SURVIVAL OUTCOMES AND PROGNOSTIC FACTORS OF MORTALITY FOR FEMALE BREAST CANCER PATIENTS IN MALAYSIA FROM 2015 TO 2019

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by

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"Whoever does not thank people has not thanked Allah."

(Sunan Abi Dawood, 4811)

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LIST OF SYMBOLS

α	Alpha
=	Equal to
≤	Equal or less than
≥	Equal or more thab
<	Less than
>	More than
n	Number of subjects
%	Percentage
P	Population's proportion
m	Ratio between two groups
b	Regression coefficient
Z	Z-score

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LIST OF ABBREVIATIONS

aHR	Adjusted Hazard Ratio
ASIR	Age-standardized Incidence Rate
ASMR	Age-standardized Mortality Rate
CI	Confidence Interval
CONCORD-3	Global surveillance of trends in cancer survival 2000-2014
df	Degree of freedom
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
GLOBOCAN	Global Cancer Observatory
HR	Hazard Ratio
IARC	International Agency for Research on Cancer
JEPem	Jawatankuasa Etika Penyelidikan Manusia
ICD-O-3	International Classification of Diseases for Oncology (3rd edition)
IQR	Inter-quartile Range
LR	Likelihood Ratio
MNCR	Malaysia National Cancer Registry
MOH	Ministry of Health
MREC	Medical Research Ethics Committee
MST	Median Survival Time
MySCAN	Malaysian Study on Cancer Survival
NCI	National Cancer Institute
NCR	National Cancer Registry
NIH	National Institute of Health
NSPCCP	National Strategic Plan for Cancer Control Program
OS	Observed Survival
SD	Standard Deviation
SEER Program	Surveillance, Epidemiology, and End Results Program
SRR	Standardized Rate Ratio
USM	Universiti Sains Malaysia
WHO	World Health Organization
WP	Wilayah Persekutuan

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ABSTRAK

KADAR KELANGSUNGAN HIDUP DAN FAKTOR PROGNOSTIK KEMATIAN DALAM~~I~~ KALANGAN PESAKIT KANSER PAYUDARA WANITA

DI MALAYSIA DARI TAHUN 2015 HINGGA 2019

Latar Belakang: Kanser payudara kekal sebagai kanser utama dalam~~I~~ kalangan wanita di Malaysia, dengan ~~jurang~~ kadar kelangsungan hidup dipengaruhi oleh faktor sosiodemografi dan klinikal.~~yang membimbangkan merentas kumpulan umur, etnik dan wilayah geografi.~~ Walaupun ~~terdapat kemajuan dalam~~ strategi pengesanan dan rawatan ~~penyakit ini~~telah berkembang, data ~~peringkat~~ kebangsaan mengenai~~ mengenai~~ kadar kelangsungan hidup dan faktor peramal~~rognostik~~ kematian masih terhad untuk menilai keberkesanan program tersebut.~~, sekali gus menyukarkan penilaian terhadap keberkesanan program saringan, diagnosis dan intervensi rawatan sedia ada.~~

Objektif: Kajian ini bertujuan untuk menganggarkan kadar kelangsungan hidup serta mengenal pasti faktor prognostik kematian dalam kalangan pesakit kanser payudara wanita di Malaysia dari tahun 2015 hingga 2019~~, menggunakan data registri kanser kebangsaan~~.

Metodologi: S~~u~~atu kajian kohort retrospektif telah dijalankan menggunakan data dari Registri Kanser Kebangsaan Malaysia. Data pesakit wanita yang didiagnosis sebagai kanser payudara dari tahun 2015 hingga 2019~~ melibatkan pesakit kanser payudara wanita yang didiagnosis antara 1 Januari 2015 hingga 31 Disember 2019. Pesakit telah~~ diikuti selama lima tahun~~ sehingga tarikh penutupan kajian pada 31 Disember 2024~~.

Kadar kelangsungan hidup dianggarkan menggunakan kaedah ~~Tempoh kelangsungan hidup dikira daripada tarikh diagnosis hingga tarikh kematian atau tarikh akhir kajian. Kaedah~~ Kaplan-Meier ~~digunakan untuk menganggarkan kadar kelangsungan hidup~~, manakala faktor prognostik dinilai dengan ~~-~~regresi hazard berkadar Cox. ~~proportional hazards digunakan untuk mengenal pasti faktor prognostik.~~

Keputusan: Sebanyak 26,867 kes kanser payudara wanita ~~telah~~ dianalisis. ~~dan k~~ Kadar kelangsungan hidup lima tahun adalah sebanyak 57.5% (95% CI: 57.2, 57.8) dengan empat faktor prognostik kematian dikenalpasti. ~~Median kelangsungan hidup keseluruhan tidak dapat dianggarkan kerana lengkung kelangsungan hidup tidak menurun di bawah ambang 50%. Empat faktor prognostik telah dikenal pasti.~~ Wanita berumur 50 tahun ke atas mempunyai risiko kematian ~~yang~~ lebih tinggi ~~secara signifikan~~ berbanding wanita yang lebih muda (nisbah hazard terlaras [aHR]: 1.24; 95% CI: 1.19, ~~–~~1.29; p<0.001). ~~Etnik turut menjadi faktor signifikan, dengan w~~Wanita Cina (aHR: 0.78; 95% CI: 0.75, ~~–~~0.81; p<0.001) dan India (aHR: 0.85; 95% CI: 0.80, ~~–~~0.91; p<0.001) pula menunjukkan risiko kematian yang lebih rendah berbanding wanita ~~wanita~~ Melayu. Tahap kanser semasa diagnosis merupakan peramal hasil kelangsungan hidup yang penting di dalam kajian ini, dengan risiko kematian meningkat dengan ketara dari ~~yang jauh lebih tinggi untuk~~ tahap ~~2~~II (aHR: 1.87; 95% CI: 1.66, ~~–~~2.10; p<0.001), tahap ~~3~~III (aHR: 4.13; 95% CI: 3.69, ~~–~~4.62; p<0.001), dan tahap IV~~4~~ (aHR: 11.03; 95% CI: 9.88, ~~–~~12.32; p<0.001) berbanding tahap I~~1~~. Morfologi tumor juga mempengaruhi kelangsungan hidup., ~~dengan karsinoma lobular (aHR: 0.93; 95% CI: 0.84–1.03; p=0.182) dan karsinoma mukinus (aHR: 0.69; 95% CI: 0.58–0.82; p<0.001) menunjukkan kesan perlindungan terhadap kematian, manakala tumor phyllodes malignan (aHR: 1.15; 95% CI: 0.94–1.41; p=0.180)~~

