Yes	1328 (84.4%)	215 (13.6%)	6 (0.38%)	28 (1.78%)	1,577 (100%)
	No	103 (12.5%)	38 (4.6%)	8 (0.97%)	672 (81.9%)	821 (100%)
OR (95% CI) (P -value)	P = 0.0001	1 Reference)	0.44 (0.29, 0.65) (0.0001)	0.06 (0.02, 0.17) (0.0001)	0.003 (0.002, 0.005) (0.0001)	-

Table 5.9. Association between treatment strategies over time and tumour subtype. * Percentage of cases in the respective treatment modality, OR: odds ratio, CI: confidence interval.

Treatment		Age group at diagnosis							
		< 20 (N=2)	20-29 (N=119)	30-39 (N=617)	40-49 (N= 1,038)	50-59 (N=792)	60-69 (N= 353)	70-79 (N= 129)	≥ 80 (N= 34)
Surgery	Yes 2,244 (100%)	2 (0.09%)	87 (3.88%)	463 (20.63%)	792 (35.29%)	563 (25.09%)	244 (10.87%)	75 (3.3.4%)	18 (0.80%)
	No 345 (100%)	0 (0%)	13 (3.77%)	53 (15.36%)	107 (31.01%)	85 (24.64%)	46 (13.33%)	32 (9.28%)	9 (2.61%)
OR (95% CI) (P -value)	<i>P</i> = 0.0001	-	0.90 (0.48,1.67) (0.75)	1.18 (0.83, 1.67) (0.35)	Ref.	0.89 (0.66, 1.21) (0.48)	0.72 (0.49, 1.04) (0.08)	0.32 (0.19,0.52) (0.001)	0.27 (0.12,0.62) (0.002)
Radiotherapy	Yes 1,819 (100%)	2 (0.11%)	69 (3.93%)	391 (21.5%)	669 (36.78%)	455 (25.01%)	169 (9.29%)	53 (2.91%)	11 (0.60%)
	No 699 (100%)	0 (0%)	30 (4.29%)	111 (15.88%)	206 (29.47%)	171 (24.46%)	114 (16.31%)	50 (7.15%)	17 (2.43%)
OR (95% CI) (P -value)	<i>P</i> = 0.0001	-	0.71 (0.45,1.12) (0.14)	1.08 (0.83, 1.41) (0.54)	Ref.	0.82 (0.65, 1.04) (0.1)	0.46 (0.34, 0.61) (0.001)	0.33 (0.23,0.49) (0.001)	0.19 (0.09,0.43) (0.001)
Chemotherapy	Yes 1,920 (100%)	2 (0.10%)	88 (4.58%)	452 (23.54%)	741 (38.59%)	464 (24.17%)	140 (7.29%)	29 (1.51%)	4 (0.21%)

	No 674 (100%)	0 (0%)	17 (2.52%)	68 (10.09%)	155 (23.0%)	184 (27.3%)	150 (22.26%)	78 (11.57%)	22 (3.26%)
OR (95% CI) (P -value)	P = 0.0001	-	1.08 (0.63,1.87) (0.77)	1.39 (1.02, 1.89) (0.036)	Ref.	0.53 (0.41, 0.67) (0.0001)	0.19 (0.15,0.26) (0.0001)	0.08 (0.05,0.12) (0.0001)	0.04 (0.01,0.11) (0.0001)
Biological	Yes 655 (100%)	0 (0%)	39 (5.95%)	159 (24.27%)	240 (36.64%)	152 (23.21%)	50 (7.63%)	13 (1.98%)	2 (0.31%)
	No 1,856 (100%)	0 (0%)	66 (3.56%)	345 (18.59%)	630 (33.94%)	467 (25.16%)	232 (12.50%)	91 (4.90%)	25 (1.35%)
OR (95% CI) (P -value)	P = 0.0001	-	1.55 (0.042) (1.02,2.37)	1.21 (0.12) (0.95, 1.5)	Ref.	0.85 (0.19) (0.67, 1.08)	0.57 (0.001) (0.40, 0.79)	0.38 (0.001) (0.21,0.68)	0.21 (0.035) (0.05,0.89)
Hormonal	Yes 1590 (100%)	1 (0.06%)	45 (2.83%)	264 (16.6%)	547 (34.4%)	418 (26.29%)	212 (13.33%)	82 (5.16%)	21 (1.32%)
	No	1 (0.1%)	55 (6.113%)	224 (24.97%)	310 (34.56%)	201 (22.41%)	78 (8.7%)	21 (2.34%)	7 (0.78%)
OR (95% CI) (P -value)	P = 0.0001	0.57 (0.04,9.09) (0.7)	0.46 (0.31,0.70) (0.0001)	0.67 (0.53, 0.84) (0.0001)	Ref.	1.18 (0.95, 1.5) (0.14)	1.54 (1.15, 2.07) (0.004)	2.21 (1.34,3.65) (0.002)	1.70 (0.71,4.04) (0.23)

Table 5.10. Association between treatment strategy over time and age groups. * Percentage of cases in the respective treatment modality, OR: odds ratio, CI: confidence interval, N= number of cases in the age group.

5.7 “Systematic review of economic evaluations of aromatase inhibitors in oestrogen receptor-positive breast cancer: quality evaluation”

5.7.1 Introduction

The high incidence and prevalence of BC impose a tremendous financial burden and carry huge socioeconomic, emotional, and public health implications. Policymakers need robust evidence on the cost-effectiveness of different treatment options to base decisions on how best to use scarce healthcare resources.

Economic evaluation is essential to the health technology assessment (HTA) process to help inform healthcare decision-makers. The quality of these studies is crucial to countries with limited HTA resources. This review will help authors from such countries to improve the quality of their studies so that policymakers will have the tools to help them make better decisions. The economic evaluation of AIs since 2010 was systematically reviewed, the quality of these studies was examined, and the evidence on drivers of cost-effectiveness was summarised. The aim was to look at the model structures and the input parameters and how the analyses were conducted. A comparative study of model structure and parametrisation using a checklist and guidelines for models was undertaken to improve our understanding of the quality of current evidence.

5.7.2 Methods

Literature search:

A comprehensive literature search for economic evaluations of AIs versus tamoxifen in females with oestrogen receptor-positive BC was performed using MEDLINE (July 16, 2021), Embase (2021 July 16), the Cochrane Library (Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, and NHS Economic Evaluation Database), and SCOPUS (July 2021).

The electronic search strategy was based on (PICOS): Population (postmenopausal females with BC), Interventions (at least one AI), Comparators (Tamoxifen), Outcomes (health outcomes such as Quality Adjusted Life Years (QALY) or Life Years Gained (LYG) or life years saved (LYS)) and Study designs (economic study, cost-effectiveness analysis, cost-utility analysis or cost-benefit analysis). The exclusion criteria were: (i) descriptive costing studies as they are not considered full economic evaluations, (ii) Conference abstracts because they lack details about the methods, and (iii) economic evaluation addressing extended adjuvant therapy. No language restrictions were imposed.

Search strategies:

Database: Ovid MEDLINE(R) and In-Process & Other Non-Indexed Citations <1946 to July 16, 2021>
 Search Strategy:

-
- 1 exp Breast Neoplasms/ (308448)
 - 2 exp Breast/ or exp Breast Diseases/ (343824)
 - 3 exp Neoplasms/ (3500221)
 - 4 2 and 3 (312787)
 - 5 (cancer* adj3 breast*).tw. (305831)
 - 6 (neoplas* adj3 breast*).tw. (2906)
 - 7 (carcinoma* adj3 breast*).tw. (42078)
 - 8 (adenocarcinoma* adj3 breast*).tw. (3970)
 - 9 (tumour* adj3 breast*).tw. (5833)
 - 10 (tumor* adj3 breast*).tw. (32467)
 - 11 (malignan* adj3 breast*).tw. (9989)
 - 12 5 or 6 or 7 or 8 or 9 or 10 or 11 (344087)
 - 13 1 or 4 or 12 (416249)
 - 14 exp Aromatase Inhibitors/ (9211)
 - 15 aromatase inhibitor*.tw. (7620)
 - 16 (Nolvadex or Soltamox or Letrozole or Femara or Exemestane or Aromasin or anastrozole or Arimidex).tw. (5081)
 - 17 14 or 15 or 16 (13185)
 - 18 13 and 17 (8051)
 - 19 exp Tamoxifen/ (21723)
 - 20 (Tamoxifen or Novaldex or soltamox).tw. (23372)
 - 21 19 or 20 (30331)
 - 22 18 and 21 (3664)
 - 23 Economics/ (27346)
 - 24 exp "Costs and Cost Analysis"/ (247080)
 - 25 Economics, Nursing/ (4005)
 - 26 Economics, Medical/ (9138)
 - 27 Economics, Pharmaceutical/ (2998)
 - 28 exp Economics, Hospital/ (25197)
 - 29 Economics, Dental/ (1918)
 - 30 exp "Fees and Charges"/ (30795)
 - 31 exp Budgets/ (13851)
 - 32 budget*.ti,ab,kf. (231134)

- 33 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf. (240609)
- 34 (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab. /freq=2 (310574)
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- 36 (value adj2 (money or monetary)).ti,ab,kf. (2529)
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- 38 economic model*.ab,kf. (3486)
- 39 markov chains/ (15091)
- 40 markov.ti,ab,kf. (23987)
- 41 monte carlo method/ (29857)
- 42 monte carlo.ti,ab,kf. (51794)
- 43 exp Decision Theory/ (12511)
- 44 (decision* adj2 (tree* or analy* or model*)).ti,ab,kf. (26876)
- 45 or/23-44 (768968)
- 46 22 and 45 (152)

Database: Embase <1980 to 2020 July 16 >

Search Strategy:

-
- 1 exp breast tumor/ (555899)
 - 2 exp BREAST/ or exp BREAST DISEASE/ (638516)
 - 3 exp neoplasm/ (4576727)
 - 4 (cancer* adj3 breast*).tw. (444077)
 - 5 (neoplas* adj3 breast*).tw. (3396)
 - 6 (carcinoma* adj3 breast*).tw. (51904)
 - 7 (adenocarcinoma* adj3 breast*).tw. (5320)
 - 8 (tumour* adj3 breast*).tw. (8329)
 - 9 (tumor* adj3 breast*).tw. (46539)
 - 10 (malignan* adj3 breast*).tw. (13849)
 - 11 5 or 6 or 7 or 8 or 9 or 10 (114654)
 - 12 2 and 3 (580096)
 - 13 1 or 11 or 12 (593571)
 - 14 exp aromatase inhibitor/ (33663)
 - 15 aromatase inhibitor*.tw. (12522)
 - 16 (Nolvadex or Soltamox or Letrozole or Femara or Exemestane or Aromasin or anastrozole or arimidex).tw. (13333)
 - 17 14 or 15 or 16 (40569)
 - 18 13 and 17 (22892)
 - 19 exp Tamoxifen/ (64640)
 - 20 (Tamoxifen or Novaldex or soltamox).tw. (35004)
 - 21 19 or 20 (68682)
 - 22 18 and 21 (13159)
 - 23 *economics/ (26388)
 - 24 exp *"costs and cost analysis"/ (77832)
 - 25 (economic adj2 model*).mp. (8277)
 - 26 (cost minimi* or cost-utilit* or health utilit* or economic evaluation* or economic review* or cost outcome or cost analys?s or economic analys?s or budget* impact analys?s).ti,ab,kw. (55161)
 - 27 (cost-effective* or pharmacoeconomic* or pharmaco-economic* or cost-benefit or costs).ti,kw. (113239)
 - 28 (life year or life years or qaly* or cost-benefit analys?s or cost-effectiveness analys?s).ab,kw. (51504)
 - 29 (cost or economic*).ti,kw. and (costs or cost-effectiveness or markov).ab. (98002)
 - 30 or/23-29 (266180)
 - 31 22 and 30 (253)

CRD database: (DARE, NHS EED and HTA):

1	MeSH DESCRIPTOR Breast Neoplasms EXPLODE ALL TREES	1798
2	(aromatase inhibitor)	38
3	(anastrozole) OR (Arimidex)	63
4	(letrozole) OR (femara)	75
5	(exemestane) OR (aromasin)	38
6	(tamoxifen) OR (soltamox) OR (nolvadex)	235
7	#2 OR #3 OR #4 OR #5	117
8	#1 AND #7	89
9	#6 AND #8	62

Scopus: (19/07/2021):

The search terms used were:

- a. "breast cancer" or breast neoplasm or carcinoma or malignan* or sarcoma or tumo?r (444,406)
- b. Search within results: estrogen receptor positive (55,727)
- c. Search within results: cost effective or pharmacoeconomic* or markov model or economic model or decision model (771)
- d. Search within results: tamoxifen or nolvadix or soltamox (529)
- e. Search within results: "aromatase inhibitor" or letrozole or femara or exemestane or aromasin or anastrozole or arimidex (267)

After deleting duplicate and screening titles and abstracts, I end up with 37 documents

Study selection

The study selection procedure encompassed three main stages. The first stage was to import all the references to Endnote and remove duplicates. The second stage was to evaluate the remaining studies based on the title and abstract, and studies that did not meet the inclusion criteria were excluded. In the third stage, the full articles of potentially relevant studies were retrieved, and those that met the inclusion criteria were included in the current review.

Data extraction

The characteristics of the identified studies were extracted in two tables. A summary of the pertinent study characteristics: publication year, country, perspective, type of model, type of

economic evaluation, time horizon, sponsorship, discount rate, and currency are extracted along with a summary of the model characteristics: source of data, methods of measuring outcomes, included costs, AI, type of sensitivity analysis, incremental cost-effectiveness ratio (ICER), stage of BC, line of treatment, population, and conclusion.

To allow direct comparison across countries, all costs were converted to International Dollars and then inflated to the reference year 2021 using the 'CCEMG—EPPI-Centre Cost Converter (v.1.6, last update: April 29, 2019), a free web-based tool for adjusting estimates of cost expressed in one currency and price year to a specific target currency and price year (Shemilt et al., 2010). Data were extracted using Microsoft Excel.

Quality assessment

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Statement was adopted to appraise the studies critically. The 28-item CHEERS checklist consists of 7 domains: Title (1 item); Abstract (1 item); Introduction (1 item); Methods (18 items); Results (4 items); Discussion (1 item); and Other relevant information (2 items) (Husereau et al., 2022). CHEERS checklist is not a scoring instrument, but the same tool based on other review studies indicating 'yes' when the criteria were met, 'no' when they were unfulfilled, and "not applicable" when they were not required for that type of study will be adopted, the studies were divided into three quality categories according to the proportion of items achieved: high (>75%), average (50–75%) and poor (< 50%) (Meregaglia & Cairns, 2015).

Sensitivity analysis was used to address uncertainty, which is divided into three categories: structural, methodological, and parameter.

Structural uncertainty

Structural uncertainty relates to whether all relevant processes are represented in the model. The adverse events mentioned in the analysis were abstracted, and it was determined whether their effect on mortality was incorporated into the analysis.

Methodological uncertainty

Methodological uncertainty refers to choices about population, time horizon, and study perspective that impact how economic evaluation estimates are calculated. This includes sensitivity analysis (SA) for extrapolating beyond the study's follow-up time. Did the analysis address different subgroups, such as older women, women at high risk of side effects (SE), women with comorbidities, and women at low risk of BC recurrence?

Parameter uncertainty

Parameter uncertainty concerns the numerical values of input parameters. The data sources on both BC recurrence and adverse event rates associated with AIs were abstracted. Then, it was determined whether the authors perform the following or not: SA on the risk of BC recurrence, SA on SE (including fracture, cardiovascular events, stroke, thromboembolic events, endometrial cancer), probabilistic sensitivity analysis (PSA), and value of information analysis (VOI) to critique the authors' handling of parameter uncertainty.

5.7.3 Results

Literature search

Records identified through database synthesis were 674 references, among which 125 were duplicates, 492 were excluded after screening and analysis of titles and abstracts for not matching the eligibility criteria, 47 articles were excluded due to date restriction, and two were excluded because of the comparators. A total of eight papers were retrieved and analysed (Mould & Contreras-Hernandez, 2011), (Djalalov et al., 2015; Ye et al., 2018; Gamboa et al., 2010; Lee et al., 2010; Lux et al., 2011, 2010; Shih et al., 2012). (Figure 5.1)

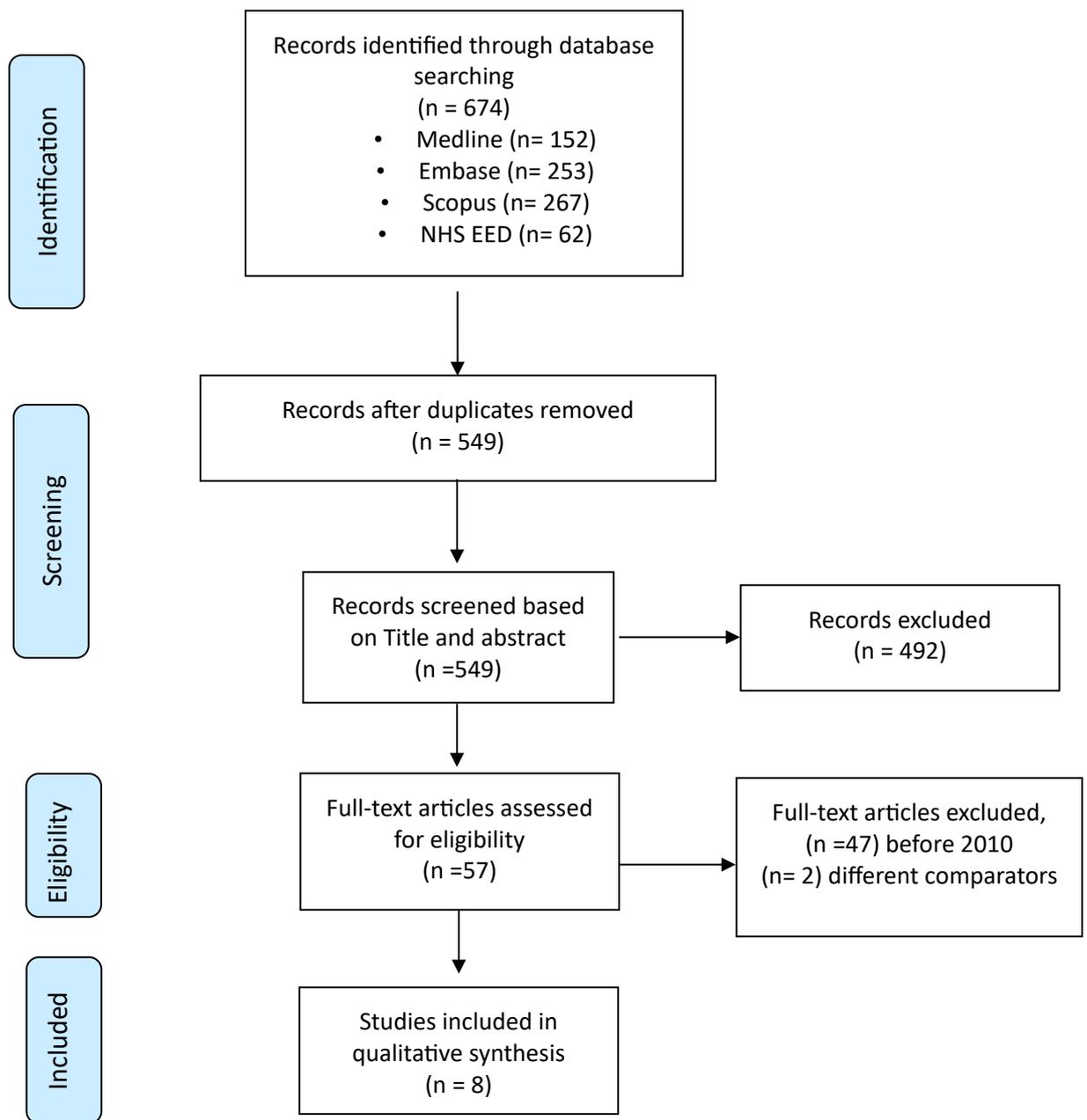


Figure 5.1 PRISMA flow diagram of included studies.

Characteristics of studies included in the review

A total of eight articles were included in the final study, of which six were published in English and two in Spanish (Mould & Contreras-Hernandez, 2011; Gamboa et al., 2010). Studies were conducted in different countries, including Mexico (Mould & Contreras-Hernandez, 2011), China (Ye et al., 2018), Canada (Djalalov et al., 2015), Singapore (Shih et al., 2012), Germany (Lux et al., 2011, 2010), Korea (Lee et al., 2010), and Colombia (Gamboa et al., 2010). The authors analysed from the health care system's perspective ($n = 6$; 75%); only two studies were conducted from a societal perspective (Lee et al., 2010; Shih et al., 2012). Seventy five percent of studies ($n = 6$) considered both QALY and LY outcomes, while the remaining two studies used recurrence rate (Mould & Contreras-Hernandez, 2011) and overall survival (Gamboa et al., 2010) as outcome measures. All economic evaluations involved were model-based analyses using Markov cohort models. All studies considered direct costs, except one study considered both direct and indirect costs (Lee et al., 2010). Shih *et al.* involved direct costs only despite conducting their study from a societal perspective (Shih et al., 2012). All studies clearly stated that the price, currencies, and costs were derived from local sources and/or national databases. The publication years ranged from 2010- 2018 (Table 5.11).

One study modelled for ten years (Mould & Contreras-Hernandez, 2011), while most studies used a lifetime horizon or ranged between 20-35 years. Discounting of costs was made in all studies; half of the studies used a 3% discount rate, and the other half used a 5% discount rate. Three studies (Lux et al., 2011, 2010; Ye et al., 2018) justify choosing this discount rate, but others did not. Most studies compared one AI vs Tamoxifen ($n=4$), one compared letrozole vs tamoxifen (Ye et al., 2018) and three compared anastrozole vs tamoxifen (Gamboa et al., 2010; Lux et al., 2010; Shih et al., 2012); the remaining studies compared anastrozole or letrozole vs tamoxifen (Lee et al., 2010; Lux et al., 2011) ($n=2$), one comparing the three AIs (anastrozole or letrozole or exemestane) vs tamoxifen (Mould & Contreras-Hernandez, 2011), and one treated the AI drug class as a group without reference to a specific drug (Djalalov et al., 2015). Efficacy data were derived from the results of clinical trials or literature (Table 5.12).

Most studies report an ICER value except for two that didn't calculate it (Djalalov et al., 2015; Mould & Contreras-Hernandez, 2011). The ICER values for anastrozole and letrozole

after conversion to 2021 International dollars ranged between \$40 and \$206,256/QALY and \$11,510 to \$45,019/ QALY, respectively.

The Markov cycle length used in all studies was yearly except for two studies that used a one-month (Ye et al., 2018) and a three-month cycle (Lux et al., 2010). Most of the studies (n=6) concluded that compared to tamoxifen, AIs were cost-effective at a commonly accepted threshold for cost-effectiveness (less than \$50k /QALY, (Cuzick et al., 2010)), except for two studies (Gamboa et al., 2010; Mould & Contreras-Hernandez, 2011) that concluded that tamoxifen is cost-effective.

Quality Assessment

The quality assessment results using the CHEERS checklist per study are summarised in (Table 5.13). The mean number of fulfilled criteria for the CHEERS checklist was 22 out of 28. The most frequent partially or not reported items were health economic analysis plan (item 4), characterising heterogeneity (item 18), characterising distributional effects (item 19), approach to engagement with patients and others affected by the study (item 21), and effect of engagement with patients and others affected by the study (item 25).

The quality of the included studies ranges between high and average; according to our criteria, 75% of the studies (n=6) were of average quality, and 25% (n=2) were of high quality.

Study Country	Perspective/ Time Horizon	Type of Model/ economic evaluation	Aromatase Inhibitor	Population Studied (Age at entry)
Ye, M. et al (2018) China	Chinese Healthcare system/ Lifetime	Markov CEA	Letrozole	Postmenopausal women with newly diagnosed early ER + ve BC after lumpectomy, 57 yrs (27-79 yrs)
Djalalov, S. et al (2015) Canada	Canadian health system/ Lifetime	Markov CEA	Treated the AI drug class as a group without reference to a specific drug	Postmenopausal women with ER + ve early BC, 65 yrs
Shih, V. et al (2012) Singapore	Societal/ Lifetime	Markov CEA and CUA	Anastrozole	Postmenopausal women with HR + ve early-stage BC who had completed primary therapy, 64 yrs
Mould-Quevedo et al (2011) Mexico	Healthcare payers/ 10 years	Markov CEA	Anastrozole Letrozole Exemestane	Postmenopausal HR+BC females. The cohort was divided into two groups. One for females with positive lymph nodes (LN+) and one for females with negative lymph nodes (LN-) NR
Lux, M. et al (2011) Germany	Healthcare system/ 20 years	Hybrid and Markov CBA*	Anastrozole Letrozole	Postmenopausal women with HR +ve BC, 76-80 yrs
Gamboa et al (2010) Colombia	Colombian health care system/ 30 years	Markov CEA	Anastrozole	Postmenopausal women with ER + ve early BC, 50 yrs
Lee, et al (2010) Korea	Societal/ 35 years	Markov CEA	Anastrozole Letrozole	Postmenopausal women with HR +ve early BC, 50 yrs
Lux, M. et al (2010) Germany	German healthcare system/ 25 years	Markov CEA	Anastrozole	Postmenopausal women with HR + ve early BC, 64 yrs

Table 5.11. Study characteristics. Key; CEA: Cost-Effectiveness Analysis, CBA: Cost- Benefit Analysis, CUA: Cost-Utility Analysis, ER: oestrogen receptor, HR: hormone receptor, NR: not reported *Paper title is CBA, but it is a CE

Author	Source of Data	Outcomes	Type of sensitivity analysis	ICER conversion to I\$ 2021	Findings
Ye, M. et al.	<p>Effectiveness: published randomized clinical trials meta-analyses (EBCTCG).</p> <p>Costs: from published Chinese studies.</p>	<p>- Progression-free LY's</p> <p>- Overall LY's</p> <p>- QALYs</p>	<p>- PSA (second-order Monte Carlo technique)</p> <p>- One-way sensitivity analyses</p>	11,510/QALY	Adjuvant endocrine therapy with Letrozole is a cost-effective strategy compared to tamoxifen in women with early BC
Djalalov, S. et al	<p>Effectiveness: Medical literature, meta-analysis (BIG 1-98 trial and ATAC trial)</p> <p>Costs: Ontario Ministry of Health and Long-Term Care, Ontario Drug Benefit Formulary Costs, published Canadian studies.</p>	QALY's (Utility weights)	<p>- PSA (Monte Carlo simulation)</p> <p>- Deterministic sensitivity analysis</p>	NR	<p>In postmenopausal women with ER +ve early BC, strategies using AIs appear to provide more benefit than strategies using TAM alone.</p> <p>Sequential strategies using TAM and an AI appear to provide benefits similar to those provided by upfront AI but at lower cost</p>
Shih, et al	<p>Effectiveness: ATAC trial, interviews with oncology nurses, local financial electronic databases, published literature</p>	<p>- Cost per LY survival</p> <p>- Cost per QALY gained</p>	Multiple one-way sensitivity analyses	<p>ICER of anastrozole was:</p> <p>- 242,815/ LY</p> <p>- 133,536 / QALY gained</p>	If the WHO recommendation of 1 to 3x GDP range is an acceptable threshold, anastrozole is deemed cost-effective compared with tamoxifen in the treatment of early-stage BC

Author	Source of Data	Outcomes	Type of sensitivity analysis	ICER conversion to I\$ 2021	Findings
	Costs: were obtained via financial electronic databases of the NCCS and the Singapore General Hospital				
Mould-Quevedo, et al	Effectiveness: Probabilities derived from published data. Costs: obtained from the Mexican Social Security Institute	- Non- recurrence rate - Time to recurrence	PSA (2nd order Monte Carlo simulation)	NR	Sequential treatment with tamoxifen/ exemestane appeared to be a cost-effective alternative among the therapies, which includes an aromatase inhibitor for women with BC in Mexico
Lux, M. et al.	Effectiveness: BIG 1-98 study, ATAC study, and EBCTG study Costs: generic prices	- Recurrence rate - Overall survival - QALY (Utility weights)	PSA (Monte Carlo simulation with 2000 scenarios).	- ICER for anastrozole is 206,256 /QALY - ICER for letrozole is 45,019/QALY	The present model, including the inverse probability of censoring weighted analysis (IPWC) for letrozole and generic prices for both AIs shows that letrozole is cost-effective.
Gamboa, et al	Effectiveness: Literature Costs: Treatment and adverse events costs derived from information provided by several health service providers over a	- Survival - Time free from disease	- PSA - One- way sensitivity analysis	- Non-discounted ICER = 29.51 /LY - Discounted ICER= 40.35/ LY	Compared to tamoxifen, adjuvant therapy with anastrozole yields an additional 0.49 disease-free years. The additional cost per disease-free year gained is 37,071 Colombian pesos. Tamoxifen has

Author	Source of Data	Outcomes	Type of sensitivity analysis	ICER conversion to I\$ 2021	Findings
	period of 12 months. Relapse costs based on the individual costs for 23 women provided by the National Institute of Cancer				a higher probability of being cost-effective at all WTP points considered in the analysis
Lee, et al	<p>Effectiveness: published studies (EBCTCG meta-analysis, the ATAC trial, and the BIG 1-98 trial)</p> <p>Costs: Drug costs were based on the 2009 pharmaceutical prices that were weighted by the prescription volume, which was issued by the Korean Health Insurance Review and Assessment Service (HIRA) in the first half year of 2009</p>	<p>- QALY's</p> <p>- LY</p>	Deterministic sensitivity analysis	<p>- for anastrozole 31,858</p> <p>- for letrozole 29,791</p>	<p>Anastrozole and letrozole were both cost-effective treatments compared to tamoxifen.</p> <p>When anastrozole and letrozole were compared indirectly in the overall population, their cost-effectiveness ratios were too similar to decide which treatment was superior to the other</p> <p>When the population was divided by nodal status, anastrozole was more cost-effective than letrozole in the node-negative group, and letrozole was more effective in the node-positive group</p>
Lux, M. P. et al.	Effectiveness: published literature and expert opinion (ATAC trial)	<p>- QALY</p> <p>- Overall survival</p>	<p>- Scenario analyses</p> <p>- Deterministic sensitivity analysis</p>	for anastrozole compared to tamoxifen was 32,616/QALY gained	Adjuvant treatment with anastrozole for postmenopausal women with HR+ EBC is a cost-effective alternative to tamoxifen

Author	Source of Data	Outcomes	Type of sensitivity analysis	ICER conversion to I\$ 2021	Findings
	<u>Costs</u> : costs were derived from standard sources.		- PSA		

Table 5.12. Model Characteristics.

Key: EBCTCG: Early Breast Cancer Trialists' Collaborative Group, ICER: incremental cost-effectiveness ratio, I\$: International dollars, ATAC: The Arimidex, Tamoxifen Alone or in Combination trial, BIG 1- 98: The Breast International Group 1-98 trial, QALY: quality-adjusted life years, LY: life year, PSA: probabilistic sensitivity analysis, NR: not reported

Ye, Djalalov, Shih, Mould- Lux, Gamboa,et Lee, Lux,
M.et S.et al et al Quevedo,et M.et al et M.et
al al al al al

	Title								
1	Title	√	√	√	√	√	√	√	√
	Abstract								
2	Abstract	√	√	√	√	√	√	x	√
	Introduction								
3	Background and objectives	√	√	√	√	√	√	√	√
	Methods								
4	Health economic analysis plan	x	x	x	x	x	x	x	x
5	Study population	√	√	√	√	√	√	√	√
6	Setting and location	√	√	√	√	√	x	√	√
7	Comparators	√	√	√	√	√	√	√	√
8	Perspective	√	x	√	√	√	√	√	√
9	Time horizon	√	√	√	√	√	√	√	√
10	Discount rate	√	√	√	√	√	√	√	√
11	Selection of outcomes	√	√	√	√	√	√	√	√
12	Measurement of outcomes	√	√	√	x	√	√	√	√

13	valuation of outcomes	√	√	√	x	√	x	√	√
14	Measurement and valuation of resources and costs	√	√	√	√	√	√	√	√
15	Currency, price date, and conversion	√	√	√	√	√	√	√	√
16	<i>Rationale and description of model</i>	√	√	√	√	√	√	√	√
17	Analytics and assumptions	√	√	√	√	√	√	√	√
18	Characterizing heterogeneity	√	x	√	x	x	√	√	x
19	Characterizing distributional effects	x	x	x	x	x	x	x	x
20	Characterizing uncertainty	√	√	√	√	√	√	√	√
21	Approach to engagement with patients and others affected by the study	x	x	x	x	x	x	x	x
	Results								

22	Study parameters	√	√	√	√	√	√	√	√
23	Summary of main results	√	√	√	√	√	√	√	√
24	Effect of uncertainty	√	√	√	√	√	√	√	√
25	<i>Effect of engagement with patients and others affected by the study</i>	√	x	x	x	x	x	x	x
Discussion									
26	Study findings, limitations, generalisability, and current knowledge	√	√	√	√	√	√	√	√
Other Relevant Information									
27	Source of funding	√	√	√	√	√	√	x	√
28	Conflicts of interest	√	√	√	√	x	√	x	x

Table 5.13. Quality assessment of Cost-effectiveness studies

Data sources:

All the study's authors used one or two RCTs as a source of data to estimate the impact of hormonal therapies on breast cancer recurrence. Most data were taken from the ATAC trial (Arimidex or Tamoxifen Alone or in combination trial) (Cuzick et al., 2010) and/or the BIG 1-98 trial (the breast international group trial) (Breast International Group (BIG) 1-98 Collaborative Group et al., 2005). The costs were obtained from national databases; Ye *et al.* and Djalalov *et al.* are the only two studies mentioned that used the generic costs of the drugs (Djalalov et al., 2015; Ye et al., 2018).

