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A comparison of the Quality of life and Depression Risk Among Breast Cancer Patients in High- and Low/Middle-Income Countries: An Integrative Literature Review

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2023 Laurea

Laurea University of Applied Sciences

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Degree Programme in Global Health

 and Crisis Management

Master of Health Care

05, 2023

Breast cancer (BC) is the most common cancer in the world and lists the 5th most common cancer related deaths worldwide. The objective of this thesis is to gather novel information on the psychosocial situation of the breast cancer patients around the world and discuss the obstacles in order to trying to make the world more equal to all breast cancer patients and their families.

Breast cancer diagnosis causes anxiety and can lead to depression and thus can be thought to cause decreased quality of life (QoL). The aim of this thesis is to critically analyze the differences in quality of live and depression among breast cancer patients in low/middle- and high-income countries and to illustrate the barriers the patients face in low/middle-income countries compared to high-income countries, when their access to modern treatments and psychological support networks are limited. Many interventions have been made in order to better the QoL and minimize depression both in low/middle-income and high-income countries and this thesis examines whether these interventions have been successful.

Depression is usually the highest among newly diagnosed patients and during the acute phase of cancer treatments. Breast cancer patients in low/middle-income countries are thought to be at higher risk of depression and lower QoL than breast cancer patients in high-income countries. An integrative literature review was chosen as a research method. The data search was carried out in CINAHL and Medline databases. From 2602 peer reviewed articles 10 articles were selected for this integrative literature review. These articles covered both low/middle- and high-income countries. The results show that all low/middle-income countries are not the same when it comes to BC depression risk, prevalence of depression and QoL showing how complex the field of research is. The low/middle-income country status alone cannot define what kind of psychological challenges the BC patients might face. Low-income African breast cancer patients seemed to be in higher depression risk compared to Asian patients in low/middle-income countries whereas patients in Asian high-income countries had higher depression risk than Caucasians in high-income countries. Health insurance was not an important factor when depression risk was evaluated but economic burden was listed as one key factor causing increased depression. Depression risk seems to be multifactorial so not only high/low country GNI can predict the risk. Interventions have not been successful to lower the depression rates and increased QoL in low/middle- and high-income countries in long term but managed to shorten the time from first clinic meeting to diagnosis among low/middle-income Indonesian BC patients. The study did not find the answers for the burning question of how to make the world more equal to BC patients and their families.

The collected data were limited so further studies are needed to examine more thoroughly which factors are contributing to higher depression risk in different low/middle-income countries and a more precise definition of low- and high-income countries is needed to create interventions to prevent depression in these countries.

Keywords: breast cancer, depression, quality of life, low-income countries, middle-income countries, high-income countries

Contents

1   Introduction

Breast cancer (BC) is the most common cancer in the world and lists the 5th most common cancer related deaths worldwide. In 2020 around 2.26 million new cases and 685 000 deaths were reported (WHO 2023). The breast cancer burden can be reduced through early detection via mammography screening programs. In high-income countries routine screenings are carried out in every 1-2 years for women around 40-75 years varying a bit from country to country (e.g Seely and Alhassan 2018). The BC mortality has been reduced 40% when screening schedule is followed (Seely and Alhassan 2018). BC incidence rates have been arising in low/middle-income countries (LMIC) (Newman 2022) but in many LMICs they have reduced access to modern treatments and screening programs leading to higher mortality (Newman 2022). Many LMICs don't have complete cancer registry data so BC disease burden is more difficult to evaluate (Martei et al. 2018).

The golden standard of breast cancer treatments includes surgery, radiation, chemotherapy, hormone therapy, and targeted therapy. The protocols vary from low/middle-income countries to high-income countries. If BC patients have access to all modern treatments the survival is generally good, especially with early diagnosis and less advanced cancer stage (Cancer Research UK 2023). On average in UK around 75 out of every 100 women will survive their cancer for 10 years or more when all the stages are included (Cancer Research UK 2023). Unfortunately, in LMIC, the mortality rates are higher, and patients are more likely to die from cancer (Martei et al. 2018). For instance, mortality-to-incidence ratios in Middle, Eastern, and West Africa come up to 0.55, compared with 0.16 in North America (Martei et al. 2018).

In modern oncology not only clinical outcomes are measured but psychological factors must be taken account when the treatment protocols are selected. The quality of life (QoL) is one of the most important outcome indicators (Biparva et al. 2022). It has been stated that QoL could be seen as a prognostic factor along with clinical parameters (Paraskevi 2012). Various factors as socioeconomic status, education, unemployment, and financial factors affect QoL.

Breast cancer diagnosis causes anxiety and can lead to depression and thus can be thought to cause decreased QoL. Depression is usually the highest among newly diagnosed patients and during the acute phase of cancer treatments. The global prevalence of depression among BC patients has been reported to be 32.2% and in LMIC the reported prevalence of depression is 21% showing a significantly lower value (Belay et al. 2022). There are also other studies suggesting that depression rates are a lot higher in LMICs, for example in Palestine 35.4% (e.g. Sadaqa et al. 2022). A systematic review and meta-analysis by Pilevarzadeh et al. (2019)

reported the prevalence of depression among BC patients being the highest in the Easter Mediterranean region with 57.1% and twice as high in LMIC compared to high-income countries. Among all cancer patients, depression has been reported to be the most common in AFRO region with 35% and the 2nd most common in South-East Asia and Easter Mediterranean region with 34% (Mejareh et al. 2021). The lowest depression rates have been measured in EURO region and Pan American region with 25% (Mejareh et al. 2021). The prevalence of depression among breast cancer patients can vary depending on a range of factors, including cultural differences, access to healthcare resources, and socioeconomic factors, which may explain some of the conflicting findings in the literature.

The aim of this study is to identify the quality of life, depression risk and prevalence of depression in high- and low/middle-income countries and illustrate and discuss the potential differences in outcome. The expected outcome would be that the patients in low/middle-income countries would face higher depression risk than the patients in high-income countries thus lowering QoL values in LMIC compared to high-income countries. This study also tries to illustrate the interventions already done in order to try to decrease the risk of depression and lower quality of life globally and discusses the burdens. An integrative literature review is selected for method to include both quantitative and qualitative research in order to answer these questions.

2 Background

Breast cancer is a leading malignancy among women. The disease has been present throughout the history and ancient Egyptians were the first ones to notate the malignancy around 3500 years ago (Mandal 2019). On the molecular level BC is all but homogenous disease as different molecular characteristics govern tumor growth and metastasis. Various molecular subtypes have different treatment strategies from surgery and radiation therapy to systemic therapies like endocrine therapy, traditional chemotherapy, and immunotherapy (Harbeck et al. 2019).

Early screening and treatments have decreased the mortality in high-income countries but in LMIC the mortality remains high. Metastasis and cancer recurrence are the main causes for poor prognosis and for decreased overall survival (OS). There are several other factors affecting the mortality and the role of psychological factors in breast cancer prognosis are studied actively (Wang et al. 2020).

Many breast cancer patients feel anxiety and depression while diagnosed. There is even some evidence that depression is connected to cancer recurrence and mortality and anxiety was associated with recurrence (e.g. Wang et al. 2020). Depression can also lead to chronic stress and animal studies and murine models have shown that chronic psychological stress promotes ovarian tumor growth and angiogenesis as well as lung metastasis (e.g. Wang et al. 2020; Chen et al. 2018; Qin et al. 2015; Thaker et al. 2006). It is thus important to recognize these vulnerable groups for early interventions.

2.1 Short introduction to cancer malignancy

Cancer can be seen as a major global burden mainly as its diversity, complex genetics, cell and tissue biology, pathology, and treatment responsiveness variations (Hanahan 2022). There are growing numbers of cancer patients around the world because of aging. Despite the new strategies for cancer treatment, cancer-related deaths are one of the leading causes of death in the world causing around 13% of all human deaths globally (Zhao et al. 2021).

Why do we get cancer? Many different factors can cause cancer, making it a complex disease. Some of these factors are genetic mutations caused by environmental factors and lifestyle choices. Before cancer develops there are usually a series of events involved that allow cells to grow and divide uncontrollably. The mutations in genome are normal but if there is a mutation that produces oncogenes with dominant gain of function as well as tumor suppressor genes leading to function-loss, these multiple factors together can promote the cancer growth (Hanahan & Weinberg 2000).

According to classical two-hit hypothesis model by Knudson (1971) cancer development requires two "hits", namely mutations, to occur in specific genes, with the first hit being inherited or acquired at birth, and the second hit occurring later in life. The first hit is most likely a germ-line mutation, which is an inherited mutation that is present in all cells of the body. This mutation is usually a loss-of-function mutation resulting in the loss of one copy of a tumor suppressor gene. Tumor suppressor genes are genes that normally prevent the development of cancer by regulating cell growth and division. The second hit is usually a somatic mutation, which is a mutation that occurs in a specific cell and is not present in all cells of the body. Loss of both copies of a tumor suppressor gene leads to the complete loss of gene function causing uncontrolled cell growth and in the end the development of cancer. Tumor-suppressor genes can be seen as important targets for cancer prevention research (Hanahan & Weinberg 2011).

Cancer research has been taken large steps forward after the famous paper "Hallmarks of Cancer" published in 2000 by Hanahan & Weinberg (2000). They postulated that the hallmarks of cancer are characteristics of tumor cells that include growth signal self-sufficiency, anti-growth signal insensitivity, avoidance of apoptosis, endless replication, angiogenesis, tissue invasion and metastasis (Figure 1) and BC tumors are not an exception. All human cancers develop because of multiples processes instead of one straightforward process (Hanahan 2022).
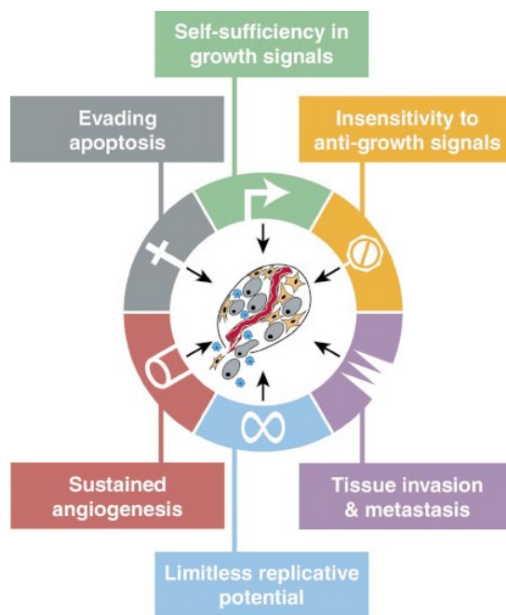
Figure 1: Hallmarks of cancer. Cancer needs multiple processes to develop. Hanahan & Weinberg (2000) suggested that almost all, maybe even all cancers, have acquired the same functional capabilities that promote immortality. When normal cells grow, divide, and die, cancer cells have endless potential to multiply and invade. Reprinted from Cell, Vol. 100, Hanahan, D. & Weinberg, R., The Hallmarks of Cancer, pages 57-70, 2000, with permission from Elsevier.