~~dikaitkan dengan risiko kematian yang lebih tinggi berbanding karsinoma duktus invasif.~~

Kesimpulan: ~~Hasil dapatan dari kajian~~Kajian kebangsaan ini menyediakan ~~anggaran~~ bukti terkini ~~yang berasaskan populasi berkenaan~~mengenai kadar kelangsungan hidup pesakit kanser payudara wanita di Malaysia~~,~~ serta ~~mendedahkan~~ faktor prognostik kematian utamanya ~~iaitu umur, etnik, tahap diagnosis dan morfologi tumor~~. P~~Penekanan harus diberikan kepada p~~engukuhan ~~strategi~~ pengesanan awal, ~~peningkatan~~ akses ~~kepada~~ rawatan yang saksama, serta penyepaduan data ~~pendaftaran kanser~~registri dengan maklumat klinikal a~~dalah penting bagi meningkatkan kadar kelangsungan hidup.~~~~dan rawatan bagi menyokong intervensi yang lebih tersasar dan berkesan.~~

Kata Kunci: kanser payudara, kadar kelangsungan hidup, faktor prognostik~~, nisbah hazard~~, registri kanser kebangsaan, Malaysia.

ABSTRACT

SURVIVAL OUTCOMES AND PROGNOSTIC FACTORS OF MORTALITY FOR FEMALE BREAST CANCER PATIENTS IN MALAYSIA FROM 2015 TO 2019

Background: Breast cancer remains the leading cancer among women in Malaysia, with ~~concerning~~ survival ~~disparities across age groups, ethnicities, and geographic regions~~influenced by sociodemographic and clinical factors.~~.~~ Despite advances~~progress~~ in ~~the~~ detection and treatment~~s of the disease~~, national ~~-~~level data on survival outcomes and mortality predictors remain limited~~, making it more challenging to evaluate the effectiveness of current screening program, diagnostic and treatment interventions~~ for evaluating program effectiveness.

Objective: This study aimed to ~~aimed to~~ estimate survival outcomes and identify~~fy~~ prognostic factors of mortality among female breast cancer patients in Malaysia from 2015 to 2019 ~~using population-based registry data~~.

Methodology: A retrospective cohort study was conducted using data from the Malaysian National Cancer Registry. ~~of f~~Data for female patients diagnosed with breast cancer ~~diagnosed~~ from ~~between 1st January~~ 2015 to ~~and 31st December~~ 2019 were followed ~~. Patients were followed~~ for ~~-~~ five years. Survival was estimated using ~~until the study closure date of 31st December 2024. Survival time was calculated from the date of diagnosis to the date of death or censoring.~~ Kaplan-Meier method, and prognostic factors were assessed with ~~was used to estimate survival outcomes, while~~ Cox proportional hazards regression. ~~was used to identify prognostic factors.~~

Result: A total of 26,867 eligible cases were analysed. ~~and t~~The ~~five-year~~5-year survival rate was 57.5% (95% CI: 57.2-57.8) with four ~~. The overall median survival time could not be estimated as the survival curve did not fall below the 50% threshold. Four independent~~ prognostic factors were identified. Women aged ≥50 years ~~and above~~ had a ~~significantly~~ higher mortality risk ~~of mortality compared to~~ than younger women (adjusted hazard ratio [aHR]: 1.24; 95% CI: 1.19–1.29; p<0.001). Ethnicity was ~~also a~~ significant ~~factor~~, with Chinese (aHR: 0.78; 95% CI: 0.75–0.81; p<0.001) and Indian (aHR: 0.85; 95% CI: 0.80–0.91; p<0.001) women showing lower risks of mortality ~~compared to~~than Malays ~~women~~. Stage at diagnosis was the~~a~~ important prognostic factors in this analysis~~predictor of outcome~~, with mortality risk increasing substantially~~markedly~~ for~~higher risks of mortality for~~ ~~stage 2~~stage II (aHR: 1.87; 95%CI: 1.66, 2.10; p<0.001), ~~stage 3~~stage III (aHR: 4.13; 95% CI: 3.69, 4.62); p<0.001), and ~~stage 4~~stage IV (aHR: 11.03; 95% CI: 9.88, 12.32; p<0.001) compared with~~to~~ ~~stage 1~~stage I. Tumor morphology was also associated with variation in ~~d~~survival outcomes.~~, with lobular carcinoma (aHR: 0.93; 95% CI; 0.84, 1.03; p = 0.182) and mucinous carcinoma (aHR: 0.69; 95% CI: 0.58; 0.47, 0.70; p<0.001) associated with protective effect from mortality, while malignant phyllodes tumors (aHR: 1.15; 95% CI: 0.94, 1.41; p = 0.180) were associated with higher risks of mortality compared to infiltrating ductal carcinoma.~~

Conclusion: This nationwide study~~ese findings~~ provides updated ~~population based~~ evidence on breast cancer survival in Malaysia and its key prognostic factors~~, revealing key prognostic disparities driven by age, ethnicity, stage at diagnosis and tumor morphology~~. Strengthening early detection ~~strategies~~, ~~improving access to~~ equitable

access to treatment~~care~~, and ~~-~~registry~~-enhance cancer registry integration with~~ clinical ~~and treatment~~ data integration are essential to enhance outcomes.~~support targeted and effective interventions.~~

Keyword: breast cancer, ~~observed~~ survival rate, prognostic factor~~, hazard ratio~~, population-based registry, Malaysia.

CHAPTER 1

INTRODUCTION

1.1 Background

1.1.1 Breast Cancer Burden

Breast cancer remains the most commonly diagnosed cancer among women worldwide and a leading cause of cancer-related mortality (Ferlay J, 2024). The global burden of breast cancer continues to rise, with significant implications for public health, healthcare resources, and patient outcomes (WHO, 2024). Although advancements in early detection and treatment have improved survival rates in many regions, outcomes still vary widely due to a range of clinical, demographic, and socio-economic differences (Arnold *et al.*, 2022).

In 2022, there were 2.3 million women diagnosed with breast cancer and 670, 000 deaths were reported globally (Ferlay J, 2024; WHO, 2024). These estimates reveal striking inequities in breast cancer burden between high- and low -human development index (HDI) countries. Developed countries like North America, Western Europe, Australia, and Canada generally reported higher incidences of breast cancer with lower mortality rates. In contrast, developing countries like sub-Saharan Africa, the Middle East, and South America, experience a growing burden of breast cancer with persistently higher mortality rates despite lower incidence.