Handling structural uncertainty:

Half of the studies (n = 4, 50%) addressed the increased mortality following adverse events (Table 5.14).

Handling methodological uncertainty:

Few economic evaluations performed sub-group analyses to address patient heterogeneity related to older women (n = 2, 25%), and no study looked at women at low risk of breast cancer recurrence. A large proportion (75%) did not assess the impact of uncertainty arising from extrapolating beyond the trial data. Five studies (62.5%) vary the discount rate in the sensitivity analysis (Table 5.14).

Handling parameter uncertainty:

All the studies reported sensitivity analysis on the risk of breast cancer recurrences. Two studies did not perform sensitivity analysis on the risk of adverse events (n = 2, 25%). Six studies (75%) performed PSA. One study conducted a VOI analysis. (Table 5.15)

Detailed information on the handling of parameter, structural and methodological uncertainty are available in (Table 5.14, Table 5.15)

No.	Increased mortality following any adverse event?	Did the analysis address the following sub-groups?								SA for extrapolating beyond the follow-up time of studies	SA for the discount rate
		Older women?	Women at low risk of breast cancer recurrence?	Women at high risk of fracture?	Women with high risk of cardiovascular disease?	Women at high risk of stroke?	Women at high risk of thromboembolism?	Women at high risk of endometrial cancer?	Women with multiple co-morbidities?		
1	√	√	x	x	x	x	x	x	x	x	√
2	√	x	x	x	x	x	x	x	x	x	x
3	x	√	x	x	x	x	x	x	x	x	√
4	x	x	x	x	x	x	x	x	x	x	x
5	x	x	x	x	x	x	x	x	x	x	x
6	x	x	x	x	x	x	x	x	x	x	√
7	√	x	x	x	x	x	x	x	x	√	√
8	√	x	x	x	x	x	x	x	x	√	√

Table 5.14. Handling structural and methodological uncertainty.

1 (Mould & Contreras-Hernandez, 2011)(Mould & Contreras-Hernandez, 2011), 2 (Ye et al., 2018)(Ye et al., 2018), 3 (Djalalov et al., 2015)(Djalalov et al., 2015), 4 (Gamboa et al., 2010)(Gamboa et al., 2010), 5 (Lux et al., 2010)(Lux et al., 2010), 6 (Lee et al., 2010)(Lee et al., 2010), 7 (Lux et al., 2011)(Lux et al., 2011), 8 (Shih et al., 2012)(Shih et al., 2012)

	Handling of parameter uncertainty							
	SA on risk of BC recurrence	SA on AE					PSA	VOI
		Fracture	Cardiovascular events	Stroke	Thromboembolism	Endometrial cancer		
1	√	√	x	x	x	√	√	x
2	√	√	√	√	√	√	√	√
3	√	√	√	x	√	√	x	x
4	√	x	x	x	x	x	√	x
5	√	√	x	x	√	x	√	x
6	√	x	x	x	x	x	√	x
7	√	√	√	x	√	√	x	x
8	√	√	√	√	√	√	√	x

Table 5.15. Parameter Uncertainty.

1 (Mould & Contreras-Hernandez, 2011)(Mould & Contreras-Hernandez, 2011), 2 (Ye et al., 2018)(Ye et al., 2018), 3 (Djalalov et al., 2015)(Djalalov et al., 2015), 4 (Gamboa et al., 2010)(Gamboa et al., 2010), 5 (Lux et al., 2010)(Lux et al., 2010), 6 (Lee et al., 2010)(Lee et al., 2010), 7 (Lux et al., 2011)(Lux et al., 2011), 8 (Shih et al., 2012)(Shih et al., 2012)

5.7.4 Discussion

In this study, we systematically reviewed and assessed the quality of eight economic evaluations comparing AIs to tamoxifen for early-stage breast cancer published between 2010 and 2021, covering the perspectives of Chinese, Korean, German, Canadian, Singapore, Colombian and Mexican healthcare systems. Compared to tamoxifen, AIs were reported to be cost-effective in postmenopausal women with early-stage BC in most studies (75%) at a commonly accepted threshold for cost-effectiveness (less than \$50k /QALY).

Two systematic reviews of economic evaluations were conducted on AIs and tamoxifen in early-stage BC. (John-Baptiste et al., 2013) identified 18 cost-effectiveness studies between 2004 and 2010, while (Frederix et al., 2012) analysed 20 articles about the cost-effectiveness of endocrine treatments published between 2000 and 2010. These reviews concluded that there is an overestimation of the cost-effectiveness of AIs and a need for standardised models to help in decision-making. Our study now finds that AIs are cost-effective based on high to average-quality study methodology. The general evaluation approaches in all studies had a significant degree of similarity. First, all the evaluations used a Markov model. Secondly, all studies used an RCT as a data source and national costs. However, despite this fact,

the reported cost-effectiveness results were inconsistent across all the evaluations; this variation could be due to the difference in treatment costs in different countries.

In two studies conducted by Lux *et al.*, there were considerable differences in ICER \$32,616/QALY and \$206,256/QALY even though they were conducted from the German healthcare perspective, using the same discount rate (3%), the same AI (anastrozole), and similar time horizon (20-25 yrs.) and only differing in the age of the participant at entry (76-80 and 64 yrs.). The higher ICER was associated with using generic drug costs.

In studies comparing letrozole to tamoxifen, the lowest ICER was associated with using generic drug prices in the latest study (2018). The ICER of the two other studies was doubled; this could be due to different discount rates, different settings, different lifetime horizons, and different ages at entry. The study in Mexico used a short time horizon of 10 years, which failed to capture the full costs and effects of chronic diseases. The difference between studies in the participant's age at entry should be considered; knowing the side effects of AIs and how they affect older ages could lead to differences in the costs of side effects in different age groups.

All studies except two used a yearly Markov model cycle length without justification; the recommended cycle length is three months because recurrences are very relevant for the outcome and using a 3-month cycle is a better representation of the course of the disease.

Regarding the quality of reporting these evaluations, we observed that the reporting was sufficient except for reporting sub-group analysis to address heterogeneity, increased mortality following adverse events, and approaches to engage patients or others affected by the study, which were partially reported. It was recognised that all the studies do not follow any checklists to evaluate the quality of their studies; we highly recommend using checklists to improve the reporting and, hence, the quality of economic evaluations.

Our review found some key drivers of cost-effectiveness that are not always discussed. First, medication adherence should be incorporated in upcoming economic evaluations. Medication non-

adherence was found to place a significant cost burden on healthcare systems (Cutler et al., 2018). Second, the drug costs, whether generic or branded, would affect the cost-effectiveness.

There are some limitations of this systematic review that must be addressed. First, this review included only fully published studies, and we did not look at grey literature and excluded conference abstracts. Second, most of the studies adopted the health care system rather than the societal perspective, limiting the generalisability of results. Third, comparing economic outcomes is difficult because of the variability in currencies and the health systems involved in different countries.

5.7.5 Conclusion

Although most studies concluded that AIs are cost-effective compared to tamoxifen in early-stage BC, these results are disputable because they did not consider the adherence, the side effect profile, and the subgroup analysis. However, the overall quality of the studies included was average according to the CHEERS checklist; characterising heterogeneity should be considered in future studies.

Chapter 6 Survival of Breast Cancer in Saudi females (Population-based and Hospital-based study)

Along with incidence, BC survival is an important measure to evaluate the progress against cancer. Chapter 4 discusses the incidence of BC, and this chapter will analyse and discuss survival.

6.1 Introduction

Survival refers to the probability of remaining alive after being diagnosed with a particular disease for a specified period. Survival analysis is an essential time-to-event data analysis that helps understand the factors affecting patient outcomes. In cancer, survival is expressed as the proportion of patients still alive at specific time points, usually five or ten years after their diagnosis.

Survival analysis uses two fundamental concepts: the survivor function $S(t)$ and the hazard function $h(t)$. The survivor function is the probability of an individual surviving beyond time x , while the hazard function is the probability of an individual observed at time t having an event at that time; $S(t)$ focuses on not failing, while $h(t)$ focuses on failing (in this study failing is experiencing death) (Clark et al., 2003).

In survival analysis, censoring is a crucial aspect. It must be adequately addressed because it is common in longitudinal studies and ignoring it may lead to biased estimates of survival probabilities and misleading results. Censoring occurs when the survival time is unknown or incomplete in some cases since only some individuals experienced the event. There are three types of censoring: right censoring, in which the patient had not experienced the relevant outcome at the end of the follow-up period, or the event of interest is beyond the study period, for example, if patients dropped out of the study because they were lost to follow-up for any reason or died because of another cause, which is the most common type of censoring in cancer studies. Left censoring is the second type, in which the cases are diagnosed with the disease on a date before the study date. The third type is interval censoring, in which the time to the event is not known precisely but is known to fall in a particular interval (Clark et al., 2003). Of the three types discussed, this study considered the right censoring only, as the other two types are not an issue in this study.

Survival can be calculated from both population-based data and hospital data. When calculated from population-based studies, trends in survival rates are evaluated, the effectiveness of cancer care in the region is assessed, and factors associated with survival outcomes are identified. In comparison, hospital-based studies can provide information on the efficacy of different treatments and their impact on patient outcomes (Jensen et al., 1991).

The statistical method most frequently used to estimate the survival probability is the Kaplan-Meier (KM) method (Lira et al., 2020). In this method, the follow-up time is divided into intervals, and the probability of each individual at the beginning of the interval developing the event of interest at the end of the interval is estimated. Then, the probabilities of surviving from one interval to the next are multiplied to give the cumulative survival probability. The KM survival curve is used to represent the survival function graphically; it shows the probability of survival at specific time intervals; in this case, the intervals are defined by the occurrence of an event (Lira et al., 2020).

The main measures used in survival analysis are OS and cause-specific survival. OS is calculated by dividing the number of diagnosed cases of the disease (in this case, BC cases) alive sometime after diagnosis by the number of total BC cases diagnosed (Dickman & Coviello, 2008). In contrast, cause-specific survival accounts only for death from BC while censoring deaths from other causes. It is calculated by dividing the number of individuals with BC who have survived for a specified period by the total number of diagnosed BC cases (Mariotto et al., 2014).

Cause-specific survival is the most common method used in survival estimations (Mariotto et al., 2014). However, in population-based registries, the cause of death is not always accurate or is unavailable. In this situation, another approach, the relative survival framework, where the cause of death is not required, can be used (Dickman & Coviello, 2008).

Relative survival is the ratio of the observed survival rate of cancer patients to the expected survival rate of a comparable group with matching age and sex during a specified interval. In relative survival, it is assumed that the BC cases would have mortality similar to that of the general population if they didn't have cancer. Relative survival provides a measure of the excess mortality experienced by patients

diagnosed with BC; it does not depend on knowing the cause of death, and life tables are required in this method (Bajpai et al., 2014).

Life tables are statistical tables that provide the number of survivors, deaths, and life expectancy based on the annual mortality ratio for each age group. Life tables are used to estimate survival probabilities over time and compare the mortality rates in a specific population to those of the general population (Anousschka van der Meulen, 2012).

In this study, overall and relative survival analysis was conducted to examine the 5-year and 10-year survival in Saudi females diagnosed with BC and the impact of various factors, including age, cancer stage or grade, molecular subtype, and year of diagnosis on survival. In addition, the study explored changes in survival caused by different treatment modalities used to manage BC.

6.2 Methodology

The data used in this analysis are the SCR and KFSH&RC data described previously in Chapter 3. Different measures were chosen for each registry to best utilise the available data in each setting, allowing for appropriate analysis and interpretation of survival outcomes. For the SCR data, both OS and relative survival were utilised to assess patient outcomes following BC diagnosis. Then, survival was analysed by age, year of diagnosis, stage, and grade. For the hospital data, OS was calculated and analysed by age, stage, year of diagnosis and treatment modalities.

Overall survival was chosen for this study over cause-specific survival, as registries frequently have incomplete or imprecise information regarding the cause of death. Using OS, where an all-cause mortality endpoint cannot be misclassified, ensures a more robust and reliable analysis of survival outcomes than a cause-specific survival (Mariotto et al., 2014) .

Survival time is the time between the starting point and the outcome of interest. To estimate survival, it is necessary to precisely define the starting point, the end of the follow-up time, and the outcome. In both registries, the date of diagnosis with BC was considered the starting point, and the

end of follow-up time was November 2019 (when the complete data was received) for the SCR data and November 2020 for hospital data. The outcome of interest is death, whether from BC or other causes; patients who remained alive until the last follow-up and those who were lost to follow-up were censored.

The data were analysed using the Stata /BE 17.0 software (Stata Corp LP, College Station, Texas 77845, USA). The Kaplan-Meier method was used to estimate the survival distribution, and the differences in survival between different groups (age, stage, year of diagnosis, treatment modality and grade) were compared using the log-rank test. Subsequently, a Cox proportional hazard model was computed to determine the significance of the difference in survival and the effect size.

Variables used in the analysis:

- Grade was categorised into three categories: 1, 2, and 3 (Amin, 2017).
- The stage at diagnosis was classified into four categories: in situ, localised, regional, and distant metastasis (Nci & Seer, 2018).
- The year of diagnosis started in 1994 for SCR data and in 2007 for the hospital data.
- Age was categorised into nine age groups, starting from 10-19 with 10-year intervals and ending at age 90 and greater. In addition to this categorisation, age was categorised into two groups: cases under 50 and cases aged 50 and above. These were to be used in the survival analysis by age at diagnosis.

Age is a confounder survival variable; if survival was longer at younger ages than at older ages, this might result from the age differences rather than the disease's prognosis. Therefore, a multivariable survival analysis was conducted to overcome this issue, and a confounder model using Cox regression for survival analysis was generated to determine if BC subtypes differ after adjusting for confounders such as age, stage, and grade (Bradburn et al., 2003).

The cumulative survival probabilities were displayed graphically in the survival curve. The curve starts at 1 (all patients are alive) and progressively declines towards zero with time. This study will present the crude survival (overall) and the 5-year relative survival.

6.2.1 SCR data

The data set relates to 80,161 Saudi female cases diagnosed with BC between 1994 and 2017. Follow-up data were available until the end of November 2019 (the date the data were received). The information available was age at diagnosis, year of diagnosis, staging, grading, date of last contact, and status of last contact.

OS was estimated by considering death as the endpoint, whether from BC or due to other causes. The survival time was presented in years, including decimal values, and calculated from the date of diagnosis to the date of last contact or the end of the follow-up period. Kaplan-Meier method was employed to estimate the survival distribution of patients diagnosed with BC, and a survival curve was generated. Survival distribution was obtained by different variables, which are the year of diagnosis with four groups of 5-year intervals from 1994 to 2013, age at diagnosis where age was categorised into two groups: cases aged less than 50 and cases aged 50 and older at diagnosis, Grade (grades 1,2,3 and 4), stage at diagnosis (localised, regional, and distant metastasis). A log-rank test was used to test for the equality of survival distributions among the groups in each variable; P -value < 0.05 was considered statistically significant. To assess the relationship between independent variables such as age, stage, and grade with survival, a multivariable analysis was performed using the Cox regression technique with stepwise methods to evaluate which predictors should be included in the model. The stepwise method used was a combination of forward addition and backward elimination. The forward stepwise method involved sequentially adding predictors to the model based on their statistical significance using a P -value < 0.05 , while the backward stepwise method began with all potential predictors and iteratively removed non-significant variables. This dual approach ensured robustness in identifying the significant predictors. The results were presented as hazard ratios and 95% confidence intervals, and the association was considered statistically significant if the P -value < 0.05 . Interaction effects were examined in the multivariable analysis to explore the potential relationships between key variables. Specifically, the interactions between age and stage, age and grade, as well as stage and grade. These interaction terms were included in the model to determine their significance and to evaluate how they influenced the OS. The likelihood ratio test was employed to compare models with and without interaction terms, providing a statistical assessment of whether the inclusion of these interactions

significantly improved model fit; interactions were considered statistically significant if the P -value < 0.05.

Relative survival was calculated by dividing the observed survival rate of cancer patients by the expected survival rate of Saudi females during the same period. The observed survival was calculated by dividing the number of patients who survived after being diagnosed with BC by the number of all patients diagnosed with BC; the endpoint was death from all causes. The expected survival was estimated from lifetables with matched age and sex obtained from the World Health Organization (regional office for South-East Asia), and the available years were 2019, 2015, 2005, and 2000. For the years with unavailable data, using the most recently available lifetables is the standard practice, assuming the probabilities are the same as those most recently available (Dickman & Coviello, 2015). The table for 2019 was used for the years from 2016 to 2019, the table for 2015 was used for the years from 2006 to 2015, the table for 2005 was used from 2001 to 2005, and the table for 2000 was used for the years from 1994 to 2000.

There are three approaches used to calculate the expected survival to estimate relative survival, Ederer I, Ederer II, and the Hakulinen method (Dickman & Coviello, 2015). The three methods differ in how long the matched individual is considered at risk. In Ederer I, the matched individual is deemed at risk for the entire follow-up period, unlike the Ederer II method, in which the matched individual is followed until the matched individual dies or is censored. In the Hakulinen method, the matched individual will be censored if the cancer patient is censored. However, if the cancer patient dies, the matched individual will still be at risk until the end of the study. In this study, the Ederer II method was used, as this method accounts for the changes in mortality rate over the entire study period, allowing for a more accurate estimation of relative survival over time.

Survival distribution was obtained by different variables, which are the year of diagnosis with four groups of 5-year intervals from 1994 to 2013 (1994-1998, 1999-2003, 2004-2008, 2009-2013), age at diagnosis where age was categorised into two groups: cases aged less than 50 and cases aged 50 and older at diagnosis, Grade (grades 1,2,3 and 4), and stage at diagnosis (localised, regional, and distant metastasis). Log-rank tests were used to compare the survival between different groups based on

variables (such as age, grade, and stage). Next, Cox proportional hazards were calculated to assess the magnitude of the difference.

A Poisson regression model for excess mortality was employed in the framework of generalised linear models to describe the association between prognostic factors, which include age, year of diagnosis, stage and grade, and excess mortality. The model adequacy was evaluated using the Akaike information criterion (AIC) and Bayesian information criterion (BIC). AIC and BIC assess the trade-off between model fit and complexity of the model, with lower values indicating a better model that avoids overfitting. Both are used to compare models and confirm the selected predictors' appropriateness.

6.2.2 Hospital data

This is a retrospective study of 2924 cases diagnosed with BC from 2007-2016 and followed up till November 2020 (the date of receiving data) in KFSH&RC. The available data were age at diagnosis, year of diagnosis, stage, treatment modalities (surgery, hormonal therapy, radiotherapy, chemotherapy, and biological therapy), date of follow-up, status, and date of death.

OS was calculated by calculating the proportion of BC patients still alive for 5 years and 10 years after being diagnosed with BC; the Kaplan-Meier method was employed using Stata software. Survival analyses were conducted to evaluate the impact of different prognostic factors on overall survival. The factors include the age in which patients were stratified into two groups (< 50 , ≥ 50), the stage (I, II, III, VI), hormone receptor status (ER+/PR+, ER+/PR-, ER-/PR+, ER-/PR-) and the treatment modalities.

The Log-rank test was used to compare survival across different groups to determine if differences in survival were statistically significant. Additionally, Cox proportional hazard models were conducted to calculate hazard ratios for each prognostic factor.

6.3 Results

6.3.1 SCR data

Overall survival (crude survival)

The dataset initially comprised 30,246 observations. Of these, 1,743 were excluded because they ended on or before entering the study's observation period (2007 to 2020). Subsequently, 28,498 subjects remained for analysis, among which 3,628 observed deaths were recorded. The maximum observed exit time, which is the time until the death occurs or until the subject is censored, was 22 years.

The five-year OS rate for BC among Saudi females was 73% (95% CI 72-74%), while the ten-year OS was 54.7% (95% CI 53-57%); the median OS was approximately eighteen years. The results are presented in Table 6.1 and graphically in Figure 6.1.

Time (years)	Number of deaths	Survival rate
5	3025	0.73
10	479	0.55
15	98	0.39

Table 6.1 Overall Survival of BC in Saudi females. CI: Confidence interval.

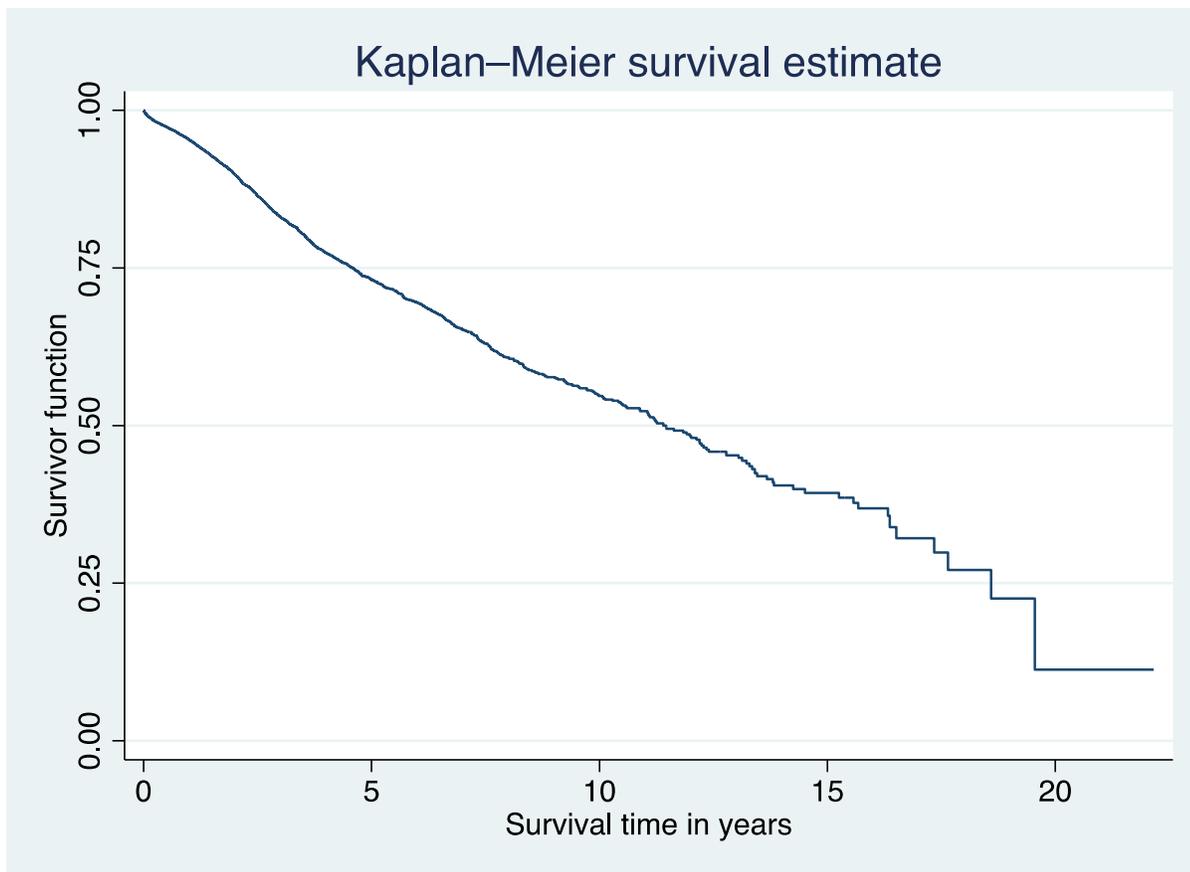


Figure 6.1. Overall survival of BC in Saudi females.

Time trends in survival (1994-2017):

To explore the evidence of survival rate differences over time, the year of diagnosis was grouped into four 5-year intervals from 1994 to 2013. The Ederer II method indicated that survival decreased in the first three periods. Cumulative five-year survival was 75% from 1994-1998, 70% from 1999 to 2003, and 69% from 2004-2008. A notable improvement in five-year survival to 78% in the last period (2009 to 2013) indicates better outcomes. The log-rank test shows a significant difference in five-year survival rates among the four diagnosis periods ($P = 0.0001$). Using the Cox proportional hazards regression model, the analysis indicated that patients diagnosed between 1999-2008 had a 22% statistically significant higher risk of mortality than those diagnosed in the earlier period of 1994-1998, while patients diagnosed between 2009 and 2013 had a lower risk of mortality compared to the reference group, with a hazard ratio indicating a 9% lower risk. However, this result is not statistically significant ($P = 0.11$) and could be due to chance.

Figure 6.2 shows that there have been improvements in BC survival over the years, with the most recent period (2009 to 2013) exhibiting the best survival, followed by the earlier 1994-1998 period. The intermediate periods of 1999-2008 showed relatively lower survival probabilities than earlier and later periods.

Period of diagnosis	N (number of deaths)	5-years Survival (95%CI)	N (number of deaths)	10-years Survival (95%CI)	Hazard Ratio (p-value)
1994-1998	274	0.75 (0.72-0.77)	112	0.58 (0.55,0.62)	Reference
1999-2003	623	0.70 (0.68-0.72)	207	0.51 (0.49,0.54)	1.21 (0.002)
2004-2008	804	0.69 (0.67-0.71)	135	0.49 (0.45,0.54)	1.22 (0.001)
2009-2013	829	0.78 (0.76-0.80)	25	-	0.91 (0.112)

Table 6.2. Time trends in Overall survival by 4 periods of diagnosis for SCR data.

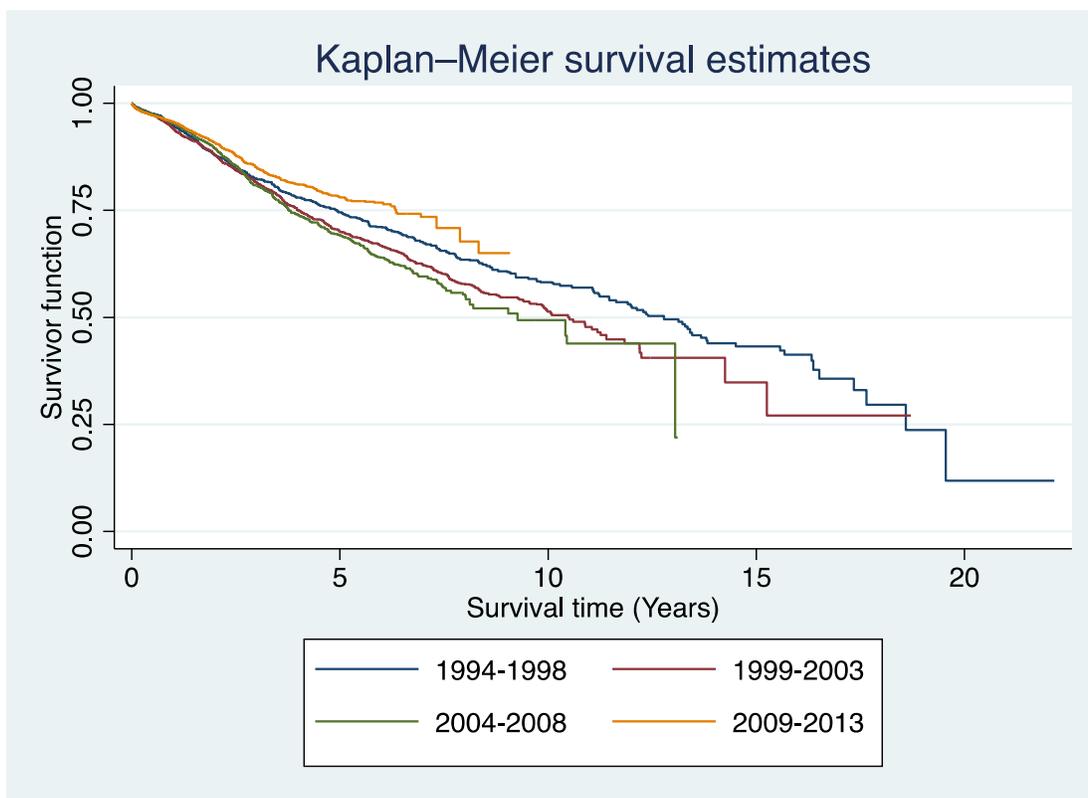


Figure 6.2. Overall survival from BC by year of diagnosis (1994-2013).

Overall Survival by age at diagnosis:

The 5- and 10-year survival was analysed by age group for the whole period from 1994 to 2013. It was found that women diagnosed with BC at a younger age had better survival than those diagnosed older. Age was categorised into two groups: cases aged less than 50 at diagnosis and those aged 50 and older. The analysis showed that 5-year survival for ages less than 50 was 79.7% (95% CI 78.5, 80.8), and for ages 50 and older, it was 76.1% (95% CI 74.5, 77.6). When applying the Log-rank test, it shows that there is a statistically significant difference between the two age groups ($P = 0.0001$). The 10-year survival for the two age groups was 69.5% (95% CI 67.5, 71.4) for ages younger than 50 and 61.9% (95% CI 58.9, 64.7) for ages 50 and older. Cox proportional hazards regression model was used to compare the 5-year survival between the two age groups and showed a hazard ratio of 1.35 ($P = 0.0001$, 95% CI 1.26, 1.45), which indicates that patients in the older age groups had a significantly higher risk of death, with 35% increased risk of death compared to the younger patients.

To better understand how age affects survival, age was categorised into eight groups, starting from 10-19 years with 10-year intervals up to 90 years and older. The survival rate was calculated for each group. The data showed that the youngest patients (under 20 years) had the highest survival rates, with a 5-year OS of 92%. For the age groups 20-29 and 30-39, there was a notable decrease in survival from 5 to 10 years, with drops of 12.7% and 14.6% in the survival rate, respectively. For the age groups from 40 to 69, the 5-year survival rate was higher compared to younger groups, but the 10-year survival rate dropped markedly. The age group 70-79 had a lower survival rate compared to younger age groups, while in the age group 80-89, the survival rate was markedly low, with only about half of the cases surviving 5 years and less than half surviving 10 years. In patients aged 90 and over, the survival rate was relatively low and had a broad confidence interval indicating uncertainty which could be due to the small number of patients (95% CI 0.14, 0.75). The survival rate tended to decrease as the age at diagnosis increased; younger patients (20-29 and 30-39) had the best survival outcomes, while survival rates significantly reduced in older age groups.

Age group	5-years Survival rate (95%CI)	10-years Survival rate (95%CI)
10-19	0.92 (0.73,0.98)	0.92 (0.73,0.98)
20-29	0.70 (0.66,0.74)	0.58 (0.52,0.63)
30-39	0.69 (0.67,0.71)	0.55 (0.51,0.58)
40-49	0.77 (0.75,0.79)	0.57 (0.54,0.60)
50-59	0.77 (0.74,0.79)	0.54 (0.49,0.58)
60-69	0.75 (0.72,0.78)	0.51 (0.45,0.56)
70-79	0.58 (0.52,0.63)	0.48 (0.40,0.55)
80-89	0.49 (0.38,0.59)	0.44 (0.32,0.55)
90+	0.47 (0.14,0.75)	-

Table 6.3. Overall survival by age group for SCR data.

