Oncology Central

The latest advancements in breast cancer survivorship

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Contents

Psycho-oncology: mental health, financial hardship and sexual well-being in cancer patients and survivors

What is psycho-oncology?

Psycho-oncology is an interdisciplinary field that covers the physical, psychological, social and behavioral aspects of oncologic disease. The aim of this field is to address these issues and provide support to patients and survivors of cancer who face numerous challenges during the course of the disease.

With medical advancements and an overall increasing life expectancy, the overall rates of cancer have also risen. Importantly, there are more people living with cancer for long periods of time as well as more people surviving cancer, which can have significant effects on a patient's physical and mental wellbeing.

This feature will explore the field of psycho-oncology, with a focus on financial hardship, mental health and sexual well-being of cancer patients and survivors, while highlighting the need for multidisciplinary care teams to optimize patient care.

How are cancer patients and survivors affected financially?

The financial effects of cancer and treatment have previously been explored, with a 2021 survey from the American Cancer Society Cancer Action Network (WA, USA) revealing that 61% of cancer patients and survivors in the USA struggled with cancer care costs. Additionally, 37% admitted having difficulty affording prescription drugs and treatment.

Now, a recent study has explored the financial challenges that young adult survivors of cancer experience during and after treatment. This study, led by Kaitlyn Lapen at Memorial Sloan Kettering Cancer Centre (NY, USA), administered a financial toxicity screening assessment tool to 2,519 patients between the ages of 15 and 39 [1,2].

The results were in keeping with the 2021 survey, finding that more than half of the survivors experienced financial toxicity, as well as difficulty affording social needs such as food, housing and transportation. Additionally, 10% did not have enough money for medications, and 7% took fewer medications than prescribed because of the cost, highlighting some of the barriers that lead to inequities in cancer care.

"Given lower quality of life and decreased adherence to treatment associated with financial toxicity, future research should focus on interventions to support the specific needs of AYA [survivors] and increase acceptance of financial assistance and navigation," concluded the study authors.

"Although economic hardships and burdens as a result of cancer diagnosis, treatment, and management may often go unaddressed, they are common and should be acknowledged. Making more people aware of the prevalence and impact of financial toxicity may also galvanize advancements in policy to mitigate financial toxicity," commented Lapen in a statement to the press.

Looking beyond material aspects of financial hardship, researchers from Northwestern University Feinberg School of Medicine (IL, USA) explored the interconnectedness of financial hardship, anxiety and depression.

The team analyzed data from 2,305 participants from the Northwestern University Improving the Management of Symptoms during and following Cancer Treatment Trial, revealing that financial hardship emerged as a prominent issue, with nearly half of the participants experiencing financial hardship [3].

The results also revealed that symptoms of anxiety and depression were linked to financial hardship, highlighting the need for a comprehensive care approach that combines financial counseling and psychological support.

Policy recommendations on financial burden

Recently, ASCO released a statement of recommendations to help reduce the financial burden cancer patients face when paying for treatment and care. The recommendation includes eliminating co-pay accumulator programs that raise out-of-pocket costs for prescription drugs, reducing or capping patient cost-sharing under Medicare Part B and ACA Marketplace plans and ultimately removing all out-of-pocket expenses for active cancer treatment.

Read the ASCO recommendations to reduce out-of-pocket costs for people with cancer

Understanding the prevalence of psychological distress

Some of the highest levels of psychological distress amid oncologic disease management and treatment side effects are reported in patients with head and neck cancers, with fear of recurrence noted as a top unmet need.

"Due to the location of the cancer, treatment may mean that there's highly visible disfigurement and long-term impact on eating, speaking and breathing," Gozde Ozakinci (University of Stirling, UK) commented. "This means that head and neck cancer patients experience high levels of psychological distress – some of the highest among all cancer groups. Despite this, efforts to understand distress for head and neck cancer patients and how it develops have been lacking."

To address this, a collaborative team from the University of Stirling, University of St Andrews, University of Bristol (all UK) and the University of Delaware (USA) and analyzed 4,891 questionnaire responses from people with head and neck cancer in the UK to assess how changes in anxiety and depression during the first year after diagnoses may relate to fears of recurrence [4, 5].