As reflected in global patterns (Figure 1.1), Malaysia exhibits a moderate incidence but relatively high mortality rate for female breast cancer, consistent with trends in many low- and middle -income countries. According to the GLOBOCAN 2022 estimates, Malaysia had an age-standardized incidence rate (ASIR) of 46.1 per 100,000 women, and an age-standardized mortality rate (ASMR) of 19.3 per 100,000

women. These figures contrast sharply with countries like the United States (ASIR: 95.9 per 100,000; ASMR: 12.2 per 100,000) and Australia (ASIR: 101.5 per 100,000; ASMR: 12.3 per 100,000), where advanced health systems contribute to early -stage detection and better survival rates (Figure 1.2) (IARC, 2022).

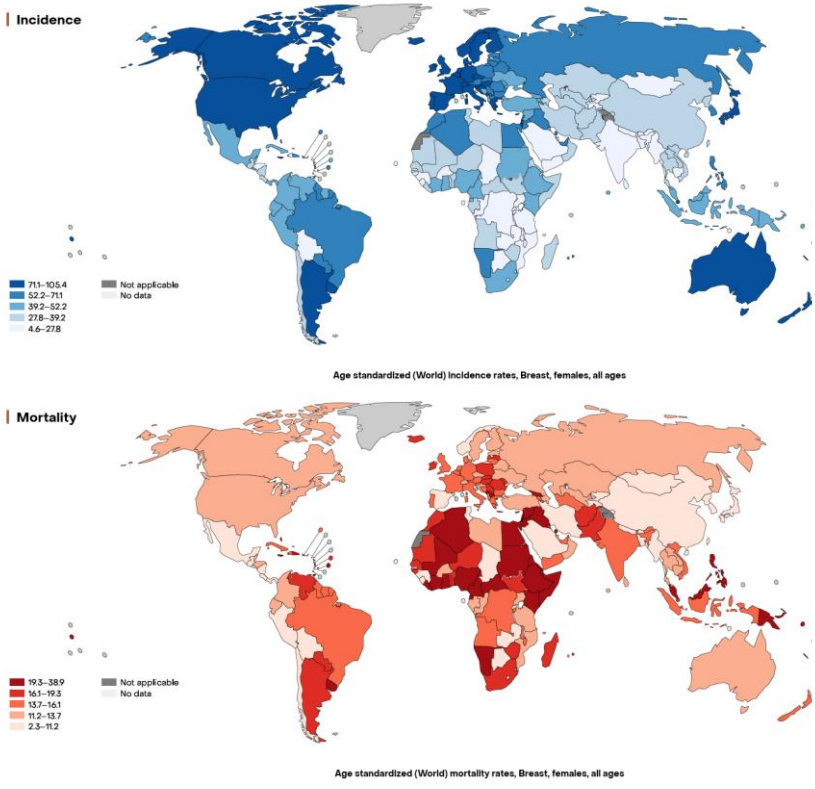

Figure 1.1: Global Maps Presenting the Age-Standardized Incidence Rates (above) and Age-Standardized Mortality Rates (below) among Female Breast Cancer in 2022 (IARC, 2022).

In comparison to the neighbouring countries, Malaysia ranks among the countries with the highest reported breast cancer incidence rates, higher than neighbouring countries like Vietnam (38.0 per 100,000) and Thailand (37.4 per 100,000), and comparable to Indonesia (41.8 per 100,00). However, Malaysia's ASMR remains concerning, particularly when compared to countries with more developed healthcare systems such as Singapore (17.8 per 100,00) and Brunei (14.3 per 100,000) (Figure 1.3) (IARC, 2022). This disparity suggests ongoing challenges in timely diagnosis, access to multidisciplinary care, and public awareness. The relatively high mortality-to-incidence ratio (MIR) in Malaysia further reflects persistent barriers in early detection and equitable healthcare delivery.

Based on the local report by Malaysia National Cancer Registry (MNCR) 2017 to —2021, breast cancer remains the most common cancers among Malaysian women with increased trend of ASIR from 34.1 per 100,000 between 2012 and 2016 (MNCR, 2019) to 38.9 per 100,000 between 2017 and 2021 (Figure 1.4) (MNCR, 2022). However, these reports mainly focus on incidence rates rather than cancer -specific mortality rates. Much of the available information relies on modelled estimates, such as those provided by GLOBOCAN, which may not fully capture the local context.

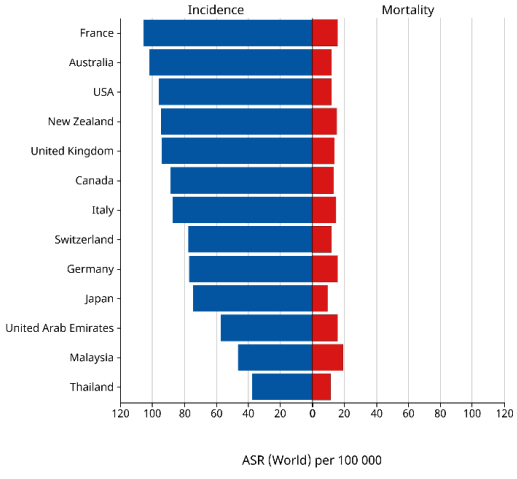

Figure 1.2: Age-Standardized Incidence Rates and Age-Standardized Mortality Rates Comparison for Female Breast Cancer among High Development Index Countries with Malaysia in 2022 (IARC, 2022)

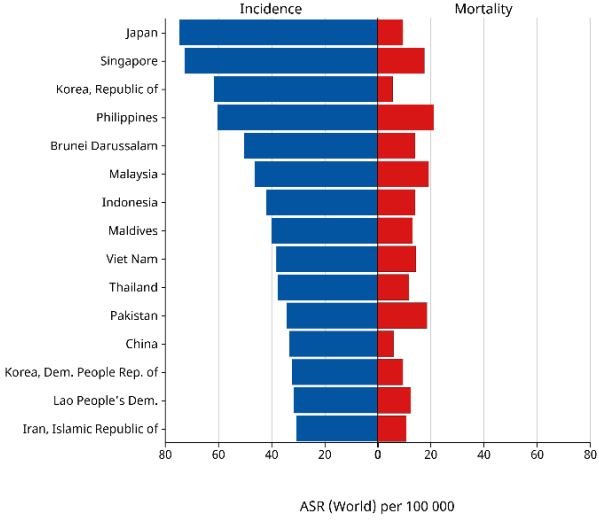

Figure 1.3: Age-Standardized Incidence Rates and Age-Standardized Mortality Rates Comparison for Female Breast Cancer among South-East Asia with Malaysia in 2022 (IARC, 2022)