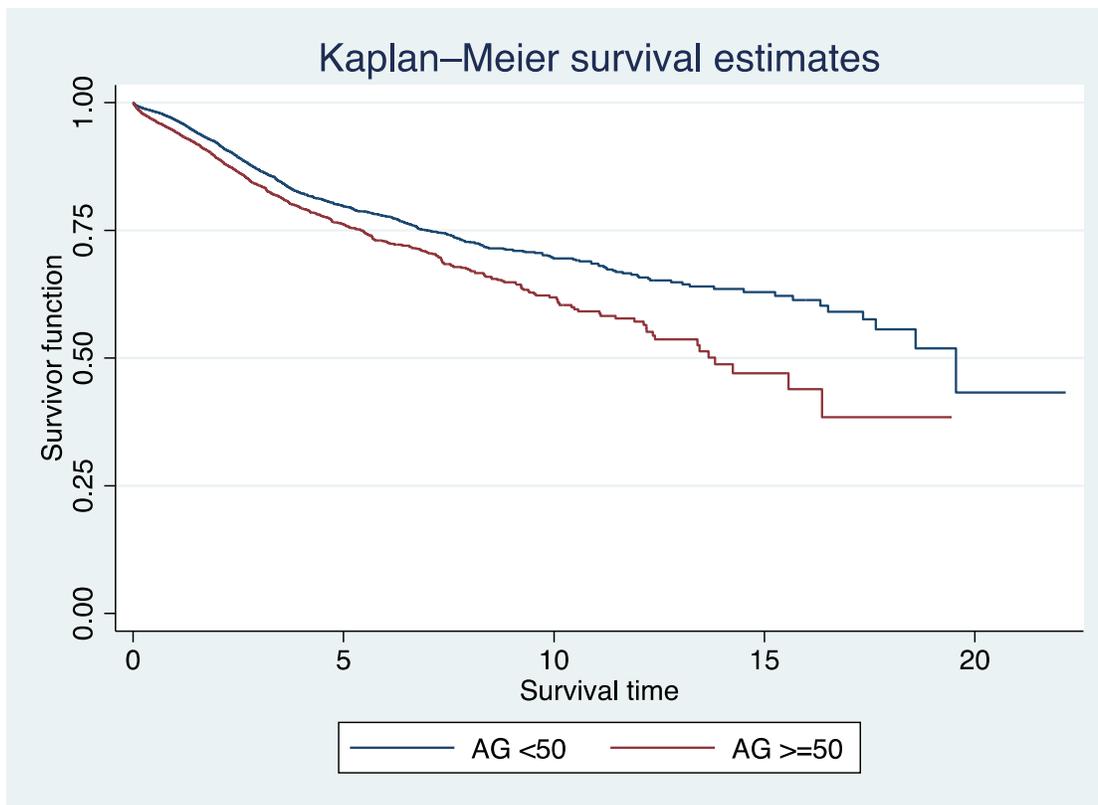


Figure 6.3. Overall survival by age at diagnosis for SCR data.

Overall Survival by grade:

When comparing survival rates by grade, 88.6% of cases in grade 1 survived for five years after being diagnosed with BC, while this percentage decreased with advanced stages to 81.6% for Grade 2, 75% for Grade 3, and 68% for Grade 4. Overall, the data indicate a clear trend of decreasing survival rates with increasing tumour grade. Grade 1 tumours had the highest survival rates among all grades, while grade 4 tumours showed stability in long-term survival rates despite having a relatively low 5-year survival rate. The decline in survival rates over time is more pronounced in Grades 2 and 3.

Grade	5-years Survival rate (95%CI)	10-years Survival rate (95%CI)
Grade 1	0.89 (0.85, 0.92)	0.75 (0.67, 0.82)
Grade 2	0.82 (0.80,0.83)	0.68 (0.65, 0.71)
Grade 3	0.75 (0.73,0.77)	0.66 (0.63,0.69)
Grade 4	0.68 (0.58, 0.77)	0.66 (0.54,0.75)

Table 6.4. Overall survival by cancer grade at diagnosis for SCR data.

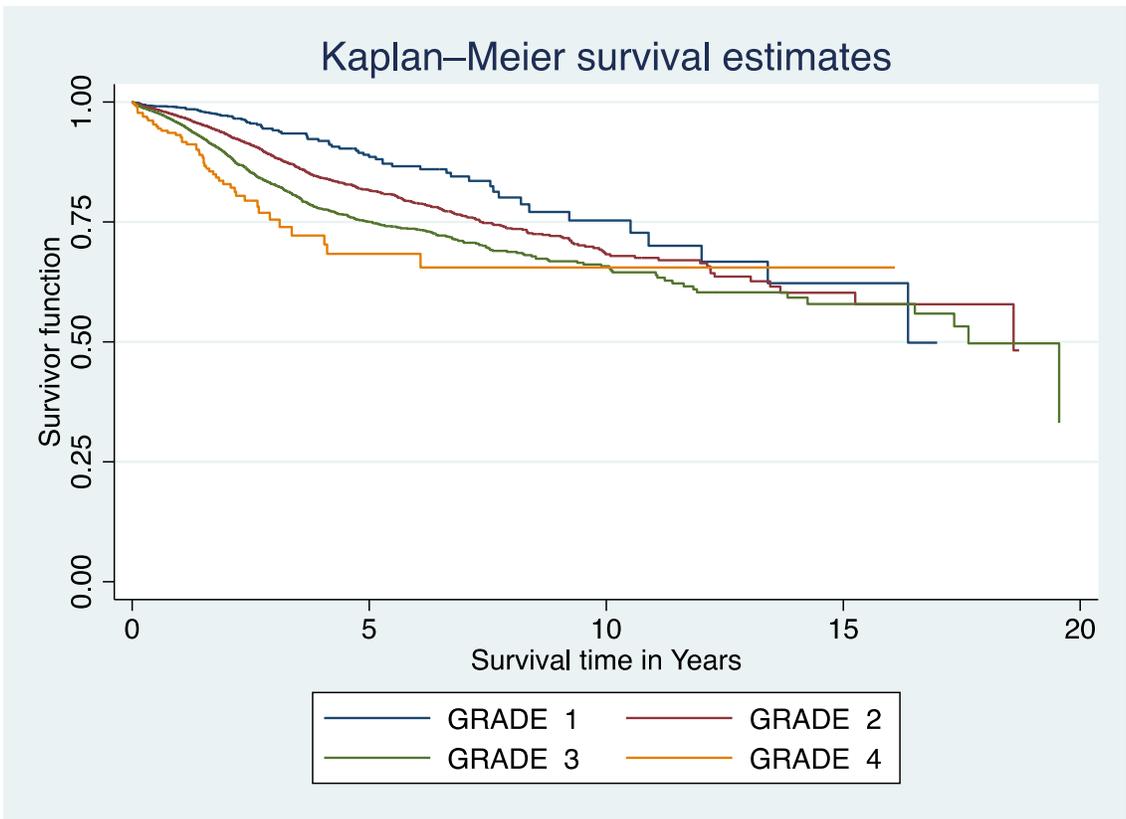


Figure 6.4. Overall survival by grade at diagnosis.

A log-rank test was performed to assess the equality of survival distributions among different grades. The test yields $X^2 = 136.68$ with $P = 0.0001$, indicating a statistically significant difference in survival distributions among the grades. Cox regression was conducted to assess this difference, showing that the risk of dying from BC increases with higher grades. Grades 2, 3, and 4 all present significantly higher hazard ratios compared to Grade 1, with Grade 4 showing the highest risk. The results are shown in the table below.

Grade	Hazard ratio (<i>p</i> -value)	95% CI
1	Reference	-
2	1.79 (0.001)	1.43,2.24
3	2.59 (0.001)	2.07,3.23
4	3.69 (0.001)	2.58,5.28

Table 6.5. Hazard ratios and 95% confidence intervals for different cancer grades at diagnosis, SCR.

Overall Survival by stage at diagnosis:

The data clearly demonstrate that survival rates of BC decrease as the disease progresses from localised to regional, then to distant metastatic stages. Patients with localised BC showed better survival among other stages stage, while those with distant metastasis had the lowest survival rates compared to regional and localised BC. The log-rank test was used to assess differences in survival by stage at diagnosis. The $X^2 = 2321.5$ with $P = 0.00001$ indicate a statistically significant difference in survival by stage at diagnosis.

Stage	5-years Survival rate (95%CI)	10-years Survival rate (95%CI)
Localised	0.90 (0.89,0.92)	0.79 (0.76,0.82)
Regional	0.81 (0.80,0.83)	0.68 (0.66,0.71)
Distant metastasis	0.50 (0.48,0.64)	0.39 (0.35,0.43)

Table 6.6. Overall survival of BC by Stage at diagnosis for SCR data.

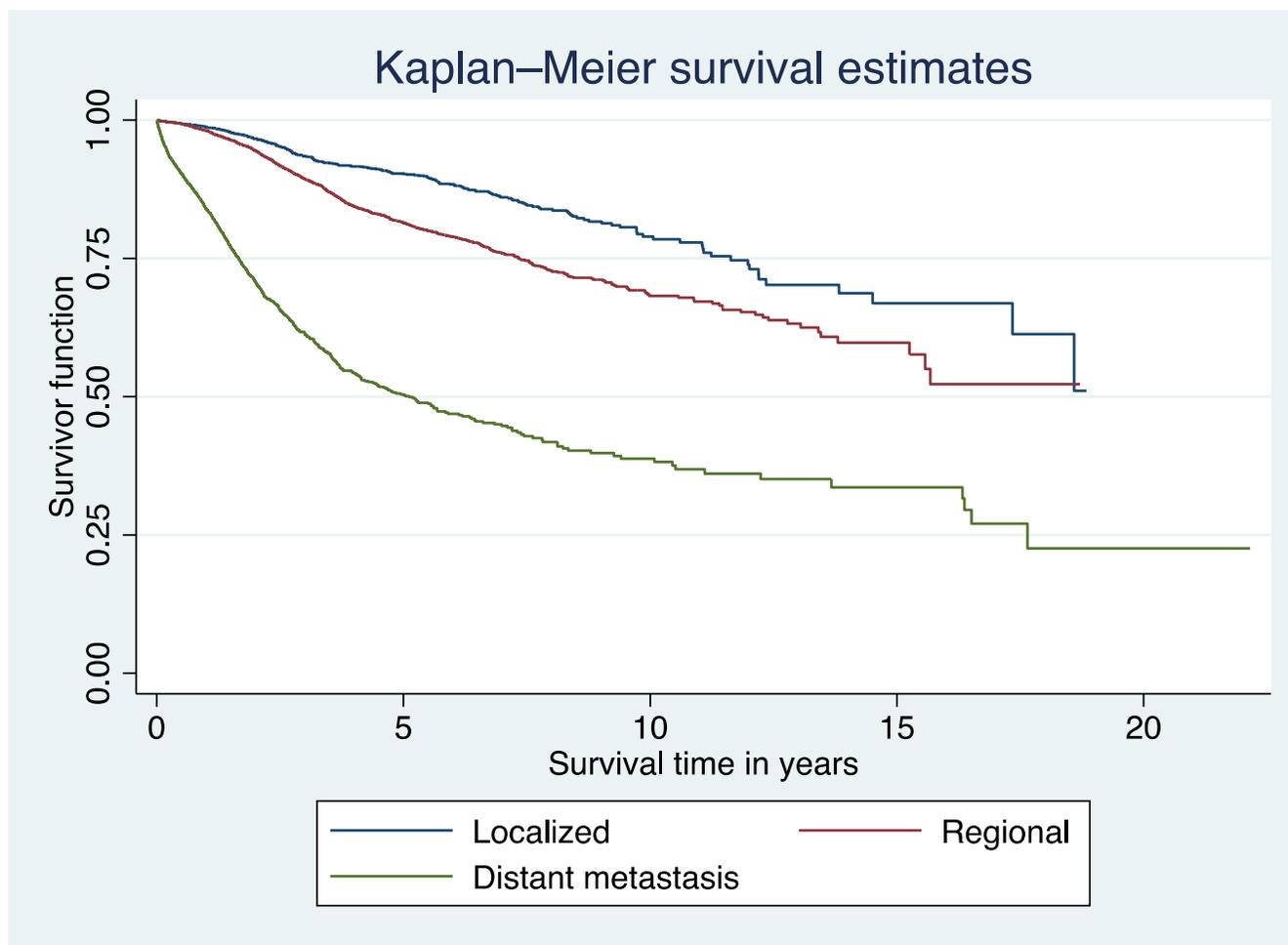


Figure 6.5. Overall survival by Stage at diagnosis.

The localised BC survival function pattern lies entirely above the regional and distant metastasis BC, meaning the cases with localised BC lived longer and had a more favourable survival experience than the other two groups.

By applying Cox regression, the hazard ratio for regional BC was 1.72 (95% CI 1.53,1.94), and for distant metastasis, it was 7.73 (95% CI 6.87, 8.68) compared to localised BC. This means regional BC is associated with a 72% higher mortality risk than localised BC, while distant metastasis presents more than a sevenfold increase in the risk compared to localised BC.

Model building:

Applying the univariate analysis showed that all variables had *P*-values less than 0.05, which means that this model will include every predictor, including age, stage, and grade. Next, a multivariable analysis using both forward and backward stepwise regression methods confirmed that all predictors, age, stage, and grade, were significant and should be included in the final model.

The multivariable Cox regression analysis indicates that age, stage, and grade are significant predictors of the death from BC. The results demonstrate that increasing age, regional cancer stage, and higher tumour grade are all associated with increased mortality risk. The model showed very high statistical significance ($P < 0.001$).

Variable	β Coefficient	95% CI	HR
Age \geq 50 (vs. <50)	0.006*	0.003,0.009	1.006
Stage			
Regional	0.54 *	0.42,0.65	1.54
Distant metastasis	1.91 *	1.79,2.02	6.91
Grade			
2	0.45*	0.25,0.65	1.45
3	0.80 *	0.60,1.00	2.22
4	0.89 *	0.57,1.23	2.45

Table 6.7. Multivariable Cox regression analysis. HR: hazard ratio, *indicates P -value < 0.05

Next, the Cox regression method considered and tested all possible interactions. The significance of interactions was assessed by examining the P -values in the model output. It was found that the interactions of age with stage, age with grade, and stage with grade do not show statistically significant effects and were not included in the model.

Interactions	β Coefficient	P- value	95% CI
Stage with age			
Regional	-0.11	0.43	-0.38,0.16
Distant metastasis	0.04	0.79	-0.23,0.30
Grade with age			
2	-0.14	0.56	-0.61,0.33
3	0.03	0.89	-0.44,0.50
4	-0.48	0.21	-1.23,0.28
Stage with grade			
Regional # grade2	0.25	0.42	-0.35,0.84
Regional #grade 3	0.61	0.04	0.02,1.20
Regional #grade 4	0.83	0.18	-0.39,2.05
Distant metastasis # grade 2	0.39	0.18	-0.19,0.98
Distant metastasis # grade 3	0.48	0.11	-0.11,1.06
Distant metastasis # grade 4	0.34	0.58	-0.86,1.54

Table 6.8. Interactions between variables and their coefficient and P-values. (Note: Age variable represents age ≥ 50 vs < 50 , with < 50 as reference)

The final model, which includes age, stage, and grade, is presented in the table below. The hazard ratios indicate that the risk of BC death increased by almost 27% for those aged 50 and older when all other variables were constant. Patients with regional BC have a 75% higher risk of mortality compared to those with localised BC. At the same time, patients with distant metastasis face a mortality hazard that is eight times higher than that of patients with localised disease. The risk of death increased by 66% in patients with Grade 2, more than twofold in Grades 3 and about threefold in Grade 4 compared to those with patients with Grade 1 BC. The results are highly significant, indicating that the highest tumour grade is associated with the most significant increase in mortality risk.

	Hazard ratio	95% CI
Age	1.27 ($P = 0.0001$)	1.16, 1.38
Stage		
Regional	1.75 ($P = 0.0001$)	1.53, 2.00
Distant metastasis	7.69 ($P = 0.0001$)	6.73, 8.79
Grade		
2	1.66 ($P = 0.0001$)	1.31, 2.09
3	2.43 ($P = 0.0001$)	1.93, 3.07
4	2.84 ($P = 0.0001$)	1.96, 4.11

Table 6.9. The final model with the hazard ratio and 95% confidence interval (CI).

Net survival (relative survival):

The dataset initially comprised 27,564 observations, with 1,748 observations excluded because their time to event was recorded as zero or negative, which means these individuals experienced death or were censored (lost to follow-up) before the study began. Subsequently, 25,811 subjects remained for analysis, among which 3,159 observed deaths were recorded, and the maximum observed exit time, which is the time until the death occurs or until the subject is censored, was 22 years.

The relative survival rates at 5 and 10 years were 99% and 94%, calculated using the Ederer II method.

Time (years)	Observed survival	Expected survival	Relative survival ((95%CI)
5	0.81	0.82	0.99 (0.98,1.00)
10	0.62	0.66	0.95 (0.92,0.98)

Table 6.10. Relative survival of BC in Saudi females for SCR data.

Relative survival by year of diagnosis:

When relative survival was analysed by the year of diagnosis and split into four groups, the data indicated fluctuations in relative survival rates across different periods. While earlier years of diagnosis showed high survival rates, a decline was observed from 1999 to 2003, followed by improvements in subsequent periods.

Period of diagnosis	5-years relative survival (95%CI)	10-years relative survival (95%CI)
1994-1998	0.94 (0.90, 0.97)	0.83 (0.77, 0.89)
1999-2003	0.87 (0.85, 0.89)	0.75 (0.69, 0.79)
2004-2008	0.92 (0.90, 0.94)	0.88 (0.82, 0.94)
2009-2013	1.02 (1.01, 1.04)	1.20 (1.16, 1.25)

Table 6.11. Relative survival by year of diagnosis for SCR data.

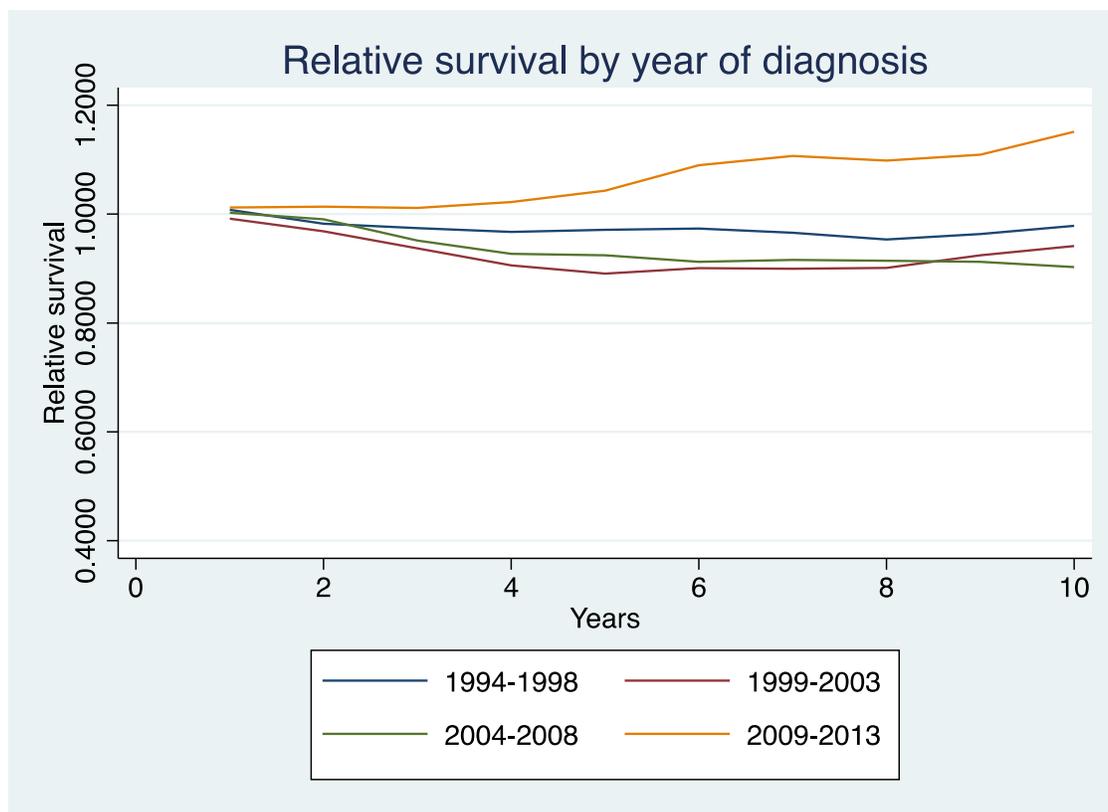


Figure 6.6. Relative survival by year of diagnosis.

Relative survival by age at diagnosis:

The age group with the lowest survival rate is individuals aged 90 and older, with a 5-year survival rate of 72%. In contrast, individuals older than 49 but younger than 90 exhibited a relative survival rate of over 100%. There was a marked increase in relative survival with advancing age at diagnosis, except for those younger than 20 and older than 89. To make the comparison more explicit, age was divided into two categories: those aged 50 or older and those younger than 50. Younger individuals demonstrated reasonable survival rates but faced a notable decline over time. In contrast, older patients show exceptionally high relative survival rates.

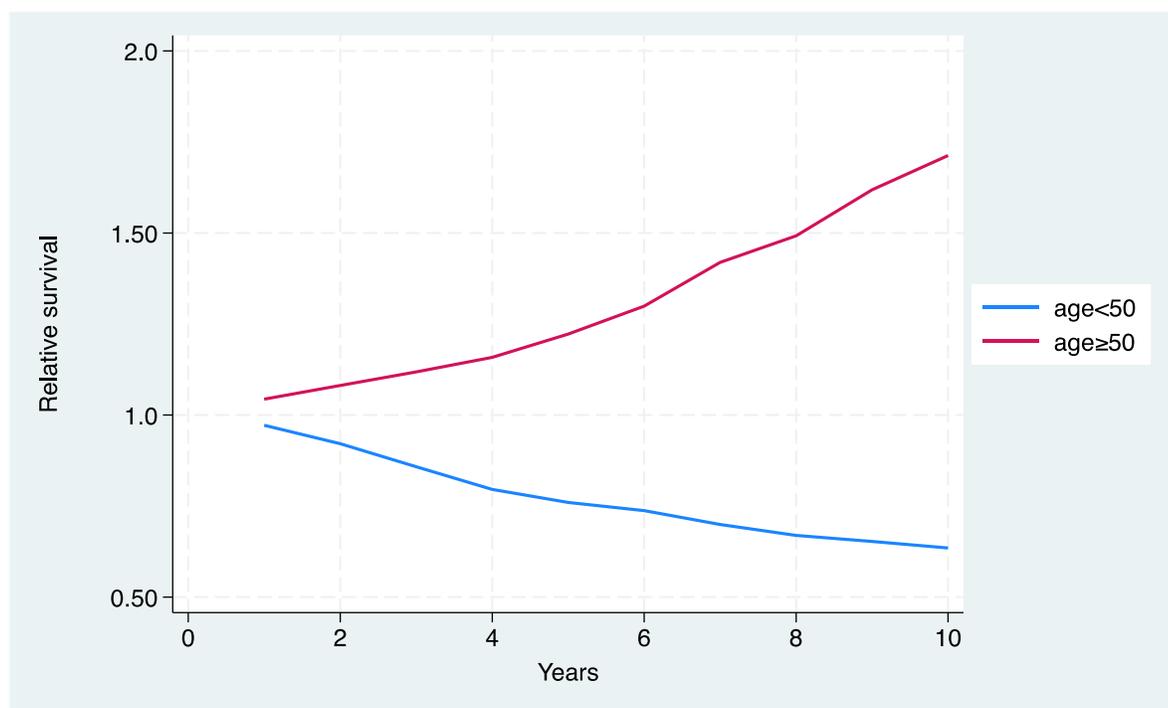


Figure 6.7. Relative survival by age at diagnosis.

Age group	5-years relative survival (95%CI)	10-years relative survival (95%CI)
<50	0.88 (0.87, 0.89)	0.75 (0.72,0.78)
≥ 50	1.18 (1.16,1.19)	1.37 (1.29,1.45)

Table 6.12. Relative survival by age group for SCR data.

Age group	5-years relative survival (95%CI)	10-years relative survival (95%CI)
10-19	0.96 (0.69,1.00)	0.97 (0.71,1.02)
20-29	0.79 (0.75, 0.82)	0.67 (0.59,0.73)
30-39	0.84 (0.80,0.85)	0.68 (0.63,0.73)
40-49	0.92 (0.91,0.93)	0.81 (0.76,0.85)
50-59	1.03 (1.01,1.04)	1.01 (0.94,1.08)
60-69	1.27 (1.24,1.29)	1.73 (1.56,1.89)
70-79	2.02 (1.95, 2.09)	7.99 (6.72,9.10)
80-89	1.76 (1.62,1.88)	1.44 (0.99,1.81)
90+	0.72 (0.59,0.82)	0.24 (0.0009-0.75)

Table 6.13. 5- and 10-year relative survival by age group with 95% confidence interval for SCR data.

In the relative survival analysis based on age group, an unexpected increase in survival rates was observed in the age group 70-79. To ensure the validity of these findings, the data were rigorously inspected for errors. The distribution of cases within each age group was examined. The life tables were verified, and the relative survival analysis was repeated. Despite these additional checks, the results remained consistent, leading to further exploration of the distribution of cases within each age group and their corresponding follow-up periods.

The relative survival analysis revealed an unexpected increase in the 5-year relative survival rate for the age group 70-79 (2.02, 95% CI:1.95- 2.09) and the 10-year relative survival rate (7.99, 95% CI: 6.72-9.10). A detailed inspection of the data showed that this age group accounted for 6.46% of the total cases, with only 7 cases (0.003%) having follow-up periods of 10 years or more.

Age group	Follow up period <10 (%)	Follow up period ≥10 (%)	Total (%)
10-19	28 (0.10)	1 (0.0)	29 (0.11)
20-29	1,082 (3.93)	32 (0.12)	1,114 (4.04)
30-39	5,033 (18.26)	72 (0.26)	5,105 (18.53)
40-49	8,294 (30.10)	88 (0.32)	8,382 (30.42)
50-59	6,662 (24.18)	48 (0.17)	6,710 (24.35)
60-69	3,735 (13.55)	32 (0.12)	3,767 (13.67)
70-79	1,772 (6.43)	7 (0.03)	1,779 (6.46)
80-89	550 (2.00)	1 (0.0)	55 (2.00)
90+	119 (0.43)	0 (0.0)	119 (0.43)
Total	27,275 (98.98)	281 (1.02)	27,556 (100)

Table 6.14. Distribution of BC cases by age group and follow-up periods for SCR data.

Relative survival by grade:

Survival was inversely related to the grade of BC, as the grade of the disease progresses, survival decreases. Lower tumour Grades (1 and 2) were associated with better survival, while higher grades (4 and 5) correlated with reduced survival rates, as shown in Figure 6.8.

Grade	5-years Survival rate (95%CI)	10-years Survival rate (95%CI)
Grade 1	1.19 (1.18,1.22)	1.25 (1.08,1.38)
Grade 2	1.04 (1.03,1.05)	0.97 (0.92,1.02)
Grade 3	0.93 (0.92,0.95)	0.93 (0.88,0.98)
Grade 4	0.85 (0.76,0.93)	0.85 (0.61,1.04)

Table 6.15. Relative survival by BC grade at diagnosis for SCR data.

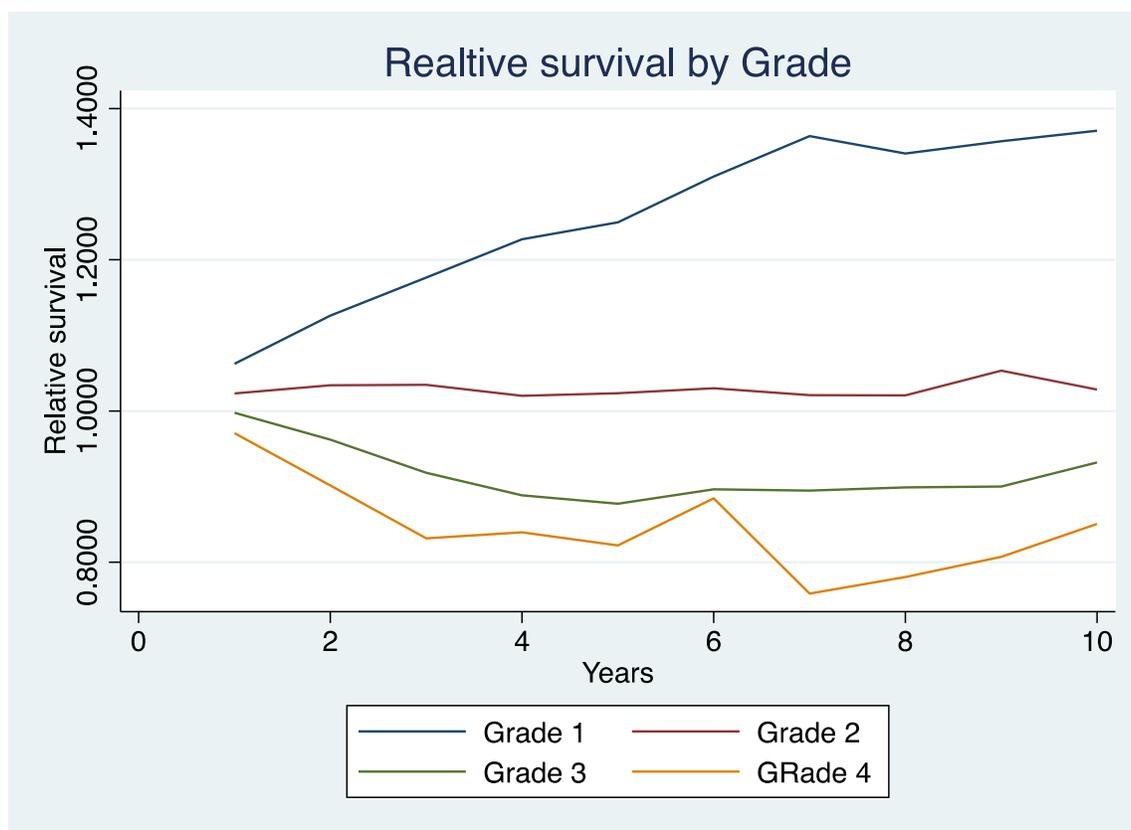


Figure 6.8. Relative survival by grade.

Relative survival by stage:

The 5-year relative survival rate for localised BC was the best among all stages, followed by those with regional BC. However, those with distant metastasis face significantly lower survival rates. This means that as the disease progresses, survival decreases. The 5-year relative survival rate for distant metastasis was 68%.

Stage	5-years relative survival (95%CI)	10-years relative survival (95%CI)
Localised	1.14 (1.13,1.15)	1.15 (1.09,1.21)
Regional	1.03 (1.02,1.04)	0.97 (0.92,1.01)
Distant metastasis	0.68 (0.66,0.70)	0.54 (0.47,0.62)

Table 6.16. Relative survival by stage at diagnosis for SCR data.

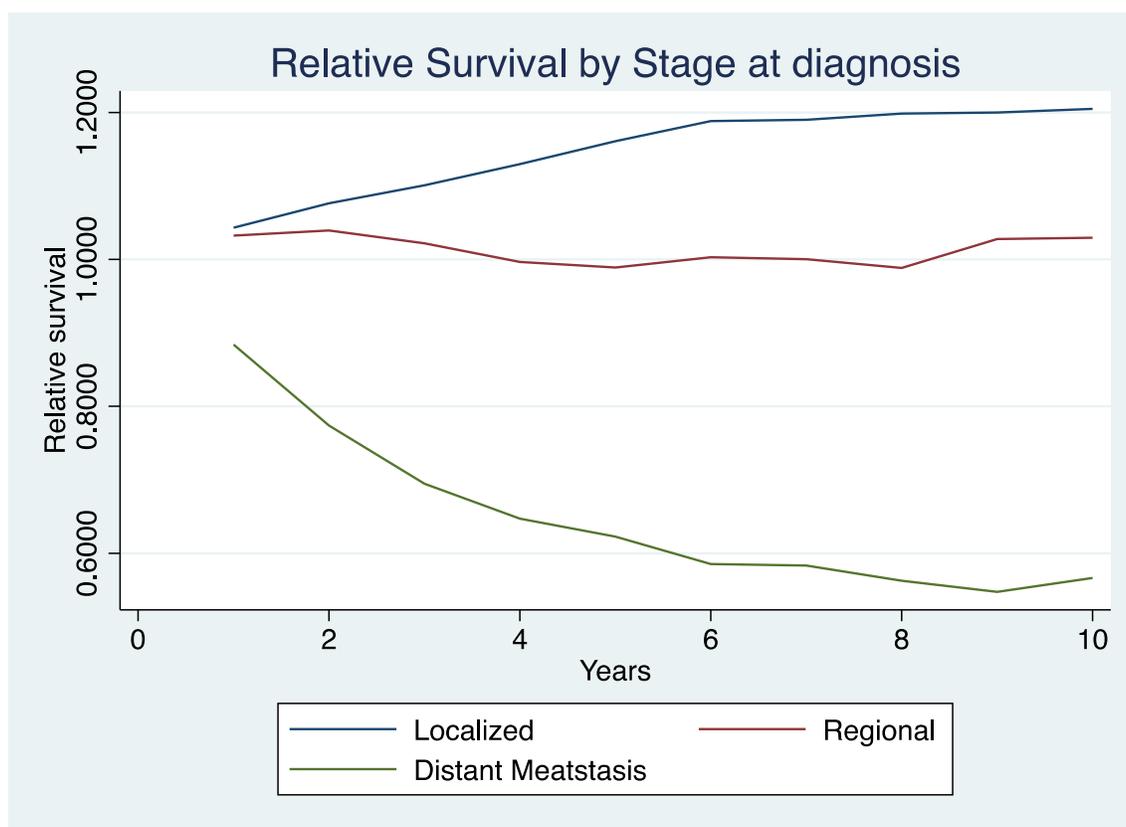


Figure 6.9. Relative survival by stage at diagnosis.