The team found that in the first 4 months of treatment, over 34% of participants had an increase in anxiety, while nearly 60% had an increase in depression. The results also indicated that early-level increases in anxiety were precursors for increased fear of recurrence in patients; therefore, targeting anxiety early in cancer treatment may mitigate fears of recurrence from developing.

Ozakinci explained: "Patients may see worry as a way of being prepared for cancer coming back and this unhelpful belief may lead to rumination, reduced quality of life and behaviors that are not helpful."

"By identifying how anxiety at the beginning of cancer treatment can impact on fears of cancer coming back, we can work with health care providers who interact with the patients and put support in place so that these anxieties are addressed."

Mental health challenges in rare cancers

While important studies, such as the one above, have been conducted in common cancers, the psychological impact of rare cancers – which affect fewer than 6 in 100,000 people per year – is less understood and has not been compared with the impact of common cancers before.

Now, in a study led by Valeria Yang at the National Cancer Center Singapore and A*STAR Institute of Molecular and Cell Biology (Singapore), the psychological outcomes of 57,470 patients with rare cancer have been assessed. The study indicated that patients with rare cancers are nearly three times more likely to develop mental health issues, such as anxiety

and depression, compared to those with common cancers. High rates of suicide (300 per 100,000 people) and PTSD (18%) were also reported in those with rare cancers [6, 7].

As there are fewer individuals with rare cancers, clinicians may be less aware of the psychological challenges faced by these patients. "While each individual diagnosis might be rare, as a whole, rare cancers actually account for 25% of all cancers. This, coupled with the rising burden of rare cancers globally, highlights the critical need for more support for this group of patients," commented Yang.

The study also highlights specific risk factors in rare cancer patients who may develop negative psychological outcomes, as well as the need for early identification of when psychological support is needed for these patients. These risk factors include chemotherapy treatment, advanced disease, lower income and social status.

While each individual diagnosis might be rare, as a whole, rare cancers actually account for 25% of all cancers.

Next, the study team is working closely with clinical specialists who support rare cancer patients. These include methods for the early identification of patients and referral to support teams such as social workers, with.t the aim of creating approaches that could be applied to managing the psychological needs of all vulnerable patient populations.

A closer look at breast cancer and psycho-oncology

Many breast cancer patients have concerns about sexual health, with previous reports citing that 85% of patients report sexual dysfunction but receive very little medical guidance. Further to this, very few studies about breast cancer treatment have focused on sexual well-being, particularly on the different outcomes following breast cancer surgery.

Now, researchers have analyzed sexual well-being in 15,857 breast cancer patients who underwent different types of surgery. The team used the Sexual Well-Being section of the validated BREAST-Q questionnaire to compare scores between patients who underwent breast-conserving therapy (BCT; 54%) and postmastectomy breast reconstruction (PBMR; 46%) [8, 9].

The results revealed that before surgery, both groups had similar sexual well-being scores, but following surgery, patients who underwent PBMR had lower sexual well-being scores than those who underwent BCT. Additionally, despite the effects of cancer and treatment on sexual-wellbeing, only 3.5% of BCT group and 5.4% of the PBMR group received a sexual medicine consultation.

"The findings highlight the need for increased attention to sexuality when discussing breast cancer treatment options," explained the study authors.

Looking at survivorship, many breast cancer survivors experience fears of cancer recurrence. For some, this fear is occasional, while for others, this fear can be constant and debilitating.

A study conducted by Indiana University-affiliated institutions investigated the impacts of this by surveying 347 breast cancer survivors, revealing that almost all aspects of life can be affected by fears of recurrence, including emotional, behavioral, cognitive, relational and professional domains. Additionally, the study found that more of these domains were affected in survivors who experienced the greatest fears of occurrence [10, 11].

"Fear of cancer recurrence is one of the most common psychological challenges for cancer survivors. Understanding affected life domains, coping strategies employed prior to intervention, and reasons for seeking guidance can inform the development and implementation of evidence-based interventions to effectively address fear of cancer recurrence among persons living with breast cancer."

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How are oncofertility advancements supporting pregnancy, breastfeeding and fertility preservation for cancer patients?

The need to tackle the long-term effects of cancer and subsequent treatment is rapidly growing, particularly as survival rates of young cancer patients continue to rise. After endocrine health, Oncofertility connects endocrine health and reproductive health, focusing on the unique challenges faced by cancer patients and survivors.