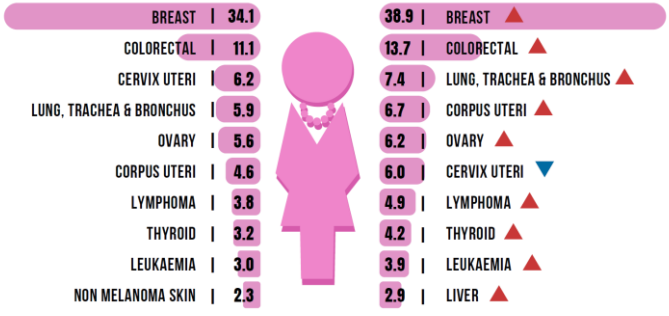

Figure 1.4: Age-Standardized Incidence Rates for 10 Most Common Cancers among Females in Malaysia between 2012 – 2016 (Left) and 2017 to– 2021 (Right) (MNCR, 2022)

1.1.2 Breast Cancer Survival

Although the burden of breast cancer is well recognized, national_-level data on mortality and survival outcomes in Malaysia are still limited. Existing mortality data is derived from model_-based estimates, while population_-based survival studies remain scarce. Most available research focuses on hospital_-based, institutional-based, or regional-based survival data, which may not be representative of the broader Malaysian population.

The most recent nationwide survival data, published in the Malaysian Study on Cancer Survival (MySCan) report, estimated a ~~5-year~~5-year relative survival rate of 66.8% among breast cancer patients diagnosed from 2007 to 2011. The survival rate (Figure 1.5) was lower than in other developed countries such as Japan, Australia, and neighbouring Singapore (MNCR, 2018) but was markedly increased compared to the overall 5-year cancer survival rate for female breast cancer patients in 2000 and 2005 (49.4%) (Abdullah NA, 2013). However, these data may no longer reflect current trends in diagnosis and treatment, given changes in healthcare delivery and awareness programs over the past decades.

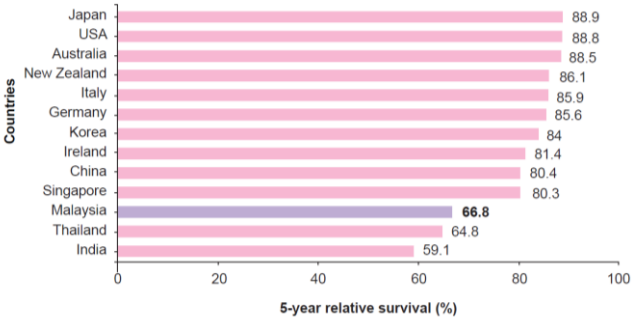

Figure 1.5: International Comparison of 5-year Relative Survival for Female Breast Cancer (NCR NCI MOH Malaysia, 2018)

Given the increasing incidence of breast cancer and persistent concerns over late-stage diagnosis and disparities in access to care, it is critical to generate updated survival data to guide public health strategies and clinical decision-making. One of the key contributors to poor outcomes is delay or absence of early cancer detection, particularly in settings where organized screening programs are limited or underutilized. Early detection through screening methods such as clinical breast examination, mammography, and imaging plays a pivotal role in identifying cancers at an earlier, more treatable stage, thereby improving diagnosis, and reducing mortality.

Numerous studies have explored survival rates and the various prognostic factors influencing mortality in breast cancer patients, such as age, ethnicity, stage of diagnosis, tumor size, hormonal receptor status, lymph node involvement and type of treatment (Maajani *et al.*, 2019). Many of these prognostic factors are strongly influenced by how early the cancer is detected. For example, patients whose cancers are identified through screening programs are more likely to be diagnosed at an earlier stage with smaller tumors and no lymph node involvement, which are the factors consistently associated with better prognosis. However, despite these clinical

understanding, variability in outcomes persists due to differences in patient demographics, geographical access to diagnostic services, availability of screening programs, and overall health system responsiveness to early cancer detection.

1.2 Problem Statement

Breast cancer remains the most common cancer among women in Malaysia, accounting for nearly one in three female cancer diagnoses and one of the leading causes of cancer-related mortality (Arnold *et al.*, 2022). Despite significant advancement in clinical technology and ongoing efforts to improve cancer care, ~~many women in Malaysia continue to be diagnosed with breast cancer at advanced age~~survival in Malaysia remains lower compared with neighbouring and other high-income countries (MNCR, 2018). Within Malaysia, survival differences have been observed across ethnicities, with variations reported among Malay, Chinese, and Indian women, as well as between regions, particularly in rural and underserved area, where access to timely diagnosis and treatment may differ (Bhoo-Pathy *et al.*, 2012b; MNCR, 2018; Nordin *et al.*, 2018; Nizuwan Azman, 2019; Winnie Ong, 2021; Lim *et al.*, 2025a). Most existing studies are hospital-based, confined to specific states, or based on earlier cohorts, limiting their applicability to the current national population.

For policymakers, accurate and updated information on breast cancer survival is essential to guide resources allocation, prioritize regions or groups in need of enhanced healthcare interventions, and design targeted public awareness campaigns to address gaps in early detection and preventive care. ~~This delayed diagnosis is not just a clinical issue but reflects broader, systemic challenges in healthcare access. These disparities are particularly evident in underserved regions and among populations with limited healthcare access, where screening programs and diagnostics services may be~~

~~inadequate or inaccessible (Winnie Ong, 2021). The impact of such delays is overwhelming, as it not only reduces the chances of successful treatment but also contributes to increased healthcare costs, longer treatment durations, and lower overall survival rates.~~

~~For policymakers, having accurate and up-to-date information on how women are surviving breast cancer is essential for shaping effective public health policies. Such data provides the evidence necessary to guide decision-making on resource allocation, prioritize regions or groups in need of enhanced healthcare interventions, and design targeted public awareness campaigns to address gaps in early detection and preventive care. However, the existing data on breast cancer survival trends is limited and often outdated, especially at the national level (Bhoo Pathy *et al.*, 2011).~~

~~While survival predictions based on individual patient characteristics, such as age, comorbidities, and tumor-specific factors, are critical in clinical settings to guide treatment decisions (Moons *et al.*, 2009), they only provide a partial understanding of breast cancer outcomes. These individual-level models are invaluable in tailoring personalized treatment approaches, but they do not capture the broader trends and systemic factors that impact survival at population level. Moreover, there is a lack of recent, nationally representative studies that examine survival trends and the factors influencing these outcomes in Malaysia.~~

The absence of comprehensive, up-to-date ~~data~~, population-based data on breast cancer survival presents a significant challenge in evaluating how well current cancer control efforts are working and where improvements are most needed to ~~. This gap limits the ability to develop targeted, evidence-based interventions that can~~ improve survival outcomes for women across Malaysia.