Model building:

A Poisson regression model was fitted to assess the association between prognostic factors and excess mortality. The model is presented in Table 6.17. The results indicate that all the included prognostic factors significantly influence excess mortality.

Individuals aged 50 years and older had a significantly lower risk of excess mortality at 66.9% compared to younger age groups (HR: 0.33). Patients diagnosed from 1999 to 2003 and 2004 to 2008 exhibited a significantly higher risk of excess mortality, with HRs of 2.76 and 1.77, respectively. Both regional and distant metastasis stages showed a significantly higher risk of excess mortality compared to localised BC. Furthermore, the risk of distant metastasis is considerably higher than that of the regional stage. Regarding the grade of BC, using grade 1 as a reference, as tumour grade increases, there is a marked rise in the risk of excess mortality. The model fit statistics indicate a reasonable fit of the model, suggesting that the model adequately captured the underlying data. Specifically, the deviance was 1855.98, and the Pearson Chi-square was 1811.16, both indicating good model alignment with the observed data. Additionally, the AIC value of 5.46 and the BIC value of -1389.04 further support the adequacy of the model, with lower AIC and BIC values indicating a better fit of the model.

Variables		HR (<i>p</i> -value)	95% CI
Age	< 50	Ref.	
	≥ 50	0.33 (0.0001)	0.25,0.44
Year of diagnosis	1994-1998	Ref.	
	1999-2003	2.76 (0.0001)	1.93,3.96
	2004-2008	1.77 (0.002)	1.24,2.53
	2009-2013	1.21 (0.294)	0.85,1.74
	2014- 2017	1.67 (0.009)	1.13,2.45
Stage	Localised	Ref.	
	Regional	6.36 (0.0001)	3.28,12.35
	Distant metastasis	44.45 (0.0001)	22.87,86.40
Grade	1	Ref.	
	2	6.52 (0.003)	1.88,22.64
	3	13.04 (0.0001)	3.76,45.29
	4	19.99 (0.0001)	5.46,3.27

Table 6.17. Multivariable Poisson regression of BC cases in SCR. HR hazard ratio, Ref. =reference, CI confidence interval, AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion

Model	Variables included	AIC	BIC	Deviance
Model 1 (Reduced)	Age, stage, grade	10.55	485.2	1502.29
Model 2 (Full)	age, stage, grade, year of diagnosis	5.46	-1389.04	1855.98

Table 6.18 Model fit statistics comparing full and reduced poisson regression models for excess mortality. AIC: Akaike Information Criterion, BIC: Bayesian Information Criterion

6.3.2 Hospital data

Overall survival:

The dataset initially comprised 2,924 observations, with 112 missing event times indicating incomplete survival information. An additional two observations were excluded because they ended on or before entering the study. Subsequently, 2,810 subjects remained for analysis, among which 316 observed deaths were recorded, and the maximum observed exit time, which is the time until the death occur, was 14 years. The overall survival rate was 80% (77-82) at 5 years and 70.7% (66-75) at 10 years.

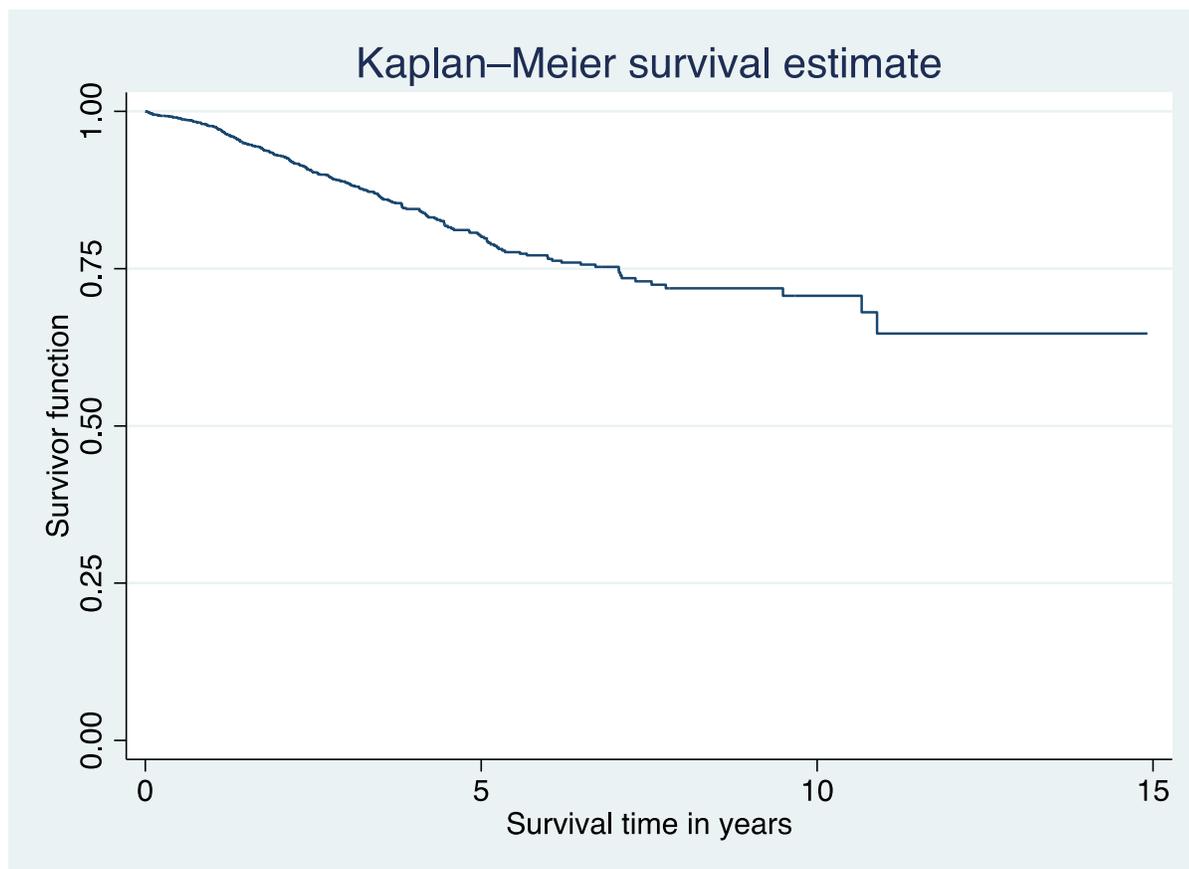


Figure 6.10. Overall Survival of BC in Saudi females in KFSH&RC.

Overall survival by stage:

When analysing survival by stage at diagnosis, results showed that the survival rate decreases as the cancer stage progresses. Patients diagnosed at stage I have a high 5-year survival rate of 85%, indicating a favourable prognosis. Patients with stage II BC show better survival than the other three stages. However, the hazard ratio 1.54 suggests a higher mortality risk than stage I. Still, the *P*-value of 0.41 indicates that this result is not statistically significant, meaning that the difference in risk is not conclusive although there was a clear trend with stage. Patients with stage III disease have a 5-year survival rate of 82% with a hazard ratio of 3.78, indicating that patients in this stage have a significantly higher risk of mortality compared to stage. Patients with stage IV BC showed poorer survival with a 46% survival rate after 5 years of diagnosis, with a hazard ratio 15-fold higher than those diagnosed with stage I, indicating an extremely high risk of mortality. Due to the lack of data for the 10-year survival rate for stages I and IV, long-term outcomes cannot be assessed for these stages. A clear trend was evident as the log-rank test showed that the difference in survival across stages was significant (*P* = 0.001). (Table 6.19)

Stage	5-years Survival rate (95%CI)	10-years Survival rate (95%CI)	HR (95%CI)	<i>p</i> -value
Stage I	0.85 (0.49,0.96)	-	Reference	-
Stage II	0.91 (0.86,0.94)	0.87 (0.81,0.92)	1.54 (0.55,4.31)	0.412
Stage III	0.82 (0.77,0.85)	0.69 (0.61,0.75)	3.87 (1.42,10.54)	0.008
Stage IV	0.46 (0.36,0.56)	-	15.64 (5.79,42.23)	0.0001

Table 6.19. Survivor function by stage at diagnosis with the 95% confidence interval (CI) at KFSH&RC.

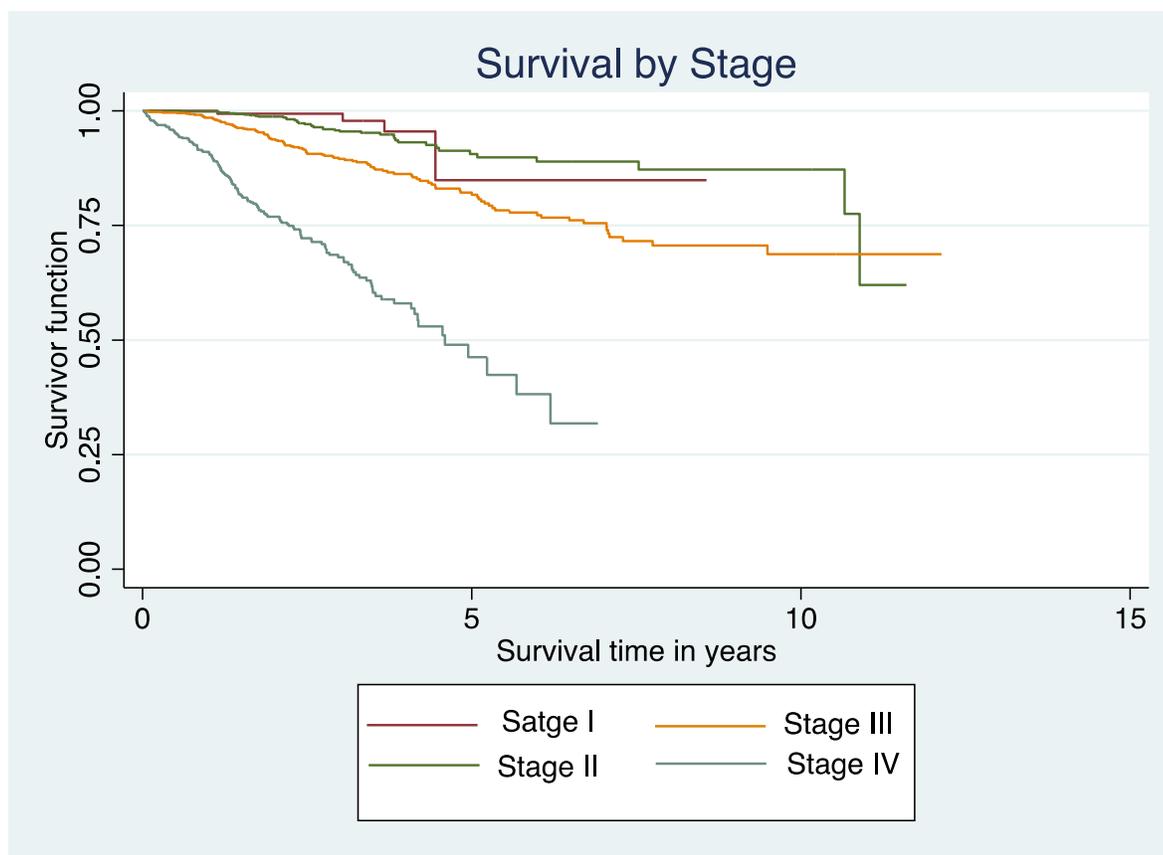


Figure 6.11. Survival by stage at diagnosis.

Overall survival by age at diagnosis:

By categorising age into two groups, the 5-year overall survival was 80.2% for those aged <50. However, the 10-year survival rate decreased to 70%. The 5-year survival rate was 79.7% for those aged 50 and older, and the 10-year survival rate was also lower at 72%. Overall, both age groups exhibit similar survival rates, with no significant difference. ($\chi^2 = 0.03$ ($P = 0.85$), HR = 1.02 ($P = 0.18$)).

Age group	5-years overall survival (95%CI)	10-years overall survival (95%CI)
<50	0.80 (0.77,0.83)	0.70 (0.64,0.75)
≥ 50	0.79 (0.75,0.84)	0.73 (0.65,0.79)

Table 6.20. Survival by age group at KFSH&RC.

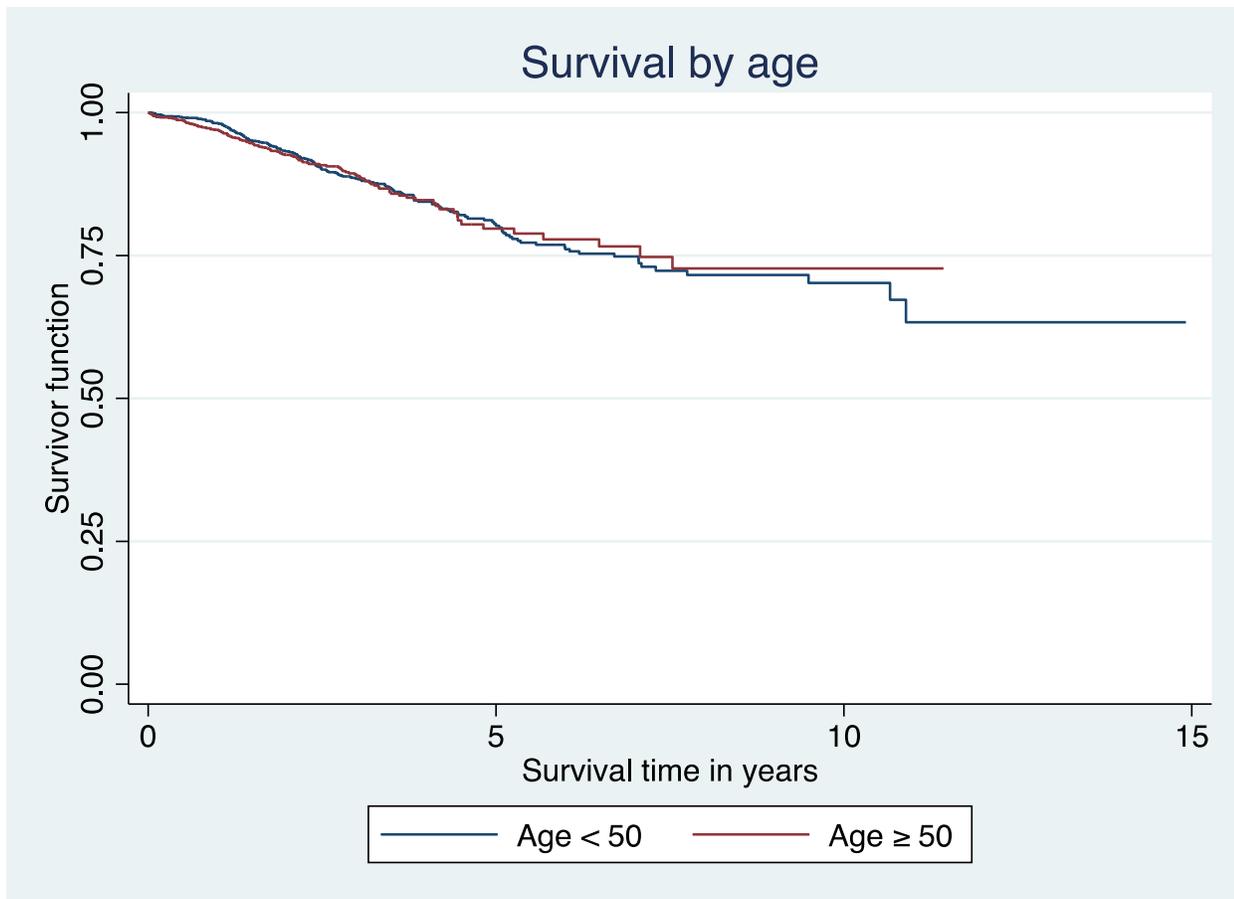


Figure 6.12. Survival by age at diagnosis.

Overall survival by hormone receptor status:

The analysis of survival based on hormone receptor status showed that patients with both ER and PR-positive receptors have better survival rates than patients with negative hormone receptors. The 5-year survival rate is 85%, and the 10-year survival rate is 74%. There is a statistically significant difference ($P = 0.0001$) between the various receptor statuses; patients with negative oestrogen receptors have poorer survival than those with positive oestrogen receptors. Having ER-/PR+ increases the mortality risk by 3.5-fold and having ER-/PR- increases the mortality risk by more than two-fold compared to those with positive receptors. The results indicate that hormone receptor status significantly influences survival outcomes. Those with ER+/PR+ status have the most favourable prognosis, while those who are ER-/PR- have the highest mortality risk.

Hormone Receptor status	5-years overall survival (95%CI)	10-years overall survival (95%CI)	HR (95%CI)	p-value
ER+/PR+	0.85 (0.81, 0.88)	0.74 (0.68, 0.79)	Reference	
ER+/PR-	0.76 (0.67, 0.83)	0.58 (0.39, 0.73)	1.93 (1.36, 2.75)	0.0001
ER-/PR+	0.74 (0.39, 0.91)	-	3.53 (1.12, 11.11)	0.031
ER-/PR-	0.71 (0.66, 0.76)	0.69 (0.63, 0.74)	2.32 (1.82, 2.96)	0.0001

Table 6.21. Survival function by hormone receptor status with hazard ratios (HR) and confidence intervals (CI) at KFSH&RC. ER: oestrogen receptor, PR: Progesterone receptor.

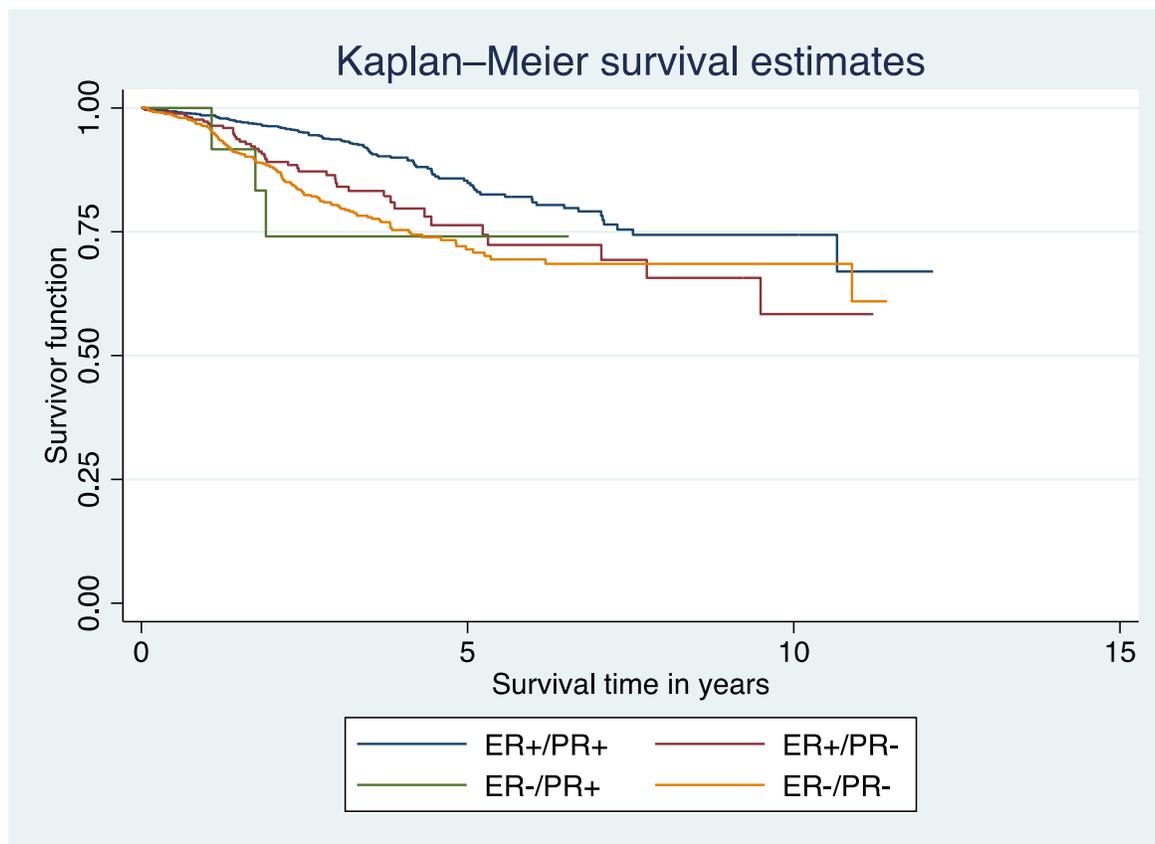


Figure 6.13. Survivor function by hormone receptor status.

Overall survival by treatment modalities:

Different treatment modalities have been applied at KFSH&RC; about 40% of the cases undergo surgery and receive chemotherapy, radiotherapy, and hormonal therapy. The 5-year OS rate was higher in patients who underwent surgery at 97% compared to other treatments. The 10-year survival rate was high in surgery, chemotherapy, and radiotherapy cases. The lowest survival rate was 57% in patients who had the combination of surgery and radiotherapy. The difference in survival between different treatments was very highly statistically significant ($\chi^2(10) = 76.79, P = 0.0001$).

Treatment modality	5-years overall survival (95%CI)	10-years overall survival (95%CI)	HR (95%CI)	p-value
Surgery	0.97 (0.88,0.99)	-	Reference	
Surgery + radiotherapy	0.57 (0.17,0.84)	0.29 (0.01,0.69)	7.15 (1.48,34.48)	0.01
Surgery + Chemotherapy + Radiotherapy	0.87 (0.78,0.93)	0.87 (0.78,0.93)	2.89 (0.65,12.75)	1.60
Surgery + Chemotherapy + Radiotherapy + Hormonal therapy	0.89 (0.77,0.95)	-	1.18 (0.26,5.36)	0.82
Surgery + Chemotherapy + Hormonal therapy	0.84 (0.45,0.96)	-	1.29 (0.23,7.04)	0.77
Surgery + Hormonal therapy	0.76 (0.37,0.93)	-	1.63 (0.31,8.42)	0.56
Chemotherapy + Surgery + Radiotherapy	0.73 (0.65,0.79)	0.67 (0.58,0.75)	5.69 (1.37,23.58)	0.02
Chemotherapy + Surgery + Radiotherapy+ Hormonal therapy	0.88 (0.83,0.92)	0.75 (0.66,0.82)	2.41 (0.58,10.02)	0.23
Chemotherapy + Surgery + Chemotherapy + Radiotherapy + Hormonal	0.89 (0.62,0.97)	0.89 (0.62,0.97)	2.03 (0.58,10.02)	0.48

Table 6.22. Survival by treatment modalities after 5 and 10 years with 95% confidence interval and hazard ratios (HR) at KFSH&RC.

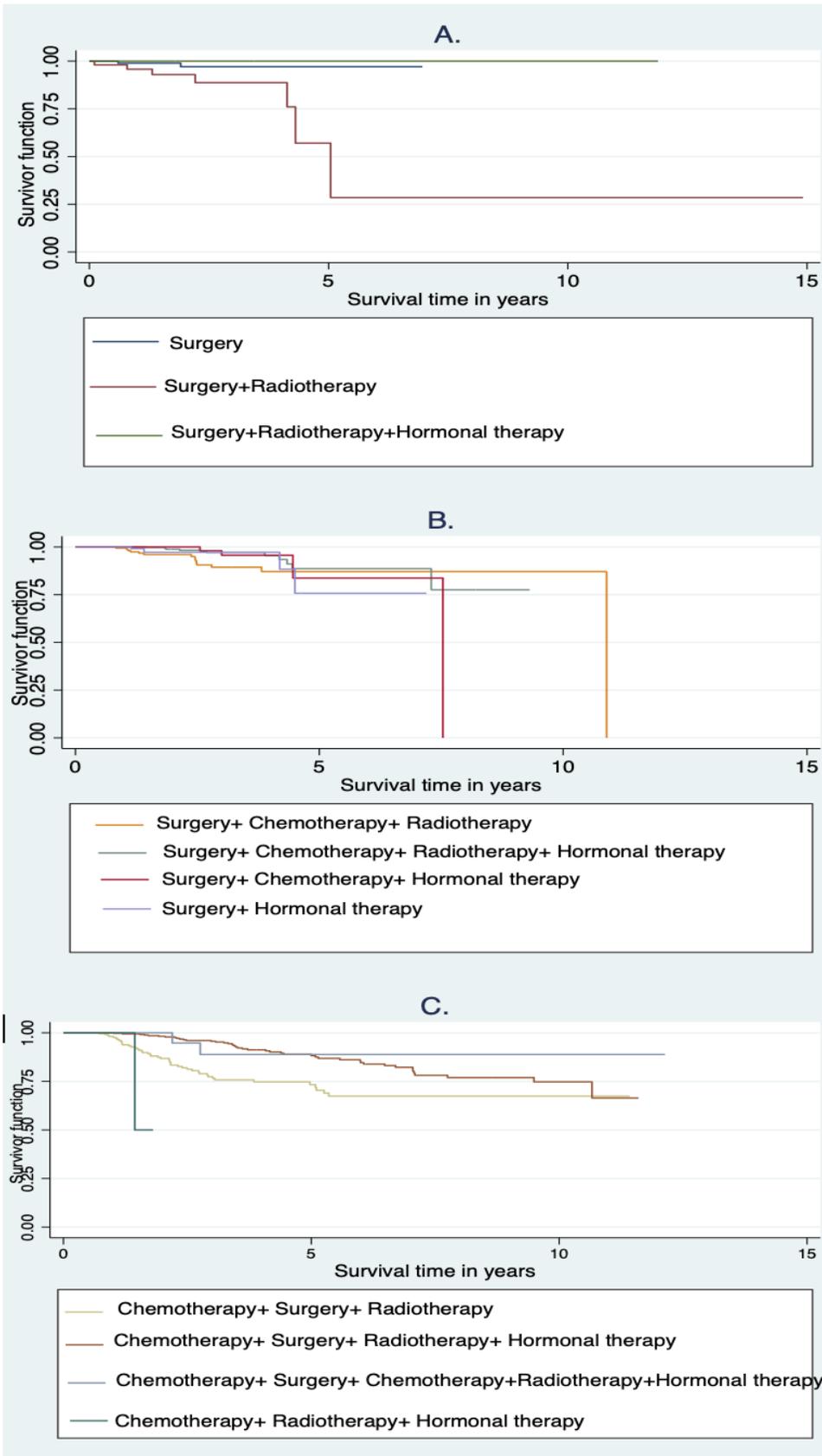


Figure 6.14. Survival analysis by different treatment modalities

The table below shows the survival by different treatment modalities after 5 and 10 years, with the hazard ratio. Some results are missing in the 10-year overall survival column, and this could be because there may not have been enough patients or follow-up time to calculate the 10-year survival or due to a large proportion of participants in the treatment groups that were censored, which affected the ability to calculate the 10-year survival rate for these groups. The use of biological treatments and chemotherapy shows no significant impact on survival. In contrast, the use of hormonal therapy is associated with a significant improvement in survival outcomes for BC patients; those who used hormonal therapy had a significantly lower risk of mortality compared to those who did not receive hormonal therapy, and this risk is reduced by 59%. Additionally, there is a statistically significant association between radiotherapy and mortality in BC patients; radiotherapy increases mortality risk by 44% in patients who received radiotherapy compared to those who did not. Surgery also improved the survival rate, showing that the 5-year survival was 84% compared to 54% when surgery is not performed; this difference is statistically significant with a hazard ratio of 0.21, indicating that the risk of mortality is reduced by 79% in patients who underwent surgery compared to those who did not.

Treatment	5-yr survival	10-yr survival	χ^2 test (<i>p</i> -value)	HR (<i>P</i> -value)
Biological			0.9 (0.34)	
No	0.81 (0.77,0.84)	0.70 (0.64,0.76)		-
Yes	0.77 (0.70,0.81)	0.72 (0.65,0.78)		-
Chemotherapy			1.23 (0.26)	
No	0.79 (0.69,0.86)	0.68 (0.49,0.82)		-
Yes	0.79 (0.77,0.82)	0.71 (0.66,0.75)		-
Hormonal			60.8 (0.0001)	
No	0.72 (0.67,0.76)	0.67 (0.61,0.72)		Ref.
Yes	0.84 (0.81,0.87)	0.72 (0.65,0.78)		0.41 (0.0001)
Radiotherapy			7.91 (0.005)	
No	0.82 (0.79,0.85)	0.73 (0.69,0.83)		Ref.
Yes	0.76 (0.69,0.83)	-		1.44 (0.005)
Surgery			154 (0.0001)	
No	0.54 (0.33,0.65)	-		Ref.
Yes	0.84 (0.81,0.86)	0.74 (0.69,0.78)		0.21 (0.0001)

Table 6.23. BC survival by treatment with the hazard ratios.

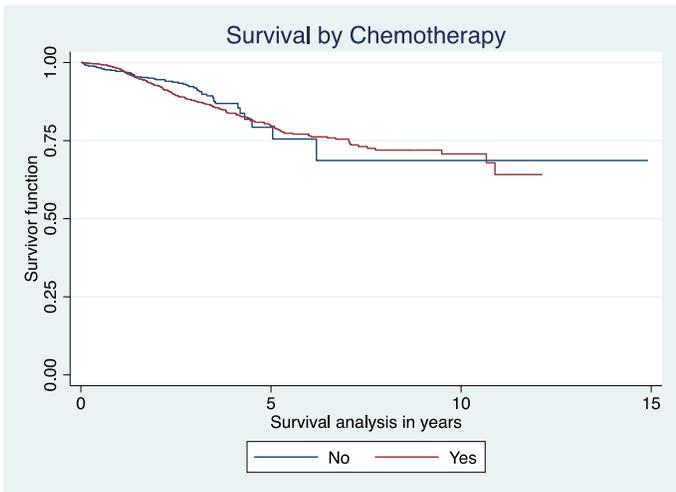
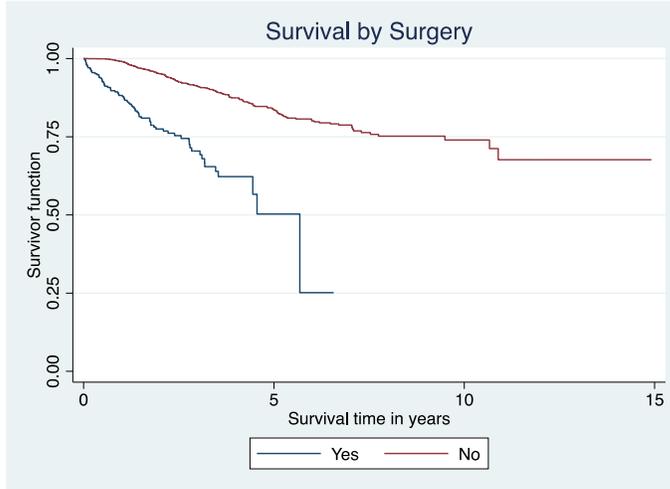
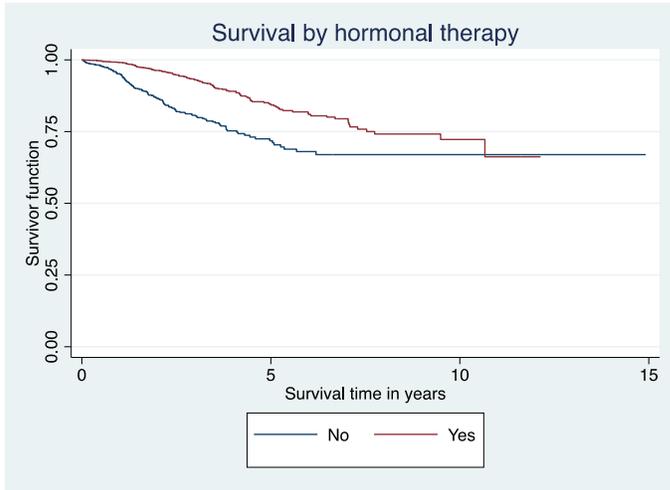
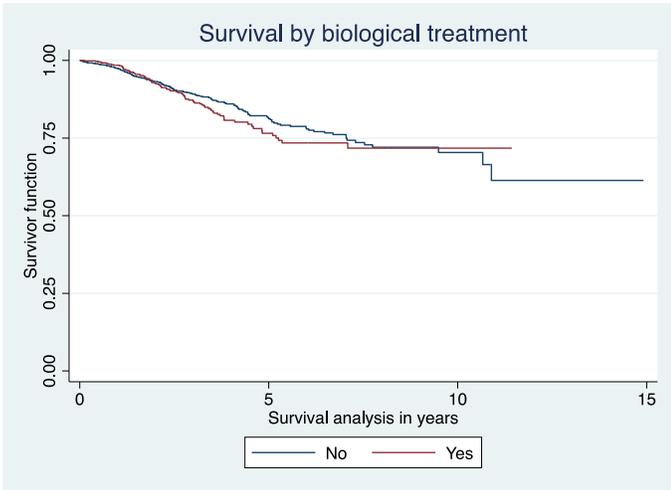


Figure 6.15. Survival by different treatment modalities

Hormonal therapy:

Hormonal therapy was used in BC treatment, including tamoxifen (39.9%), aromatase inhibitors (20.3%), luteinising hormone-releasing hormone (LHRH) (0.4%), or a combination of tamoxifen with AIs (6.3%). Analysis of the survival by hormonal therapy showed an increase in survival when using hormonal therapy, and the risk of mortality was reduced by 56% compared to those not taking hormonal therapy. Further analysis was done for the different types of hormonal treatment and found that the 5-year survival rate when using tamoxifen was 86%, which is higher than using AI's, which was 80%. Still, the log-rank test did not show a significant difference in survival between tamoxifen and AI's ($P = 0.61$). While the 10-year survival rate using AI's (80%) was higher than those using tamoxifen (68%). The combination therapy shows a 5-year survival rate of 84%, but the 10-year survival rate of 73% suggests a decline in long-term survival, similar to tamoxifen.