In 2000, Hanahan & Weinberg (2000) were not able to address how these hallmarks can allow evolving preneoplastic cells to develop and reach their malignancy potential. Since then, the classical hallmark model has been updated to show which surrounding atmospheres can promote the malignancy (Figure 2). The main promotors are nowadays known to be genome instability and tumor-promoting inflammation (Hanahan 2022).

Inflammation either promotes or suppresses tumor progression. Chronic inflammation can be seen as a promoter whereas acute inflammatory reactions can lead to dendritic cell maturation and thus leading to anti-tumor immune responses via antigen presentation (Zhao et al. 2021). One way how chronic inflammation can cause malignancy is via production of reactive oxygen species (ROS) and reactive nitrogen species (RNS). These species can cause DNA damage and mutations that can lead to the development of cancer (Coussens & Werb 2002). Inflammation can also promote angiogenesis, which is necessary for tumors to grow and spread (Balkwill & Mantovani 2001).
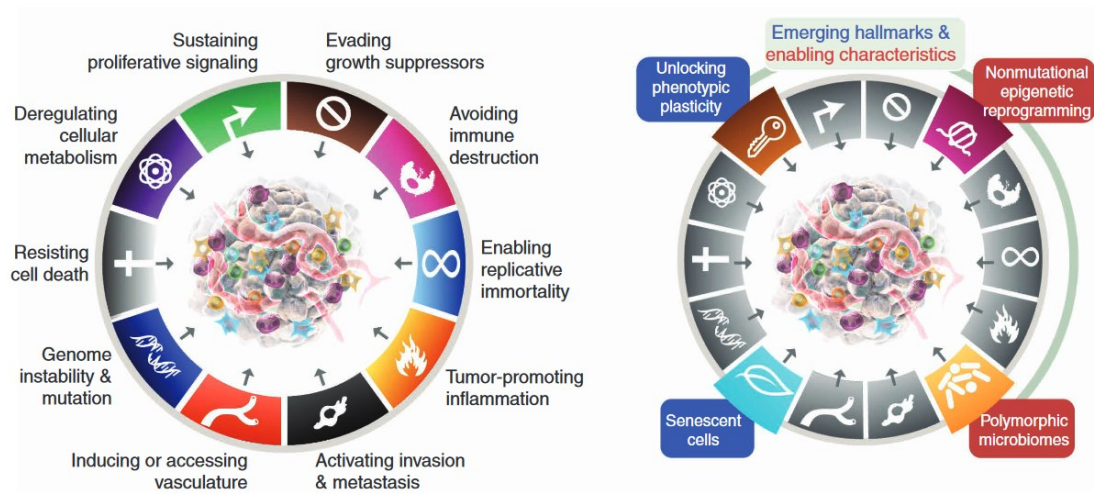
Figure 2: Updated Hallmarks of cancer with surrounding atmospheres. The new model includes a mechanism to avoid immune destruction thus making cancer cells "cold" for immune system. Also, tumor inflammation, known as "tumor-associated inflammation," is a process where different cells interact with each other. These interactions between cancer cells, immune cells, and other components of the tumor microenvironment can promote a suitable environment for cancer growth. Reprinted from Cancer Discovery, 2022, 12 (1): 31-46, Hanahan, D., Hallmarks of Cancer: New Dimensions, with permission from AACR.

To conclude, cancer cells often have mutations in specific genes that allow them to grow and divide uncontrollably (Vogelstein & Kinzler 2004). These genes are up- and downregulated with different pathways. In addition to genetic mutations, changes in the tumor microenvironment can also contribute to cancer progression. The presence of immune cells, blood vessels, and other components of the tissue surrounding the tumor are all factors that can affect the microenvironment (Hanahan & Coussens 2012). Cancer cells can evade the immune system with a variety of mechanisms that are downregulation of immune cell recognition and suppression of immune cell activity (Sharma & Allison 2020). Telomeres in cells protect the ends of chromosomes in DNA from becoming tangled. When the cell divides the telomeres become a bit shorter with every dividing. Telomerase is an enzyme that maintains the length of telomeres. Telomerase enzyme adds short DNA sequences to the ends of chromosomes. In normal cells this activity is low or not happening at all leading to telomere shortening and, in the end, controlled cell apoptosis. In cancer cell telomerase activity is upregulated which allows cells to continue to divide indefinitely leading to cancer. Upregulation of telomerase activity is a hallmark of many types of cancer (Shay & Wright 2019).

2.2 Breast cancer tumor types and their treatment protocols

Breast cancer tumor types can be traditionally defined in accordance with hormonal and growth factor responsiveness (Wang et al. 2020). The classification of breast cancer is based on the expression of hormone receptors, human epidermal growth factor receptor 2 (HER2), and other biomarkers. Molecular profiling has become an important tool for classification (Sørlie 2004). In this subchapter the major subtypes of breast cancer are shortly discussed.

Hormone receptor-positive (HR+) breast cancer subtype is a common BC type. Approximately 75% of breast cancers are of this type (NCI 2023). Hormone receptor-positive breast cancers express estrogen and/or progesterone receptors on the surface of the tumor cells. These receptors can promote tumor growth in response to hormones. HR+ BC treatments rely on hormone therapy to block the effects of these hormones (NCI 2023). Luminal A and Luminal B breast cancer are both HR+ breast cancers, but Luminal B tumors tend to have higher levels of Ki-67 which is a marker of cell proliferation. Luminal B tumors are more aggressive than Luminal A tumors (Rakha & Ellis 2010). Luminal A type BC can often be treated with only hormone therapy, but Luminal B type needs a combination of hormone therapy and chemotherapy and in some cases even targeted therapies (Finn et al. 2016).

Around 15-20% of breast cancers are HER2-positive breast cancers. They overexpress the HER2 protein on the surface of the tumor cells (NCI 2023). HER2-positive breast cancer is often more aggressive than other subtypes and is often treated with targeted therapies such as trastuzumab and pertuzumab (NCI 2023).

Triple-negative breast cancer (TNBC) subtype is diagnosed for approximately 10-15% of all breast cancer cases. It does not have hormone receptors on the surface of the tumor cell and does not show HER2 overexpression (Sørlie 2004). TNBC tends to be more aggressive than other subtypes and is often treated with chemotherapy (NCI 2023). Basal-like breast cancer subtype is like TNBC and expresses basal-like markers such as cytokeratin 5/6 and epidermal growth factor receptor (Sørlie 2004). Basal-like breast cancers can be treated with chemotherapy and targeted therapies. PARP-inhibitors can be used for patients with BRCA mutations which are more common among patient groups having TNBC subtype breast cancers (Tutt et al., 2018).

All in all, breast cancer treatment strategies depend on several factors such as the stage of the cancer, the type and subtype of the cancer and the patient's overall health (NCI 2023). Surgery is often the first line of curative treatment with or without neoadjuvant chemotherapy. Radiotherapy can be given as adjuvant or neoadjuvant therapy. Other therapy forms are chemotherapy, hormone therapy, targeted therapy, and immunotherapy (NCI 2023).

2.3   Breast cancer treatment in high- and low/middle-income countries

Breast cancer treatment varies greatly between high-income countries (HICs), low-income countries (LICs), and middle-income countries (MICs) due to differences in healthcare systems, resources, and availability of trained healthcare professionals.

In high-income countries, breast cancer treatment typically involves a multidisciplinary approach with surgery, chemotherapy, radiation therapy, and targeted therapy. Breast cancer patients in HICs have access to the latest treatments and technologies, including advanced imaging and genetic testing (American Cancer Society 2023). In low-income countries, breast cancer treatment is often limited due to a lack of resources and trained healthcare professionals. Many breast cancer patients in LICs do not have access to basic cancer screening, they lack diagnosis, and treatment services. They also have limited access to essential medicines, such as chemotherapy drugs and pain relief medications (Erfani et al. 2021). In middle-income countries, breast cancer treatment varies depending on the level of healthcare infrastructure and resources available. While some MICs have made significant progress in improving breast cancer care, many still face challenges with access to diagnostic services and appropriate treatments making the situation similar to LICs. The cost of breast cancer treatment is also a major concern for patients in MICs, as it can be prohibitively expensive (Erfani et al. 2021). In this thesis LIC and MIC are analyzed together as selected research papers suggest.

The World Health Organization (WHO) has developed guidelines for breast cancer control in low- and middle-income countries and released a road map (WHO BC Roadmap 2023). These guidelines focus on strengthening healthcare systems, promoting early detection and diagnosis, and improving access to essential cancer treatments.

2.4   Physiology and biopsychosocial aspects of cancer related depression

Many factors affect the quality of life among cancer patients. Many cancer patients face cancer-related depression. Giese-Davis et al. (2011) have suggested that cancer-related depression is connected to changes in the levels of hormones and neurotransmitters in the body. Cortisol released from adrenal glands is one of the most well-known hormones linked to depression. The patients with depression have higher levels of cortisol compared to healthy individuals (Belvederi Murri et al. 2014). Additionally, the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis responsible for regulating cortisol release, has been suggested to play part in the development of depression (Pariante & Lightman 2008). Thyroid hormones and sex hormones have also been linked to depression. For example, patients with hypothyroidism have a higher risk of depression (Kotkowska & Strzelecki 2022). Neurotransmitters serotonin, norepinephrine and dopamine can also play a part in the

development of depression. Additionally, inflammation and oxidative stress, which are common among cancer patients, have been linked to depression (Walker et al. 2013).

Psychosocial factors such as stress, lack of social support, and different coping strategies also play a crucial role in cancer-related depression. For example, patients with higher levels of social support have lower levels of depression (Chang et al. 2019). Cancer-related depression can also impact the patient's quality of life, physical symptoms, and treatment outcomes. For instance, depression can lead to a reduced tolerance of chemotherapy, increased pain, and decreased adherence to treatment (Kroenke et al. 2010). Therefore, identifying and treating depression in cancer patients is crucial for improving their overall well-being and treatment outcomes.

2.5   The quality of life and depression risk among breast cancer patients in high- and low/middle-income countries

Depression and quality of life are closely connected among breast cancer patients. Breast cancer patients have been linked to a higher incidence of depression and other psychiatric symptoms than other patients with malignancies (Zhu et al. 2020). A breast cancer diagnosis can be emotionally overwhelming and can lead to many different feelings like sadness, anxiety, and depression. These emotional responses can significantly affect the patient's quality of life. Depression in breast cancer patients has been linked to decreased overall quality of life, decreased social functioning, and poorer physical functioning (e.g. Biparva et al. 2022).

Breast cancer patients in low/middle-income countries often face greater challenges in accessing healthcare services, managing symptoms, and coping with the psychological impact of their diagnosis. These challenges may have a significant impact on their quality of life and increase the risk of depression. A systematic review and meta-analysis by Mejareh et al. (2021) examined global, regional, and national prevalence of depression among cancer patients and found out that AFRO region patients had the highest risk of depression. Female breast cancer patients had a higher prevalence of depression compared to men having other cancers. The study also suggested that socioeconomic factors, such as education and income level, were associated with depression risk. Similarly, a study by Skiba et al. (2022) found that breast cancer survivors in the United States had lower rates of depression compared to those in Mexico border. The authors suggested that cultural differences and varying levels of access to healthcare resources and social support may contribute to these differences as well as diet and lack of physical activity. Another study by Milbury et al. (2017) found that breast cancer patients in China had higher levels of depression and lower QoL compared to those in the United States.