1.3 Rationale of the Study

This study provides timely evidence to addresses the critical gap in population-based breast cancer survival data in Malaysia. the existing literature by providing up-to-date, population-based survival estimates for female breast cancer patients in Malaysia using national registry data. By analysing examining the key prognostic factors and survival trends and key prognostic factors using the national cancer registry data, across diverse demographic groups, the study offers updated survival estimates and valuable insights into disparities in breast cancer outcomes on mortality determinants relevant to local populations. The findings will help support more informed, evidence-based decisions, and enabling policymakers to monitor progress of the National Strategic Plan for Cancer Control Programme (NSPCCP) 2021-2025, particularly its goals on early detection, timely diagnosis, and equitable access to treatment. Furthermore, the results can inform resource allocation, guide public health interventions, and support the integration of cancer registry data with clinical information for precision cancer care in Malaysia. strengthen cancer prevention strategies, improve healthcare resource allocation, enhance early detection efforts and ultimately, save more lives.

Analysing survival outcomes and identifying key influencing factors will be essential in shaping effective public health interventions. Additionally, the findings will provide a valuable baseline for future cohort comparisons, enabling longitudinal assessments of cancer care improvements in Malaysia over time. This study aims to contribute to a deeper understanding of survival dynamics within Malaysia's diverse population, providing a solid foundation for future policy initiatives and cancer control strategies that can improve outcomes for all women across the country.

As an observational study using secondary data, this research presents minimal risk to the patients, as it does not require direct patient engagement. This approach

~~allows for the identification of critical areas of concern without the emotional burden often associated with direct interaction with patients. By using readily available data, researchers can focus on deriving meaningful insights while minimizing potential emotional and social impacts on breast cancer patients and the wider community~~In addition, this study provides a valuable baseline for future cohort comparisons, allowing longitudinal assessments of improvements in cancer care over time. By enhancing understanding of survival dynamics across Malaysia's diverse population, the research contributes to the development of targeted strategies and policies aimed at improving outcomes for women nationwide.

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1.4 Research Questions

1. What are the survival outcomes for female breast cancer patients in Malaysia from 2015 to 2019?
2. What are the prognostic factors of mortality among female breast cancer patients in Malaysia from 2015 to 2019?

1.5 Objectives

1.5.1 General Objective

To study the survival outcomes and prognostics factors of mortality for female breast cancer patients in Malaysia from 2015 to 2019 using national cancer registry data.

1.5.2 Specific Objectives

1. To determine survival outcomes for female breast cancer patients in Malaysia from 2015 to 2019.
2. To identify prognostic factors of mortality among female breast cancer patients in Malaysia from 2015 to 2019.

1.6 Research Hypothesis

Demographic and clinical -related prognostic factors are associated with the hazard of mortality among female breast cancer patients in Malaysia from 2015 to 2019.

CHAPTER 2

LITERATURE REVIEW

2.1 Breast Cancer Survival

2.1.1 Global Perspectives of Breast Cancer Survival

The survival rate for breast cancer is quite different all over the world. The ~~5-year~~5-year survival rate varies from 80% or more in developed countries to 60% in middle-income countries and less than 40% in low-income countries with the pooled ~~five-year~~5-year survival rates of 0.73 (95% CI 0.71, 0.75) as found in the meta-analysis of 130 studies published between 1978 and 2016 (Maajani *et al.*, 2019). While this provides a useful benchmark, the wide range in time period and heterogeneity of settings limit the specificity of this figure to present-day contexts or individual countries. The American Cancer Society in 2015 also reported similar findings in which wide disparities seen in ~~five-year~~5-year survival rate where developed countries such as the United States, Canada, Australia, Brazil and many Northens and Western Europe has 85% or higher survival rates while many developing countries such as South Africa, Mongolia, Algeria and India has 60% or lower survival rates (American Cancer Society, 2015). These differences highlight significant inequities potentially linked to healthcare systems, level of awareness, access, and early detection to cancer care.

More recent global data reflect both progress but persistent disparities. According to GLOBOCAN 2022 and the CONCORD-3 study, ~~five-year~~5-year survival for breast cancer has exceeded 85 to 90% in high-income countries driven by early detection programs, widespread access to treatment and advanced therapeutic options. Conversely, lower- and middle-income countries continue to report significantly lower survival rates, often below 60% largely due to delayed diagnosis, limited treatment infrastructure, and financial barriers to care (Allemani *et al.*, 2018; IARC, 2022). These

more recent survival patterns emphasize that economic development, health system capacity, and public health investment are key determinants of breast cancer outcomes worldwide. As such, understanding country -specific survival trends and the factors influencing them is crucial for designing effective cancer control strategies, particularly in middle-income settings like Malaysia.

Within Asia region, Malaysia's ~~five year~~5-year relative survival for breast cancer patients diagnosed between 2007 and 2011 was 66.8% (95% CI 66.0, 67.6), which is comparable to the neighbouring country, Thailand (68.7%, 95% CI: 66.6, 70.8) but lower than Singapore (80.3%, 95% CI: 78.4, 82.2), South Korea (86.6% , 95% CI: 85.8, 87.5) and Japan (89.9% , 95% CI: 88.9, 89.9) (Allemani *et al.*, 2018; MNCR, 2018). Such variations within the same continent are attributed to distinct socioeconomic levels between middle- and high -income countries, which affect early detection and optimal access to medical care (Ji *et al.*, 2020). However, comparing regions, might overlook important differences within countries especially in diverse, multi-ethnic nations like Malaysia.

2.1.2 Burden and Trends of Breast Cancer Survival in Malaysia

Several studies have observed a rising trend in survival rates among female breast cancer patients in Malaysia over time. A study by Abdullah et.al 2013, found that the observed survival among female breast cancer patients diagnosed between 2000 and 2005 was 49.4% with median survival time 68.1 months (Abdullah NA, 2013). The observed survival increased to 61.9% (95% CI: 61.1, 62.6) for patient diagnosed between 2007 to 2011 and 60.5% (95% CI: 57.6, 63.6) for those diagnosed between 2012 and 2016 (Nik Ab Kadir *et al.*, 2022). This improvement in overall survival is consistent with the international findings. However, while this trend is encouraging,

inconsistencies in survival estimates and overlapping confidence intervals may suggest plateauing progress or limitation in registry data quality.