Hormonal therapy	5-years overall survival (95%CI)	10-years overall survival (95%CI)
Tamoxifen	0.86 (0.82,0.89)	0.68 (0.62,0.73)
AI's	0.80 (0.71,0.87)	0.80 (0.71,0.87)
Combination	0.84 (0.69,0.92)	0.73 (0.51,0.86)

Table 6.24. Survival analysis by different hormonal therapies with the confidence interval at KFSH&RC.

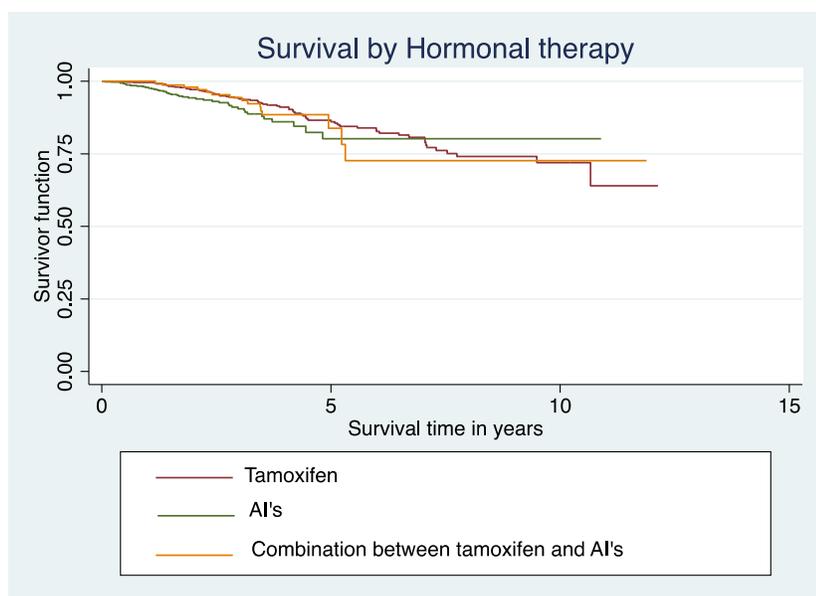


Figure 6.16. Survival by hormonal therapy.

6.4 Discussion

One of the main objectives of this study was to explore BC survival in Saudi females by age, stage, genotype, and treatment modalities, as well as to investigate the changes in survival driven by risk factors.

This study's results showed that the 5-year survival rate was 73%, which is similar to the results reported by a study conducted in KSA, with a 5-year survival rate of 72% (Al-Shamsi et al., 2023). In contrast, the rates were lower in KSA compared with those reported in high-income countries and inconsistent with studies that reported survival to be above 80% in developed countries (Sun et al., 2017). For example, the overall 5-year survival rate in the UK was 80.2% from 2000 to 2021 (Barclay et al., 2024). In this study, the survival outcomes varied depending on the data source and survival measure used. The relative survival from the SCR was considerably higher than the overall survival from the SCR; this discrepancy highlights the impact of adjusting for competing risks when estimating net survival. The higher survival rates observed in hospital data compared to registry-based OS may reflect differences in patient population, treatment quality or completeness of follow-up, it could be that cancer registries capture all diagnosed cases including those who may not have received treatment or those who are diagnosed late or with comorbidities while the hospital data include patients who had access to treatment. This hospital is one of the specialised cancer hospitals that provide more advanced treatments compared to data in the registry data that includes patients from different hospitals with different facilities. Additionally, the data on follow-up in the hospital could be more accurate and complete compared to the registry data which would affect the survival rates.

The survival analysis reveals a noticeable decline in 5- and 10-year survival rates over time, which could be attributed to delayed diagnosis, poorer treatment options, or data that could be incomplete or less accurate. However, the most recent period (2009-2013) exhibited an increase in 5-year survival rates; but it lacks statistical significance suggests that statistical variation might partially explain the observed improvement. This improvement may be attributed to several factors, it could be the approval of new therapeutic medications (e.g., AIs) such as anastrozole and exemestane, which were approved in KSA by the Saudi FDA in 2000 and 2003, respectively (SFDA,2024) and shown to improve survival rates of BC patients (Mauri et al., 2006). Another contributing factor could be the establishment of the first

BC screening centre in 2007 in Riyadh, followed by another centre in 2009 in the eastern province (Gosadi, 2019); females are undergoing screening, which aids in the early detection of BC and enhances survival.

The influence of age at diagnosis on survival in this study aligns with findings in other studies (Teng et al., 2024); older patients experienced lower survival rates, with those aged 70 and above demonstrating the lowest rates (Brandt et al., 2015). However, survival among middle-aged patients exhibits variability, with low rates between ages 30 and 39 (69%), which improves for ages 40 to 49 (77%). When interpreting these findings, caution is warranted, as the decline in survival among older patients may be attributed to late-stage diagnosis, a higher burden of comorbidities, or reduced access to aggressive treatment options due to frailty affecting survival rates (Jackson et al., 2023). Nonetheless, the results were statistically significant, indicating that the effect is due to age and is less likely to be attributable to chance. These findings underscore the need for tailored plans to improve outcomes in older populations and ensure access to early detection and effective treatment strategies across all age groups.

As anticipated, survival rates correlate inversely with BC stages and grades, with advanced grades showing poorer outcomes. The observed threefold increase in mortality risk for Grade 4 patients emphasises the need for early detection and intervention strategies. The association between low-grade tumours and a better prognosis is attributed to their slower progression and greater responsiveness to treatment. Conversely, Grade 4 tumours demonstrate stability in long-term survival despite a relatively low five-year survival rate. This may indicate that the aggressive nature of high-grade tumours is mitigated over time due to more intensive early treatment approaches.

In contrast, the survival rates in women who were diagnosed with Grades 2 and 3 tumours displayed a more noticeable decline over time, suggesting that these intermediate-grade tumours may encounter challenges in long-term management. These results are consistent with the results of global studies (Saadatmand et al., 2015). This could be due to their biological characteristics, which may limit the effectiveness of standard treatments and require a more tailored therapeutic approach.

Furthermore, survival rates varied significantly by clinical stage. Patients with localised BC demonstrated the highest survival, while distant metastasis is strongly associated with lower survival rates. This finding aligns with the results from other studies, such as this study that reported that the survival rate decreased with the advancing stage (Ugnat et al., 2004). This emphasises the critical importance of early detection and highlights the challenges of managing advanced-stage BC.

The same results were obtained when analysing the overall survival by stage using data from the hospital; survival rate decreased with advanced stage at diagnosis. However, the hazard ratio of 1.54 for patients with stage II compared to stage I suggests a higher mortality risk, but the associated *P*-value of 0.41 indicates that this difference is not statistically significant. However, the consistent trend suggests that the lack of significance in hospital data may be due to the insufficient sample size or limited follow-up duration, reducing the ability to detect a true difference. Additionally, several factors could contribute to this variability, including differences in treatment approach or access to therapies for stage II patients, which may affect outcomes, creating variability in survival.

The analysis of relative survival rates offers valuable insights into the long-term outcomes of BC patients compared to the general population. It reveals a pattern of improvement over the years, this trend has been particularly pronounced since 2003 and may be linked to advances in medical care, treatments, and early detection protocols. An interesting finding in this study is that older patients have higher survival rates than the general population with matched characteristics; however, younger individuals, particularly those aged 20 to 39, present lower survival rates; this might be attributed to delayed diagnosis or the aggressiveness of the disease in this age group, or it could be related to lack of competing causes of death in this age group. This finding was consistent with other studies, for example (Ugnat et al., 2004), which showed that relative survival was poor for cases younger than 40 years. Moreover, the analysis highlights the impact of disease grade and stage at diagnosis on survival outcomes, with earlier stages showing higher relative survival rates than advanced stages. These findings underscore the importance of ongoing efforts to encourage screening programmes and tailor treatment strategies to further improve outcomes for breast cancer patients.

Furthermore, the unexpected increase in survival rates for the age group 70-79 may be attributed to the limited number of cases with extended follow-up periods in this age group (7 cases, 0.03%). These data could have resulted in unreliable estimates due to the overrepresentation of survivors within this small subset of patients. Another cause could be that patients in this age group might receive more focused medical attention and care, including regular monitoring and follow-up. These findings emphasise the importance of adequate follow-up data when analysing survival outcomes, particularly in older age groups. Further investigation is warranted to determine whether this anomaly reflects a true epidemiological phenomenon or is an artefact of data limitations, as the results contradict the results from other studies that showed a lower 5-year relative survival of 74% (Dabakuyo et al., 2008)

The findings regarding hormone receptor status reveal significant differences in OS rates and hazard ratios across subgroups, underlining the critical role of hormone receptor status in BC prognosis. Patients with positive receptors are considered to have the most favourable status, with the highest 5-year survival rate of 85%. This aligns with the findings of other studies, such as the study conducted in the United States, which found that positive hormone subtypes experienced better survival than negative subtypes (Howlader et al., 2018). In contrast, lower survival rates were noted for the other subgroups, with the lowest survival rate of 71% observed in the double-negative group, reflecting the lack of hormone receptor response to treatment options. This finding also aligns with the results of other studies, such as (Dunnwald et al., 2007), which reported that all subtypes had lower survival rates than ER+/PR+. This underscores the need for more targeted strategies for these subgroups. These results highlight the importance of hormone receptor testing at diagnosis and its integration into treatment planning to improve outcomes.

The impact of treatment strategies on BC survival outcomes is crucial and emphasises the role of comprehensive care in improving patient prognosis. Analysis of treatment modalities reveals that surgery is the cornerstone of therapeutic intervention, and it showed higher survival rates when combined with adjuvant therapies. Notably, combining surgery with adjuvant therapies demonstrates superior survival outcomes, emphasising the importance of a multidisciplinary approach. This is consistent with the study that reported surgery followed by adjuvant treatment as the gold standard of BC treatment (Miller et al., 2014). The impact of chemotherapy and biological therapy on survival rates

appears less pronounced. The combination of chemotherapy, radiotherapy and surgery led to lower survival rates, indicating worse outcomes compared to surgery alone.

Conversely, the effect of hormonal therapy on long-term survival is pronounced; the addition of hormonal therapy to multimodal treatments appeared to improve survival rates. Interestingly, the combination of surgery and hormonal therapy alone had a 5-year survival rate of 76% compared to the combination of surgery and radiotherapy which had a 5-year survival rate of 57%, emphasising the potential benefit of this less intensive regimen in selected patients, possibly with hormone-positive receptors. These findings indicate that treatment outcomes depend on both the complexity of the regimen and the underlying tumour characteristics.

In discussing the impact of different hormonal therapies on survival outcomes, patients receiving tamoxifen or aromatase inhibitors exhibit different outcomes over time. While Tamoxifen shows better short-term survival, aromatase inhibitors demonstrate the potential for improved long-term outcomes. It was reported that AIs improve survival outcomes compared to tamoxifen (Flatley & Dodwell, 2016). However, in this study, the difference in survival between AI's and tamoxifen was not statistically significant ($P = 0.61$), which suggests that this difference could be due to chance. These findings highlighted the importance of tailoring the approach to optimise the survival rates of BC patients.

This study was one of the few to analyse survival rates from cancer registry data over a long period (over 23 years). It also analysed survival by treatment modalities and hormone receptor status using hospital data. Notably, only a limited number of studies have examined survival rates among the Saudi population. For example, a study was conducted in 2018 using data from the SCR, including 5,411 patient records. This study covered a shorter period of only nine years (2004 to 2013) than the present study (Alotaibi et al., 2018). Another study estimated the BC survival among Saudi patients living in Riyadh diagnosed between 1994 and 1996 and followed up until 2002; although it was described as a population-based study, it included only patients living in Riyadh (Ravichandran & Al-Hamdan, 2014).

This study encountered some limitations. First, using the registry data may have inaccurate information on the cause of death. For instance, death may be attributed to an inaccurate cause due to

misdiagnosis, or in some cases, when BC metastasises, the cause of death might be recorded as metastatic cancer rather than indicating BC as the underlying cause, which may introduce bias in the data. To address this issue, a relative survival analysis was employed to overcome this bias. Still, another problem arose: the lifetables needed for relative survival analysis were only available for a few years. However, this was managed using the recommendations of using the available life tables for previous or future years. The second limitation was the uneven distribution of BC cases by age and follow-up period, which affected the relative survival results for this age group. The study's retrospective design was considered a limitation; the completeness of data and the accuracy, such as the cause of death, cannot be identified if missing. If certain information was not originally documented or documented inaccurately, the ability to complete it or verify it is limited. Missing information could be due to errors during the data entry or lack of follow-up documentation or because patients are being treated in multiple institutions without an integrated record system. Another limitation is the long follow-up period, which may lead to variability in the diagnostic procedures, treatment regimens, and screening process. This study did not assess changes in survival across different birth cohorts, such analysis require age-period-cohort models and specific data structure which is beyond the scope and design of this current study.

6.5 Conclusion

In conclusion, this study highlights the factors influencing BC patients' survival outcomes in KSA, emphasising the interaction between tumour characteristics, treatment modalities, and patient demographics. Accordingly, treatment planning and follow-up care must be tailored to each individual's needs. Improving survival outcomes could be further enhanced through the refinement of treatment regimens and the enhancement of early detection. Additionally, the variability in long-term survival across different hormonal therapies and age groups suggests areas for further research, particularly to investigate the underlying biological mechanisms and ensure that care pathways are optimised. Such insights could inform targeted interventions, thereby improving the quality of life and long-term outcomes for BC female patients in KSA. Future research is recommended to explore cohort and temporal trends in BC survival using appropriate age-period-cohort modeling approaches.

Chapter 7 Quality of Life of women with breast cancer in Saudi Arabia

7.1 Introduction

The increase in the incidence rate of BC among Saudi females highlights the importance of quality-of-life (QoL) studies. Following a BC diagnosis, women's QoL is significantly impacted by cancer symptoms and the side effects of treatment (Heidary et al., 2023). Cancer symptoms, such as pain, fatigue, and nausea, can severely impact their ability to perform everyday activities. Additionally, the side effects of treatment, including chemotherapy and radiation, often contribute to a decline in overall QoL (Cardoso et al., 2023).

When discussing quality of life, it is essential to distinguish between two terms, quality of life (QoL) and health-related quality of life (HRQoL), which are often mistakenly used interchangeably (Karimi & Brazier, 2016). QoL is a broader concept covering all aspects of human life, defined by the World Health Organization (WHO) as "individuals' perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concern" (Salvatore et al., 2020). In contrast, HRQoL focuses on the effects of illness and treatment on patient well-being. It is defined as "the impact of a disease and its treatment on a person's perception of their ability to lead a full and productive life" (Ward, 1999). Breast cancer can negatively affect HRQoL due to the disease process itself or its treatment, as patients undergo several rounds of treatments with side effects.

HRQoL is assessed through health-state utilities, which are typically derived from the stated preferences of the general population. Health-state utility is measured on a scale from 0 to 1, where 0 represents death, 1 represents full health, and negative values represent health states considered worse than death (Yang et al., 2023). The main approaches to measuring HRQoL are utility/preference-based measures, psychometric-based measures, and, less commonly, the Patient Generated Index (Brazier et al., 2017). It is commonly evaluated using self-reported methods such as written questionnaires, computer-administered versions, and in-person or telephone-based interviews.

Psychometric-based measures are available in generic and disease-specific measures. Generic instruments measure general health and provides a single value that can be used to calculate QALYs. Disease-specific tools focus on specific disease and provides multiple values corresponds to different domains which cannot be used to calculate QALYs. Mapping the values of disease-specific measures onto generic measures by using regression technique is the solution to this problem.

In Saudi Arabia, few studies about the effect of breast cancer on HRQoL in Saudi females have been conducted and few studies have been conducted reported using the generic EQ-5D, which is the most common tool used for calculating QALYs. In a systematic review conducted between 2015 and 2020 to explore publications that used EQ-5D in the Saudi population, only 13 articles were identified, and none of these used EQ-5D in cancer populations (Althemery, 2021). Most studies published in KSA used EORTC-QLQ C30 (Nageeti et al., 2019; Almutairi et al., 2016; Abu-Helalah et al., 2022; Imran et al., 2019) or SF-36 to (Al-Karni et al., 2024; Ahmed et al., 2018) evaluate QoL in Saudi cancer patients. This means that specific QoL measures are more commonly used in the Saudi literature than generic ones. Responses from disease-specific measures cannot be used in pharmacoeconomic studies unless they are mapped onto generic preference-based measures, such as EQ-5D, to allow the calculation of utility values and QALYs. Additionally, there are no published studies or randomised controlled trials to obtain utility values directly from them; information about utility values in general and specifically in oncology in Saudi literature is lacking (Ahmed et al., 2018).

Few studies in KSA have assessed the quality of life of Saudi female breast cancer patients; further studies in this area are recommended (Althemery, 2021; Ahmed et al., 2018). The lack of information on quality of life and its associated factors among BC females in KSA means there is a need for the work described in this chapter, which aims to assess the quality of life of Saudi females and to measure health utility in Saudi female BC patients in different age groups, disease stages and treatment modalities via mapping utility values obtained by disease-specific tools (EORTC QLQ-C30 & BR23) onto a generic measure (EQ-5D-3L) to evaluate the impact of BC on QoL using the data collected from patients with BC in KFSH&RC.

The work reported in this chapter aims to enable the development of tariffs based on EQ-5D for KSA, which are currently lacking. These tariffs can be used to inform decision-making and health technology assessment (HTA) in future Saudi health economic studies.

7.2 Methodology

A cross-sectional questionnaire-based study was conducted in an outpatient oncology clinic at King Faisal Specialist Hospital & Research Centre (KFSH&RC) from February to September 2023.

7.2.1 Sample population

The target population for the study was Saudi female BC patients from all age groups and different disease stages, treated at KFSH&RC for at least six months with different treatment modalities who were able to provide informed consent to participate and fill out the questionnaire. Participants were excluded from the study if they were pregnant, terminally ill or in severe pain, or were patients with psychiatric or mental diseases.

The sample size was calculated to be 292 using OPENEPI 6 software based on an estimated population of 500 patients seen monthly in the oncology clinic at KFSH&RC, a frequency of 70% prevalence of problematic QoL as reported in a previous study (Mortada et al., 2018), with a 5% margin of error and a 95% confidence interval.

7.2.2 Ethical considerations

Ethical approval was obtained from Newcastle University (Ref: 23508/2022) and the KFSH&RC on 18 January 2023. The patients from the outpatient clinic were included in the study after the purpose of the study was explained clearly to all participants, assuring strict confidentiality. A statement regarding confidentiality and consent was included at the beginning of the survey, informing participants that by completing the survey, they agreed to participate in the study (Appendix A).

7.2.3 Data collection tools

Data were collected using a three-part survey to address the various objectives of the study: (1) basic background socio-demographic and clinical characteristics, (2) the Arabic version of the generic health-related QoL instrument EQ-5D-3L, (3) the Arabic version of EORTC QLQ C-30, and the breast cancer-specific version BR-23. These instruments were selected because they are the most used in literature and because translated validated Arabic versions are available (Whitehead & Ali, 2010).

Details of the three parts of the questionnaire are provided below:

1. Demographics and medical history: marital status, age, menopausal status, educational level, medical history, date of diagnosis, region, employment status, financial level, number of children (if applied), and BC Family history in the first-degree relatives, disease stage, metastasis, and treatment modalities. (Appendix A)

2. The Arabic version of the generic health-related QoL instrument EQ -5D 3L consists of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain has three levels. Participants were asked to rate their ability to perform each function from one to three on a scale where 1 indicates no problem, 2 indicates a moderate problem, and 3 indicates an extreme problem. This yields a one-digit number for each function, when combined, gives a 5-digit number which describes the respondent's health status. It has 243 health states, and a corresponding utility value is available for each state.

The second part of the EQ-5D-3L consists of an EQ Visual Analogue Scale (EQ VAS) from 0 to 10, with 0 labelled as “the worst health you can imagine” and ten as” the best health you can imagine”.

The Arabic version of the EQ-5D-3L was purchased from the EuroQol group (<http://www.euroqol.org/eq-5d/eq-5d-products/eq-5d-3l-translations.html>). (Appendix B)

3. Arabic version of EORTC QLQ C-30 and the breast cancer-specific version BR-23: The QLQ-C30 consists of 30 items in nine multi-item scales: five functional scales (Physical, Role, Cognitive, Emotional, and Social functioning), three symptom scales (Fatigue, Pain, and Nausea or Vomiting), a global health status/QoL scale, and a number of single items assessing additional symptoms commonly reported by

cancer patients (dyspnea, loss of appetite, insomnia, constipation and diarrhoea) and perceived financial impact of the disease. The QLQ-BR23, which assesses the quality of life of breast cancer patients specifically, has 23 items that incorporate five multi-item scales to assess body image, sexual functioning, systemic therapy side effects, breast symptoms and arm symptoms. In addition, single items assess sexual enjoyment, future perspective and being upset by hair loss. The participants were asked to select one answer for most items to indicate the extent to which their diagnosis impacts on that item. In each case, participants can select from responses labelled from one to four. One indicates “not at all”, 2 indicates “a little”, 3 indicates “quite a bit”, and 4 indicates “very much”. For the global health status questions, participants indicate their perceived health status on a scale with a range from 1 for “very poor” to 7 for “excellent”. The Arabic versions of QLQ-C30 and BR-23 have been tested and found to be reliable and valid (Awad et al., 2008). It was purchased from the European Organization for Research and Treatment of Cancer (EORTC, www.eortc.org). (Appendix C)

All instruments were obtained in their officially translated and validated Arabic version, except for the demographic questionnaire, which was written in Arabic and reviewed by my internal supervisor (Prof. Eman Mortada). It was then translated into English for review by my Newcastle supervisors. Pre-testing was performed on seven people from the family and friends

The EORTC QLQ C-30 was used in this study because it is the most commonly used instrument to measure the quality of life of cancer patients and has been translated into more than 110 languages, including Arabic (Aaronson et al., 1993). The EQ-5D is the generic instrument recommended by NICE; population values are available for several countries but, unfortunately, not Saudi Arabia. Using country-specific norms as a value set for the utility analysis is the best approach because there are differences in how people report their problems in different countries and how they value these problems. In the current study, these norms are unavailable, so the possible option is to use the norms from other countries; EUROQOL recommends using the United Kingdom value set by Dolan (Dolan & Roberts, 2002).

The participants completed the questionnaire in electronic format (using a QR code to access it) during their follow-up visits to the clinic. Although a paper version of the questionnaire was available, it was not used by any participants, older women were generally comfortable using smartphones. Some

received assistance from nurses to open the questionnaire, while accompanying family members supported others.

7.2.4 Data management & Statistical analysis

Data were coded and entered into Excel and then exported to the Statistical Package for the Social Sciences (SPSS) version 29.0.2.0 for further cleaning and analysis. The demographics and clinical characteristics of the sample were described using frequencies and percentages.

EQ-5D-3L:

The EQ-5D-3L summary statistics were produced, including the number of patients and the proportions of categorical responses for the five EQ-5D dimensions.

For the Saudi population, EQ-5D-3L preference utility score data were not available. Therefore, the health state index score was calculated from individual health profiles using a UK value set based on the Time Trade-Off method. The raw scores from the EQ-5D-3L were converted into an index ranging from -0.6 to one, with one defined as a full health state; zero is death, and negative scores are the most severe states considered as “worse than death” states for respondents.

Mean, standard deviation (SD), median, and quartile scores were calculated for the study population. The EQ VAS score (between 0 and 10) was also summarised using mean, SD, and median scores. The Kolmogorov-Smirnov normality test yielded a significant result ($P < 0.001$), meaning the data are not normally distributed. A Mann-Whitney or Kruskal-Wallis test was applied to determine if there is a statistically significant difference between EQ-5D-3L and the characteristics of the respondents. The correlation between the EQ-5D-3L index score and the EQ-VAS score was measured using Spearman’s correlation.

EORTC- QLQ- C30 and EORTC- QLQ- BR23:

The EORTC scoring system was followed, where the functional domain scores and item scores were standardised from the raw item scores through a linear transformation to have a range of 0 to 100. The scoring of the missing items also followed the EORTC scoring system. For scale scores, first determine if at least half of the items on the scale have been answered. If so, use only completed items and calculate the scale score, ignoring any missing items. If less than half of the items are answered, the scale score should be set to missing. For single-item measures, any missing response automatically results in the score being set to missing, as there is no additional data to compensate (Fayers et al., 2001).

A higher score represents a “better” level of functioning or a “worse” level of symptoms. A high score for a functional scale represents a high/ healthy level of functioning, while a high score for the symptom scales represents a high level of symptomatology or problems. In QLQ-C30 and QLQ-BR-23, the group with an overall QoL score or a functional scale of $\leq 33.3\%$ were considered problematic. In contrast, a symptom score of $\geq 66.7\%$ is problematic (Ahn et al., 2007).

A Kolmogorov-Smirnov normality test was conducted, among the continuous variables of the scores for both EORTC QLQ C-30 and BR-23 was done to examine the distribution of the sample population, and the data were found to be not normally distributed ($P < 0.001$). Thus, median and interquartile ranges (IQ) were used to describe the QLQ-C30 and BR-23. The equality of the distribution of the scores across the categories of each categorical variable was tested using the non-parametric test, a Mann-Whitney test or a Kruskal-Wallis test; a statistical significance was considered if $P < 0.05$.

Linear regression:

A univariate linear regression model was applied to explore the association of sociodemographic and clinical characteristics mentioned before with EQ-5D-3L and the EORTC symptom and functioning scale scores.

Multiple linear regression was conducted after checking if its assumptions were met. First, the linearity of the regression model was checked by creating a scatter plot between the predicted values and the model's residuals. Second, multicollinearity was tested to check for a strong relationship between the independent variables in the model. This was checked by examining the correlation matrix of the independent variables and by calculating the variation influence factor. Third, data were checked for homoscedasticity by inspecting the scatterplot of the residuals, which concerns the distribution of the residuals; they should be evenly spread across the range of predicted values.

Multiple linear regression examined and assessed the predictor's contribution to the variations in the outcome and compute the coefficient of determination. The significant demographics and clinical factors from the univariate analysis were used as model predictors, while the QLQ-C30 symptom and functioning scale scores and EQ-5D-3L were set as dependent variables.

R squared was computed to understand how much variation in the dependent variables could be explained by the independent variables, and a *P*-value of less than 0.05 was considered statistically significant, indicating a 95% confidence interval level in the results.

7.2.5 Mapping process

Mapping or “crosswalk” is a technique used to link the outcomes of different measures of health outcomes and then use this relationship to predict the unobserved utility values (Longworth & Rowen, 2011). In this study, mapping was conducted from the specific tool QLQ-C30 to the generic preference-based measure EQ-5D-3L.

The appropriate method used the adjusted limited dependent variable mixture model (ALDVMM). This study uses the bespoke mixture model for directly mapping to EQ-5D-3L utility scores based on the adjusted limited dependent variable mixture model approach; this method was applied in STATA/BE 17.0 using the “aldvmm” command using the UK tariff. The adjusted limited dependent variable mixture model can be run between one and four components; the three-component model was recommended by (Worboys et al., 2023). Each component in the mixture is normally distributed and capable of

reflecting a mass of observations at the upper full health limit. It does not produce values in the non-feasible area, which are above 1, below -0.594, and between 0.883 and 1 (Gray et al., 2021). Spearman's rank correlation was used to determine the correlation between the dependent variable (EQ-5D-3L) and the independent variable (QLQ-C30).

The performance of each model was evaluated by determining the goodness of fit using AIC and BIC (Gray et al., 2021). Predictive ability was determined by calculating the root mean squared error, which is the squared root of the mean of the squared differences between observed and predicted EQ-5D-3L index scores, and mean squared error, which indicates the "error" in the estimates in the data set used to estimate the regression; smaller root mean squared error and mean squared error values indicate better performance (Kiadaliri & Englund, 2016).

7.3 Results

The total number of patients participated in this study and completed the questionnaire was 300. Six were excluded because they were non-Saudis, and 19 were excluded due to duplication. A total of 275 subjects were included in the study. The response rate was 94.25% based on the sample size calculated which was 297.

Table 7.1 shows the characteristics of participants. The mean age was 47.7 years, and the median was 47 years (IQR = 16). Most respondents were married (75%) and postmenopausal (70%); 48% were not employed, and about half were in the 5000-15,000 SR income category. The most common comorbidities reported were thyroid disorders, asthma, epilepsy, diabetes, and hypertension.

Most of the study participants were in early-stage BC (42%), 80% were recently diagnosed with BC (within five years), and 45% were treated with chemotherapy; the clinical characteristics of participants are shown in Table 7.2.

Characteristic	N (%)
Age group (Y)	
< 30	8 (2.9%)
30-39	61 (22.2%)
40-49	86 (31.3%)
50-59	79 (28.7%)
≥ 60	41 (14.9%)
Mean	47.68 (SD=10.9)
Marital status	
Married	206 (74.9%)
Not married (single, divorced, widowed)	69 (25.1%)
Have children	
Yes	237 (86.5%)
No	37 (13.5%)
Menopausal status	
Premenopausal	83 (30.2%)
Postmenopausal	192 (69.8%)
Education level	
Diploma/ High-school or less	142 (51.6%)
Bachelors	114 (41.5%)
Higher degrees	19 (6.9%)
Employment status	
Employed	102 (37.1%)
Own business	5 (1.8%)
Non- employed	135 (49.1%)
Retired	33 (12.0%)

Income (SR)	
< 5000	91 (33.1%)
5000-15,000	152 (55.2%)
> 15,000	31 (11.3%)
Active/ Sporting	
Yes	122 (44.4%)
No	153 (55.6%)
Family history of cancer	
Yes	66 (24.0%)
No	209 (76.0%)
Comorbidities	
Yes	110 (40.0%)
No	162 (58.9%)
Region	
Central	141 (51.3%)
Eastern	40 (14.5%)
Northern	36 (13.1%)
Southern	51 (18.5%)
Western	7 (2.5%)

Table 7.1 Socio-demographic of female BC patients at KFSH&RC. Y: year, SR: Saudi Riyals

Characteristic	N (%)
Breast Cancer stage	
Stage I	69 (25.1%)
Stage II	46 (16.7%)
Stage III	49 (17.8%)
Stage IV	29 (10.5%)
Unavailable	82 (29.8%)
Years since diagnosis (Y)	
< 2	127 (46.2%)
2 - 4	94 (34.2%)
≥5	51 (18.5%)
Metastasis	
Yes	90 (32.7%)
No	131 (47.6%)
Unknown	54 (19.6%)
Breast cancer Treatment	
Surgery	54 (19.6%)
Chemotherapy	126 (45.8%)
Hormonal therapy	63 (22.9%)
Radiation	4 (1.5%)
Unknown	28 (10.2%)

Table 7.2. Clinical characteristics of female BC patients at KFSH&RC.

7.3.1 Quality of life using QLQ-C30 and BR-23

The participants scored a median global health status/QoL score of 50 (IQR = 41.67), and functional scale scores ranged from a median of 83.3 (IQR = 33.3) for role functioning to a median of 66.7 (SD = 41.76) for emotional functioning. On the symptom scale, fatigue, appetite loss, constipation, and sleep disturbance had the highest scores (all ≥ 33.3), meaning worse QoL. In contrast, all other symptoms scored lower than 33, which can be interpreted as good health.

In the QLQ-BR23, on the functional scale, all the items scored below 66, which is considered problematic except body image, which had a median score of 75 (IQR = 50). In the symptom scales, the best score was observed for breast symptoms, with a median of 16.7 (IQR = 41.7).