Controversially, there are some studies suggesting that depression risk is not following income and treatment statistics but instead there could be multiple cultural factors behind the numbers. A study by Ashing-Giwa et al. (2014) found that African American and Latina breast cancer survivors in the US reported higher rates of depression compared to White survivors, despite having similar levels of income and education. A study by Brintzenhofe-Szoc et al. (2012) found out that low-income, rural breast cancer patients in the US reported higher levels of depression and lower quality of life compared to urban patients, despite both groups having access to similar healthcare services.

To conclude, while the specific factors that contribute to depression risk among breast cancer patients may differ between high- and low/middle-income countries, it is clear that breast cancer patients in low/middle-income countries are at a higher risk of depression compared to those in high-income countries. The purpose of this integrative review is to find the data supporting the correlation between higher depression rate and decreased quality of life, and lower country GNI (low/middle-income) where GNI is a Gross National Income. GNI can be defined as the total amount of money earned by people and businesses within a country. This review also tries to find answer whether the interventions made have been lowering the depression rates and bettering QoL both in low/middle- and high-income countries.

3   Method

3.1   Goals, objectives, and research questions

The goal of this thesis is to critically analyze the differences in quality of live and prevalence of depression and depression risk among breast cancer patients in low/middle- and high-income countries and to illustrate the barriers the patients face in low/middle-income countries compared to high-income countries, when their access to modern treatments and psychological support networks are limited. The objective of this thesis is to gather novel information on the psychosocial situation of breast cancer patients around the world in order to make the world more equal to all breast cancer patients and their families. An integrative literature review is chosen to illustrate these goals and to answer the following research questions:

1) What kind of interventions there have been to decrease the depression rates and better the quality of life among BC patients in low/middle- and high-income countries?
2) Is there a correlation between the lower quality of life and higher prevalence of depression, and lower GNI?

3.2   Integrative literature review as a method

An integrative literature review is a type of literature review that involves a systematic and comprehensive approach to synthesizing existing research findings from multiple sources on a particular topic. It seeks to provide a comprehensive and cohesive overview of the existing literature on a specific research question or topic by integrating findings from various studies, including both quantitative and qualitative research (e.g. Whittemore & Knafl 2005; Hopia et al. 2016).

An integrative literature review typically involves several steps, including defining the research question or topic, identifying relevant literature through a comprehensive search of databases and other sources, critically appraising, and evaluating the quality of the included studies, extracting relevant data, and synthesizing the findings to identify common themes, patterns, and gaps in the literature. The purpose of an integrative literature review is to provide a comprehensive and holistic understanding of the current state of knowledge on a particular topic and to identify areas for future research (e.g. Pati & Lorusso 2018).

An integrative literature review differs from other types of literature reviews, such as systematic reviews or meta-analyses, which have more specific methodologies and focus on quantitative research evidence. Integrative literature reviews are often used in fields such as nursing, healthcare, psychology, and social sciences, where a synthesis of diverse literature is needed to provide a comprehensive overview of a topic (e.g. Whittemore & Knafl 2005; Hopia et al. 2016).

The five steps of a successful integrative literature review formulated by Whittemore & Knafl (2005) typically include:

1. Formulating the research question: The first step in conducting an integrative literature review is to clearly define the research question or topic of interest. This involves identifying the key concepts, variables, or phenomena that will be the focus of the review. The research question should be specific, measurable, and relevant to the research context.

2. Searching and selecting relevant literature: Once the research question is formulated, the next step is to search for relevant literature using appropriate databases, libraries, and other resources. The literature search should be comprehensive and systematic, and include both published and unpublished sources, such as journal articles, books, dissertations, conference proceedings, and grey literature. Relevant literature should be critically evaluated for quality and relevance to the research question and selected for inclusion in the review.

3. Analyzing and synthesizing literature: After selecting the relevant literature, the next step is to critically analyze and synthesize the findings, concepts, and theories presented in the literature. This involves identifying common themes, patterns, and trends across the selected literature, and integrating the findings to draw meaningful conclusions. Various methods, such as thematic analysis, content analysis, and meta-analysis, can be used to analyze and synthesize the literature.

4. Evaluating the gaps and inconsistencies in literature: In this step, the integrative literature review assesses the limitations, gaps, and inconsistencies in the existing literature. This involves identifying areas where the literature is lacking, contradictory, or incomplete, and critically evaluating the strengths and weaknesses of the existing research. This step may also involve identifying potential biases or limitations in the literature, such as publication bias or methodological limitations.

5. Writing the integrative literature review: The final step is to organize and present the findings of the integrative literature review in a coherent and well-structured manner.

3.3 Research problem identification with the help of PICO model

Research problem identification is a process of identifying a gap, issue, or challenge in existing knowledge or practice that forms the basis for conducting research. It involves identifying an area of interest or concern that requires further investigation or exploration to better understand, address, or solve a problem or issue. Research problem identification is a crucial step in the research process as it helps define the focus and purpose of the study (e.g. Creswell 2014). The PICO approach is a framework commonly used in evidence-based practice (EBP) to formulate clinical research questions. PICO stands for Patient/Population, Intervention, Comparison, and Outcome. It provides a structured approach to clearly define and articulate research questions or clinical queries, which helps guide the search for relevant evidence and supports the development of evidence-based practice. Table 1 shows the PICO model for this study. The research questions to be answered are:

1) What kind of interventions there have been to decrease the depression rates and better the quality of life among BC patients in low/middle- and high-income countries?
2) Is there a correlation between the lower quality of life and higher prevalence of depression, and lower GNI?

P (Problem)	Is there a correlation between the lower quality of life and higher prevalence of depression, and lower GNI? What kind of interventions there have been to decrease the depression rates and better the quality of life among BC patients in low/middle- and high-income countries?
I (Intervention)	Successful interventions to prevent depression and reduced quality of life in low/middle-, and high-income countries.
C (Comparison)	Depression prevalence and quality of life among BC patients in high-income countries with access to multidisciplinary treatments and psychological support network. What kind of barriers there are to reach the same level?
O (Outcome)	Increased knowledge of depression risk and poorer quality of life among BC patients globally for all people working in oncology and wanting to increase the knowledge of global health perspective.

Table 1: PICO model for depression and quality of life among BC patients.

3.4   Literature search plan and review of data

Data search is the step 2 while conducting the integrative literature review. All data was collected by the author alone. The best not biased result would be to have at least two individuals doing the data searches independently and separately and, in the end, combine the results but as noted, all searches are done by author alone which can lead to bias.

The databases chosen for the data search were CINAHL and MEDLINE. The chosen timeline was 2010-2023 as breast cancer treatment strategies have drastically changed after the novel targeted therapies. The search terms are introduced in Table 2 with hits. A more general test search was also carried out to see if there are enough studies without country GNI limitations. The literature search was aiming to be as logical and systematic as possible to answer the research questions introduced in Table 1.

Search terms	Database	Hits	Title	Abstract	All text
Breast cancer AND depression AND quality of life (Test search)	CINAHL	881	46	615	967
Breast cancer AND depression AND quality of life AND developed countries	CINAHL	14	0	5	14
Breast cancer AND depression AND quality of life AND high-income countries	CINAHL	2	0	1	4
Breast cancer AND depression AND quality of life AND low- and middle-income countries	CINAHL	3	0	2	5

Breast cancer AND depression AND quality of life AND intervention AND high-income countries	CINAHL	1	0	1	3
Breast cancer AND depression AND quality of life AND intervention AND low- and middle-income countries	CINAHL	3	0	2	3
Breast cancer AND depression AND quality of life (Test search)	MEDLINE	1670	81	1352	169
Breast cancer AND depression AND quality of life AND developed countries	MEDLINE	10	0	7	86

Breast cancer AND depression AND quality of life AND high-income countries	MEDLINE	4	0	1	1
Breast cancer AND depression AND quality of life AND low- and middle-income countries	MEDLINE	7	0	4	4
Breast cancer AND depression AND quality of life AND intervention AND high-income countries	MEDLINE	1	0	1	1
Breast cancer AND depression AND quality of life AND intervention AND low- and middle-income countries	MEDLINE	6	0	3	3

TOTAL		2602	127	1994	1260

Table 2: Data search with search terms from two databases.

The data search from two different databases, CINAHL and MEDLINE gave 2602 hits in total (see Table 2). Based on abstract only the search narrowed to 1994 hits. Only headline searches left valuable articles out of range, so abstracts were selected to deeper analysis and duplicates were removed. The abstract needed to include one or more research question concepts. When test search and duplicates were removed 11 articles met the primary selection criteria. Test search was removed in order to limit the hits to more accurate country division (low/middle- and high-income).

The selected articles had following inclusion criteria: English language, publication date 2010-2023, peer reviewed articles and articles were accessed via Karolinska Institute library services. Exclusion criteria included all other languages than English and not peer reviewed articles to maintain a high quality. The eligible articles must be also in line with the research questions introduced in PICO-model (Table 1).

The PRISMA checklist is a tool used in systematic reviews and meta-analyses to ensure the transparent and complete reporting of the study methods, results, and conclusions. PRISMA words mean "Preferred Reporting Items for Systematic Reviews and Meta-Analyses". The checklist is used to guide authors in the preparation of a clear and complete systematic review report (Shamseer et al. 2015).