Several hospital-based studies in Malaysia, particularly those studies that were limited to one centre analysis, have consistently reported relatively high survival rates. Azman *et al.* (2019) found an 89% five~~5~~-year survival rate in a tertiary oncology centre in Pulau Pinang, while a private centre in Subang Jaya which deliver cancer care services, reported overall ~~five-year~~5-year relative survival of 88% (Abdullah *et al.*, 2015). While these findings were promising, they were primarily based on selected populations in urban centres that cannot provide generalizability.

The most recent local hospital-based analysis reported an increase in ~~five-year~~5-year observed survival rates among Malaysian women with breast cancer, rising from 73.0% (95% CI: 71.0, 75.0) in 2005 to– 2009 cohort to 75.0% (95% CI: 73.2, 76.8) in 2010 to– 2014 cohort, and 78.9% (95% CI: 77.3, 80.5) in 2015 to– 2019 cohort (Jaya-Prakason *et al.*, 2024). This upward trend reflects improvements in early detection and access to advanced systemic therapies. However, as the study was conducted across three tertiary referral hospitals in Klang Valley, the findings may not be generalizable to the broader population, especially in rural or under-resourced regions, and raise concerns about difference outcomes across different healthcare settings.

2.2 Prognostic Factors of Mortality

Breast cancer prognosis is influenced by a range of well-established factors that have been extensively documented in the global literature. These prognostic factors can be broadly categorized into demographic characteristics (such as age at diagnosis, ethnicity and socio-economic status), tumor_~~-~~specific attributes (including tumor size, histological grade, lymph node involvement, and hormone receptor status), and

treatment-related variables (such as type and timing of surgery, chemotherapy, radiotherapy, and hormonal therapy).

Among these, tumor staging at diagnosis remains one of the most significant predictors of survival, with earlier detection often correlating with improved outcomes. Hormone receptor status, particularly estrogen and progesterone receptor expression and HER2 status also play a crucial role in guiding treatment decisions and estimating prognosis. Understanding the relative impact of these factors is essential for refining risk stratification, enhancing clinical decision-making, and improving long-term outcomes for breast cancer patients (Nur Aishah bt Mohd Taib, 2008; Moons *et al.*, 2009; Abubakar *et al.*, 2018; Nordin *et al.*, 2018; Phung *et al.*, 2019; Nik Ab Kadir *et al.*, 2022).

2.2.1 Age at Diagnosis

Age at diagnosis is widely recognized as a crucial prognostic factor influencing cancer survival outcomes. A recent meta-analysis synthesizing data from 30 countries demonstrated that individuals diagnosed at age 60 years and above have a significant increased hazard of mortality, with ~~a hazard ratio (~~HR~~)~~ of 1.45 (95% CI: 1.21, –1.72) (Abdul Rahman *et al.*, 2024). This finding highlights the global trend where older patients tend to experience poorer survival, potentially due to cumulative biological aging, comorbidities, reduce physiological reserve, and a higher likelihood of receiving conservative treatment.

Recent international research strengthens the case that age is an independent predictor of poorer survival in breast cancer (Ji *et al.*, 2020; Yang *et al.*, 2022; Liu *et al.*, 2024; Shin *et al.*, 2024). For example, Liu *et al.* (2024) examined patterns of distant metastasis and survival outcomes in de novo metastatic breast cancer and found that older age at diagnosis (≥65 years old) was associated with distinct metastatic patterns

(lung metastasis HR: 2.96 (95% CI: 2.41, 3.65); lymph node metastasis HR: 1.39 (95% CI: 1.15, 1.69) and worse survival outcomes (HR 1.65 (95% CI: 1.44, 1.88). Similarly, Ji et.al (2020) also found elderly women aged more or equal to 65 years old had HR of 1.362 (95% CI: 1.261, 1.473). In addition, Shin *et al.* (2024) observed that younger patients with ER-positive, ERBB2-negative breast cancer had a higher risk of survival (HR: 0.53 (95% CI: 0.34, 0.82)) and lower risk of late recurrence (HR: 0.91 (95% CI: 0.88, 0.93)), underscoring age as an independent prognostic factor across age groups. Moreover, Yang *et al.* (2022) compared very young (≤35 years old) and older women (≥50 years old) with breast cancer in China and reported that older women had a HR of 1.30 (95% CI: 1.04, 1.61). These studies support the previous meta-analysis findings.

In the Malaysian context, there is a scarcity of published studies examining prognostic factors for mortality among breast cancer patients. Most available evidence reported that age at diagnosis is not a statistically significant variable (Nor Idawaty Ibrahim, 2012; Nordin *et al.*, 2018; Nizuwan Azman, 2019; Nik Ab Kadir *et al.*, 2022). This might be due to small sample size and potential selection bias limiting its generalizability. However, one study conducted in Pulau Pinang found that age at diagnosis was a significant predictor of breast cancer survival with women aged more than 60 years old had an adjusted HR of 1.34 (95% CI: 1.12, 1.61). The study also found that elderly women had the shortest mean survival time (91.2 months), and the lowest survival rate (71.4%) compared to their younger counterparts (Tan *et al.*, 2021).

2.2.2 Ethnicity

Ethnicity has been increasingly recognized as a significant prognostic factor in breast cancer outcomes. Interestingly, a meta-analysis from 30 countries reported that there is a potential protective effect from developing breast cancer among Asian population

((HR 0.84 (95% CI: 0.76, 0.93)). Possible explanations for this finding include cultural variations in health-seeking behaviours, genetic factors, earlier detection through screening programs in some Asian subregions, or differences in healthcare infrastructure. However, without accounting for important factors like socio-economic status, healthcare access, and comorbid conditions, the apparent protective effect might simply reflect differences that were not fully measured in the analysis.

In the United States, African American women have a lower incidence of breast cancer compared to non-Hispanic White women, with age-standardized incidence rates of 122.9 and 124.4 per 100,000 population, respectively. However, African American women experience higher mortality from the disease, with an age-standardized mortality rate of 28.2 per 100,000, compared to 20.3 per 100,000 among non-Hispanic White women. This is postulated to be due to later stage at diagnosis and more aggressive tumor subtypes such as triple-negative breast cancer among African American group (Newman and Kaljee, 2017). Similarly, based on another study by Moore et. al (2015), indigenous populations in Australia (Queensland, Standard Rate Ratio (SRR): 0.72 (95% CI: 0.62, 0.84); Western Australia, SRR: 0.52 (95% CI: 0.42, 0.64), and the USA except Alaska (SRR: 0.40 (95% CI: 0.38, 0.41) exhibit lower breast cancer rates compared to the non-Indigenous group. The Standardized Rate Ratio was in comparison with the white population of the USA (Moore *et al.*, 2015). However, Moore's study was unable to investigate corresponding mortality patterns and incidence trends over time.