Table 7.3 summarises the mean and median scores of the EORTC QLQ—C30 global health status, functional, and symptoms scales and the BR-23 functional and symptoms scales.

Dimensions	N	Mean (SD)	Median (IQR)
QLQ -C30			
Global health status	275	52 (25.65)	50 (33.3;75.0)
Functional scales			
Physical functioning (PF)	275	65.8 (24.01)	66.7 (46.7;86.7)
Role functioning (RF)	275	76.0 (30.07)	83.3 (66.7;100)
Emotional functioning (EF)	275	65.2 (30.36)	66.7 (50.0;91.7)
Cognitive functioning (CF)	275	69.1 (29.97)	83.3 (50.0;100)
Social functioning (SF)	275	72.3 (31.03)	83.3 (66.7;100)
Symptom scales			
Fatigue (Fa)	275	42.8 (30.34)	33.3 (11.1;58.3)
Nausea and vomiting (NV)	275	20.6 (26.86)	16.7 (0.0;33.3)
Pain (PA)	275	38.0 (31.61)	25.0 (16.7;66.7)
Dyspnea (DY)	275	24.5 (31.94)	0 (0.0;33.3)
Sleep disturbance (SL)	275	47.6 (37.31)	33.3 (0.0;66.7)
Appetite loss (AP)	275	28.4 (32.28)	33.3 (0.0;33.3)
Constipation (CO)	275	30.1 (33.11)	33.3 (0.0;33.3)
Diarrhea (DI)	275	15.2 (26.42)	0 (0.0;33.3)
Financial impact (FI)	275	29.2 (36.12)	0 (0.0;66.7)
QLQ-BR23			
Functional scales			
Body image (BRBI)	270	67.6 (33.62)	75.0 (50;100)
Sexual functioning (BRSEF)	254	21.9 (26.32)	33.3 (33.3;66.7)
Sexual enjoyment (BRSEE)	92	49.6 (29.44)	33.3 (33.3;66.7)
Future perspective (BRFU)	270	44.7 (39.65)	33.3 (0.0;75.0)
Symptom scales			
Systemic therapy side effect (BRST)	272	32.0 (23.54)	28.6 (9.5;43.3)
Breast symptoms (BRBS)	275	26.6 (27.34)	16.7 (0.0;41.7)
Arm symptoms (BRAS)	275	39.4 (31.02)	33.3 (11.1;66.7)
Upset by hair loss (BRHL)	268	48.6 (42.82)	33.3 (0.0;100)

Table 7.3. Summary statistics of the calculated HRQoL using QLQ-C30, BR-23.

Median differences between sociodemographic and clinical variables with EORTC QLQ-C30 functional scales:

The global health status results were highest in the youngest women and students, but the only significant difference in the QoL was found in menopausal status ($P = 0.04$) and participating in sport ($P = 0.02$). There was a statistically significant difference in physical functioning on many characteristics, including age ($P = 0.008$), educational level ($P = 0.002$), menopausal status ($P = 0.02$), income ($P = 0.06$), and comorbidities ($P < 0.001$). The scores were higher in the youngest ages, with high educational levels, premenopausal, moderate-income levels, sports and those with no other diseases. The role function was significant in married respondents only ($P = 0.05$), while the emotional function was significantly high in the southern, western, and central regions ($P = 0.04$), those with no comorbidities ($P = 0.01$), holding a bachelor's degree and with 5000-15,000 SR income ($P = 0.05$). The cognitive function was significantly high in respondents with no other diseases ($P = 0.001$) and in younger age groups ($P = 0.01$). Regarding social functioning, higher scores were reported in those with no comorbidities ($P = 0.04$). Mean scores of EORTC QLQ C30 global health and functional scales according to different variables are presented in Table 7.4.

The global health status and QLQ-C30 functional scales by clinical characteristics showed that physical functioning was significantly higher in respondents with no metastasis ($P = 0.002$) and those using hormonal therapy and chemotherapy ($P = 0.04$). While social functioning was significantly higher in patients who underwent surgery or used hormonal therapy ($P = 0.045$) (Table 7.5).

Characteristic	Global health /QoL Median (IQR)	Functional scales in QLQ- C30 Median (IQR)				
		PF	RF	EF	CF	SF
Age in years						
< 30	79.2 (66.7)	90.0 (23.3)	100 (41.7)	75.0 (22.9)	100 (12.5)	100 (16.7)
30-39	50.0 (45.8)	73.3 (30.0)	100 (33.3)	66.7 (33.3)	83.3 (50.0)	83.3 (50.0)
40-49	50.0 (50.0)	76.7 (40.0)	100 (33.3)	75.0 (58.3)	75.0 (50.0)	66.7 (66.7)
50-59	50.0 (33.3)	60.0 (33.3)	83.3 (33.3)	66.7 (50.0)	83.3 (33.3)	83.3 (33.3)
≥ 60	41.7 (45.8)	60.0 (50.0)	83.3 (41.7)	75.0 (29.2)	66.7 (33.3)	100 (33.3)
<i>P</i> -value	0.55	0.008*	0.88	0.65	0.01*	0.06
Marital status						
Married	50.0 (41.7)	66.7 (40.0)	100 (33.3)	70.8 (41.7)	83.3 (50.0)	83.3 (33.3)
Not married	41.7 (41.7)	73.3 (43.3)	66.7 (58.3)	66.7 (50.0)	66.7 (66.7)	66.7 (50.0)
<i>P</i> -value	0.17	0.29	0.05*	0.29	0.31	0.15
Having children						
Yes	50.0 (41.7)	66.7 (40.0)	100 (33.3)	70.8 (41.7)	83.3 (50.0)	83.3 (33.3)
No	50.0 (41.7)	73.3 (40.0)	66.7 (58.3)	66.7 (54.2)	83.3 (66.7)	66.7 (50.0)
<i>P</i> -value	0.67	0.92	0.15	0.19	0.61	0.47
Menopausal status						
Premenopausal	50.0 (50.0)	73.7 (33.3)	83.3 (33.3)	66.7 (33.3)	83.3 (50.0)	83.3 (33.3)
Postmenopausal	50.0 (33.3)	66.7 (40.0)	83.3 (33.3)	66.7 (41.7)	83.3 (50.0)	83.3 (45.8)
<i>P</i> -value	0.03*	0.02*	0.75	0.83	0.99	0.57

Educational level						
Diploma /High-school or less	50.0 (33.3)	60.0 (35.0)	83.3 (33.3)	66.7 (41.7)	66.7 (50.0)	83.3 (33.3)
Bachelors	50.0 (50.0)	73.3 (26.7)	83.3 (33.3)	75.0 (45.8)	83.3 (33.3)	83.3 (37.5)
Higher degrees	50.0 (50.0)	86.7 (46.7)	100 (66.7)	58.3 (66.7)	50.0 (66.7)	66.7 (100)
<i>P</i> -value	0.22	0.002*	0.98	0.05*	0.08	0.17
Employment status						
Employed	50.0 (45.8)	73.3 (40.0)	100 (33.3)	66.7 (50.0)	83.3 (50.0)	66.7 (66.7)
Own-Business	41.7 (50.0)	66.7 (43.3)	66.7 (41.7)	66.7 (70.8)	66.7 (50.0)	83.3 (25.0)
Non- employed	50.0 (33.3)	66.7 (40.0)	83.3 (33.3)	66.7 (50.0)	83.3 (50.0)	83.3 (33.3)
Retired	50.0 (50.0)	66.7 (23.3)	100 (33.3)	75.0 (29.2)	83.3 (33.3)	83.3 (33.3)
<i>P</i> -value	0.36	0.45	0.74	0.31	0.47	0.17
Income						
< 5,000	50.0 (25.0)	60.0 (40.0)	83.3 (33.3)	66.7 (50.0)	66.7 (33.3)	83.3 (50.0)
5000-15,000	50.0 (41.7)	73.3 (33.3)	100 (33.3)	75.0 (33.3)	83.3 (50.0)	83.3 (33.3)
> 15,000	50.0 (33.3)	60.0 (33.3)	66.7 (66.7)	66.7 (41.7)	66.7 (33.3)	66.7 (66.7)
<i>P</i> -value	0.49	0.006*	0.06	0.05*	0.15	0.28
Sport						
Yes	50.0 (41.7)	80.0 (30.0)	100 (33.3)	75.0 (41.7)	83.3 (50.0)	83.3 (33.3)
No	41.7 (33.3)	60.0 (36.7)	83.3 (33.3)	66.7 (45.8)	66.7 (50.0)	83.3 (33.3)
<i>P</i> -value	0.02*	0.002*	0.11	0.09	0.16	0.78
Family history						
Yes	50.0 (50.0)	66.7 (40.0)	83.3 (50.0)	66.7 (58.3)	66.7 (50.0)	83.3 (66.7)
No	50.0 (33.3)	66.7 (40.0)	83.3 (33.3)	75.0 (41.7)	83.3 (50.0)	83.3 (33.3)
<i>P</i> -value	0.97	0.89	0.45	0.24	0.40	0.34

Comorbidities						
Yes	50.0 (33.3)	60.0 (40.0)	83.3 (50.0)	66.7 (50.0)	66.7 (50.0)	66.7 (50.0)
No	50.0 (43.8)	73.3 (33.3)	100 (33.3)	75.0 (33.3)	83.3 (37.5)	83.3 (33.3)
<i>P</i> -value	0.09	<0.001*	0.12	0.01*	0.001*	0.04*
Region						
Central	50.0 (50.0)	66.7 (40.0)	100 (33.3)	75.0 (33.3)	83.3 (50.0)	83.3 (33.3)
Eastern	33.3 (31.3)	60.0 (40.0)	66.7 (66.7)	66.7 (56.3)	66.7 (62.5)	66.7 (58.3)
Northern	50.0 (25.0)	76.7 (36.7)	83.3 (33.3)	66.7 (45.8)	66.7 (45.8)	83.3 (33.3)
Southern	50.0 (33.3)	73.3 (40.0)	100 (33.3)	75.0 (41.7)	83.3 (50.0)	83.3 (33.3)
Western	50.0 (33.3)	66.7 (46.7)	100 (33.3)	75.0 (58.3)	83.3 (50.0)	83.3 (50.0)
<i>P</i> -value	0.09	0.54	0.07	0.04*	0.18	0.30

*Table 7.4. Global health and functional scales in QLQ -C30 by sociodemographic. *Statistically significant.*

Characteristic	Global health /QoL Median (IQR)	Functional scales in QLQ- C30 Median (IQR)				
		PF	RF	EF	CF	SF
Disease stage						
I	41.7 (45.8)	73.3 (40.0)	83.3 (33.3)	75.0 (41.7)	83.3 (33.3)	83.3 (33.3)
II	50.0 (41.7)	66.7 (40.0)	83.3 (33.3)	75.0 (58.3)	83.3 (50.0)	83.3 (41.7)
III	50.0 (33.3)	73.3 (33.3)	83.3 (66.7)	66.7 (37.5)	66.7 (58.3)	66.7 (66.7)
IV	50.0 (50.0)	66.7 (36.7)	66.7 (41.7)	66.7 (45.8)	83.3 (41.7)	83.3 (50.0)
<i>P</i> -value	0.89	0.54	0.46	0.76	0.79	0.28
Years since diagnosis						
< 2	50.0 (41.7)	66.7 (40.0)	83.3 (33.3)	66.7 (33.3)	83.3 (50.0)	83.3 (33.3)
2-4	50.0 (41.7)	73.3 (40.0)	83.3 (33.3)	75.0 (43.8)	83.3 (50.0)	83.3 (37.5)
≥ 5	41.7 (16.7)	60.0 (40.0)	100 (33.3)	66.5 (50.0)	66.7 (50.0)	66.7 (66.7)
<i>P</i> -value	0.34	0.15	0.68	0.46	0.09	0.08
Metastasis						
Yes	50.0 (25.0)	60.0 (33.3)	75.0 (33.3)	66.7 (50.0)	66.7 (50.0)	66.7 (66.7)
No	50.0 (50.0)	73.3 (28.3)	100 (33.3)	75.0 (27.1)	83.3 (50.0)	83.3 (33.3)
<i>P</i> -value	0.16	0.002*	0.12	0.11	0.34	0.051
Treatment modalities						
Surgery	50.0 (33.3)	66.7 (33.3)	91.7 (33.3)	75.0 (27.1)	66.7 (33.3)	83.3 (33.3)
Chemotherapy	50.0 (41.7)	73.3 (40.0)	83.3 (33.3)	66.7 (58.3)	83.3 (50.0)	66.7 (66.7)
Hormonal	50.0 (41.7)	73.3 (40.0)	83.3 (33.3)	66.7 (50.0)	83.3 (50.0)	83.3 (33.3)
Radiation	25.0 (29.2)	33.3 (36.7)	58.3 (54.2)	66.7 (31.3)	58.3 (41.7)	75.0 (33.3)
<i>P</i> -value	0.37	0.04*	0.59	0.58	0.24	0.045*

Table 7.5. Global health and functional scales in QLQ -C30 by clinical characteristics.

Symptom scales showed a non-statistically significant difference with respect to age, having children, menopausal status, educational level, employment status, and family history, which could potentially be attributed to chance. Fatigue, nausea or vomiting, dyspnea, sleep disturbance, pain, and constipation have been shown to occur less in patients with no other medical conditions. The pain was significantly higher in patients with a low-income level. Appetite loss was significantly higher in non-married respondents, those at low-income levels, and those who reported being inactive. There was a statistically significant difference across regions ($P < 0.001$) indicating substantial regional variability in financial impact on individuals.

Characteristic	FA	NV	PA	DY	SL	AP	CO	DI	FI
Age group (Y)									
< 30	22.2 (33.3)	0.0 (29.2)	0.0 (33.3)	0.0 (58.3)	0.0 (83.3)	16.7 (33.3)	0.0 (33.3)	0.0 (25.0)	0.0 (75.0)
30-39	33.3 (38.9)	16.7 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
40-49	33.3 (47.2)	0.0 (20.8)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
50-59	44.4 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (100.0)	33.3 (66.7)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)
≥ 60	44.4 (55.6)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (50.0)	33.3 (66.7)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.25	0.37	0.12	0.92	0.23	0.23	0.79	0.89	0.36
Marital status									
Married	33.3 (47.2)	16.7 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (75.0)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)
Not married	33.3 (55.6)	16.7 (33.3)	33.3 (50.0)	33.3 (33.3)	33.3 (66.7)	33.3 (50.0)	33.3 (66.7)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.08	0.06	0.19	0.052	0.77	0.01*	0.37	0.08	0.86
Having children									
Yes	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)

No	33.3 (55.6)	16.7 (33.3)	33.3 (66.7)	0.0 (33.3)	33.3 (38.3)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.80	0.36	0.96	0.89	0.87	0.74	0.89	0.72	0.69
Menopausal status									
Premenopausal	33.3 (47.2)	16.7 (33.3)	33.3 (54.2)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	16.7 (33.3)	0.0 (33.3)	33.3 (66.7)
Postmenopausal	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.52	0.96	0.21	0.89	0.07	0.62	0.12	0.86	0.24
Educational level									
Diploma /High-school or less	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	16.7 (41.7)
Bachelors	33.3 (44.4)	16.7 (33.3)	33.3 (41.7)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)
Higher degrees	33.3 (88.9)	0.0 (33.3)	33.3 (83.3)	33.3 (33.3)	66.7 (66.7)	0.0 (33.3)	33.3 (100.0)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.72	0.56	0.48	0.79	0.10	0.26	0.64	0.90	0.86
Employment status									
Employed	33.3 (50.0)	16.7 (33.3)	33.3 (58.3)	0.0 (33.3)	33.3 (100.0)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
Own-Business	44.4 (55.6)	33.3 (58.3)	50.0 (58.3)	33.3 (33.3)	33.3 (50.0)	33.3 (50.0)	33.3 (33.3)	33.3 (50.0)	0.0 (33.3)
Non- employed	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (66.7)	33.3 (66.7)	0.0 (33.3)	33.3 (66.7)
Retired	33.3 (44.4)	0.0 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.27	0.39	0.06	0.74	0.59	0.08	0.38	0.08	0.29
Income									
<5,000	44.4 (55.6)	16.7 (33.3)	50.0 (50.0)	33.3 (33.3)	33.3 (66.7)	33.3 (66.7)	33.3 (66.7)	0.0 (33.3)	33.3 (66.7)
5000-15,000	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)
>15,000	33.3 (77.8)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	0.0 (66.7)	33.3 (66.7)	0.0 (33.3)	0.0 (33.3)

<i>P</i> -value	0.06	0.19	0.005*	0.11	0.052	0.02*	0.08	0.05*	0.27
Sport									
Yes	33.3 (33.3)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
No	33.3 (55.6)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (66.7)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
<i>P</i> -value	0.08	0.25	0.058	0.33	0.12	0.04*	0.18	0.94	0.02*
Family history									
Yes	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)
No	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.36	0.42	0.19	0.89	0.66	0.74	0.49	0.80	0.97
Comorbidity									
Yes	44.4 (47.2)	16.7 (33.3)	33.3 (50.0)	33.3 (41.7)	33.3 (66.7)	33.3 (66.7)	33.3 (66.7)	0.0 (33.3)	16.7 (66.7)
No	33.3 (44.4)	0.0 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.01*	0.04*	<0.01*	<0.01*	0.002*	0.23	<0.001*	0.01*	0.29
Region									
Central	33.3 (44.4)	0.0 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (100.0)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
Eastern	55.6 (44.4)	16.7 (33.3)	33.3 (45.8)	33.3 (33.3)	66.7 (66.7)	33.3 (66.7)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
Northern	33.3 (33.3)	16.7 (33.3)	33.3 (45.8)	33.3 (33.3)	33.3 (33.3)	33.3 (33.3)	33.3 (58.3)	33.3 (33.3)	33.3 (66.7)
Southern	33.3 (55.6)	16.7 (33.3)	16.7 (83.3)	33.3 (33.3)	33.3 (41.7)	16.7 (41.7)	33.3 (41.7)	0.0 (8.3)	33.3 (66.7)
Western	33.3 (33.3)	0.0 (50.0)	0.0 (33.3)	0.0 (33.3)	33.3 (66.7)	0.0 (66.7)	0.0 (66.7)	0.0 (0.0)	0.0 (66.7)
<i>P</i> -value	0.20	0.17	0.10	0.17	0.57	0.18	0.38	0.02*	<0.001*

Table 7.6. Median and IQR in Symptom scales in QLQ -C30 by sociodemographic characteristics.

With respect to clinical characteristics, no significant differences were noted in the symptom scales by the disease stage or years since diagnosis, but there was a statistically significant difference with metastasis and treatment modalities. Patients with metastatic cancers were shown to have worse symptoms of fatigue, nausea and vomiting, dyspnea, sleep disturbances, appetite loss, diarrhoea and financial impact ($P < 0.050$). Nausea and vomiting were found to be worse in patients receiving radiation therapy, while appetite loss was worse in those receiving chemotherapy and radiation. Patients who underwent surgery had the lowest score (better state) in constipation.

Characteristic	Symptom scales in QLQ-C30								
	Median (IQR)								
	FA	NV	PA	DY	SL	AP	CO	DI	FI
Disease stage									
I	33.3 (50.0)	0.0 (16.7)	33.3 (50.0)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
II	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	33.3 (33.3)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)	0.0 (33.3)
III	44.4 (50.0)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (100.0)	0.0 (50.0)	33.3 (33.3)	0.0 (33.3)	0.0 (66.7)
IV	44.4 (38.9)	16.7 (41.7)	33.3 (50.0)	33.3 (33.3)	66.7 (83.3)	33.3 (66.7)	33.3 (66.7)	0.0 (50.0)	33.3 (33.3)
<i>P</i> -value	0.31	0.24	0.11	0.22	0.88	0.47	0.53	0.46	0.46
Years since diagnosis									
1-2	33.3 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
2-4	33.3 (55.6)	16.7 (33.3)	33.3 (54.2)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (66.7)	0.0 (33.3)	0.0 (66.7)
3-5	44.4 (44.4)	16.7 (33.3)	33.3 (50.0)	0.0 (33.3)	33.3 (66.7)	33.3 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)

<i>P</i> -value	0.63	0.58	0.51	0.71	0.42	0.38	0.19	0.55	0.49
Metastasis									
Yes	44.4 (33.3)	16.7 (37.5)	33.3 (50.0)	33.3 (41.7)	66.7 (66.7)	33.3 (66.7)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
No	33.3 (55.6)	0.0 (16.7)	33.3 (66.7)	0.0 (33.3)	33.3 (66.7)	0.0 (33.3)	33.3 (33.3)	0.0 (33.3)	0.0 (33.3)
<i>P</i> -value	0.03*	0.003*	0.051	0.009*	<0.001*	<0.001*	0.67	0.011*	0.006*
Treatment modalities									
Surgery	33.3 (44.4)	0.0 (16.7)	33.3 (37.5)	0.0 (33.3)	33.3 (41.7)	0.0 (33.3)	16.7 (33.3)	0.0 (0.0)	0.0 (33.3)
Chemotherapy	33.3 (50.0)	16.7 (41.7)	33.3 (50.0)	33.3 (33.3)	33.3 (50.0)	33.3 (66.7)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)
Hormonal	33.3 (44.4)	16.7 (33.3)	33.3 (33.3)	0.0 (33.3)	33.3 (66.7)	0.0 (33.3)	33.3 (66.7)	0.0 (33.3)	0.0 (66.7)
Radiation	72.2 (66.7)	25.0 (54.2)	58.3 (41.7)	33.3 (75.0)	50.0 (83.3)	33.3 (66.7)	33.3 (25.0)	16.7 (33.3)	16.7 (33.3)
<i>P</i> -value	0.06	0.01*	0.18	0.21	0.77	0.002*	0.004*	0.052	0.61

Table 7.7. Symptom scales in QLQ -C30 by clinical characteristics.

Median differences between sociodemographic and clinical variables with EORTC-QLQ-BR23:

Table 8 shows the QLQ-BR-23 scales by patient characteristics. Body image was significantly higher in the age group between 30 and 39, those who are unemployed or retired, and respondents with a bachelor's degree. The statistically significant sexual functioning scores in younger, married, and premenopausal women who were active and had no comorbidities were higher, indicating better sexual functioning. The future perspective was significantly higher in those with high school educational levels, retired patients, and those from the western region.

Concerning the symptoms scale of the BR23, it was found that there were no significant differences in symptom scales for any of the variables considered except for comorbidities, therapy side effects and hair loss; all symptoms were worse in patients with other diseases ($P < 0.050$). Systemic therapy side effects and hair loss were higher in women with low income. All symptom scales were constant when employment status was own business, so it has been omitted.

Characteristic	Functional scales in BR23				Symptom scales in BR-23			
	Median (IQR)				Median (IQR)			
	BRBI	BRSEF	BRSEE	BRFU	BRST	BRBS	BRAS	BRHL
Age group (Y)								
<30	66.7 (-)	58.3 (-)	50.0 (-)	66.7 (-)	7.10 (-)	58.3 (-)	0.0 (-)	16.7 (-)
30-39	100.0 (25.0)	50.0 (33.3)	66.7 (41.7)	66.7 (75.0)	23.8 (29.8)	25.0 (27.1)	22.2 (47.2)	16.7 (100.0)
40-49	70.8 (47.9)	50.0 (33.3)	50.0 (33.3)	33.3 (66.7)	30.9 (46.4)	16.7 (52.1)	44.4 (44.4)	66.7 (100.0)
50-59	66.7 (33.3)	33.3 (16.7)	33.3 (0.0)	33.3 (100.0)	28.6 (19.1)	16.7 (41.7)	22.2 (55.6)	33.3 (66.7)
≥60	66.7 (33.3)	33.3 (33.3)	33.3 (33.3)	66.7 (100.0)	42.9 (38.1)	41.7 (50.0)	66.7 (55.6)	66.7 (66.7)
<i>P</i> -value	0.02*	<0.001*	0.10	0.64	0.66	0.849	0.14	0.40
Marital status								
Married	75.0 (50.0)	50.0 (33.3)	33.3 (33.3)	33.3 (66.7)	28.6 (33.3)	16.7 (41.7)	33.3 (55.6)	33.3 (100.0)
Not married	66.7 (58.3)	33.3 (66.7)	33.3 (66.7)	66.7 (100.0)	33.3 (42.9)	41.7 (33.3)	66.7 (33.3)	33.3 (66.7)
<i>P</i> -value	0.95	<0.001*	0.27	0.23	0.29	0.08	0.82	0.53
Having children								
Yes	75.0 (100.0)	41.7 (33.3)	33.3 (33.3)	66.7 (100.0)	28.6 (33.3)	16.7 (35.4)	33.3 (55.6)	33.3 (100.0)
No	66.7 (68.8)	33.3 (29.2)	33.3 (50.0)	0.0 (58.3)	30.9 (50.0)	41.7 (41.7)	38.9 (58.3)	33.3 (91.7)
<i>P</i> -value	0.82	0.91	0.11	0.86	0.76	0.88	0.99	0.12
Menopausal status								
Premenopausal	79.2 (56.3)	50.0 (33.3)	66.7 (33.3)	33.3 (66.7)	26.2 (42.9)	25.0 (56.3)	33.3 (55.6)	66.7 (100.0)
Postmenopausal	75.0 (50.0)	33.3 (33.3)	33.3 (33.3)	66.7 (100.0)	28.6 (25.8)	16.7 (41.7)	33.3 (55.6)	33.3 (100.0)
<i>P</i> -value	0.93	0.006*	0.17	0.16	0.93	0.85	0.58	0.48
Educational level								

Diploma /High-school or less	75.0 (60.4)	50.0 (33.3)	33.3 (33.3)	66.7 (100.0)	33.3 (38.1)	25.0 (60.4)	44.4 (58.3)	66.7 (66.7)
Bachelors	83.3 (39.6)	33.3 (33.3)	33.3 (33.3)	33.3 (91.7)	23.8 (32.1)	16.7 (29.2)	22.2 (41.7)	33.3 (66.7)
Higher degrees	70.8 (89.6)	41.7 (45.8)	33.3 (66.7)	33.3 (66.7)	19.0 (34.5)	16.7 (35.4)	38.9 (55.6)	0.0 (83.3)
<i>P</i> -value	0.023*	0.79	0.49	0.03*	0.66	0.19	0.25	0.33
Employment status								
Employed	66.7 (54.2)	50.0 (33.3)	33.3 (33.3)	33.3 (66.7)	28.6 (45.2)	16.7 (37.5)	44.4 (55.6)	33.3 (100.0)
Non- employed	83.3 (33.3)	50.0 (33.3)	66.7 (33.3)	66.7 (66.7)	28.6 (29.4)	16.7 (45.8)	22.2 (55.6)	66.7 (100.0)
Retired	83.3 (50.0)	33.3 (0.0)	33.3 (0.0)	100.0 (33.3)	33.3 (23.8)	33.3 (25.0)	33.3 (44.4)	33.3 (33.3)
<i>P</i> -value	<0.001*	0.08	0.14	0.016*	0.06	0.79	0.77	0.42
Income								
< 5,000	65.8 (34.4)	17.6 (26.2)	57.9 (28.8)	43.7 (40.5)	37.0 (24)	29.9 (28.7)	42.2 (31.1)	57.8 (40.2)
5,000- 15,000	69.9 (32.7)	23.9 (26.7)	47.8 (30.3)	47.3 (40.4)	29.2 (22.8)	25.7 (27.4)	38.2 (30.5)	43.8 (43.2)
> 15,000	60.9 (36.4)	24.4 (24.1)	40.7 (22.2)	34.5 (32.7)	31.1 (24.1)	21.8 (22.4)	36.6 (33.9)	43.3 (44.8)
<i>P</i> -value	0.34	0.07	0.25	0.30	0.04*	0.35	0.47	0.03*
Sport								
Yes	66.7 (58.3)	50.0 (33.3)	66.7 (33.3)	33.3 (100.0)	33.3 (28.6)	25.0 (50.0)	55.6 (66.7)	100.0 (66.7)
No	83.3 (43.8)	33.3 (33.3)	33.3 (33.3)	66.7 (100.0)	23.8 (38.1)	16.7 (35.4)	27.8 (55.6)	33.3 (100.0)
<i>P</i> -value	0.13	0.03*	0.63	0.87	0.19	0.66	0.28	0.053
Family history								
Yes	75.0 (50.0)	33.3 (33.3)	33.3 (33.3)	66.7 (75.0)	28.6 (23.3)	16.7 (33.3)	22.2 (55.6)	33.3 (100.0)
No	75.0 (52.1)	50.0 (33.3)	33.3 (33.3)	33.3 (91.7)	30.9 (41.7)	20.8 (56.3)	38.8 (55.6)	66.7 (66.7)
<i>P</i> -value	0.47	0.56	0.49	0.11	0.68	0.72	0.47	0.54

Comorbidities								
Yes	75.0 (33.3)	33.3 (16.7)	33.3 (33.3)	33.3 (66.7)	33.3 (33.3)	25.0 (33.3)	44.4 (55.6)	66.7 (66.7)
No	83.3 (50.0)	50.0 (33.3)	33.3 (33.3)	33.3 (100)	23.8 (38.1)	16.7 (41.7)	33.3 (55.6)	33.3 (100.0)
<i>P</i> -value	0.11	0.01*	0.39	0.09	0.004*	0.03*	0.01*	0.05*
Region								
Central	79.2 (50.0)	33.3 (33.3)	33.3 (33.3)	28.6 (66.7)	28.6 (23.8)	16.7 (37.5)	27.8 (55.6)	33.3 (100.0)
Eastern	75.0 (79.2)	50.0 (58.3)	33.3 (66.7)	0.0 (50.0)	42.9 (66.7)	16.7 (70.8)	44.4 (50.0)	33.3 (100.0)
Northern	75.0 (62.5)	33.3 (50.0)	33.3 (66.7)	33.3 (66.7)	26.2 (51.2)	25.0 (27.8)	38.9 (52.8)	50.0 (100.0)
Southern	83.3 (50.0)	50.0 (33.3)	66.7 (33.3)	33.3 (66.7)	40.5 (48.8)	16.7 (70.8)	38.9 (52.8)	66.7 (91.7)
Western	83.3 (-)	50.0 (-)	66.7 (-)	66.7 (-)	4.80 (-)	8.30 (-)	22.2 (-)	0 (-)
<i>P</i> -value	0.68	0.95	0.36	0.03*	0.22	0.66	0.59	0.99

Table 7.8. Functional and symptom scales in QLQ BR- 23 by sociodemographic.

In regard to the functional and symptom scales in QLQ BR23 by clinical characteristics, it was found that there was no significant difference across the disease stages, but there was a statistically significant difference in arm symptoms for patients diagnosed five years or before ($P < 0.05$) and those with metastatic cancers. Body image was found to be statistically significant among patients with metastatic cancers. Additionally, all symptom scales showed statistically significant difference across treatment modalities, with patients reporting worse symptoms during radiation therapy. Furthermore, hair loss was significantly more pronounced in patients receiving chemotherapy and radiation.

Characteristic	Functional scales in BR23 Median (IQR)				Symptom scales in BR-23 Median (IQR)			
	BRBI	BRSEF	BRSEE	BRFU	BRST	BRBS	BRAS	BRHL
Disease stage								
I	75.0 (50.0)	50.0 (33.3)	66.7 (33.3)	33.3 (66.7)	38.1 (42.9)	25.0 (66.7)	44.4 (77.8)	100.0 (66.7)
II	75.0 (83.3)	50.0 (33.3)	33.3 (33.3)	66.7 (83.3)	28.6 (33.3)	16.7 (25.0)	55.6 (55.6)	0.0 (100)
III	83.3 (58.3)	33.3 (25.0)	33.3 (41.7)	50.0 (100.0)	23.8 (26.2)	16.7 (41.7)	38.9 (52.8)	33.3 (75.0)
IV	62.5 (58.3)	41.7 (33.3)	33.3 (66.7)	50.0 (75.0)	30.9 (45.2)	29.2 (50.0)	27.8 (36.1)	66.7 (100.0)
<i>P</i> -value	0.51	0.92	0.62	0.76	0.13	0.49	0.43	0.15
Years since diagnosis								
1-2	75.0 (52.1)	33.3 (33.3)	33.3 (33.3)	33.3 (50.0)	28.2 (33.7)	25.0 (35.4)	22.2 (38.9)	33.3 (100.0)
2-4	75.0 (54.2)	50.0 (33.3)	33.3 (33.3)	33.3 (66.7)	23.8 (37.3)	16.7 (37.5)	44.4 (61.1)	66.7 (100.0)
3- 5	83.3 (41.7)	50.0 (33.3)	33.3 (33.3)	66.7 (100.0)	33.3 (42.9)	25.0 (75.0)	55.6 (44.4)	33.3 (100.0)
<i>P</i> -value	0.32	0.80	0.95	0.83	0.58	0.17	0.004*	0.64
Metastasis								
Yes	75.0 (100.0)	33.3 (33.3)	33.3 (33.3)	66.7 (100.0)	28.6 (34.9)	25.0 (33.3)	44.4 (44.4)	33.3 (100)
No	79.2 (100.0)	33.3 (33.3)	33.3 (33.3)	33.3 (66.7)	33.3 (41.3)	16.7 (33.3)	33.3 (55.6)	66.7 (100.0)
<i>P</i> -value	0.5*	0.39	0.93	0.26	0.053	0.08	0.01*	0.95
Treatment modalities								
Surgery	66.7 (50.0)	33.3 (16.7)	33.3 (33.3)	66.7 (66.7)	28.6 (23.0)	25.0 (41.7)	33.3 (61.1)	33.3 (100.0)
Chemotherapy	83.2 (52.0)	50.0 (33.3)	50.0 (33.3)	33.3 (66.7)	35.7 (32.1)	16.7 (39.6)	33.3 (55.6)	66.7 (100.0)
Hormonal	75.0 (54.2)	41.7 (33.3)	50.0 (33.3)	66.7 (100.0)	23.8 (35.7)	20.8 (37.5)	33.3 (44.4)	33.3 (100.0)
Radiation	70.8 (-)	50.0 (-)	33.3 (0.0)	66.7 (0.0)	61.9 (-)	70.8 (-)	77.8 (-)	66.7 (-)
<i>P</i> -value	0.27	0.44	0.88	0.18	<0.001*	0.02*	0.05*	0.04*

Table 7.9. Functional and symptom scales in QLQ BR- 23 by clinical characteristics.