As patients look forward to life after cancer, many face difficulties with fertility as a result of either their treatment or the disease itself. Within oncofertility, fertility preservation has become a key area of focus, with this now becoming a standard element of cancer care plans. This feature explores clinician-patient discussions around fertility, emerging fertility preservation techniques and highlights evidence that breastfeeding after breast cancer is safe.

Are fertility preservation discussions falling short for early-onset cancer patients?

A questionnaire conducted by Vanderbilt-Ingram Cancer Centre (TN, USA) investigators as part of the Reproductive Health After Cancer Diagnosis and Treatment (REACT) study revealed that only 50% of people with early-onset cancer recalled discussing fertility preservation options with their clinician before beginning cancer treatment.

The REACT study aims to improve clinicians' and researchers' understanding of the unmet care needs of early-onset cancer patients (patients aged 18–49), including unmet needs around fertility and fertility preservation.

The study collected questionnaire results from 473 patients, yet only 240 patients reported discussing fertility preservation options with healthcare professionals before treatment initiation. The reported discussions differed by cancer type, with thyroid, lung, ovarian and colorectal cancer patients reporting the lowest prevalence of fertility preservation discussions.

While a study on perceptions and experiences may introduce recall bias, it still raises important insights around the appropriate timing for fertility preservation discussions and the experiences of young cancer patients [1, 2].

What advancements have been made in access to ovarian tissue cryopreservation?

Ovarian tissue cryopreservation (OTC) is a fertility preservation option that was once considered experimental, but now, is considered a standard treatment and is being offered at select clinics.

Researchers from the University of Calgary (Canada) have established an OTC program for young cancer patients, offering fertility preservation or prepubertal patients impacted by cancer.

As the survival rates of pediatric cancer approach 90% in Canada, the need for fertility preservation options is becoming increasingly important to give patients and families hope for the future and the chance to have biological children, if they want to [3].

A person born with ovaries has all the eggs of their lifetime at birth, however, aggressive treatments used to treat pediatric and adolescent cancers can affect fertility and may cause premature menopause [3]. At the University of Calgary, when families and children facing aggressive treatment first meet with an oncologist, they are introduced to fertility preservation options as part of their care plan, including OTC.

OTC involves removing one or both ovaries laparoscopically before the initiation of cancer treatment. Strips of ovarian tissue containing unfertilized eggs are then removed and frozen [2]. After a patient has undergone cancer treatment and is considered cancer-free and ready to have children, the tissue is transplanted in a peritoneal pocket near the location of the removed ovary, in the hope that normal ovarian function will return [4]. This offers patients the best chance of conceiving a child.

This technique is effective in preserving the fertility of early-onset cancer patients, however, many patients still require assisted reproductive technology, such as IVF, in order to conceive a child [4].

Calgary is one of the only centers in Canada that offers OTC and combined treatment of endocrine health and reproductive health. However, as the field of oncofertility continues to advance, OTC may be routinely offered as part of standard care in other locations.

The researchers from the University of Calgary aim to expand their fertility preservation program to include patients with testes as well as those with ovaries.

"All initiatives to make oncofertility available to young cancer survivors should be applauded, and efforts should continue to make sure these services are equitably accessible too" commented Miranda Fidler-Benaoudia (University of Calgary) [3].

Is breastfeeding after breast cancer safe?

Two international studies presented at ESMO Congress 2024 (13–17 September 2024, Barcelona, Spain) provided the first evidence that breastfeeding after receiving treatment for breast cancer is safe and does not lead to an increased risk of recurrence or new breast tumors. One of the studies also provided evidence that pausing breast cancer treatments to have a child is safe.

While breast cancer is more commonly found in middle-aged and older women, it can occur at any age, with 7% of new diagnoses occurring in women under 40. As a result, there may be a number of breast cancer patients receiving breast cancer treatment before they decided to conceive and breastfeed a child.

The POSITIVE trial analyzed women with hormone-receptor-positive breast cancer who ceased endocrine therapy to conceive a child and breastfeed. After this, the women resumed treatment, ideally within 2 years.

After a 41-month follow-up period, the study concluded that temporarily pausing endocrine therapy to conceive a child and breastfeed is safe. The rates of breast cancer recurrence were modest, with the women doing just as well as a historical control group. Additionally, at 2-years post birth, the number of women with breast cancer recurrence or new breast cancer was similar between those who breastfed and those who did not.