The PRISMA checklist includes 27 items organized into a flow diagram that follows the process of identifying and selecting studies for inclusion in a systematic review. Figure 3 shows the flow chart of data used in this study. The PRISMA checklist includes items related to the title, abstract, introduction, methods, results, discussion, and funding sources. Each item on the checklist should be reported in the systematic review report, or an explanation provided for why it is not applicable (Shamseer et al. 2015).
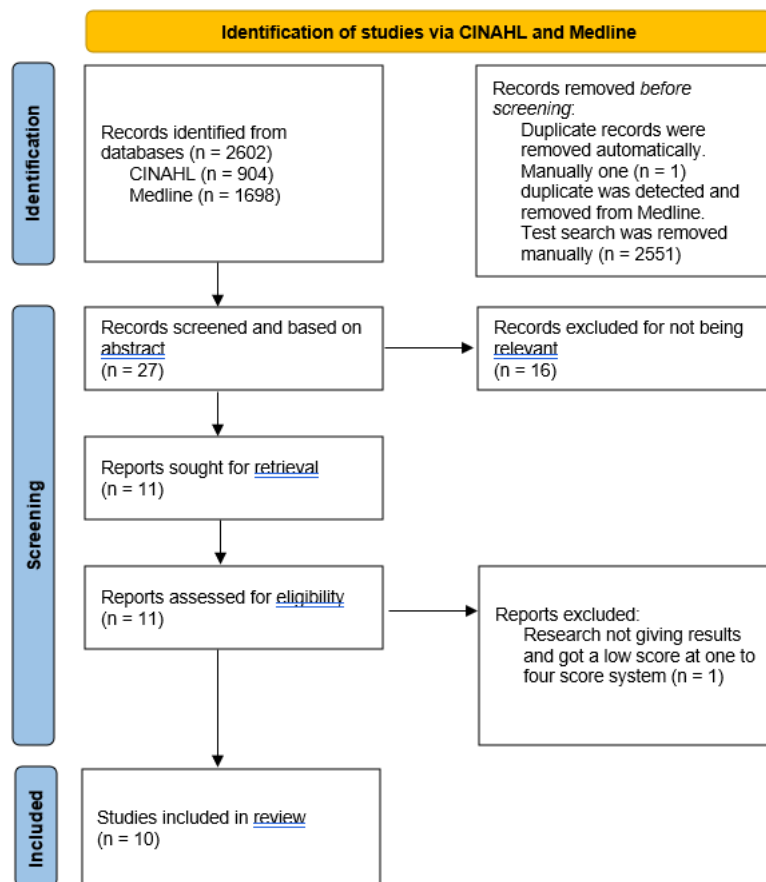
Figure 3: PRISMA flow chart. (Page et al. 2021)

The PRISMA checklist is intended to improve the quality of systematic reviews and meta-analyses by ensuring that all relevant information is reported in a transparent and consistent manner. It also helps readers to critically appraise the completeness and reliability of the systematic review report. The checklist can be used by authors, editors, and peer reviewers to improve the reporting and quality of systematic reviews and meta-analyses (Shamseer et al. 2015).

3.5   Evaluation of data

The evaluation process of chosen articles is the key element to produce a trustworthy integrative literature review. Integrative literature reviews can be seen as an important tool for synthesizing and evaluating research findings across multiple studies. Data evaluation is a crucial step in the process of conducting an integrative literature review, as it involves assessing the quality and relevance of the data sources that will be included in the review (Whittemore & Knafl 2005).

The study design is an important factor to consider when assessing quality. Randomized controlled trials (RCTs) are generally considered to be the gold standard for assessing

intervention effectiveness, while observational studies are typically used to identify associations between variables. A study's sample size can affect the precision and generalizability of its findings. Larger sample sizes are generally preferred, as they can provide more accurate estimates of effect sizes and improve the generalizability of the findings. The methods used to collect data can also affect study quality. Studies that use valid and reliable measures are generally considered to be of higher quality (Cooper 2016).

Bias is a potential threat to the validity of study findings. Common types of bias include selection bias, measurement bias, and publication bias. It's important to consider whether a study is at risk of bias and how it may affect the study's results. The statistical analysis used in a study can also affect its quality. Studies that use appropriate statistical methods and report effect sizes and confidence intervals are generally considered to be of higher quality. Overall, assessing study quality involves considering a range of factors that can affect the validity and reliability of a study's findings (Cooper 2016).

The data evaluation was done with a one to four score system. Hawker et al. (2002) illustrates nine categories of evaluation model which have been used in this work. Table 3 summarizes the evaluation criteria used in this thesis. The evaluation criteria scores are presented in Table 4 (Appendix 1) that shows the list of publications selected to evaluation process and their points. The average evaluation score was 32 with the lowest score being 29 and the highest 36. Articles that got below 30 points were excluded. All articles that were used in results are introduced in appendices (Appendix 2).

Evaluation model	Good (4 points)	Fair (3 points)	Poor (2 points)	Very poor (1 point)
Abstract and title	Title and abstract provide accurate picture of article	Abstract has most information	Defective abstract	Abstract missing
Introduction and aims	Adequate background literature review with clearly specified aim and	Little background and literature review and defined	Either background or aim and research questions missing.	Background, literature review, aim and research question missing

	research questions	research questions		
Method and data	Method and data collection profoundly explained	Method imperfect and data collection plainly explained	Method and data poorly explained	Method and data missing
Sampling	Details of sampling defined	Some details of sampling given	Sampling is mentioned but details are not defined	Sampling missing
Data analysis	Precise definition of data analysis	Some details of analysis defined	Minimal details of analysis	Analysis missing
Ethics and bias	Inclusive analysis of ethics and bias	Some details of ethics and bias addressed	Minimal description of ethics and bias	Analysis of ethics and bias missing
Results	Logical result that are relevant to aims and research questions	Results are listed and logically explained but the relation between results and aims is narrowly explained	Results are listed but not logically. The relation between results and aims not explained	Results missing nor irrelevant to aims
Transferability or generalizability	Analyses the sampling and its accountability to be transferred widely. Needs high score also in the	Some analysis of sampling and its accountability. Also score 3 or 4 points in the evaluation of sampling.	Minimal analysis of sampling and its accountability.	Analysis of sampling and its accountability missing or low score in sampling

	evaluation of sampling.			
Implications and usefulness	Provides new points of view on the subject. Suggests further research. Suggest new policies or actions.	Provides two out three components described in 4 points score section of usefulness	Provides one out of three components described in 4 points score section of usefulness	All the components are missing
Total	36			9

Table 3: Evaluation criteria table. The maximum points the article can get is 36 and the lowest point is 9. (Hawker et al. 2002)

3.6   Data analysis

Data analysis is the process of examining, transforming, and interpreting data. The final 10 articles were studied again thoroughly and the results that the research articles presented were synthesized in order to get an outcome. The compiled data needs to be categorized, coded and summarized providing synthesis of results to avoid bias (e.g. Lubbe et al. 2012). All 10 articles were compared with the research questions shown in Table 1. The compiled data from 10 articles were divided into subgroups based on information, topic, or sample characteristics. The results were critically analyzed and connected to the original research questions and divided into two categories 1) low/middle-income countries, 2) high-income countries. Both groups have subgroups 1) depression, 2) QoL, 3) interventions.

The data from groups and subgroups were then reviewed again by checking one research question at time and then all questions together. The answers were analyzed and interpreted in order to build up new knowledge out of data.

4   Results

Totally 11 articles met initially the inclusion criteria and were selected to deeper analysis. Articles had coverage from low/middle-income to high-income countries answering well the original research questions. This thesis follows the same classification of high- and low/middle-income countries that the authors had used. It is important to mention that the classification is all but clear as the World Bank classifies low-income countries with GNI per

capita to be 1 086$ or less, lower middle-income economies with a GNI per capita between 1 086$-4 255$, upper middle-income economies with a GNI per capita between 4 256$-13 205$ and high-income countries above 13 205$ per capita (World Bank 2023). The classifications that the articles use were not defined and especially the problems within Asian countries and their classification should be thus noted.

Article 1 by Setyowibowo et al. (2017) was an RCT study protocol of a self-help psychoeducation program to reduce diagnosis delay in Indonesia which belongs to LMIC according to authors, and results have been already published. These two papers were analyzed together. Article 7 by Holtdirk et al. (2020) was an RCT evaluating a novel Internet intervention for breast cancer survivors in Germany and the results have been published as well so these two papers were analyzed together. Article 8 by Singleton et al. (2019) was also an RCT examining the effectivity of a text message intervention to support women's physical and mental health after breast cancer treatments in Australia and in this RCT the results are already published so these articles were evaluated together.

Article 2 by *The ACTION Study Group* (2017) examined health-related quality of life and psychological distress among cancer survivors in Southeast Asia in eight low- and middle-income countries. The study protocol was a longitudinal study. Articles 3 by Habimana et al. (2023) and 4 by Alwi et al. (2022) were cross-sectional studies examining prevalence and associated factors of depression and anxiety among cancer patients in Rwanda and predictors of health-related quality of life after completion of chemotherapy among Malaysian BC survivors. Rwanda is a low-income country, but Malaysia is belonging to middle-income countries. Article 6 by Jang et al. (2022) was a cross-sectional study of quality of life and prolonged symptoms in Korean breast cancer survivors. Korea is a high-income country with rapid development and known for its culture of serious overwork. Article 10 by Cheng et al. (2018) was a cross-sectional study that studies via questionnaires cognitive challenges while at work and work output in breast cancer survivors in a rapidly evolving economy in China. Article 11 by Fradelos et al. (2017) was a cross-sectional study about psychological distress and resilience in women diagnosed with breast cancer in Greece.

Article 5 by Uphoff et al. (2020) was a Cochrane library review of behavioral activation therapy for depression in adults with non-communicable diseases in United States where cancer is listed such a disease representing a high-income country. Cochrane reviews are recognized as one of the most reliable sources of evidence on the effectiveness of healthcare interventions. Article 9 by Delgado-Sanz et al. (2011) was a systematic review about health-related quality of life in Spanish breast cancer patients representing the high-income country, but it got only 29 evaluation points and did not offer modern research results and was thus discarded. All included articles are summarized in appendices (Appendix 2).

4.1 Depression and QoL among BC patients in low/middle-income countries

Breast cancer survival rates vary widely depending on the country. In high-income countries survival rates are as high as 90% but around 60% in middle-income countries and are as low as below 40% in low-income countries (The ACTION study group 2017). Depression and anxiety are common within all cancer patients around the world and particularly in low/middle-income countries (Habimana et al. 2023). Habimana et al. (2023) conducted a cross-sectional study at Butaro Cancer Center of Excellence in Rwanda to estimate the prevalence and depression with cancer patients. According to World Bank (World Bank Rwanda 2023) Rwanda are within the limit of belonging to MIC nowadays so whether Rwanda is a low- or lower middle-income country depends on the classification. They reported the prevalence of depression being 42.6% and anxiety being 40.9% among all cancer patients included in this study and 44% of the cancer patients had BC and within breast cancer patients the greater risk of depression was reported (AOR = 2.07, 95% CI (1.01–4.22)]). The global prevalence of depression among BC patients has been reported to be 32.2% (Belay et al. 2022) so Rwanda's BC depression rate is significantly higher than global BC depression rate. The study made in Ethiopia (Belay et al. 2022) reported as high as 58.6% depression rates among BC patients which is significantly higher than global depression rate or the rate Habimana et al. (2023) reported.

Habimana et al. (2023) also found out that if chemotherapy was combined with psychotherapy that decreased the mental disorders among the patients leading to better outcome than patients getting only chemotherapy. They did not report what kind of psychotherapy was offered so no conclusions can be drawn if behavioral activation therapy or standard therapy was offered thus making it impossible to compare the results with Uphoff et al. (2020).

The ACTION study was a longitudinal study in eight low/middle-income countries in Southeast Asia with 5249 first time cancer survivors followed up at 1 year after diagnosis. The ACTION study did not concentrate on one specific type of cancer, but results were introduced with subgroups of different cancers where breast cancer was one subgroup. 32% of participants had breast cancer. Results of the study showed that families living in low/middle-income countries in Southeast Asia had difficulties to manage the economic costs associated with cancer spending more than 30% of household income for cancer-related costs after one year of diagnosis (The ACTION study group 2017). In addition to economic burden outcome also health-related quality of life and psychological distress after one year of diagnosis was measured.