Predictors of quality of life among breast cancer females (Multiple linear regression):

The linear regression model assumptions were checked and met. The linearity of the regression model was assessed, and it showed that a linear function of the independent variable is good enough to estimate the dependent variables. The multicollinearity was tested by examining the variation influence factor values, which found that none of the variation influence factor values was above 5, and by examining the correlation matrix. None of the correlations was above 0.8, meaning there is no multicollinearity problem. By inspecting the scatterplot of the residuals, the data does not have an obvious pattern, which means the homoscedasticity assumption was met. These findings demonstrate that the key assumptions required for linear regression analysis were met.

The predictors accounted for only 7.2% of the variation in global health (R-squared = 0.072), indicating limited explanatory power. This result was not statistically significant ($P = 0.2$).

In the QLQ-C30 functional scale, the only significant domains were physical and social functioning, in which the predictors explained the 15.8% ($P < 0.001$) and 10.2% ($P = 0.02$) of the variation, respectively. The predictors significantly associated with physical functioning were age, comorbidities, metastasis and sports. The predictors significantly associated with social functioning were employment status, comorbidities and metastasis.

In the QLQ-C30 symptom scale, the predictors explained 12.1% ($P = 0.004$) of the variation in pain, and the significant predictors were sport, region, and comorbidities. Comorbidity was a significant predictor of both dyspnea and constipation. Sleep disturbance predictors explained 9.3% of the variation, where income and comorbidity were the significant predictors. The predictors explained 10.9% of the variation in financial impact, and the region was the significant predictor.

In the BR23 functional scale, the predictors explained 19.6% ($P < 0.001$) of the variation in sexual functioning, with age, marital status and educational levels as the significant predictors. In

body image, the predictors explained 15.5% ($P < 0.001$) of the variation, with employment status and comorbidity as significant predictors. While in the BR23 symptom scale, the predictors explained 10.5% ($P = 0.02$) of the variation in arm symptoms, the significant predictor was the year since diagnosis.

Variable	QLQ-C30 Functional scale											
	Global health /QoL		Physical functioning		Role functioning		Emotional functioning		Cognitive functioning		Social functioning	
	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value	β	P-value
Age	-2.45	0.19	-3.66	0.03*	-3.26	0.14	0.19	0.09	-1.06	0.63	1.90	0.40
Marital status	-3.94	0.33	-3.17	0.39	-9.11	0.06	-4.47	0.35	-4.68	0.32	-6.25	0.19
Having children	2.82	0.56	3.06	0.52	5.90	0.35	3.74	0.55	3.67	0.55	-1.77	0.78
Menopausal status	-5.44	0.15	-2.75	0.42	-0.29	0.95	-1.59	0.72	1.16	0.79	-2.85	0.53
Education level	0.39	0.83	1.81	0.25	-0.96	0.64	-1.11	0.59	-0.31	0.88	-1.00	0.63
Employment status	0.53	0.75	2.19	0.14	3.97	0.04	4.1	0.04*	3.84	0.05*	5.44	0.006*
Income	0.49	0.86	3.44	0.17	0.79	0.81	-0.68	0.84	2.82	0.38	0.001	1.00
Activity (sports)	5.72	0.08	8.32	0.005*	8.19	0.03*	8.14	0.04*	6.08	0.11	2.97	0.45
Family history	0.74	0.85	-1.67	0.62	-3.26	0.46	-4.98	0.26	-3.24	0.46	-4.05	0.37
Comorbidities	-2.48	0.47	-6.64	0.03*	-5.98	0.14	-9.76	0.02*	-10.96	0.006*	-9.87	0.02*
Region	-0.90	0.48	0.06	0.96	0.38	0.79	0.37	0.81	0.66	0.65	0.85	0.57
Disease stage	0.43	0.39	0.44	0.34	0.82	0.17	0.40	0.50	0.02	0.97	0.71	0.24
Years since diagnosis	-2.42	0.25	-1.45	0.44	3.13	0.20	-1.98	0.42	-3.80	0.12	-4.05	0.12
Metastasis	-0.83	0.22	-1.11	0.05*	-0.73	0.32	-.91	0.22	-0.37	0.61	-1.69	0.02*
Treatment	0.26	0.73	0.93	0.16	0.11	0.89	0.04	0.96	1.07	0.22	1.01	0.25
R-squared	0.072		0.158		0.078		0.080		0.09		0.102	
p-value	0.19		<0.001*		0.14		0.12		0.058		0.02*	

Table 7.10. A linear regression model with parameter estimates for QLQ C30 functional scale. β : Standardised coefficient Beta

	QLQ C30 Symptom scale									
Variable	Pain		Dyspnea		Sleep disturbance		Constipation		Financial impact	
	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value
Age	3.58	0.12	-0.57	0.81	3.49	0.21	-0.76	0.75	-2.79	0.29
Marital status	6.92	0.16	7.78	0.12	-2.08	0.72	5.06	0.33	0.25	0.97
Having children	-4.03	0.53	1.96	0.77	-4.53	0.56	2.59	0.71	5.38	0.47
Menopausal status	-1.09	0.81	0.19	0.96	6.02	0.27	4.20	0.39	-4.38	0.41
Education level	0.34	0.87	0.12	0.96	1.85	0.47	1.96	0.39	0.50	0.84
Employment status	-1.58	0.43	-3.51	0.08	-4.13	0.09	-2.28	0.28	-1.97	0.39
Income	-5.12	0.13	-4.19	0.22	-10.33	0.01*	-3.76	0.29	-5.75	0.13
Activity (sports)	-8.40	0.04*	-4.97	0.22	-7.33	0.12	-4.27	0.31	-7.06	0.12
Family history	4.61	0.31	1.63	0.72	-0.78	0.89	3.15	0.51	-0.08	0.99
Comorbidities	9.86	0.02*	16.08	<0.001*	11.68	0.02*	15.46	<0.001*	8.99	0.06
Region	3.41	0.03*	1.63	0.29	-0.98	0.59	0.78	0.63	5.04	0.004*
Disease stage	-1.07	0.08	-0.004	0.99	-0.26	0.72	0.61	0.34	1.29	0.06
Years since diagnosis	-2.04	0.42	1.93	0.45	3.91	0.19	1.59	0.56	2.22	0.44
Metastasis	0.75	0.31	1.10	0.15	1.29	0.15	0.99	0.21	0.41	0.63
Treatment	-0.86	0.34	0.23	0.80	-0.27	0.80	-0.94	0.32	-0.53	0.60
R-squared	0.121		0.109		0.093		0.095		0.109	
p-value	0.004*		0.012*		0.047*		0.042*		0.012*	

Table 7.11. A linear regression model with parameter estimates for QLQ C30 symptom scale (only scales with significant results are listed in the table). * statistically significant.

QLQ BR23	Functional scale				Symptom scale	
Variable	Body image		Sexual functioning		Arm symptoms	
	β	<i>P</i> -value	β	<i>P</i> -value	β	<i>P</i> -value
Age	2.16	0.37	-6.14	0.002*	1.34	0.56
Marital status	-0.19	0.97	-15.48	<0.001*	1.66	0.73
Having children	-3.18	0.64	-1.14	0.84	-1.96	0.76
Menopausal status	-7.17	0.14	-5.75	0.13	-1.58	0.73
Education level	-1.21	0.58	-3.63	0.04*	-1.37	0.52
Employment status	10.42	<0.001*	-0.97	0.56	-2.74	0.17
Income	4.23	0.23	2.32	0.42	-4.57	0.17
Activity (sports)	-0.13	0.98	6.09	0.07	-4.45	0.26
Family history	-0.73	0.88	-1.99	0.60	2.28	0.61
Comorbidities	-10.52	0.02*	-4.28	0.22	7.61	0.06
Region	2.06	0.20	-1.05	0.42	0.95	0.53
Disease stage	0.89	0.16	0.62	0.23	-1.05	0.08
Years since diagnosis	-3.28	0.22	0.71	0.74	7.74	0.002*
Metastasis	-1.31	0.10	-0.83	0.20	1.25	0.09
Treatment	1.50	0.11	-0.43	0.56	-1.63	0.07
R-squared	0.155		0.196		0.105	
<i>p</i>-value	<0.001*		<0.001*		0.018*	

Table 7.12. A linear regression model with parameter estimates for QLQ BR23 (only scales with significant results are listed in the table). * statistically significant

7.3.2 Quality of life using EQ-5D-3L

The mean index score for the EQ-5D-3L was 0.634 (SD 0.306), the median was 0.77, and the mode was 0.97, with values ranging from -0.484 to 1. 15 observations (5.45%) were below zero, indicating a worse-than-death health state, and 40 observations (14.55%) scored 1, indicating full health. A gap existed between full health and the next feasible value (0.883).

Regarding the EQ-VAS, the mean VAS was 70 (SD 22.9), and the median was 70. A statistically significant correlation was found between the EQ-5D-3L index and the EQ-VAS scores ($r_s=0.473$, $P < 0.001$).

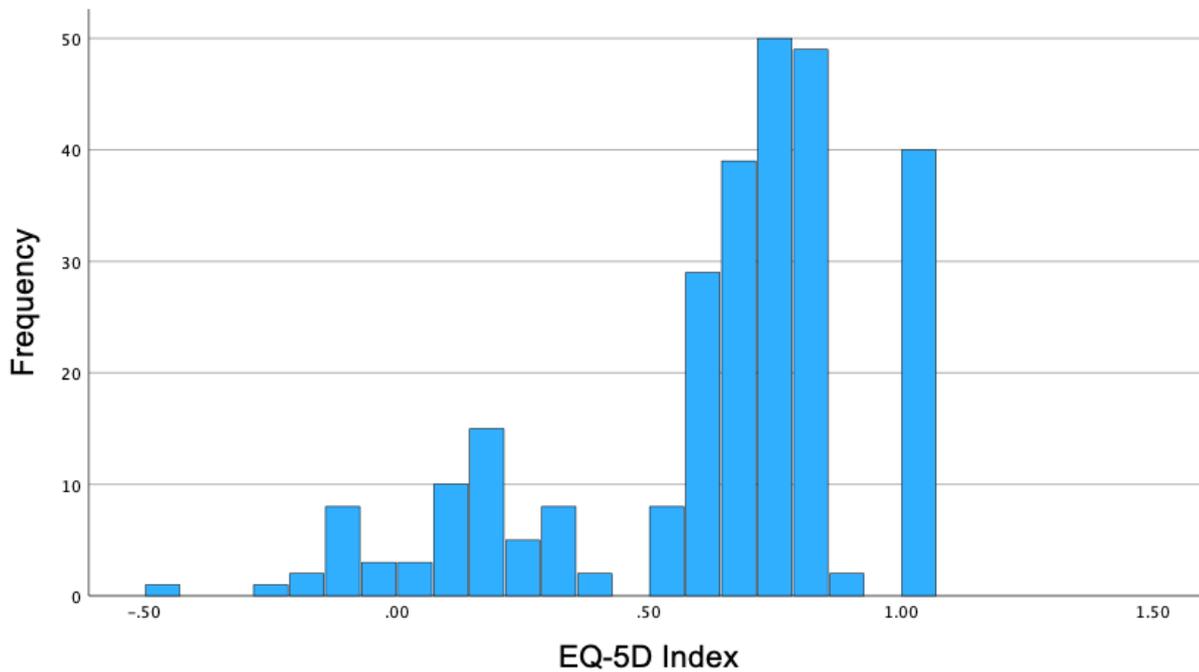


Figure 7.1 The EQ-5D-3L index frequency distribution.

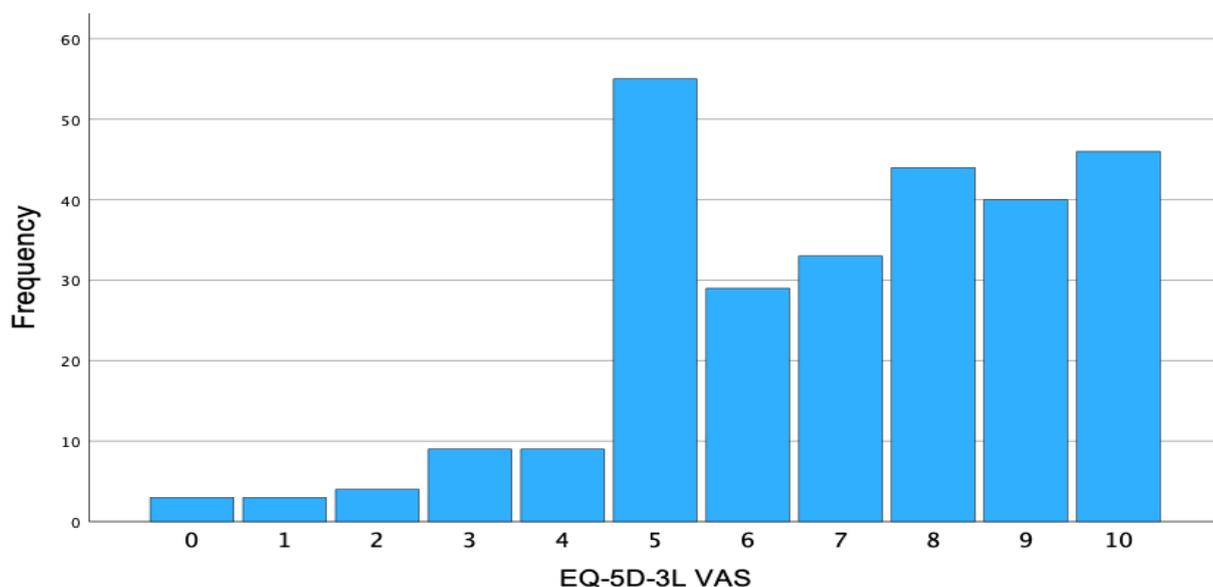


Figure 7.2. The EQ-5D-3L VAS frequency distribution.

The percentages of “no problems” vary for each dimension, ranging from the highest percentage in the self-care dimension (85%) to the lowest for the pain or discomfort dimension (31%). Moderate problems were highest in the pain or discomfort dimension (60%), followed by the anxiety or depression dimension (50%). Regarding level three, 10% of the respondents were unable to perform their usual activities. The distribution of reported problems in various severity levels and dimensions is shown in Table 7.13.

EQ-5D-3L	Level 1 (No problem)	Level 2 (Moderate problem)	Level 3 (Extreme problem)	Total
Mobility	137 (49.8%)	133 (48.4%)	5 (1.8%)	275 (100%)
Self-care	236 (85.8%)	35 (12.7%)	4 (1.5%)	275 (100%)
Usual activities	140 (50.9%)	106 (38.5%)	29 (10.6%)	275 (100%)
Pain/ discomfort	86 (31.3%)	165 (60.0%)	24 (8.7%)	275 (100%)
Anxiety/ depression	116 (42.2%)	138 (50.2%)	21 (7.6%)	275 (100%)

Table 7.13. EQ-5D-3L frequencies reported by level and dimension.

EQ-5D-3L health scores:

Table 7.14 and Table 7.15 show the median (IQR) of the EQ-5D-3L index and EQ-VAS scores by sociodemographic and clinical characteristics. The EQ-5D-3L index and VAS scores showed no significant differences for any variables.

Characteristic	EQ-5D-3L	EQ-5D VAS
	Median (IQR)	Median (IQR)
Age group (Y)		
< 30	0.90 (0.33)	85.0 (40.0)
30-39	0.81 (0.23)	70.0 (40.0)
40-49	0.79 (0.25)	80.0 (30.0)
50-59	0.77 (0.21)	70.0 (30.0)
≥ 60	0.81 (0.29)	70.0 (40.0)
<i>P</i> -value	0.33	0.07
Marital status		
Married	0.81 (0.23)	80.0 (40.0)
Not married	0.79 (0.34)	60.0 (40.0)
<i>P</i> -value	0.31	0.08
Having children		
Yes	0.81 (0.20)	70.0 (40.0)
No	0.77 (0.27)	60.0 (40.0)
<i>P</i> -value	0.89	0.48
Menopausal status		
Premenopausal	0.81 (0.23)	80.0 (40.0)
Postmenopausal	0.81 (0.21)	70.0 (40.0)
<i>P</i> -value	0.26	0.09
Educational level		
Diploma /High-school or less	0.77 (0.19)	70.0 (40.0)
Bachelors	0.82 (0.23)	80.0 (40.0)
Higher degrees	0.72 (0.36)	65.0 (40.0)
<i>P</i> -value	0.07	0.32
Employment status		
Employed	0.81 (0.23)	80.0 (40.0)

Own-Business	0.77 (0.42)	80.0 (50.0)
Non- employed	0.78 (0.23)	70.0 (40.0)
Retired	0.81 (0.23)	80.0 (40.0)
<i>P</i> -value	0.79	0.67
Income		
< 5,000	0.77 (0.27)	70.0 (40.0)
5,000- 15,000	0.81 (0.23)	80.0 (40.0)
> 15,000	0.77 (0.29)	70.0 (40.0)
<i>P</i> -value	0.12	0.09
Family history		
Yes	0.77 (0.25)	80.0 (40.0)
No	0.81 (0.23)	70.0 (40.0)
<i>P</i> -value	0.22	0.52
Comorbidities		
Yes	0.77 (0.22)	70.0 (30.0)
No	0.81 (0.23)	80.0 (40.0)
<i>P</i> -value	0.08	0.31
Region		
Central	0.81 (0.20)	70.0 (40.0)
Eastern	0.75 (0.24)	70.0 (30.0)
Northern	0.81 (0.27)	65.0 (40.0)
Southern	0.81 (0.23)	80.0 (30.0)
Western	0.84 (0.36)	60.0 (40.0)
<i>P</i> -value	0.09	0.51

Table 7.14. EQ-5D-3L health scores by sociodemographic. EQ-5D-3L: EuroQol 5-Dimension 3-Level, VAS: Visual Analogue Scale.

Characteristic	EQ-5D-3L	EQ-5d VAS
Disease stage	Median (IQR)	Median (IQR)
I	0.77 (0.26)	80.0 (40.0)
II	0.77 (0.27)	70.0 (40.0)
III	0.77 (0.22)	70.0 (40.0)
IV	0.77 (0.35)	70.0 (30.0)
<i>P</i> -value	0.80	0.88
Years since diagnosis		
1-2	0.81 (0.25)	70.0 (40.0)
2-4	0.81 (0.26)	80.0 (30.0)
3-5	0.77 (0.19)	70.0 (40.0)
<i>P</i> -value	0.74	0.33
Metastasis		
Yes	0.77 (0.16)	70.0 (30.0)
No	0.81 (0.26)	80.0 (30.0)
<i>P</i> -value	0.25	0.09
Treatment modalities		
Surgery	0.77 (0.24)	80.0 (30.0)
Chemotherapy	0.81 (0.18)	70.0 (40.0)
Hormonal	0.81 (0.19)	70.0 (40.0)
Radiation	0.67 (0.41)	55.5 (20.0)
<i>P</i> -value	0.18	0.36

Table 7.15. EQ-5D-3L health scores by clinical characteristics. EQ-5D-3L: EuroQol 5-Dimension 3-Level, VAS: Visual Analogue Scale.

The univariate analysis showed that age, marital status, menopausal status, family history, comorbidities, and disease stage were significantly correlated with the EQ-5D-3L index.

All the significant variables in the univariate analysis were included in a multivariable linear regression model to identify factors significantly associated with the EQ-5D-3L index. The predictors explained 7.9% of the variation in the EQ-5D-3L index scores ($P = 0.001$); family history of cancer ($P = 0.04$), disease stage ($P = 0.02$) and marital status ($P = 0.02$) were the factors most strongly associated with EQ-5D-3L (Table 7.16). While for the EQ-VAS, the model was non-significant ($P = 0.3$).

Variable	EQ-5D-3L index	
	β	P-value
Univariate analysis		
Age	-0.130	0.03*
Marital status	-0.126	0.04*
Having children	0.064	0.28
Menopausal status	-0.123	0.04*
Education level	0.082	0.18
Employment status	0.007	0.91
Income	0.050	0.41
Activity (sports)	0.108	0.08
Family history	-0.123	0.04*
Comorbidities	-0.139	0.02*
Region	0.043	0.48
Disease stage	0.127	0.04*
Years since diagnosis	0.000	0.99
Metastasis	-0.085	0.16
Treatment	0.075	0.22
Multivariable analysis		
Age	-0.058	0.39
Marital status	-0.146	0.02*
Menopausal status	-0.085	0.19
Family history	-0.118	0.04*
Comorbidities	-0.092	0.14
Disease stage	0.135	0.02*
R-squared	0.079	
P-value	0.001*	

Table 7.16. Univariate and Multivariable linear regression analysis with parameter estimates for EQ-5D-3L index. *Statistically significant.

7.3.3 Mapping

Spearman correlation coefficients were calculated to assess the relationship between EQ-5D-3L and QLQ-C30; there was a positive, moderate correlation ($r_s=0.49$, $P < 0.001$).

The ALDMM models were estimated using different numbers of components, including only the global health and the global health square variables as predictors of component probabilities. Table 7.17 shows summary fit statistics for adjusted limited dependent variable mixture model models with 1 to 4 components. The mean absolute error decreases from 0.211 for 1 component to 0.203 for four components, indicating improved prediction accuracy as more components are added. The root mean square error remains relatively stable across models, suggesting that performance does not vary significantly with the number of components.

When the summary fit statistics of all four adjusted limited dependent variable mixture models are inspected, the model with four components is preferred. It provides the best fit based on the lowest Root Mean Squared Error and Mean Absolute Error. The predicted mean is close to the observed data and has the lowest Akaike information criteria value (AIC).

ALDMM	MAE	RMSE	AIC	BIC	Mean	Absolute difference*
1 Component	0.211	0.270	153.89	164.89	0.627 (0.135)	0.007
2 Components	0.207	0.270	36.38	61.69	0.644 (0.129)	-0.010
3 Components	0.207	0.272	33.33	62.27	0.644 (0.116)	-0.010
4 Components	0.203	0.268	19.568	73.819	0.645 (0.123)	-0.011

Table 7.17. Comparisons of fit statistics.

Note: ALDMM: adjusted limited dependent variable mixture model, MAE: Mean Absolute Error, RMSE: Root Mean Squared Error, AIC: Akaike Information Criteria, BIC: Bayesian Information Criteria. * The observed mean was 0.63

7.4 Discussion

This study aimed to assess health-related quality of life among Saudi females with BC and explore if it is related to sociodemographic and clinical factors. It also measured the health utility values via mapping, which are needed for calculating the QALYs that in health economic studies. The main findings of this study are that patients with BC had a poor overall QoL. The participants scored high on role, social, and cognitive functioning scales; however, physical and emotional functioning was low. On the other hand, sleep disturbance, fatigue, appetite loss, and constipation score most highly, indicating these are the most distressing symptoms experienced by the participants in this study. On the QLQ-BR-23 functional scale, body image showed a better score, while on the symptom scale, the worst symptoms were arm symptoms and upset by hair loss.

By comparing this study's results to those reported by a systematic review and meta-analysis for the QoL of BC in women worldwide, this study showed poor overall QoL among Saudi females (52 ± 41.7) compared to women with BC worldwide (64.72) (Javan Biparva et al., 2022). The scores were shown to be lower than the EORTC QLQ-C30 reference values (66.7; 50-83.3) (Scott et al., 2008) and lower than scores reported by other studies around the world, such as in China (70.24 ± 8.7) (Chen et al., 2023), Singapore (67 ± 25) (Luo et al., 2005), Morocco (68.5 ± 18.5) (El Fakir et al., 2016) and in Gulf countries as in Qatar (75.6 ± 22.7) (Bener et al., 2017), and Bahrain (63.9 ± 21.3) (Jassim & Whitford, 2013). On the other hand, the scores were higher than those reported in a Kuwaiti study (45.3 ± 15.3) (Alawadi & Ohaeri, 2009).

When comparing the results of this study with previous studies in Saudi Arabia, Saudi studies reported a wide variation in the QoL scores; some demonstrated a high QoL with mean scores ranging from 74.5 in a study conducted in Jeddah (Fetaini et al., 2020) to 63.15 in a study conducted in Riyadh (Al-Shammari & Khalil, 2020), in contrast to other studies that reported a poor QoL with mean scores as low as 31.2 (Almutairi et al., 2016). This study revealed that the overall QoL score was 52.

This variation in the findings could be because the results are obtained from different regions around Saudi Arabia. However, the same variation was noticed when focusing on studies conducted in Riyadh; a score of 63.15 ± 18.4 was reported in a study from the same hospital where this study was conducted (Al-Shammari & Khalil, 2020), and a score of 31.2 ± 20.5 in a study that recruited patients from outpatient clinics in different settings in Riyadh (Almutairi et al., 2016). Interestingly, a recent study published in 2024 (Al-Karni et al., 2024) showed results consistent with this study's results, where a poor HRQoL was demonstrated.

Furthermore, the difference in the global health status could be due to the difference in the setting and design of this study compared to other studies. In this study, participants from different patients with different treatment strategies and different backgrounds were approached, which introduced a variability due to differences in treatment stages and recovery phases. In contrast, other studies often assessed the same patient at two different times, such as before and after treatment or surgery, or patients were followed up in time and interviewed in different periods after being diagnosed. Unlike longitudinal studies, this method does not capture changes in QoL or health status over time, making it difficult to attribute outcomes directly to specific treatments or interventions. Consequently, this may influence the interpretation and generalisability of the findings.

This study reported lower QoL scores among Saudi females, which could be since QoL tends to be higher in patients with BC in their 50s and 60s (Javan Biparva et al., 2022). Furthermore, this study showed that the median age of Saudi BC females is 47; the age distribution could explain the variation in QoL scores compared to other countries. Although the findings were inconsistent with the results of previous Saudi studies, they were comparable with the results of a recent study (Al-Karni et al., 2024). This could be explained by the changes in the lifestyle of Saudi women, which affect their perception of the disease and eventually affect the quality of their lives.

Regarding the functional scales, compared to BC women worldwide (77.3), this study showed lower scores in physical functioning scales (66.7±40) but higher than other studies conducted in Saudi Arabia, in which the scores ranged between 62.14 to 47.5. In contrast, role, cognitive, and social functioning showed higher scores of 83.3 in all three scales than results from meta-analysis studies of women worldwide, which were 70.8, 77.3, and 76.2, respectively, and also higher than results from Saudi studies; the higher findings of role and social functioning might be due to family support.

Regarding the EORTC QLQ-C30 symptom scale, the most disturbing symptoms were fatigue, sleep disturbance, appetite loss, and constipation, followed by pain, which aligns with the findings of studies worldwide that reported fatigue, pain and sleep disturbance as the worst scores (Javan Biparva et al., 2022), as well as the study by (Abu-Helalah et al., 2022) which reported pain, fatigue and sleep disturbance as the worse symptoms but in contrast to the study reported by (Fetaini et al., 2020) in which all symptoms were reported as disturbing with high scores.

With respect to the functional scale of the QLQ BR-23, higher scores of body image were reported (75) compared to other studies, such as the cross-sectional study done on 264 females in three different Saudi

regions (Abu-Helalah et al., 2022), but lower than the results reported by the study done In Germany, which showed a body image score of 83.3 (Waldmann et al., 2007).

In the QLQ BR-23 symptom scale, women experienced arm symptoms and were more upset by hair loss than other symptoms. These findings were inconsistent with those from the study conducted in Germany, where upset by hair loss was higher than other symptoms, followed by systemic therapy side effects. This could be explained by knowing that in this study, 45% of the participants used chemotherapy and 1.5% used radiotherapy, while in the Germany study, 85.2% used radiotherapy and 59.7% used chemotherapy.

With respect to sociodemographic factors and EORTC QLQ C30 functioning scales, physical and cognitive functioning were inversely affected by age. Some studies suggest that older people have better QoL than younger people (Javan Biparva et al., 2022); on the other hand, this study contradicts those previous findings, as younger people have better physical and cognitive functioning scores, and findings were consistent with results from another study (Imran et al., 2019). This could be related to the physiological and psychological impacts of ageing; younger individuals may have better physical and cognitive functioning due to higher energy levels and fewer age-related health issues. In contrast, older individuals often face chronic conditions, physical limitations, and cognitive decline, which could negatively impact their QoL. However, some studies reporting better QoL in older adults may reflect differences in life satisfaction or lower physical and cognitive performance expectations in this group. The contrasting results in this study might also be influenced by the sample's characteristics or cultural and societal factors affecting younger and older participants differently.

There was no significant median difference across employment status, having children, or family history. However, there was a significant difference in physical and emotional functioning across the education and income levels, with better functioning observed in participants with higher educational levels and moderate income; this could be explained by the fact that education helps patients understand their medical situation and increases awareness. Despite the availability of free medical services provided by the government in KFSH&RC, this study showed that higher income still significantly enhances the quality of life of BC patients.

The results of this study differ from the findings of another study (Al Zahrani et al., 2019), which reported poorer functions in younger women and those with high education levels but supported by the results of another study in KSA (Abu-Helalah et al., 2022), which reported younger age and high education level as good predictors of physical functioning.

A significant difference was found in physical functioning and age group, menopausal status, educational level, income status, regular exercising, and comorbidities. Physical functioning was better in younger ages, premenopausal, with high education, as well as in those who exercise regularly and are free from other diseases or comorbidities. Therefore, clinicians should pay more attention to supporting older women with low education levels and those with other diseases, as these affect their quality of life.

Role functioning was significant across marital status; married women were found to have good scores in role functioning, which could be due to the support they received from their spouses. It was observed that participants with comorbidities scored high in all aspects except role functioning. The presence of co-morbid diseases affects physical, emotional, cognitive, and social functioning scores. These results align with a previous study (Al-Karni et al., 2024), which reported that comorbidities were associated with poor HRQoL.

Contrary to other studies, QoL was generally unaffected by factors like disease stage or years since diagnosis; it was only affected by metastasis; non-metastatic patients had better physical functioning than those suffering from metastasis women. Previous studies have reported that patients with metastasis tend to have poor QoL (Al Zahrani et al., 2019)

The treatment modalities affect physical functioning and social functioning; patients who underwent surgery or received hormonal therapy tend to have higher scores in social functioning compared to other treatment strategies, while those using chemotherapy had lower scores. Regarding physical functioning, using hormonal therapy and chemotherapy was associated with higher scores, while using radiation was associated with lower scores.

Several studies have shown that chemotherapy negatively affects quality of life, while radiotherapy has been shown to improve it (Fetaini et al., 2020), which contradicts this study's results. Although chemotherapy is commonly associated with low quality of life scores, the results of this study could be interpreted as the significant improvement experienced after treatment with chemotherapy, which improves physical functioning.

Regarding the QLQ-C30 symptom scale, the most distressing symptom reported was sleep disturbance (33.3), which is lower than the results reported in another study (Al-Shammari & Khalil, 2020). Next came fatigue, appetite loss, constipation and pain. In assessing the median differences between sociodemographic and the QLQ C30 symptom scales, the only significant ones were observed for marital status, income level, region, those who sport regularly, and comorbidities.

Appetite loss was significant among unmarried women, those with low incomes, and those who were not physically active. This could be due to different levels of emotional support provided for married women by their spouses, which encourage regular eating habits that lower the effect of appetite loss. The association between comorbidities and all symptom scales, except appetite loss and financial impact, was reported. On the other hand, there was no significant association between the QLQ C30 symptom scales and the disease stage or years since diagnosis.