The second study followed 4732 young women carrying a utation who survived breast cancer, 474 of which subsequently gave birth and breastfed their babies. Following a median follow-up of 7-years post birth, the study found that there was no difference in the number of breast cancer recurrences or new breast tumors in those who breastfed their baby and those who did not [5].

How are oncofertility advancements shaping the future of cancer care?

Together these articles show the advancements that have been made in oncofertility, such as providing evidence that pausing endocrine therapy to conceive a child and breastfeed is safe, as well as the development of fertility preservation techniques and programs, all of which help to provide support for the reproductive health of a cancer patient.

While these advancements offer hope to patients and their families, they also reveal opportunities for further research, such as into fertility preservation techniques for patients with testes. Additionally, they highlight the need for better communication between healthcare professionals and patients about reproductive health, fertility preservation options and life after cancer.

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5. Studies provide first evidence that breastfeeding after breast cancer is safe

Breastfeeding choices for cancer patients: insights from the POSITIVE trial

Fedro Peccatori is the Director of the Fertility and Procreation Unit within the Division of Gynecologic Oncology at the European Institute of Oncology (Milan, Italy). He is a medical and gynecologic oncologist whose clinical activities mainly include the diagnosis and treatment of breast cancer, gynecologic malignancies and tumors in young adults. His main research projects deal with fertility preservation and counseling in young oncological patients, pharmacological protection of ovarian function during chemotherapy, clinical and molecular characterization of pregnancy-associated cancers and research protocols for the treatment of breast and gynecological malignancies.

In this interview, Fedro Peccatori (Istituto Europeo di Oncologia, Milan, Italy) discusses the POSITIVE trial, which is assessing the impact on women with Stage I–III hormone receptor-positive breast cancer taking a break from endocrine treatment to breastfeed. He highlights the importance of discussing breastfeeding with pregnant breast cancer survivors in prenatal counseling and concludes by discussing future work that needs to be done to understand the long-term impact of pausing treatment to breastfeed.

What factors or conditions should be considered when recommending breastfeeding for breast cancer patients post-treatment?

Any woman who wishes to breastfeed after breast cancer should be supported in doing so. Breastfeeding counseling should be non-directive and explore each woman's attitudes, offering support when needed. All reproductive choice options should be discussed as part of preconceptional or prenatal counseling. I really like the idea of having a "birth plan" during pregnancy to address possible issues about breastfeeding after breast cancer well in advance.

The POSITIVE trial evaluates the safety of pausing endocrine treatment in patients with hormone receptor-positive breast cancer who want to become pregnant. It is a prospective, international, multicenter, single-arm trial that enrolled 518 patients who were 42 years or younger across 20 countries over 5 years.

Eligible patients had Stage I–III hormone receptor-positive breast cancer and had a strong desire to become pregnant. The trial allowed 18–30 months of endocrine treatment, followed by 3 months of wash out, and up to 2 years' break to allow for conception, delivery and breastfeeding. After that, patients were strongly suggested to restart and complete endocrine treatment.

The analysis of data about breastfeeding from the POSITIVE trial are quite clear: breastfeeding after breast cancer should be supported as it is feasible and safe, at least in the short-run. On the other hand, even if the advantages of breastfeeding for the infant are definitive, women who choose not to breastfeed after breast cancer should be equally supported. Of note, one of the factors favoring breastfeeding in the POSITIVE cohort was breast-conserving surgery. In the study, we could not explore the reason why women with unilateral mastectomy breastfed less but this is an interesting point to address in the future.

What other endpoints were explored in the trial?

The primary endpoint of the POSITIVE trial was the breast cancer free interval. Secondary endpoints were the distant recurrence-free interval, pregnancy outcomes, offspring outcomes, use of assisted reproductive technology, adherence to endocrine treatment and breastfeeding. Results after a median follow up of 41 months were published in the New England Journal of Medicine and Journal of Clinical Oncology and breastfeeding data are those presented at the European Society for Medical Oncology Congress 2024 that will be eventually published in a peer-reviewed journal [1,2].

How do you hope to see these findings impacting clinical guidelines for breast cancer aftercare?

Given these data, speaking about breastfeeding to women who are pregnant after breast cancer should be an essential part of the prenatal counseling of breast cancer survivors. The POSITIVE trial is the largest prospective series investigating breastfeeding frequency, pattern and impact on breast cancer relapse in women with hormone receptor-positive early breast cancer who temporarily interrupted endocrine treatment to seek pregnancy.