Lower psychological distress was seen among female patients with breast cancer and cervical cancer (The ACTION study group 2017) which is controversial compared to findings of

Habimana et al. (2023) who reported poorer outcome within women with breast cancer in Rwanda. The ACTION study group (2017) reports that 43% of women with generic cancer felt symptoms of depression after one year's time and around 40% of women who had BC were also depressive so the BC depression rate in selected Asian countries is lower than in Rwanda, but the result is not significantly lower. Patients with advanced stage of disease at diagnosis and those in a poor socioeconomic status had a higher risk for poor outcomes (The ACTION study group 2017). In all cancer groups a high income and paid work were associated with fever cases of anxiety and depression and better quality of life as health insurance did not affect these factors. The ACTION study group (2017) also reports that patients with a poor socioeconomic status are less likely to get appropriate follow-up care and discussion help with their healthcare providers.

Alwi et al. (2021) states that the evidence of health-related quality of life (QoL) is an important factor and outcome measure in breast cancer management but the evidence of QoL still remains sparse in low/middle-income countries. Alwi et al. (2021) carried out a cross-sectional study in University of Malaysia Medical Centre and selected 160 breast cancer patients. The aim was to examine the level of QoL, cognitive impairment and psychological distress among Malaysian early-stage BC patients one year up to three years following chemotherapy (Alwi et al. 2021). They reported that 31.9% showed cognitive impairment and 3.2% showed moderate to severe anxiety levels after the follow-up. They also reported that none of the participants demonstrated depression at 1 to 3 years following chemotherapy (Alwi et al. 2021). This means that most Asian breast cancer survivors have poorer health related QoL compared to Caucasian patients in high-income countries (Alwi et al. 2021). Also, Alwi et al. (2021) reports lower mean global health status compared to the findings of The ACTION study group (2017).

Controversially, Alwi et al. (2021) reported minimal anxiety and depression symptoms at 1 to 3 years following chemotherapy which is completely opposite finding compared to Habimana et al. (2023) and The ACTION study group (2017). Alwi et al. (2021) also mentions that complementary and alternative medicine (CAM) as a coping strategy is increasingly common among breast cancer patients in Malaysia which can lead to improved emotional distress, but this would need further scientific studies. Some of the results can be explained with staging as the study was conducted with early-stage BC patients and it generally accepted that advanced stage also means higher risk of depression.

The economic burden can be seen as a dominating factor in health-related quality of life and psychological stress specifically in low/middle-income Asian countries where workload was also higher than average. Women with breast cancer reported lower values of psychological stress than men with other cancer types in low/middle-income Asian countries (The ACTION study group 2017). The same trend was not seen in Rwanda, Africa, where women with breast

cancer had the greater risk of getting depression. Also, among Malaysian breast cancer patients the depression rates were significantly lower as no one within a study group reported depression in 1 to 3 years follow-up (Alwi et al. 2021). The economic burden was not highlighted as a dominant factor in Rwanda.

Future studies are needed to confirm if different work cultures and attitudes play a role in these different results. In middle-income Asian country Malaysia BC patients have poorer health related QoL compared to high-income countries, but they face minimal anxiety and depression symptoms compared to low/middle-income Asian countries studied in The ACTION study group (2017) or Rwanda. Some parts of this difference could be explained with wider CAM use in Malaysia, but this aspect needs further studies.

4.2   Are challenges different in high-income countries?

Breast cancer is one of the leading cancer-related death causes in high-income countries (Fradelos et al. 2017). Despite the good prognosis, specifically in high-income countries, all the cancer treatments and uncertainties cause stress and breast cancer patients are thus dealing with many physical and mental problems. Fradelos et al. (2017) point out that there is a growing interest in resilience as a way of coping after cancer diagnosis. They carried out a study among Greek breast cancer patients if there is a relation between resilience and mental health status. Fradelos et al. (2017) found out that BC patients from Greece have moderate levels of resilience where older patients had higher level of resilience. Women with lower resilience also reported higher amount of cancer symptoms. Their findings also indicate a correlation between levels of resilience and depression and anxiety levels. Depression levels were negatively related to resilience while there was a positive correlation between anxiety meaning that resilience may protect women from depression and anxiety. Patients who had depression showed less anxiety symptoms and feelings per se.

Uphoff et al. (2020) identified high-income country RCT studies of behavioral activation for depression in adults with one of four non-communicable diseases: cardiovascular disease, diabetes, cancer, and chronic respiratory conditions and included two studies one being women with breast cancer in US hospital clinics. The Cancer Care Ontario Program in Evidence-Based Care guideline recommends psychosocial and/or pharmacological interventions for depression in people with cancer. This collaborative care includes behavioral activation therapy that is recommended for the treatment of major depression or persistent subthreshold symptoms (Uphoff et al. 2020). This BC study's intervention consisted of eight weeks of face-to-face behavioral therapy compared to problem-solving therapy. Uphoff et al. (2020) reports treatment efficacy being greater for behavioral activation therapy than for comparators in the short term and medium term and effects were reduced in the long term.

There was no evidence of a different depression symptoms between the groups (Uphoff et al. 2020) and no difference for quality of life and anxiety symptoms.

Jang et al. (2022) studied health related QoL and influencing factors in breast cancer survivors in Seoul, Korea from treatment for at least to 1 year returning to normal life and work. They reported mean QoL being lower than expected when compared to studies done in United States. Psychological distress was as high as 67.8% along with anxiety being 47.2% and depression 36.7%. Jang et al. (2022) also reports that overwork was not a significant predictor of QoL even that 30% of employed women reported working up to 90 hours weeks.

Cheng et al. (2018) examined cognitive challenges while at work and work output in breast cancer survivors in China. The outcome was to determine if work output was related to cognitive limitations while at work. Both the study group and control group had similar educational backgrounds, job types and levels of job stress. The breast cancer survivor group met cognitive limitations at work and lower levels of work output than control group which can lead to lower QoL (Cheng et al. 2018). Jang et al. (2022) had reported that overwork was not lowering QoL in Korea, but their study did not estimate if the work output was similar than within healthy individuals.

Breast cancer patients in high-income countries generally have a good prognosis as BC can be seen as a chronic illness but this does not necessarily mean lower depression and QoL compared to low-income countries. Challenging work life in high-income country Korea was not affecting QoL but in China the work output was reported to be lower after treatments.

Resilience can be seen as a protecting factor against depression, anxiety and lower QoL. Patients in high-income countries are expected to have better resilience than patients in low/middle-income countries as patients in high-income countries may have access to more resources, such as advanced healthcare with all modern treatments, education, and social support networks, which can help them to build resilience. However, patients may also face unique challenges, such as high levels of stress and pressure in competitive work environments or social isolation and disconnection compared to patients in more community-based cultures.

Patients in high-income countries tend to be diagnosed at earlier stages than patients in low/middle-income countries which is naturally leading to better quality of life and reduced depression as cancer stage correlates with lower QoL and higher depression rates. Jang et al. (2022) reported depression rate to be 36.7% among BC patients in Korea which is lower than the rate of 40% in The ACTION study group (2017) and in Rwanda (above 42.6%). This result was expected as many previous studies had reported lower depression risk in high-income countries. These results would suggest that lower GNI correlates with higher depression and lower quality of life but as mentioned the significantly lower depression risk in middle-income

GNI Malaysia reported by Alwi et al. (2021) and its possible connection to CAM use would need more studies.

4.3 Interventions to reduce depression leading to better QoL in both high- and low/middle-income countries

Depression is common in breast cancer survivors which is connected to worse prognosis. Holtdirk et al. (2020) mentions that many women receive short-term psychological support in the acute phases of diagnosis and treatment, but this support is rarely available in subsequent phases in high-income countries. Self-efficacy can be seen as a key factor in better QoL, and different methods can be used to better self-efficacy among BC patients (Singleton et al. 2022a).

In LMIC Indonesia only 30% of patients with BC symptoms who came into hospital continue through the examination and biopsies to get a confirmed BC diagnosis and many women are already in advanced stage of cancer when starting the treatment (Setyowibowo et al. 2017). The incidence of BC in low/middle-income countries is lower as compared to high-income countries (25.8 vs 95 per 100.000), but a major concern in low/middle-income countries is the higher mortality despite its lower incidence (12.7 vs 17.1 per 100.000) (Setyowibowo et al. 2017). The general problem in low/middle-income countries is delayed breast cancer detection as many patients seek help only when their cancer has progressed to advanced stages. This can also lead to higher depression rates compared to high-income countries.

Various psycho-educational interventions have been designed for women with breast cancer as lack of health behavior education is seen as a major problem to late diagnosis in low/middle-income countries (Setyowibowo et al. 2017). Web-based programs have lately been offered for psycho-educational interventions to patients and their caregivers (e.g. Holtdirk et al. 2021), but specifically in many low-income countries the patients don't have access to internet within particularly vulnerable patient groups with low education, low socio-economic status, and those in rural areas (Setyowibowo et al. 2017). The PER-ANTARA study protocol was introduced in Indonesia in 2017 where selected patients got printed and audio-visual health education and psychoeducation materials (Setyowibowo et al. 2019). The primary outcome of this RCT was to decrease a diagnosis delay in terms of the time between the date of the first consultation at the hospital and the date of final breast cancer diagnosis based on pathological examination. Secondary outcomes were increasing breast cancer knowledge, to decrease anxiety and depression, and to better quality of life. Setyowibowo et al. (2019) postulates that PER-ANTARA protocol had a small to medium effect in reducing the time to diagnosis by an average of 13.3 days but did not reduce anxiety and depression or improve quality of life.

In high-income Germanic countries the RCT Optimune was launched to examine the holistic Internet interventions to provide additional psychological support (Holtdirk et al. 2020). Optimune contains 16 topics such as stress management, emotion regulation, healthy dieting and regular exercise after breast cancer treatment, sleep management, and CBT techniques to improve mental health. The outcome was to improve quality of life over the course of 3 to 6 months. The recruited participants are thought to report better QoL, more physical activity and improved dietary habits. The results showed significant effects on QoL and dietary habits but the effect on physical exercise was not significant (Holtdirk et al. 2021). Holtdirk et al. (2021) also mentioned that psychological distress may be linked with chronic systemic inflammation. Chronic systemic inflammation can lead to worse prognosis over time. Holistic internet interventions can be seen as useful to better QoL but the follow-up time in Holtdirk et al. (2021) was too short to draw long-term conclusions. As Uphoff et al. (2020) found out, the long-term effects to QoL did not improve with more holistic methods.

In high-income country Australia the RCT EMPOWER-SMS was launched to evaluate the efficacy, feasibility, and acceptability of a text-message intervention for breast cancer survivor's self-efficacy, quality of life, and mental and physical health (Singleton et al. 2019). Mobile health interventions can be seen as effective strategies for providing health information remotely as over 5 billion people own mobile phones globally (Singleton et al. 2022). EMPOWER-SMS delivered four text messages per week for 6 months. Messages were positive and self-personalized. The trial did not improve the primary outcome self-efficacy or secondary outcomes but did have a small significant improvement on endocrine therapy medication adherence (Singleton et al. 2022a).