While in Southeast Asian, a study based on Singapore and Malaysia hospital-based breast cancer registry revealed that Malay women presented at younger age with large tumors and more advanced stage compared to Chines and Indian. The five~~5~~-year

overall survival rates were highest among Chinese women (75.8%), followed by Indian (68.0%), and Malays (58.5%). Even after adjusting for variables such as age, stage, tumor characteristics, and treatment, Malay ethnicity remained independently associated with poorer survival outcomes (Bhoo-Pathy *et al.*, 2012a). These findings suggest that factors beyond clinical presentation, possibly including tumor biology, psychosocial elements, and treatment responsiveness, contribute to observed disparities.

The influence of ethnicity on breast cancer outcomes in Malaysia demonstrates significant regional variations, reflecting the country's diverse cultural, socioeconomic, and healthcare landscapes. Although state-level analyses on ethnicity remain limited, available evidence, reveal heterogenous findings regarding the prognostic impact of ethnicity across different regions of Malaysia.

For instance, a study conducted in Kelantan by Nordin *et al.* (2018) found that Malays women had significantly poorer survival outcomes compared to women of other ethnicities. The adjusted hazard ratio for mortality among Malays was 2.52 (95% CI: 1.52, 4.13), suggesting more than double the risk of death from breast cancer relative to non-Malay women (Nordin *et al.*, 2018). In contract, a study conducted in Penang by Azman *et al.* (2019) observed relatively lower hazard ratios among Chinese and Indian women, with crude hazard ratio of 0.82 (95% CI: 0.42, 1.58) and 0.99 (95% CI: 0.43, 2.29), respectively (Nizuwan Azman, 2019). Although these results were not statistically significant, they values suggest a trend towards better survival in these ethnic groups, possibly reflecting differences in health literacy, early detection, and access to care.

Meanwhile in Sarawak, a state with a diverse population including Chinese, Malays, and Indigenous groups such as the Iban and Bidayuh, a study highlighted

significant ethnic disparities in breast cancer presentation and outcomes. It was observed that triple-negative breast cancer, an aggressive subtype with poorer prognosis, was more prevalent among Indigenous women (37.0%) and Malays (33.0%) compared to Chinese women (23.0%) (Abubakar *et al.*, 2018). These differences illustrate the complexity of interpretating ethnicity as an isolated prognostic factor in Malaysia. Instead, they highlight the need to view ethnicity within a broader socio-environmental and regional framework, as ethnic identity may serve as a proxy for other underlying factors that influence survival.

2.2.3 States/Regions

Breast cancer outcomes in Malaysia are not only influenced by biological and socioeconomic factors but are also significantly influenced by geographic location, often represented by the patient's state or region of residence. Geographic disparities manifest in unequal healthcare infrastructure, differential access to early detection and treatment services, and variations in health-seeking behaviour across the country (Nguyen-Pham *et al.*, 2014; Nordin *et al.*, 2018; Lim *et al.*, 2025b). These disparities are particularly more obvious between urban centres, such as Selangor, Kuala Lumpur, and Penang, and less developed states like Kelantan, Sabah, and Sarawak ((Nordin *et al.*, 2018; Lim *et al.*, 2025b).

Bhoo-Pathy *et al.* (2012) highlighted that geographical barriers, including long travel times and limited specialist availability, significantly reduced access to optimal care in Southeast Asia, including Malaysia. These factors are particularly acute in East Malaysia, where inter-island travel and limited oncology facilities challenge timely treatment (Bhoo-Pathy *et al.*, 2012a). Supporting this, Lim et.al (2025), highlighted that many rural Sarawakian women are diagnosed at later stages due to limited screening

infrastructure, socio-cultural beliefs, and logistical barrier like transportation and costs (Lim *et al.*, 2025b).

International studies echo these findings and provide theoretical grounding for understanding geographic disparities as prognostic factors in breast cancer outcomes. A study in Queensland, Australia, examined the relationships between geographic remoteness, area-level socioeconomic disadvantage, and the risk of advanced breast cancer. The findings revealed that women living in socioeconomically disadvantaged (OR 1.31, 95% CI: 1.07, 1.69) and remote areas and (OR 1.18, 95% CI: 0.99, 1.53) were more likely to be diagnosed with advanced breast cancer. Correspondingly, the five~~5~~-year survival rates were the lowest among its groups, at 89.9% and 88.4% respectively, underscoring the prognostic significance of place of residence in shaping breast cancer outcome (Dasgupta *et al.*, 2012).

However, to date, no other study has been done in Malaysia or elsewhere has directly evaluated this theory in relation to geographic administrative divisions such as state or region. This is probably due to such classifications not being clinically defined and are often considered administrative in nature, making it challenging to establish a direct causal relationship with clinical outcomes. Nonetheless, these geographic factors may still serve as useful proxies for underlying disparities in healthcare access, infrastructure, and service delivery, and thus warrant further investigation.

2.2.4 Staging

Globally, the stage at diagnosis remains one of the most significant prognostic factors in breast cancer survival. Delayed presentation is strongly associated with advance-stage disease, limited treatment options, and poorer survival outcome. A recent meta-analysis by Abdul Rahman *et al.* reported that disease staging was the strongest predictor of breast cancer-specific survival. The pooled hazard ratio (HR) indicated a

markedly elevated risk of mortality with advancing stage with HR of 12.12 (95% CI: 5.70, 25.76) for ~~stage 4~~stage IV, followed by 3.42 (95% CI: 2.51, 4.67) for ~~stage 3~~stage III and (1.93 (95% CI: 1.48, 2.51) for ~~stage 2~~stage II, in comparison to ~~stage 1~~stage I (Abdul Rahman *et al.*, 2024).

Similar trends have been observed in the United States. Using data from the Surveillance, Epidemiology, and End Results (SEER) program, DeSantis *et al.* (2019) reported a ~~five-year~~5-year survival rate for patients diagnosed during 2009 through 2015 was 98.0% for ~~stage 1~~stage I, 92.0% for ~~stage 2~~stage II, 75.0% for ~~stage 3~~stage III, and only 27.0% for ~~stage 4~~stage IV. These figures highlight the urgent need for early detection strategies in reducing breast cancer mortality (DeSantis *et al.*, 2019).