I hope this evidence, together with the evidence coming from patients harboring BRCA pathogenic variants, will be incorporated into clinical guidelines and help women exploit their reproductive choice to achieve real reproductive autonomy.

What are the next steps for the study?

We need to continue the follow-up of patients in the POSITIVE study to understand if the temporary interruption of endocrine treatment is safe in terms of providing a breast cancer free interval and to understand if breastfeeding is safe in the long run. POSITIVE is an academic trial with no support from pharmaceutical companies and we are seeking forward-thinking donors interested in supporting the completion of this practice-changing study.

The opinions expressed in this interview are those of the author and do not necessarily reflect the views of Oncology Central or Taylor & Francis Group.

The POSITIVE study is sponsored and conducted globally by the ETOP IBCSG Partners Foundation in collaboration with the Breast International Group (BIG) and by the Alliance for Clinical Trials in Oncology in North America.

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RESEARCH ARTICLE

Perceived social support mediates cancer and living meaningfully intervention effects on quality of life after breast cancer surgery

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ABSTRACT

Aim: To explore the role of perceived social support in enhancing psychological resilience and quality of life in postoperative breast cancer patients.

Materials & methods: The Managing Cancer and Living Meaningfully (CALM) intervention was used to improve indicators such as psychological resilience in breast cancer patients, while the role of perceived social support in this was assessed.

Results: The intervention group exhibited significant improvements compared with the control group in psychological resilience ($F = 9.059$, $p < 0.01$). The analysis showed that increased social support in the control group partly mediated the link between psychological resilience and quality of life.

Conclusion: CALM improves overall well-being, indicating that incorporating it into standard care for post-mastectomy patients can positively impact their mental health.

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breast cancer; quality of life; resilience; social support

1. Background

Breast cancer, a prevalent malignancy with rising incidence rates, originates from malignant transformations in the breast's glandular or ductal epithelial cells [1]. It remains a formidable health concern for women globally, given its physical implications and the profound psychological distress it imposes on patients [2]. Researchers such as Andrea Chirico, Holger Cramer and others consistently highlight the simultaneous presence of anxiety and depression among breast cancer patients, leading to a substantial deterioration in their overall quality of life [3,4].

Breast cancer surgeries, such as modified radical surgery and breast-conserving surgery, are common interventions for breast cancer management [5]. These surgeries elicit various emotional and psychological complexities in patients [6]. Patients undergoing surgery for breast cancer often experience heightened anxiety, fear and uncertainty before the procedure, followed by a range of emotional responses post-surgery, including relief, sadness, grief or apprehension related to changes in body image [7].

Patients undergoing breast cancer surgery may experience physical effects such as pain, discomfort, restricted mobility and fatigue, which can contribute to emotional distress [8]. Furthermore, long-term psychological challenges related to body image, self-consciousness and relationship changes may arise, highlighting the importance of proactive identification and management of mental well-being to enhance overall wellness and quality of life in these patients [9]. Recognizing the complex interplay between physical and psychological aspects is vital for providing comprehensive care that addresses the multifaceted challenges faced by individuals affected by breast cancer [10].

In recent years, psycho-oncology has witnessed the rise of psychological interventions as a promising avenue for addressing the mental health requirements of individuals grappling with cancer, affording them invaluable support and guidance throughout their cancer trajectory [11]. The Managing Cancer and Living Meaningfully (CALM) intervention has gained notable recognition among these interventions. Tailored to the unique needs of cancer patients, CALM aims to facilitate the discovery of purpose and significance in life, fortify coping mechanisms and enhance emotional well-being [12]. By honing in on the psychological dimensions of the cancer experience, these interventions endeavor to alleviate distressing symptoms and foster resilience among patients.

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While previous research has demonstrated the efficacy of CALM interventions in alleviating anxiety and depressive symptoms among individuals diagnosed with diverse cancer types, their potential value in supporting breast cancer patients remains promising [13]. However, despite these encouraging findings, the mechanisms underlying the impact of CALM interventions on mental health outcomes for patients with breast cancer are still poorly understood. To enhance our understanding of the intricate dynamics experienced by post breast cancer surgery, it is crucial to explore the interactions between CALM interventions, mental health outcomes, quality of life, perceived social support and psychological resilience, thereby providing further insights into this complex domain.