Various interventions have been made to meet the psychological challenges among BC patients. It has been challenging to find a method to increase long-term QoL and decrease depression among BC patients both in high- and low/middle-income countries. The holistic internet platforms have so far given the most optimistic results when it comes to short-time QoL. Internet interventions can be seen more integrative and holistic as people with the same disease burden can support each other and change information. Community support seems to be one of the key factors in order to decrease the psychological burden of BC. The future challenge is to find similar community support actions that would be suitable also in more rural areas in low-income countries where it is more challenging to find and connect with people facing the same burdens for support.

5   Discussion and further recommendations

Depression is a common mental health condition that can affect anyone, regardless of income level or country of residence. However, research (e.g. Pilevarzadeh et al. 2019) suggests that

the prevalence of depression is higher in low/middle-income countries compared to high-income countries. This may be due to factors such as poverty, lack of access to mental health services, social and economic inequality, and previous exposure to violence and trauma.

Quality of life is a broad term that encompasses various aspects of an individual's well-being, including physical health, mental health, social relationships, and living conditions. In general, people living in high-income countries tend to have higher quality of life compared to those living in low-income countries and the same goes for BC patients (e.g. Koohi et al. 2017). This may be due to factors such as better access to healthcare, education, and social support services, as well as higher levels of economic stability.

Breast cancer diagnosis can cause anxiety and depression equally in low/middle- and high-income countries and affect quality of life. Depression is usually the highest among newly diagnosed patients and during the acute phase of cancer treatment (Belay et al. 2022). Depression risk and quality of life can vary significantly between high- and low/middle-income countries due to various socio-economic, cultural, and environmental factors (Figure 4). The global prevalence of depression among BC patients has been reported to be 32.2% (Belay et al. 2022) and in LMIC the prevalence of depression is thought to be higher (e.g. Pilevarzadeh et al. 2019). Some controversial results of prevalence of depression in LMIC have been suggested, for example Belay et al. (2022) reported the prevalence of depression in LMIC being 21% when Pilevarzadeh et al. (2019) have suggested significantly higher values around 55%.

Several interventions have been introduced in order to better quality of life among BC patients around the world (e.g. Singleton et al. 2022b). Psychotherapy, particularly cognitive-behavioral therapy (CBT) has been one of the most traditional interventions to better QoL. Other traditional interventions include antidepressant medications, support groups, mind-body techniques, exercise, education and information, social support, and integrated care. Many of these interventions require a country where the patients have access to multidisciplinary care, and this does not necessarily happen in low/middle -income countries.
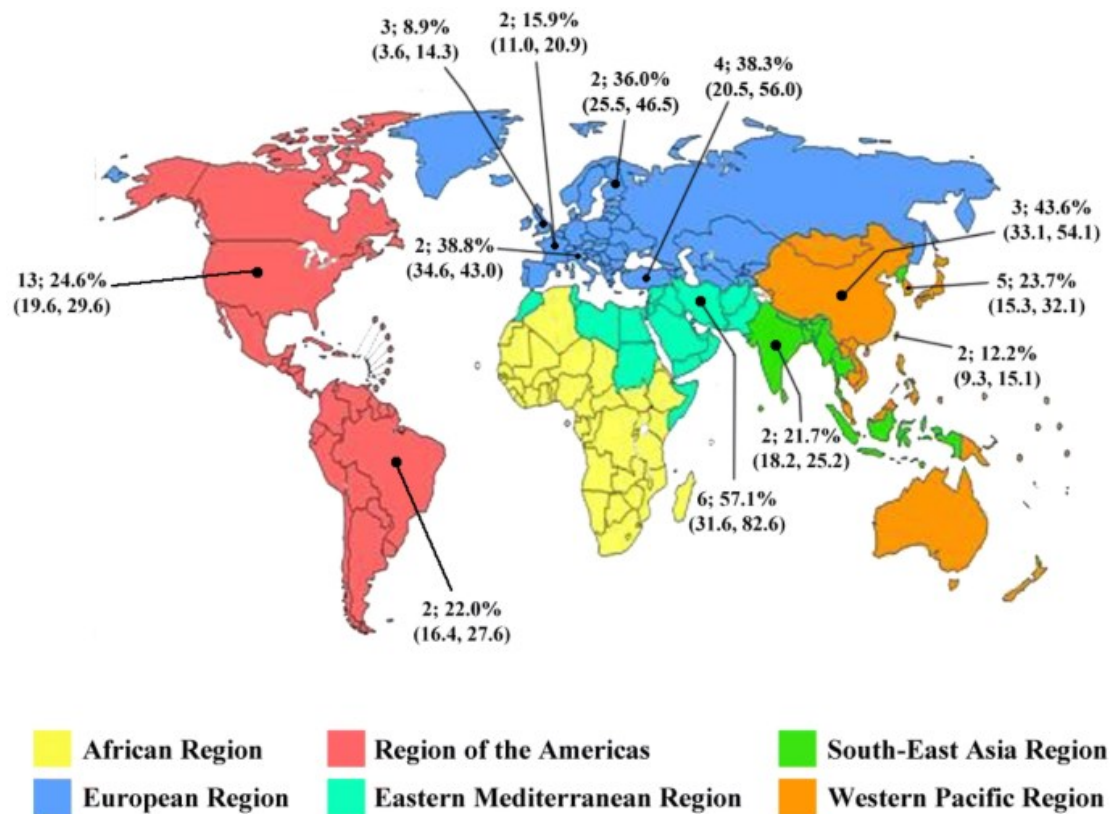
Figure 4: Pooled prevalence of depression. Pilevarzadeh et al. (2019) found out that the pooled prevalence of depression among breast cancer patients by WHO regions were showing that depression rates are higher in low/middle-income countries than high-income countries. *Reproduced with permission from Springer Nature.*

5.1   Aims and objectives

The aim of this thesis is to answer the following two research questions:

1) What kind of interventions there have been to decrease the depression rates and better the quality of life among BC patients in low/middle- and high-income countries?
2) Is there a correlation between the lower quality of life and higher prevalence of depression, and lower GNI?

The objective of this thesis was to gather novel information on the psychosocial situation of breast cancer patients around the world in order to make the world more equal to all breast cancer patients and their families.

As the results of this integrative literature review show, all low/middle-income countries are not the same when it comes to BC depression risk and QoL showing how complex the field of research is so not only the low/middle-income country status can define what kind of

psychological challenges the BC patients might face. To answer to the research question 2, African breast cancer patients seem to be in higher depression risk compared to Asian patients in low/middle-income countries. The middle-income Malaysia is an exception according to results as BC patients did not face any depression within the diagnosis and 1–3-year follow-up time but reported lower health related QoL compared to Caucasian patients in high-income countries. Some of this difference can be explained with cancer staging as this study was conducted with early-stage patients. Patients in Asian high-income countries have higher depression risk than Caucasians in high-income countries. Health insurance was not an important factor when depression risk was evaluated but economic burden was listed as a one key factor causing increased depression.

The results thus suggest that there is some correlation between higher depression and lower QoL and the country GNI but Malaysia was an exception when it comes to depression and not all high-income countries have similar rates so many cultural aspects might affect to depression and QoL. These results are mostly in line with existing research data as Figure 4 shows. Pilevarzadeh et al. (2019) found out that BC depression in South-East Asia region was 21.7% being a lot lower than in European and American regions which this study did not support as according to support data of this study the prevalence of depression was actually higher in Asian LMIC than among the Caucasians.

Many interventions have been tested to reduce depression and to better QoL among breast cancer patients both in low/middle- and high-income countries. The results show that these interventions have been internet-based platforms as well as automated but personalized weekly SMS messages as well as printed and audio-visual materials. The holistic internet platforms have so far given the most optimistic results when it comes to short-time QoL. It seems that platforms with discussion forums are the best for coping as support and meeting the people with same burdens help to develop better resilience which can lead to reduced depression and better QoL. Unfortunately, the interventions have not been tested in the poorest countries so the research question 1 can be only answered in middle-income and high-income countries and so far, more modern methods cannot significantly better QoL and lower the depression rates.

This integrative literature review did not manage to answer the objective how to make the world more equal to all breast cancer patients and their families as the included studies clearly show that there is still lack of research when it comes to breast cancer patients living in more rural areas in low/middle -income countries.

5.2 Strengths and obstacles

The used integrative literature search methodology and inclusion of studies and selection made by author alone may possibly lead to bias. The search words could have been more

precise or more general depending on the focus of the thesis. The schedule of this project made more advanced searches limited and the author could have been consulting the KI or Laurea library for more specific search terms. The strength of this study is the articles used as they all are published in known magazines and peer reviewed.

Article evaluation was based on Hawker et al.'s (2002) appraisal tool which can lead to potential limitations or challenges. The tool relies on the author's subjectivity in judgement when assessing the quality of qualitative research. Different reviewers may interpret the criteria differently, leading to variability in the ratings and potentially affecting the overall reliability of the appraisal. The tool focuses on specific criteria related to the methodological quality of qualitative research, such as study design, data collection, analysis, and ethical considerations. However, it may not capture other important aspects of qualitative research, such as the theoretical framework, reflexivity, or the richness and depth of data which can lead to limited scope. There is no universal consensus on which tool is the most appropriate or comprehensive for appraising qualitative research. Different tools may emphasize different aspects or have different criteria, leading to variations in the assessment process and potential inconsistency between studies. All the selected articles could thus be checked with different tools to get the widest scope and objectivity.

In this analysis, the structure of the support data and reviewed publications was followed, but it is worth mentioning that the results may be limited by the fact that other studies still fell prey of an old misconception, by which the world is divided in two groups, in this case high- and low/middle-income countries. Furthermore, the high and low thresholds are not consistent. The World Bank is currently dividing the economies to four income groups: low, lower-middle, upper-middle, and high, based on GNI per capita (World Bank Economies 2023). Also, The World Economic Forum (World Economic Forum 2023) stopped using the terms "developing" and "developed" in their official reports. They have started to use the same four-tiered categorization starting from 2016.