These international findings reflected in local population-based data from the Malaysian National Cancer Registry. According to the Malaysian Study on Cancer Survival (MySCan) 2018, the hazard ratios 7.52 (95% CI: 6.83, 8.28) for ~~stage 4~~stage IV, 2.71 (95% CI: 2.46, 3.00) for ~~stage 3~~stage III and 1.41 (95% CI: 1.28, 1.56) for ~~stage 2~~stage II, all compared to ~~stage 1~~stage I. In addition, the registry also reported that the overall ~~five-year~~5-year relative survival for breast cancer was 87.5% for ~~stage 1~~stage I, followed by 80.7% for ~~stage 2~~stage II and the survivals deteriorated at a faster rate for ~~stage 3~~stage III (59.7%) and ~~stage 4~~stage IV (23.3%) (MNCR, 2018).

Late-stage presentation remains a persistent challenge in Malaysia with more than 40% of breast cancer cases in Malaysia were diagnosed at advanced stage. The MySCan (2018) report indicated that between 2007 and 2011, 23.2% of patients were diagnosed at ~~stage 3~~stage III and 18.1% at ~~stage 4~~stage IV (MNCR, 2018). This pattern continues to increase in more recent registry periods with 25.1% (~~stage 3~~stage III) and 22.8% (~~stage 4~~stage IV) reported from 2012 to 2016 (MNCR, 2019), and 28.3% (~~stage 3~~stage III) and 22.2% (~~stage 4~~stage IV) reported between 2017 and 2021 (MNCR,

2022). Contributing factors include sociodemographic disparities, cultural stigma, limited awareness, and unequal access to screening and diagnostic services, especially in rural or underserved regions.

In addition to the national trend, state-level studies in Malaysia also highlighted significant disparities in the stage of breast cancer at diagnosis, which directly impacts survival. In Kelantan, Nordin et.al. (2018) reported a similar finding in which more than 40.0% breast cancer patients were diagnosed at advanced stages (16.4% at ~~stage 3~~stage III and 24.6% at ~~stage 4~~stage IV). This late presentation likely contributed to the significantly higher mortality observed among Malay women in the study. The author attributed this trend to sociocultural factors, delayed health-seeking behaviour, and limitations in regional screening infrastructure (Nordin *et al.*, 2018).

Similarly, a study conducted in Sabah revealed that a considerable proportion of patients presented with advanced disease. Specifically, 36.6% were diagnosed at ~~stage 3~~stage III and 15.6% at ~~stage 4~~stage IV, indicating that over half of the patients presented at late stages. The study highlighted that patients presenting with advanced disease were often from rural areas, had lower education levels, and were more likely to default treatment, sometimes opting for traditional alternatives. These findings emphasize the challenges faced in rural regions regarding timely diagnosis and adherence to treatment protocols. (Leong *et al.*, 2007).

These regional disparities indicate the importance of targeted interventions to improve early detection and treatment adherence, particularly in rural and underserved areas. Addressing sociodemographic barriers, enhancing public health education, and improving access to screening facilities are crucial steps toward reducing late-stage presentations and improving survival outcomes across all regions in Malaysia.

2.2.5 Topography

Tumor topography refers to the specific anatomical location of a tumor within the breast, typically categorized into five regions: upper outer quadrant (UOQ), upper inner quadrant (UIQ), lower outer quadrant (LOQ), lower inner quadrant (LIQ), and central (retro-areolar) region (Dickie, 2024). This classification is not only relevant for clinical management and surgical planning but has also been examined for its prognostic value. Early hypothesis proposed that tumor location could influence survival outcomes due to differences in lymphatic drainage pathways and proximity to internal mammary lymph nodes, though removal of the internal mammary lymph nodes (IMLNs) has not demonstrated improvement in overall survival (Eckert *et al.*, 2024). In particular, tumors in the inner quadrants w ere suspected to be associated with a higher risk of nodal metastasis and delayed detection due to less prominent symptoms, thereby potentially leading to worse prognosis, which was lower ~~5-year~~5-year disease-free survival (DFS) than those with outer quadrant tumors (67.7% vs 83.4% respectively; HR = 1.941, p ~~= value~~ 0.034) (Chang *et al.*, 2016).

Several international studies also explored the prognostics significance of tumor topography. Sarp et.al. (2007) reported that breast tumors located in the lower inner quadrant were associated with 2.3-fold increased risk of mortality compared to tumors in the upper quadrant (HR~~:~~ 2.3, 95% CI: 1.1, 4.5), suggesting that inner quadrant tumors may follow a more aggressive clinical course. This finding aligns with earlier anatomical theories emphasizing the challenging assessment and management of internal mammary node involvement (Sarp *et al.*, 2007).

Similarly, Seth et.al (2009), in an analysis of breast cancer-specific survival using population-based data, found that tumors situated in the central quadrant were significantly more likely to have higher tumor stage (p = 0.003), larger size (p ~~=~~

<0.001), metastatic lymph nodes ($p < 0.001$) and higher mortality ($p = 0.011$). However, the study also highlighted that tumor location is not an independent prognostic factor (Rummel Seth, 2015). A study using the SEER database further emphasized these observations, concluding that inner quadrant tumors had higher breast cancer-specific mortality (UIQ – HR÷ 1.142 (95% CI: 1.085, 1.203) and LIQ – HR÷ 1.222 (95% CI 1.152, 1.296)) , potentially due to limited surgical access and less comprehensive lymph node dissection (Bao *et al.*, 2014).

However, it is worth noting that many of these studies were conducted before molecular subtyping became standard component of breast cancer classification, which now plays a pivotal role in guiding prognosis and therapeutic decisions.

In contrast to international literatures, studies focusing on tumor topography in Malaysia remain scarce. Most local studies have concentrated on traditional clinical and sociodemographic predictors of breast cancer survival, such as stage at diagnosis, age, ethnicity, receptor status, and treatment modalities. Although the Malaysia National Cancer Registry collects tumor site information using International Classification of Disease for Oncology (ICD-O) topography codes (C50.0 to– C50.9), this classification was often not routinely analysed in terms of prognostic impact. Limited awareness of its prognostic relevance among healthcare providers and prioritization of variables with more immediate clinical utility, such as hormone receptor status and staging, further limiting the ability to assess the prognostic value of tumor location in Malaysia.

2.2.6 Morphology

The histologic subtype, or morphology, of breast cancer is a well-established prognostic factors that significantly influences clinical outcomes, therapeutic response, and disease progression. While traditional classification often emphasized the distinction between invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC), the