Perceived social support encompasses the subjective perception of receiving assistance, understanding and acceptance from various sources, including family, friends, healthcare professionals, support groups and others. It encompasses multiple dimensions, such as emotional support (empathy, listening, understanding), instrumental support (practical assistance) and informational support (guidance, advice) [14]. Perceived social support is crucial in fostering a sense of belonging, reassuring and facilitating adaptive coping strategies among breast cancer patients [15]. Psychological resilience, characterized by adapting to and recovering from adversity, protects against cancer-related stress [16,17]. Moreover, resilience can safeguard body image and prevent negative self-esteem following mastectomy. Breast cancer patients with higher resilience tend to perceive more excellent social support, including emotional encouragement, practical assistance and guidance [18].

Research consistently affirms the transformative impact of heightened resilience and robust social support on breast cancer patients, translating into not only improved emotional well-being and reduced pain but also enhanced coping mechanisms and increased life satisfaction [19]. This study candidly acknowledges the challenges posed by external factors, notably the disruptive impact of the COVID-19 pandemic. However, amidst these obstacles, the findings accentuate the invaluable role of social cohesion within the group, underscoring its positive influence on participants' mental health. These insights serve to reinforce the enduring importance of integrating social and group factors into psychological interventions for cancer survivors [20]. Additionally, another study sheds light on the indispensable role of peer and social support in fostering active sports participation, recognizing their critical function in overcoming internal and external barriers, including issues such as lack of motivation, fatigue and time constraints [21].

The primary objective of this study is to examine the effects of the CALM intervention on the mental health of postoperative breast cancer patients, specifically focusing on anxiety, depression and quality of life. Additionally, we aim to investigate the potential mediating role of perceived social support in the relationship between psychological resilience and quality of life. By analyzing the interconnections among the CALM intervention, mental health outcomes and psychological resilience, we aim to uncover the mechanisms that underlie the positive impact of the CALM intervention on mental well-being. Three hypotheses guide our study. First, we hypothesize that postoperative breast cancer patients exhibit low levels of psychological resilience. Second, we predict that the CALM intervention will enhance psychological resilience among postoperative breast cancer patients. Last, we hypothesize that perceived social support mediates the association between changes in psychological resilience and quality of life. The complexity of these relationships is visually represented in Figure 1, which highlights and tests each hypothesis.

2. Materials & methods

2.1. Trial design

This study utilized a randomized controlled trial design to assess the effectiveness of the CALM intervention in breast cancer patients. The participants were randomly assigned to either the Intervention Group (IG) or the Control Group (CG) (Figure 2).

2.2. Participants

The study was conducted at the Second Affiliated Hospital of Anhui Medical University. A total of 124 breast cancer patients were included in the study, with 62 patients in the intervention group and 62 patients in the control group. The participants were recruited between September 2021 and June 2022, and all provided informed consent. The eligibility criteria included age above 18 years, a confirmed diagnosis of breast cancer and scheduled breast cancer surgery. Exclusion criteria included a history of central nervous system disorders and prior use of cognitive function-enhancing drugs or treatment for severe anxiety and depression.

2.3. Interventions

Table 1 provides a comprehensive overview of the various interventions and actions comprising the CALM treatment for breast cancer patients, including therapeutic alliance, open communication, behavioral interventions, group supervision, random assignment, privacy measures, eligibility assessment, translation and the incorpo-