Hans Rosling, adviser to the WHO and UNICEF, also supported the division into 4 categories (Rosling et al. 2019). As Rosling et al. (2019) show, the division of the world in two groups, such as low/high income or developing/developed countries was somewhat accurate ~50 years ago, but that is not currently the case. While countries fell into distinct categories when looking at several metrics, including health-related matters (e.g., Figure 5 to illustrate, but similar to other metrics related to human development), the world has changed drastically, in a positive way, with most countries being in the area considered "developed" and presenting more continuous distribution.
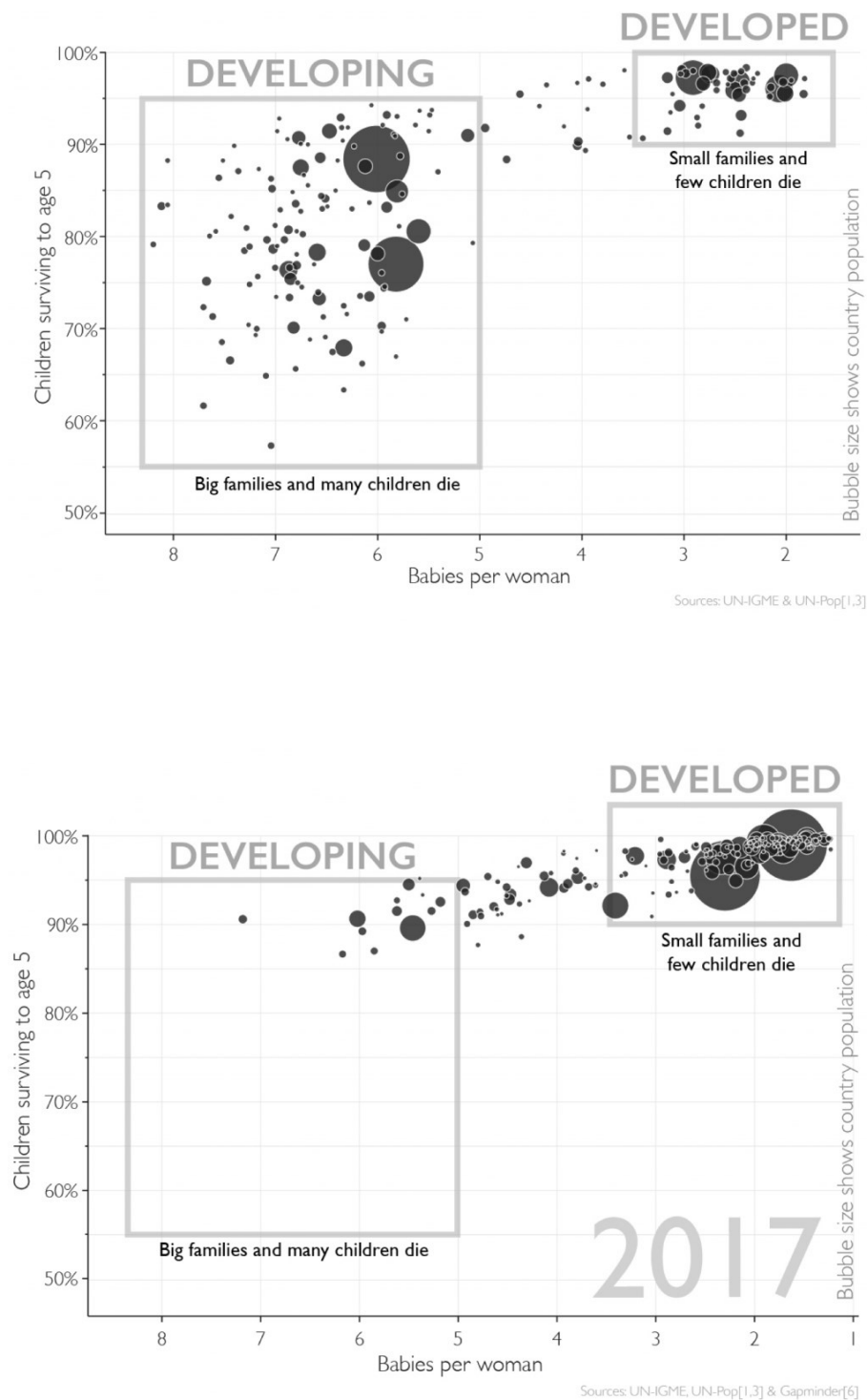
Figure 5: Division of the world 1965 and 2017. Relationship between number of children per woman and survival rate at age five. We can see that the division of the world in two distinct groups of countries (top panel, 1965 data) has changed considerably to more recent times (lower panel, 2017 data), making it hard to talk about developing/developed or poor/rich countries (Rosling et al. 2019 *Reproduced with permission from Gapminder.org*).

In the case of income, Rosling et al. (2019) propose as well a four-level division, where most of the population is in fact not in the lowest, nor the highest income levels (Figure 6).
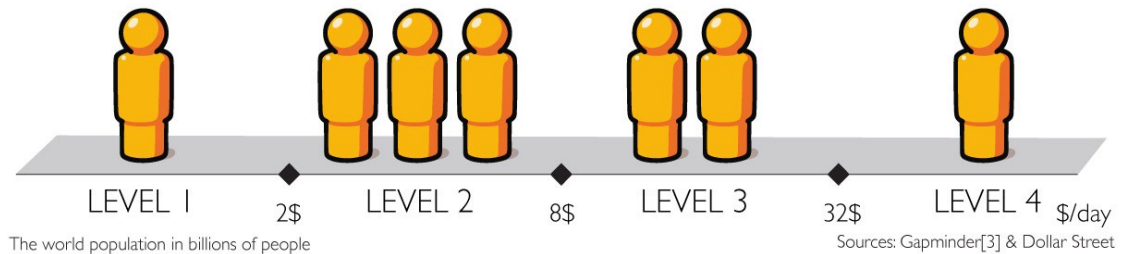

Figure 6: More granular division of the world into four income levels. We can see that most of the population is in the middle and not in what we would find if looking only at high- or low-income, which would be the extremes. (*Reproduced with permission from Gapminder.org*)

In addition, it should be noted that we have not delved into country-specific healthcare systems, taking the assumption that in high income there is better healthcare and support, which may not necessarily be the case (or not available to all the population). Decisions in global matters need to take into account a current and correct representation of the world and its populations.

Also, lack of studies in low-income countries as well as lack of definition by GNI was also challenging as the author did not have experience in health care systems in the countries mentioned in this study. This can easily lead to false interpretation as the patients included in these studies might be the richest in low/middle-income countries.

5.3   Future recommendations

The interventions to decrease depression and increase QoL among breast cancer patients have not been successful so far. Also, the integrated studies did not cover African region which can be seen challenging when it comes to prevalence of depression. The further studies are needed to examine more thoroughly which factors are contributing to higher depression risk in different low/middle-income countries and more precise definition of country categorization is recommended to create interventions to prevent depression in these countries in order to make the world more equal to BC patients and their families. The studies should also be homogenous meaning that depression prevalence and QoL should be compared with patients that have the same cancer burden (tumor staging and aggressivity).

As depression risk among BC patients is multifactorial it is worth mentioning that different cultural factors could be considered when patients meet multidisciplinary cancer teams. This thesis can offer new insights to all professionals working with multicultural BC patients to

help to understand why two patients from same economies can thus have different responses to breast cancer treatments and why are they facing different levels of depression.

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Figures

Tables

Appendices

Appendix 1: The selected 11 articles and their evaluation points

	Article	Points
1	Setyowibowo, H., Sijbrandij, M., Iskandarsyah, A. *et al*. 2017. A protocol for a cluster-randomized controlled trial of a self-help psycho-education programme to reduce diagnosis delay in women with breast cancer symptoms in Indonesia. *BMC Cancer* **17**, 284. https://doi.org/10.1186/s12885-017-3268-7 (Results) Setyowibowo, H., Hunfeld, J.A.M., Iskandarsyah, A., et al. 2020. A self-help intervention for reducing time to diagnosis in Indonesian women with breast cancer symptoms. Psycho-Oncology. 29:696–702. https://doi.org/10.1002/pon.5316	34
2	The ACTION Study Group. 2017. Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: results from a longitudinal study in eight low- and middle-income countries. *BMC Med* **15**, 10. https://doi.org/10.1186/s12916-016-0768-2	36
3	Habimana, S., Biracyaza, E., Mpunga, T., Nsabimana, E., Kayitesi, F., Nzamwita, P., Jansen, S. 2023. Prevalence and associated factors of depression and anxiety among patients with cancer seeking	30

	treatment at the Butaro Cancer Center of Excellence in Rwanda. Front Public Health. Feb 16;11:972360. doi: 10.3389/fpubh.2023.972360. PMID: 36875374; PMCID: PMC9978744.	
4	Alwi, S.S.M, Narayanan, V., Taib, M.N.A, Che, D.N. 2022. Predictors of health-related quality of life after completion of chemotherapy among Malaysian early-stage breast cancer survivors. Support Care Cancer. Mar;30(3):2793-2801. doi: 10.1007/s00520-021-06686-9. Epub 2021 Nov 29. PMID: 34841453.	30
5	Uphoff, E., Pires, M., Barbui, C., Barua, D., Churchill, R., Cristofalo, D., Ekers, D., Fottrell, E., Mazumdar, P., Purgato, M., Rana, R., Wright, J., Siddiqi, N. 2020. Behavioural activation therapy for depression in adults with non-communicable diseases. Cochrane Database Syst Rev. Aug 6;8(8):CD013461. doi: 10.1002/14651858.CD013461.pub2. PMID: 32841367; PMCID: PMC8094508.	36
6	Jang, M.K., Kim, S., Park, C., Collins, E., Quinn, L., Ferrans, C. 2022. Quality of Life and Prolonged Symptoms in Korean Breast Cancer Survivors. Cancer Nursing 45(1):p E124-E133. doi: 10.1097/NCC.0000000000000894	30
7	Holtdirk, F., Mehnert, A., Weiss, M. *et al*. 2020. Protocol for the Optimune trial: a randomized controlled trial evaluating a novel Internet	35

	intervention for breast cancer survivors. *Trials* **21**, 117. https://doi.org/10.1186/s13063-019-3987-y (Results) Holtdirk, F., Mehnert, A., Weiss, M., Mayer, J., Meyer, B., Bröde, P., Claus, M., Watzl, C. 2021. Results of the Optimune trial: A randomized controlled trial evaluating a novel Internet intervention for breast cancer survivors. PLoS One. 16(5):e0251276. doi: 10.1371/journal.pone.0251276. PMID: 33961667; PMCID: PMC8104369.	
8	Singleton, A., Partridge, S.R., Raeside, R. *et al*. 2019. A text message intervention to support women's physical and mental health after breast cancer treatments (EMPOWER-SMS): a randomised controlled trial protocol. *BMC Cancer* **19**, 660. https://doi.org/10.1186/s12885-019-5886-8 (Results) Singleton, A.C., Raeside, R., Partridge, S.R. *et al*. 2022a. Supporting women's health outcomes after breast cancer treatment comparing a text message intervention to usual care: the EMPOWER-SMS randomised clinical trial. *J Cancer Surviv*. https://doi.org/10.1007/s11764-022-01209-9	36
9	Delgado-Sanz, M.C., García-Mendizábal, M.J., Pollán, M. *et al*.	29

	2011. Heath-related quality of life in Spanish breast cancer patients: a systematic review. *Health Qual Life Outcomes* **9**, 3. https://doi.org/10.1186/1477-7525-9-3	
10	Cheng, A.S.K., Zeng, Y., Liu, X. *et al.* 2018. Cognitive challenges while at work and work output in breast cancer survivors employed in a rapidly evolving economy. *J Cancer Surviv* **12**, 753–761. https://doi.org/10.1007/s11764-018-0712-x	30
11	Fradelos, E.C., Papathanasiou, I.V., Veneti, A., Daglas, A., Christodoulou, E., Zyga, S., Kourakos, M. 2017. Psychological Distress and Resilience in Women Diagnosed with Breast Cancer in Greece. Asian Pac J Cancer Prev. Sep 27;18(9):2545-2550. doi: 10.22034/APJCP.2017.18.9.2545. PMID: 28952298; PMCID: PMC5720664.	30

Table 4: 11 selected articles and their evaluation points.