The symptom scale was affected by the treatment modalities and metastasis; nausea or vomiting was significant in patients who used radiation therapy, while loss of appetite was a significant symptom with radiation and chemotherapy, which is expected as a known side effect of both treatments. Constipation was a recognised symptom in all treatment modalities except for surgery. Metastatic cancers are a significant predictor of all symptoms except for pain and constipation compared to nonmetastatic cancers.

In this study, the functional scale of BR23 showed higher scores for body image. Arm symptoms and hair loss were the most disturbing symptoms. These findings were compatible with the results from previous studies (Imran et al., 2019). The score of hair loss in this study was 48.6 ± 42.8 which is higher than the score reported by another study (45.8 ± 39.7) (Imran et al., 2019) but lower than (61.6 ± 41.4) and ($54.2 \pm 4-0.9$) that were reported in another two studies (Nageeti et al., 2019; Abu-Helalah et al., 2022).

In relation to the predictors of QoL on the QLQ-BR23 scale, it was found that body image differed significantly by age, education level, and employment status. Women younger than 50, those with bachelor's degrees and those not employed or retired reported better body image scores. This could be due to the stress employed patients face when dealing with people on a daily basis in the workplace. Inconsistent with these results, a cross-sectional study conducted in Australia including 123 females found that body image was not affected by age or employment status (Ettridge et al., 2022), this result may be influenced by the limitations acknowledged by the authors, particularly the use of tools that were not tested for validity in that specific population and are not BC specific tools.

In contrast to the findings of other studies, which showed clinical staging as a significant predictor of body image, arm symptoms, breast symptoms, and being upset by hair loss (Almutairi et al., 2016), this study showed no significant association between clinical stage and the BR-23 symptom scale, also the surgical treatment did not affect the body image as expected. On the other hand, comorbidities were significantly associated with high scores in all symptom scales of BR-23.

Employed patients and those with higher education levels were more worried about the future perspective, which aligns with the study in KSA (Fetaini et al., 2020). In contrast, patients with metastasis were significantly associated with lower body image scores and higher systemic therapy side effects, which aligns with another study conducted in the western region of KSA (Imran et al., 2019).

Hair loss, breast symptoms, arm symptoms, and systemic therapy side effects were higher when using radiation compared to other treatment modalities. Hair loss was also associated with chemotherapy. Those findings are expected since these are known side effects of radiation and chemotherapy. Patients who were recently diagnosed with BC tend to complain less about arm symptoms compared to those who were diagnosed five years ago. This is well explained by the long-term effects of breast cancer therapy, such as oedema, which causes arm pain (Tommasi et al., 2022).

The results from EQ-5D-3L (0.634) showed better QoL than those obtained from QLQ-C30; this could be explained by the different aspects covered by each tool. The cancer-specific tool (QLQ-C30) focused mainly on symptoms specific to cancer, while the EQ-5D-3L measures the quality of life in broader aspects. Another cause of this difference could be related to using the UK tariffs in scoring the EQ-5D-3L because of the lack of norms specific to Saudi Arabia, since health preferences differ across populations due to cultural and healthcare system variations, applying UK-based tariffs may not accurately reflect Saudi's health perceptions. Moreover, the results of this study showed that the EQ-5D-3L health utility values were not affected by age or disease stage, unlike other studies that showed a decrease in utility with advanced stages.

This study used adjusted limited dependent variable mixture model to map QLQ-C30 utility scores to the EQ-5D-3L overall QoL score, demonstrating a moderate relationship between the two instruments. The model showed that the EORTC QLQ-C30 scale mapped successfully into EQ-5D-3L values. This mapping provided utility values from data obtained using the QLQ-C30, which will enable conducting cost-utility studies when utility values are not collected in clinical studies.

7.5 Strength and limitations

This study is one of a few that has assessed the QoL of BC in Saudi female and the association between QoL and sociodemographic and clinical predictors. It is also one of few studies to map the specific EORTC QLQ-C30 to the generic EQ-5D-3L tools in the Saudi population to provide utility values for pharmacoeconomic studies. To my knowledge, this is the first mapping study to map QLQ-C30 to EQ-5D-3L

in Saudi breast cancer patients. The results will enable policymakers to convert cancer-specific questionnaire scores to preference-based scores.

This study was a single centre-based study; thus, results cannot be generalised for the whole population. Additionally, questionnaires can assess association but not causality. Another limitation was that this study used a structured questionnaire, which renders the possibility of having a discussion with the patients about aspects considered important from their perspective. Another issue to be considered is patients' hesitation to take the questionnaire, which has been seen in the clinic and could increase the possibility of selection bias. Patients who were not willing to participate in the current study claim to have bad memories of remembering the specific details of their disease, such as the date of diagnosis, and others do not like to complete the survey while waiting for their appointments because they are stressed and worried.

In this study, the survey was distributed using QR codes, allowing participants to complete the questionnaire at their convenience using their smartphones, which makes it quick. In addition, participants could not submit their responses unless all questions were answered, ensuring the data's completeness. But this also could be a weakness as mandatory questions could lead to frustration, and some patients feel forced to answer some questions, especially those related to sexual life or income, as they consider them private issues, especially in conservative communities. This could lead to bias as some demographics will not participate, such as those who will not complete the survey because of technical issues or do not want to answer private questions. There is also a potential bias in the sample due to varying levels of access and willingness to use smartphones or other devices to complete the survey. Individuals without access to smartphones or who are less comfortable with technology, such as older patients or individuals with lower socioeconomic status, may be underrepresented in the survey results.

7.6 Conclusion

The results of this study produce preliminary insight into the QoL of BC among Saudi females; it found that females with BC experienced poor QoL, with low physical and emotional functioning. The key disturbing symptoms include sleep disturbance, fatigue, appetite loss, and constipation. Even though the data were obtained from a tertiary referral hospital, the results can't be generalised for the population of women with BC in Saudi Arabia because the data were obtained from a small sample of women attending a single centre for treatment for BC. Further work recruiting a larger representative sample from other institutions and regions of Saudi Arabia is recommended for future research.

Chapter 8 Conclusions

This study examined the epidemiology of BC among Saudi females by exploring incidence, survival rates, and QoL. By utilising data from the cancer registry and KFSH&RC, the analysis employed quantitative methods to provide a better understanding of BC outcomes in Saudi females. Integrating registry data, hospital data, and patient-reported outcomes bridges the gap between statistical measures of disease progression, clinical management, and patients' experience, highlighting survival trends and BC's broader effects on well-being.

By analysing the registry's data over 23 years, it can be concluded that the incidence of BC in Saudi females has increased significantly over the years. The crude incidence rate was 13.6 per 100,000 per year, sharply increasing from 6.3 in 1994 to 26.4 in 2017. Similarly, the age-standardised incidence rate increased from 7.4 to 29.4 per 100,000 during the same period, reaching an overall rate of 15.7 per 100,000 per year. The median age at diagnosis was 49 years, with over half (52%) of the cases diagnosed before age 50, which is lower than the median age of 62 observed in high-income countries. This study found that the disease was diagnosed in advanced stages and grades.

These findings align with the Saudi literature, which reported an increase in the ASR over the years (Basudan, 2022; Albeshan & Alashban, 2021). A recent study published in 2024 found that the ASIR increased from 15.5/100,000 in 1990 to 46/100,000 in 2021 (AL Zomia et al., 2024). The increase in incidence rates was due to many factors. It could be attributable to improved diagnostic modalities, high awareness of the disease and its consequences for new generations, improvement in healthcare access, or lifestyle changes which may increase the risk of obesity, such as physical inactivity and unhealthy diet (Alquaiz et al., 2021).

This study also showed that there has been no change in the pattern of BC incidence among Saudi females over the years regarding the median age at diagnosis and the stage and grade at diagnosis. Most studies in Saudi literature between 1999 and 2021 reported that the age at diagnosis was less than 50 years (Ezzat et al., 1999; Alabdulkarim et al., 2018; Albeshan & Alashban, 2021), which aligns with the results of this study. The young age at diagnosis could be related to many factors, such as the population demographics in the region or the genetic factors such as BRCA1 and BRCA2 genes.

Regarding the stage at diagnosis, the Saudi literature reported stages II and III account for more than 50% of the cases. A recent study found that stages II and III represent 55.2% of the cases (Omer et al., 2024). Another study reported an increase in the localised and a decrease in the regional BC (Albeshan & Alashban, 2021). This study showed an increase in earlier-stage diagnosis, which may be explained by the improvement

in diagnosis and the introduction of the screening programme. Still, the incidence of late-stage diagnosis is high, which could be attributed to the limitations of healthcare access for high-risk populations or lack of awareness of BC symptoms.

Regarding survival analysis, the study showed lower survival rates of Saudi females compared to high-income countries, the 5-year overall survival rate in this study was 73%, while in the UK, it was 80% (Barclay et al., 2024). However, there was an improvement in the survival rate over the years. The overall 5-year survival rate increased from 69% in 2004-2008 to 78% in 2009-2013, meaning that survival has been improving recently approaching the global rates, which are 80%. This improvement could be related to the approval of new therapeutic medications that were associated with improving survival rates (Mauri et al., 2006). Additionally, it could be due to the early detection of BC due to the introduction of screening programmes, which may enhance survival.

Survival was related to age; it tended to decrease as the age increased, showing a 5-year relative survival of 79.1% in patients younger than 50 and 76.1% in patients 50 years and older. The best survival rate was in the 40-49 age group compared to younger and older groups. Survival was also correlated inversely with the stage and grade of the disease, and worse survival was associated with higher stages and grades. The risk of death increased with distant metastasis compared to regional and localised.

The hospital data analysis revealed that hormonal receptor status was positive in most cases (65%), while Her2/neu was negative in 56% of the cases. Positive receptors are associated with better prognosis, less aggressiveness, and good response to hormonal therapy. Cases with positive receptors tend to have better survival than negative ones. The relationship between treatment and survival showed that hormonal therapy had a beneficial effect on survival.

The study also showed that Saudi BC management guidelines and practices applied at KFSH&RC align with global guidelines by adopting a multidisciplinary, personalized treatment strategy based on age, menopausal status, and receptor status. Different treatment modalities are available within Saudi practice, including surgery, chemotherapy, radiotherapy, and hormonal therapy. BC management varies significantly across different age groups, and treatment strategies are tailored to the patient's characteristics, including age, stage, receptor status, and menopausal status.

The QoL study results showed poor overall QoL in Saudi females. The physical and emotional functioning were the lowest compared to the role, social, and cognitive functioning scales. The high role and social

functioning scores could be related to family support, which may provide emotional stability that helps patients engage in personal and social roles. Concerning the symptom scales, the most disturbing were fatigue, insomnia, appetite loss and constipation. The worst symptoms on the QLQ-BR23 scale were hair loss and arm symptoms. Physical and cognitive functioning scores were increased as the age decreased, while high education levels and moderate-income levels were associated with better physical and emotional functioning.

This study was able to derive a utility value for BC which reflects the impact of BC on the QoL by mapping the specific tool QLQ-C30 to the generic preference-based measure EQ-5D-3L. The utility value obtained has not been previously reported in the existing literature, which represents novel contribution by providing utility values that can be used in pharmacoeconomic studies to calculate QALYs and enhance decision-making in HTA.

The results of the QoL studies in KSA are conflicting; some studies reported a high QoL (74.5) (Fetaini et al., 2020), while others reported a poor QoL (31.2) (Almutairi et al., 2016). This could be due to the different settings of the studies, different regions across KSA, using single centre data, or it could be attributed to the different methods used to collect data, as in some studies, the QoL was calculated based on the before and after results were the study depends on measuring the QoL based on the same patients but with different times, before specific treatment and after or before and after surgery or directly after diagnosis and then after treatment started.

In conclusion, the incidence has increased over the years, and the median age at diagnosis was 49 with advanced stages and grades. Additionally, the survival rates have improved over the years, which means that with an increase in the incidence rate, there is an improvement in the survival rates; this could be attributed to the cases being diagnosed in early stages, leading to better survival. On the other hand, the QoL of BC females was poor, and this may be related to the fact that the disease is diagnosed in late stages, which is accompanied by poor prognosis and could also be due to side effects of treatment or this could be since most of the cases are young compared to the results from global studies and this would affect their life by limiting their ability to carry out daily activities or affect their ability to work. Combining all these results highlights the importance of early detection, correct diagnosis and tailoring treatment according to stage, age, menopausal status, tolerance of side effects, and receptor status.

This is the first study that used the national cancer registry data to describe the incidence and survival over 23 years. Additionally, it is the only study in KSA that mapped the QLQC30 into EQ5D, and the resulting

utility value could be used in cost-utility studies to calculate QALYs. The observed trends in incidence and survival highlight the importance of early detection and timely access to quality care, which is vital in improving patient outcomes. Additionally, the inclusion of QoL assessment provides valuable insights into the patient's experience of living with BC, emphasising the need for an approach that addresses both the medical and psychosocial aspects of care.

These findings can be of value to policymakers and healthcare practitioners in many aspects. The awareness campaign should increase, especially in regions with high incidence rates, such as Makkah, Riyadh and the eastern region. The screening programme should continue to target females at the age of 49, as this was the median age at diagnosis for Saudi females, to capture all the cases in their early stages. Prioritising patient-centred approaches involves tailoring diagnostic and treatment plans to reflect each patient's specific physical, social, and emotional needs, healthcare providers can improve treatment adherence and enhance overall patient satisfaction and outcomes. The low utility scores emphasise the need for interventions to improve the QoL. Since the utility value was derived by mapping QLQ-C30 into EQ-5D, it is important to acknowledge the variability or bias the mapping process could introduce, which could affect the accuracy and reliability of the utility values, leading to misrepresentation of patients' QoL.

Based on the findings of this study, a comprehensive approach is required to enhance BC management and outcomes in the Saudi population. One key recommendation is to conduct a longitudinal study exploring the impact of early detection on long-term survival and quality of life. Additionally, multiregional studies within KSA should be prioritised to compare geographical differences in BC incidence and survival rates, highlighting any region-specific factors influencing outcomes. Targeting women aged 40-49 in genetic studies is essential to uncover the underlying causes of BC related to genetic factors in these early ages. Furthermore, QoL studies are vital to identifying factors affecting patient well-being, while utility value research is essential for informing policymakers and pharmacoeconomic studies. These recommendations aim to bridge the existing gaps to improve breast cancer care.

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Appendices

Appendix A Demographics and clinical questionnaire

Evaluation of Health- Related Quality of life in Saudi females with Breast Cancer

أدعوك للمشاركة في هذا الاستبيان الذي يهدف الى دراسة العوامل المؤثرة في جودة الحياة لمريضات سرطان الثدي في السعودية. الوقت المتوقع لاتمام هذا الاستبيان لا يتجاوز خمس دقائق. سيتم التعامل مع معلوماتك الشخصية بكل سرية ولن يتمكن أي شخص من الاطلاع عليها بأستثناء الشخص القائم على الدراسة

Demographics and medical history:

معلومات عامة:

1	MR#	رقم الملف الطبي:
2	Nationality: ○ Saudi ○ Non-Saudi	الجنسية: ○ سعودية ○ غير سعودية
3	Age:	العمر:
4	Marital status: ○ Married ○ Single ○ Divorced ○ Widowed	الحالة الاجتماعية: ○ متزوجة ○ عزباء ○ مطلقة ○ أرملة
5	Number of children (if any)	عدد الأبناء (ان وجد):
6	Education level: ○ Diploma/ High-school or less ○ Bachelors ○ Higher degrees	المؤهل العلمي: ○ دبلوم /ثانوي او اقل ○ جامعي ○ دراسات عليا
7	Region: ○ Central ○ Eastern ○ Northern ○ Western ○ Southern	منطقة الإقامة: ○ الوسطى ○ الشرقية ○ الشمالية ○ الغربية ○ الجنوبية
8	Employment status ○ Employed ○ Own business	الحالة الوظيفية: ○ موظفة ○ اعمال حرة

	<input type="radio"/> Non- employed <input type="radio"/> Retired	<input type="radio"/> غير موظفة <input type="radio"/> متقاعدة
9	Income (SR) <input type="radio"/> < 5000 (low) <input type="radio"/> 5000-15,000 (middle) <input type="radio"/> > 15,000 (high)	متوسط الدخل المادي الشهري: <input type="radio"/> اقل من ٥٠٠٠ <input type="radio"/> بين ٥٠٠٠ الي ١٥٠٠٠ <input type="radio"/> أكثر من ١٥٠٠٠
10	Do you have any other diseases (Comorbidities)? <input type="radio"/> Yes <input type="radio"/> No	هل تعاني من أمراض مزمنة: <input type="radio"/> نعم <input type="radio"/> لا
11	If your answer yes to the previous question, mention the disease you have.	اذ كانت اجابتك على السؤال السابق بنعم، اذكر اسم المرض/ الأمراض المزمنة التي تعاني منها .
12	Do you do any kind of sports? <input type="radio"/> Yes <input type="radio"/> No	هل تمارسي أي نوع من أنواع الرياضة؟ <input type="radio"/> نعم <input type="radio"/> لا
13	If your answer yes to the previous question, how many times you sport weekly? <input type="radio"/> Once <input type="radio"/> Twice <input type="radio"/> Three times <input type="radio"/> More than 3 times	إذا كانت اجابتك على السؤال السابق بنعم، كم مرة تقريبا تقومين بممارسة الرياضة؟ <input type="radio"/> مرة في الاسبوع <input type="radio"/> مرتين اسبوعيا <input type="radio"/> ثلاث مرات اسبوعيا <input type="radio"/> أكثر من ثلاث مرات
14	Date of diagnosis:	تاريخ تشخيص الإصابة بسرطان الثدي:
15	Do you have any family members diagnosed with BC? <input type="radio"/> Yes <input type="radio"/> No	هل سبق وتم تشخيص أحد افراد الاسرة بسرطان الثدي: <input type="radio"/> نعم <input type="radio"/> لا
16	Menopausal status: <input type="radio"/> Premenopausal <input type="radio"/> Postmenopausal	حالة الدورة الشهرية: <input type="radio"/> منقطعة <input type="radio"/> مستمرة
17	At which stage you were diagnosed: <input type="radio"/> Stage I <input type="radio"/> Stage II <input type="radio"/> Stage III <input type="radio"/> Stage IV <input type="radio"/> I don't Know	في أي مرحلة تم تشخيص أصابتك بسرطان الثدي: <input type="radio"/> المرحلة الأولى (مبكره) <input type="radio"/> المرحلة الثانية <input type="radio"/> المرحلة الثالثة <input type="radio"/> المرحلة الرابعة (متقدمة) <input type="radio"/> لا أعلم
18	What was the type of treatment you received?	ما هو نوع العلاج المستخدم؟

	<ul style="list-style-type: none"> ○ Surgery ○ Chemotherapy ○ Hormonal therapy ○ Radiation ○ I don't know 	<ul style="list-style-type: none"> ○ الجراحة ○ العلاج الكيميائي ○ العلاج هرموني ○ العلاج الشعاعي ○ لا أعلم
19	<p>After being diagnosed with breast cancer, dose your cancer transferred or metastaised to other organs?</p> <ul style="list-style-type: none"> ○ Yes ○ No ○ Not sure 	<p>بعد أن تم تشخيصك بسرطان الثدي، هل انتقلت الخلايا السرطانية الى اماكن أخرى في الجسم؟</p> <ul style="list-style-type: none"> ○ نعم ○ لا ○ غير متأكدة
20	<p>If your answer was yeas to the previous question, mention the site of metastasis</p> <ul style="list-style-type: none"> ○ Bones ○ Lungs ○ Liver ○ Brain ○ Lymph nodes ○ I don't know 	<p>اذا كانت اجابتك على السؤال السابق بنعم، حددي المكان الذي انتقل اليه المرض</p> <ul style="list-style-type: none"> ○ العظام ○ الرئة ○ الكبد ○ الدماغ ○ الغدد الليمفاوية ○ لا أعلم

Appendix B EQ-5D 3L Questionnaire (Arabic and English versions)



English version for the UK

(Validated for Ireland)

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems in walking about
- I have some problems in walking about
- I am confined to bed

SELF-CARE

- I have no problems with self-care
- I have some problems washing or dressing myself
- I am unable to wash or dress myself

USUAL ACTIVITIES (e.g. work, study, housework, family or leisure activities)

- I have no problems with performing my usual activities
- I have some problems with performing my usual activities
- I am unable to perform my usual activities

PAIN / DISCOMFORT

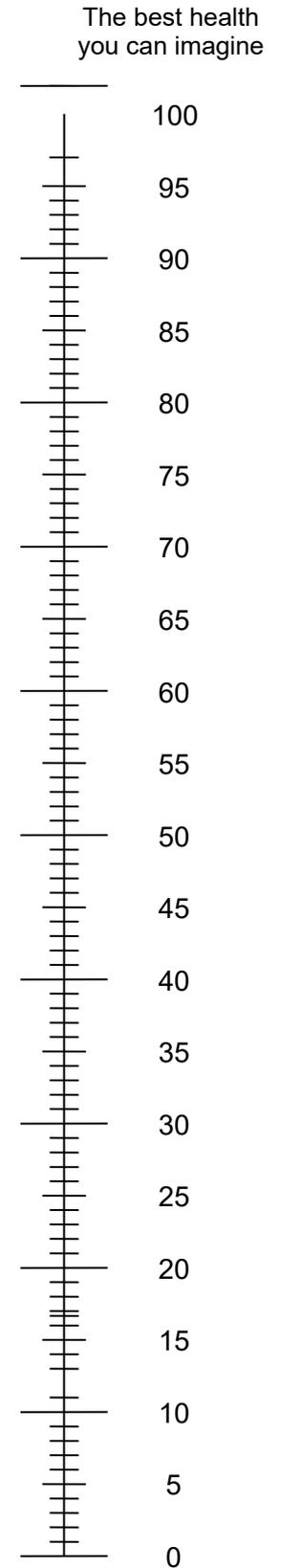
- I have no pain or discomfort
- I have moderate pain or discomfort
- I have extreme pain or discomfort

ANXIETY / DEPRESSION

- I am not anxious or depressed
- I am moderately anxious or depressed
- I am extremely anxious or depressed

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Please mark an X on the scale to indicate how your health is TODAY.
- Now, write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =



إستبيان صحي

النسخة العربية للمملكة العربية السعودية

(Arabic version for Kingdom of Saudi Arabia)

ضع علامة (√) في المربع الخاص بعبارة واحدة في كل مجموعة من المجموعات التالية، لتشير إلى أفضل عبارة تصف حالتك الصحية اليوم.

القدرة على الحركة

- ليس لدي أي مشاكل أثناء المشي
- أعاني بعض المشاكل أثناء المشي
- أنا ألزم السرير

العناية الشخصية

- لا أعاني أي مشاكل في الاعتناء بنفسني
- لدي بعض المشاكل عند الاستحمام أو إرتداء الملابس بمفردي
- ليس لدي القدرة على الاستحمام أو إرتداء الملابس بمفردي

الأنشطة المعتادة (مثل العمل، الدراسة، الأعمال المنزلية، الأنشطة الأسرية أو الترفيهية)

- ليس لدي أي مشاكل في ممارسة نشاطاتي المعتادة
- لدي بعض المشاكل في ممارسة نشاطاتي المعتادة
- ليس لدي القدرة على ممارسة نشاطاتي المعتادة

الإحساس بعدم الراحة / الألم

- لا أشعر بأي ألم أو بعدم الراحة
- أشعر بدرجة متوسطة من الألم أو عدم الراحة
- أشعر بدرجة شديدة من الألم أو عدم الراحة

القلق / الإكتئاب

- لا أعاني أي قلق أو إكتئاب
- أعاني درجة متوسطة من القلق أو الإكتئاب
- أعاني درجة شديدة من القلق أو الإكتئاب

أفضل حالة صحية
يمكن تخيلها



لمساعدة الأشخاص في التعبير عن حالتهم الصحية، قمنا برسم مقياس مدرج (يشبه مقياس الحرارة) بحيث يشير الرقم 100 إلى أفضل حالة صحية يمكن تخيلها والرقم صفر إلى أسوأ حالة صحية يمكن تخيلها.

نود منك أن توضح على هذا المقياس مدى جودة أو سوء صحتك الشخصية اليوم، حسب رأيك.

من فضلك إفعل ذلك برسم خط يبدأ من المربع الموجود بجانب المقياس و ينتهي في النقطة على المقياس التي تعكس مدى جودة أو سوء حالتك الصحية اليوم.

حالتك الصحية اليوم

أسوأ حالة صحية يمكن
تخيلها

Appendix C EORTC QLQ-C30 and BR-23 (English and Arabic versions)



EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

Your birthdate (Day, Month, Year):

Today's date (Day, Month, Year):

31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you have a dry mouth?	1	2	3	4
32.	Did food and drink taste different than usual?	1	2	3	4
33.	Were your eyes painful, irritated or watery?	1	2	3	4
34.	Have you lost any hair?	1	2	3	4
35.	Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36.	Did you feel ill or unwell?	1	2	3	4
37.	Did you have hot flushes?	1	2	3	4
38.	Did you have headaches?	1	2	3	4
39.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40.	Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41.	Did you find it difficult to look at yourself naked?	1	2	3	4
42.	Have you been dissatisfied with your body?	1	2	3	4
43.	Were you worried about your health in the future?	1	2	3	4
During the past <u>four</u> weeks:		Not at All	A Little	Quite a Bit	Very Much
44.	To what extent were you interested in sex?	1	2	3	4
45.	To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46.	Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Did you have any pain in your arm or shoulder?	1	2	3	4
48.	Did you have a swollen arm or hand?	1	2	3	4
49.	Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50.	Have you had any pain in the area of your affected breast?	1	2	3	4
51.	Was the area of your affected breast swollen?	1	2	3	4
52.	Was the area of your affected breast oversensitive?	1	2	3	4
53.	Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4



نحن مهتمون بمعرفة بعض المعلومات عنك وعن صحتك. الرجاء الإجابة بنفسك عن كل من الأسئلة التالية وذلك بوضع دائرة حول الإجابة الأكثر ملائمة لك. لا يوجد جواب "صحيح" أو "خطأ". جميع المعلومات ستعامل بسرية تامة.

ادخل الحروف الأول من اسمك: □□□□□□

(تاريخ ميلادك (اليوم، الشهر، السنة): □□□□□□□□

تاريخ اليوم (اليوم، الشهر، السنة): □□□□□□□□□□3h

إطلاقاً	قليلاً	بما فيه الكفلية	كثيراً جداً
1	2	3	4
هل لديك صعوبة في بذل مجهود جسدي شاق (متعب) مثل حمل كيس مشتريات ثقيل أو حقيبة؟			
1	2	3	4
هل لديك صعوبة بالمشي لمسافة <u>طويلة</u> ؟			
1	2	3	4
هل لديك صعوبة بالمشي لمسافة <u>قصيرة</u> خارج البيت؟			
1	2	3	4
هل تحتاج للبقاء في السرير أو الكرسي خلال اليوم؟			
1	2	3	4
هل تحتاج للمساعدة في الأكل أو ارتداء الملابس أو الاغتسال أو استخدام المراحيض؟			
خلال الأسبوع الماضي:			
1	2	3	4
هل كنت محدوداً/ مقيداً عند القيام بعملك أو نشاطات يومية أخرى؟			
1	2	3	4
هل كنت محدوداً/ مقيداً في ممارسة هواياتك أو نشاطات في أوقات الفراغ؟			
1	2	3	4
هل شعرت بضيق بالنفس؟			
1	2	3	4
هل شعرت بألم؟			
1	2	3	4
هل كنت بحاجة للراحة؟			
1	2	3	4
هل عانيت من مشاكل في النوم (أرق/ صعوبة في النوم/ نوم متقطع)؟			
1	2	3	4
هل شعرت بالضعف؟			
1	2	3	4
هل فقدت شهيتك للطعام (القدرة على الأكل)؟			
1	2	3	4
هل شعرت بالغثان (العيان)؟			
1	2	3	4
هل تقيأت؟			
1	2	3	4
هل عانيت من إمساك؟			

انتقل إلى الصفحة التالية من فضلك

كثيرا جدا	بما فيه الكفلية	قليلا	إطلاقا	خلال الأسبوع الماضي:
4	3	2	1	17. هل كان لديك إسهال؟
4	3	2	1	18. هل كنت متعبا؟
4	3	2	1	19. هل عانيت من ألم أتر سلبيا على نشاطاتك اليومية؟
4	3	2	1	21. هل كان لديك صعوبة بالتركيز في بعض الأمور مثل قراءة الجريدة أو مشاهدة التلفاز؟
4	3	2	1	21. هل شعرت بالتوتر؟
4	3	2	1	22. هل شعرت بالقلق؟
4	3	2	1	23. هل شعرت بالانزعاج؟
4	3	2	1	24. هل شعرت بكتئاب؟
4	3	2	1	25. هل كانت لديك صعوبة بتذكر الأشياء؟
4	3	2	1	26. هل حالتك الجسدية أو علاجك الطبي أتر سلبيا على حياتك <u>العائلية</u> ؟
4	3	2	1	27. هل حالتك الجسدية أو علاجك الطبي أتر سلبيا على حياتك <u>الاجتماعية</u> ؟
4	3	2	1	28. هل حالتك الجسدية أو علاجك الطبي أديا إلى مشاكل مالية؟

في الأسئلة التالية الرجاء الإشارة بدائرة حول الأرقام الأكثر ملائمة لك بين ١-٧

29. كيف تقيم صحتك عموما خلال الأسبوع الماضي؟

7	6	5	4	3	2	1
ممتاز						سيء جدا

31. كيف تقيم جودة حياتك عموما/ مستوى حياتك عموما خلال الأسبوع الماضي؟

7	6	5	4	3	2	1
ممتاز						سيء جدا

يلتزم المريضات بعض الاحيان باصابتهم/هن بالاعراض أو المشاكل التالية، يرجى الإشارة الى الدرجة التي عانيت/ي فيها من مثل هذه الاعراض او المشاكل خلال الاسبوع الماضي:

				خلال الأسبوع الماضي:	
كثيرا جدا	بعض الشيء	قليلا	أبدا		
4	3	2	1	هل شعرت بجفاف في الفم؟	31.
4	3	2	1	هل اختلف مذاق الأكل أو الشرب عن الطعم الاعتيادي؟	32.
4	3	2	1	هل شعرت بألم أو التهاب في العينين أو هل كانتا دامعتين؟	33.
4	3	2	1	هل تساقط شعرك؟	34.
				اجب/أجيبني على هذا السؤال فقط إذا كنت تعاني/تعانين من تساقط الشعر:	35.
4	3	2	1	هل كنت منزعج / منزعجة بسبب تساقط شعرك؟	
4	3	2	1	هل كنت مريض/ة أو متوعدة/ة الصحة؟	36.
4	3	2	1	هل شعرت باحمرار أو تورد الوجه؟	37.
4	3	2	1	هل شعرت بالصداع؟	38.
				هل شعرت انك اقل جاذبية (اقل مرغوبة/ لست مرغوبة	39.
4	3	2	1	جنسياً) بسبب مرضك أو علاجك؟	
4	3	2	1	هل كنت تشعر/ين انك اقل أنوثة/رجولة بسبب مرضك أو علاجك؟	40.
4	3	2	1	هل كانت لك صعوبة عند النظر إلى نفسك عاري/ة؟	41.
4	3	2	1	هل كنت غير راضي/ة عن جسدي؟	42.
4	3	2	1	هل كنت قلق/ة بخصوص صحتك في المستقبل؟	43.
				خلال الأسابيع الأربعة الماضية:	
كثيرا جدا	بعض الشيء	قليلا	أبدا		
4	3	2	1	إلى إي درجة كانت عندك رغبة بالجماع؟	44.
4	3	2	1	إلى إي درجة كنت نشيط/ة جنسيا (بجماع أو بدونه)؟	45.
4	3	2	1	أجب/أجيبني على هذا السؤال فقط إذا كنت نشيط/ة جنسيا:	46.
4	3	2	1	إلى إي درجة كان الجماع ممتعا بالنسبة لك؟	

انتقل إلى الصفحة التالية من فضلك

				خلال الأسبوع الماضي:	
كثيرا جدا	بعض الشيء	قليلا	أبدا		
4	3	2	1	.47	هل شعرت بأي ألم في الذراع أو في الكتف؟
4	3	2	1	.48	هل عانيت من تورم في اليد أو الذراع؟
4	3	2	1	.49	هل كان صعبا عليك رفع ذراعك أو تحريكه جانبيا؟
4	3	2	1	.50	هل كنت تشعر/ين بالألم في منطقة ثديك المصاب؟
4	3	2	1	.51	هل كانت منطقة ثديك المصاب متورمة؟
4	3	2	1	.52	هل كانت منطقة ثديك المصاب شديدة الحساسية؟
				.53	هل عانيت من مشاكل البشرة حول منطقة صدرك المصاب
4	3	2	1		أو فيها (مثلا الحكّة، الجفاف، التقشر)؟

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