All papers getting 30 or more evaluation points were included in the results.

Appendix 2: Research table of the studies included in the literature review

Reference	Country	Purpose and aim of the study	Design and study sample	Data and methods	Results
Setyowibowo et al. 2017 and 2020 A protocol for a cluster-randomized controlled trial of a self-help psycho-education programme to reduce diagnosis delay in women with breast cancer symptoms in Indonesia. A self-help intervention for reducing time to diagnosis in Indonesian women with breast cancer symptoms.	Indonesia (LMIC)	To study if a self-help intervention can: -reduce diagnosis delay in women with BC - increase breast cancer knowledge, to decrease anxiety and depression, and to better quality of life Printed and audio-visual health education and psychoeducation materials offered to BC patients.	A cluster-randomized controlled trial (RCT) will be conducted in 132 patients in four hospitals in Bandung, West Java, Indonesia. Cross-over allowed. Data will be collected at baseline (pre-assessment), 7 days after the intervention (postassessment), and at 3 months (follow-up assessments).	A total of 132 patients were recruited. 67 patients were in the intervention group and 65 patients in control group (treatment as usual). Provided at successive periods in a randomly determined order. BC knowledge was measured by the Breast Cancer Knowledge Test (BCKT), symptoms of anxiety and depression were measured by the Hospital Anxiety and Depression Scale (HADS), quality of life was measured by the World Health Organization Quality of Life-BREF (WHOQOL-BREF) and health status was measured by the EQ-5D-5L. A linear mixed model analysis was conducted to analyse the outcomes.	PERANTARA material reduced the time to definitive diagnosis by 13.3 days. No significant difference was found between the groups in BC knowledge, symptoms of anxiety, depression, quality of life, or health status.
The ACTION study group 2017 Health-related quality of life and psychological distress among cancer survivors in Southeast Asia: results from a longitudinal study in eight low- and middle-income countries.	Eight low- and middle-income Asian countries	To study health-related quality of life and psychological distress among cancer survivors. To assess HRQoL and the prevalence of psychological distress amongst cancer survivors in Southeast Asia and identify risk factors of these outcomes.	A longitudinal study in eight LMICs in Southeast Asia with 5249 first time cancer survivors followed up at 1 year after diagnosis.	HRQoL was assessed using the EORTC QLQ-C30 and EQ-5D. Psychological distress (anxiety and depression) was assessed using the Hospital Anxiety and Depression Scale. General linear models and multiple logistic regression were used to identify independent predictors of HRQoL and psychological distress.	Cancer survivors in LMICs in Southeast Asia have impaired HRQoL and many have psychological distress. Patients with advanced cancer stages at diagnosis and those in a poor socioeconomic position were most at risk of such poor outcomes. Lower psychological distress was seen among female patients with breast cancer and cervical cancer. 43% of women with generic cancer felt symptoms of depression after one year's time and around 40% of women who had BC were also depressive.
Habimana et al. 2023 Prevalence and associated factors of depression	Rwanda	To determine the prevalence and factors of depression and anxiety among patients with cancer in Rwanda.	A cross-sectional study among 425 patients with cancer from the Butaro Cancer Center of Excellence. 44% of patients had BC.	Socio-demographic questionnaires and psychometric instruments. Bivariate logistic regressions were computed to	The prevalence of depression is 42.6% and anxiety is 40.9% among all cancer patients. Within breast cancer patients the greater risk of depression was

and anxiety among patients with cancer seeking treatment at the Butaro Cancer Center of Excellence in Rwanda.				identify significant factors to be exported into the multivariate logistic models.	reported (AOR = 2.07, 95% CI (1.01–4.22)]). Patients with cancer initiated to chemotherapy had a greater likelihood of being depressed than those initiated to chemotherapy and counseling.
Alwi et al. 2022 Predictors of health-related quality of life after completion of chemotherapy among Malaysian early-stage breast cancer survivors.	Malaysia	To examine the level of QoL, cognitive impairment, psychological distresses, and the predictors of QoL among breast cancer survivors 1 to 3 years following chemotherapy.	Cross-sectional study 160 breast cancer patients from the University of Malaya Medical Centre (UMMC). Their QoL was evaluated with the Malay version of the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) version 3.0. Cognitive functioning and psychological distress were evaluated using the Malay version of the Montreal Cognitive Assessment (MoCA-BM) and Hospital Anxiety and Depression Scale (HADS).	Data analysis was performed with Pearson's correlation and multiple regression analyses.	At 1- to 3-year post-chemotherapy, the mean EORTC QLQ-C30 global health status of the breast cancer survivors was relatively low. QoL was low. 31.9% of them demonstrated cognitive impairment, and another 3.2% showed moderate to severe anxiety levels. No one reported depression.
Uphoff et al. 2020 Behavioural activation therapy for depression in adults with non-communicable diseases	US	To examine the effects of behavioural activation compared with any control group for the treatment of depression in adults with NCDs. To examine the effects of behavioural activation compared with each control group separately (no treatment, waiting list, other psychological therapy, pharmacological treatment, or any other type of treatment as usual) for the treatment of depression in adults with NCDs.	Systematic review. CCMD-CTR, CENTRAL, Ovid MEDLINE, Embase, four other databases, and two trial registers on 4 October 2019 were search to identify RCTs of behavioural activation for depression in participants with NCDs, together with grey literature and reference checking.	Two studies were included, data from 181 participants. Both studies recruited participants from US hospital clinics; one included people who were recovering from a stroke and the other women with breast cancer. For both studies, the intervention consisted of eight weeks of face-to-face behavioural therapy, with one study comparing to poststroke treatment as usual and the other comparing to problem-solving therapy.	Treatment efficacy was greater for behavioural activation than for comparators in the short term. Effect was reduced in long-term. There was no evidence of a difference in depression symptoms between behavioural activation and comparators. One study found no difference for quality of life or anxiety symptoms.
Jang et al. 2022	Korea	To examine health-related QOL and influencing factors in BCS in Seoul,	A cross-sectional study.	Data from questionnaire analyzed with	Mean QOL scores were 49% of the variance explained by depressive

Quality of Life and Prolonged Symptoms in Korean Breast Cancer Survivors.		Korea, who have recovered from treatment for at least 1 year and returned to normal life and work.	199 patients completed a self-administered questionnaire.	correlation and regression analysis.	symptoms, physical fatigability, cognitive impairment, and social support. Psychological distress was high (67.8%), along with anxiety (47.2%) and depressive symptoms (36.7%). QoL was lower in Korean BCS than comparable studies in the United States.
Holtdirk et al. 2020 and 2021 Protocol for the Optimune trial: a randomized controlled trial evaluating a novel Internet intervention for breast cancer survivors Results of the Optimune trial: A randomized controlled trial evaluating a novel Internet intervention for breast cancer survivors.	Germany	To examine if QoL improves by offering cognitive behavioural therapy (CBT) and addressing exercise and dietary habits after the acute treatment phase by offering internet-based platform. To examine the holistic Internet interventions to provide additional psychological support. To improve quality of life over the course of 3 to 6 months.	RCT 16 topics such as stress management, emotion regulation, healthy dieting and regular exercise after breast cancer treatment, sleep management, and CBT techniques to improve mental health. 363 female breast cancer survivors. Participants were randomly assigned to an intervention group (*n* = 181), in which they received care as usual plus 12-month access to *Optimune* immediately after randomization, or a control group (*n* = 182), in which they received CAU and *Optimune* after a delay of 3 months.	Primary endpoints were quality of life (QoL), physical activity, and dietary habits at three months. A Priori power analysis Analyses of Covariance (ANCOVA) were conducted for the primary outcomes to test for between-group differences at the 3-month timepoint. Statistical analyses were performed with R-Studio 1.3	Intention-to-treat (ITT) analyses revealed significant effects on QoL and dietary habits but no effect on physical exercise.
Singleton et al. 2019 and 2022a. A text message intervention to support women's physical and mental health after breast cancer treatments (EMPOWER-SMS): a randomised controlled trial protocol. Supporting women's health outcomes	Australia	To evaluate the efficacy, feasibility and acceptability of a co-designed lifestyle-focused text-message intervention (EMPOWER-SMS) for breast cancer survivors' self-efficacy, quality of life (QOL), mental (anxiety, depression, stress) and physical (endocrine therapy medication adherence, physical activity, BMI) health.	Single-blind RCT To compare EMPOWER-SMS to usual care at 6-months (intention-to-treat). Participants 160 breast cancer patients.	Participants were randomised in a 1:1 (EMPOWERSMS: control) allocation ratio, using a secured central computer-based randomisation service. The outcomes were compared between EMPOWER-SMS and control groups at six-months, adjusting for the baseline measure of the outcome, with a significance level of 0.05. Dichotomous outcomes were analysed using log-binomial regression	Although EMPOWER-SMS was delivered as planned, it did not improve the primary outcome (self-efficacy) or secondary outcomes Significantly less EMPOWER-SMS participants missed ≥ 1 endocrine therapy medication doses compared to control.

after breast cancer treatment comparing a text message intervention to usual care: the EMPOWER-SMS randomised clinical trial.				and for continuous outcomes, the analysis of covariance (ANCOVA).	
Cheng et al. 2018 Cognitive challenges while at work and work output in breast cancer survivors employed in a rapidly evolving economy	China	To determine whether work output was related to cognitive limitations while at work	A cross-sectional study. Measures of demographics, job type, job stress, general distress (anxiety, depression), fatigue, work-related cognitive limitations, and work output were obtained using self-report measures. Both groups 267 participants.	A multivariable regression analysis. All statistical analyses were performed using the IBM SPSS program version 24 for Windows.	The BCS group reported higher levels of fatigue, general distress, and lower levels of work output.
Fradelos et al. 2017 Psychological Distress and Resilience in Women Diagnosed with Breast Cancer in Greece	Greece	To examine resilience in women diagnosed with breast cancer and its association with depression and anxiety.	A cross-sectional study. 144 women diagnosed with breast cancer answered a questionnaire consisted of four parts: Sociodemographic data, the Patient Health Questionnaire Two-Item Depression Scale, the Generalized Anxiety Disorder Questionnaire and the Connor-Davidson Resilience Scale 25.	Reliability of the instruments was tested with Cronbach's Alpha. Normality was checked by the Kolmogorov-Smirnov test. Pearson correlation coefficient was used to identify the relationship between the studied variables. Logistic regression analyses were used to determine which factors affect the depression and anxiety of cancer patients.	The mean value of resilience showed moderate resilience among patients. 54.5% of participants indicated a depressed mood. The anxiety severity measured with the GAD-2, where the mean was 2.1 and 46.8% of patients suffered from high anxiety. According to results, resilience can negative influence depressive symptomatology. Lower levels of depression can lead to fewer anxiety symptoms.