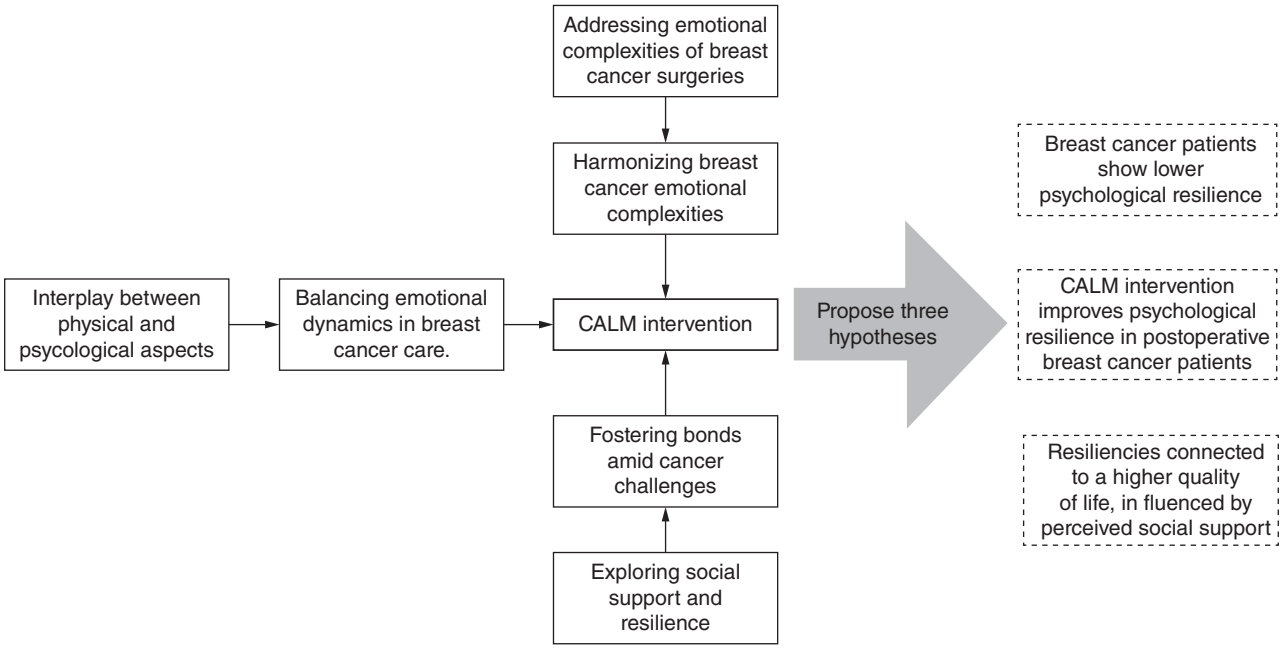

Figure 1. CALM in breast cancer care: surgical emotions, comprehensive well-being and support dynamics.
CALM: Managing cancer and living meaningfully.

ration of VR technology, all aimed at improving patient outcomes and offering personalized and accessible care. Patients were randomly assigned to either the intervention group receiving CALM treatment or the control group receiving usual care.

A six-member team, including four postgraduates, one psychologist and one oncologist, administered the CALM intervention to the intervention group. The control group received the usual care without additional psychological treatment. The CALM therapists underwent extensive training and clinical supervision before delivery. Senior clinicians oversaw intervention quality and effectiveness. The CALM therapists delivered six CALM interventions, each lasting 30 min over 12 weeks. Psychological scales measured at 6 weeks, 12 weeks after the first intervention and 12 weeks after the last intervention assessed effectiveness. Group supervision meetings ensured protocol adherence and skill development. Therapists submitted case reports and recorded interviews for analysis and evaluation.

In this study, CALM therapists were fastidiously selected from a cohort of esteemed professionals pursuing master's or doctoral degrees in oncology. Their expertise was honed through a comprehensive training and supervised process orchestrated by seasoned clinical investigators, encompassing 6 h of formal instruction and practical exercises. The training placed paramount importance on essential factors such as empathy, cultural sensitivity and a person-centered approach meticulously tailored to the unique needs of breast cancer patients. Detailed case reports rigorously gauged proficiency, offering a thorough panorama of their application to intervention measures. Beyond formal training, these therapists exhibited a profound understanding of the challenges faced by breast cancer patients, approaching their work with genuine empathy. Their commitment extended beyond addressing the intervention's technical aspects to encompass each participant's emotional and mental well-being. This comprehensive expertise ensured the effectiveness and impact of CALM intervention in fostering psychological resilience among diverse participant groups.

2.4. Crucial steps in CALM interventions

2.4.1. Patient assessment & tailoring

Each patient underwent a thorough assessment to comprehend their unique psychological needs, fears and challenges associated with cancer. The CALM intervention was then tailored meticulously to address these specific concerns.

2.4.2. Psychoeducation

The intervention commenced with an extensive psychoeducational component. Patients were enlightened about the factual nature of cancer, dispelling common misconceptions and addressing the multifaceted meanings associated with the disease. This phase aimed to provide a clear and accurate understanding of the illness.

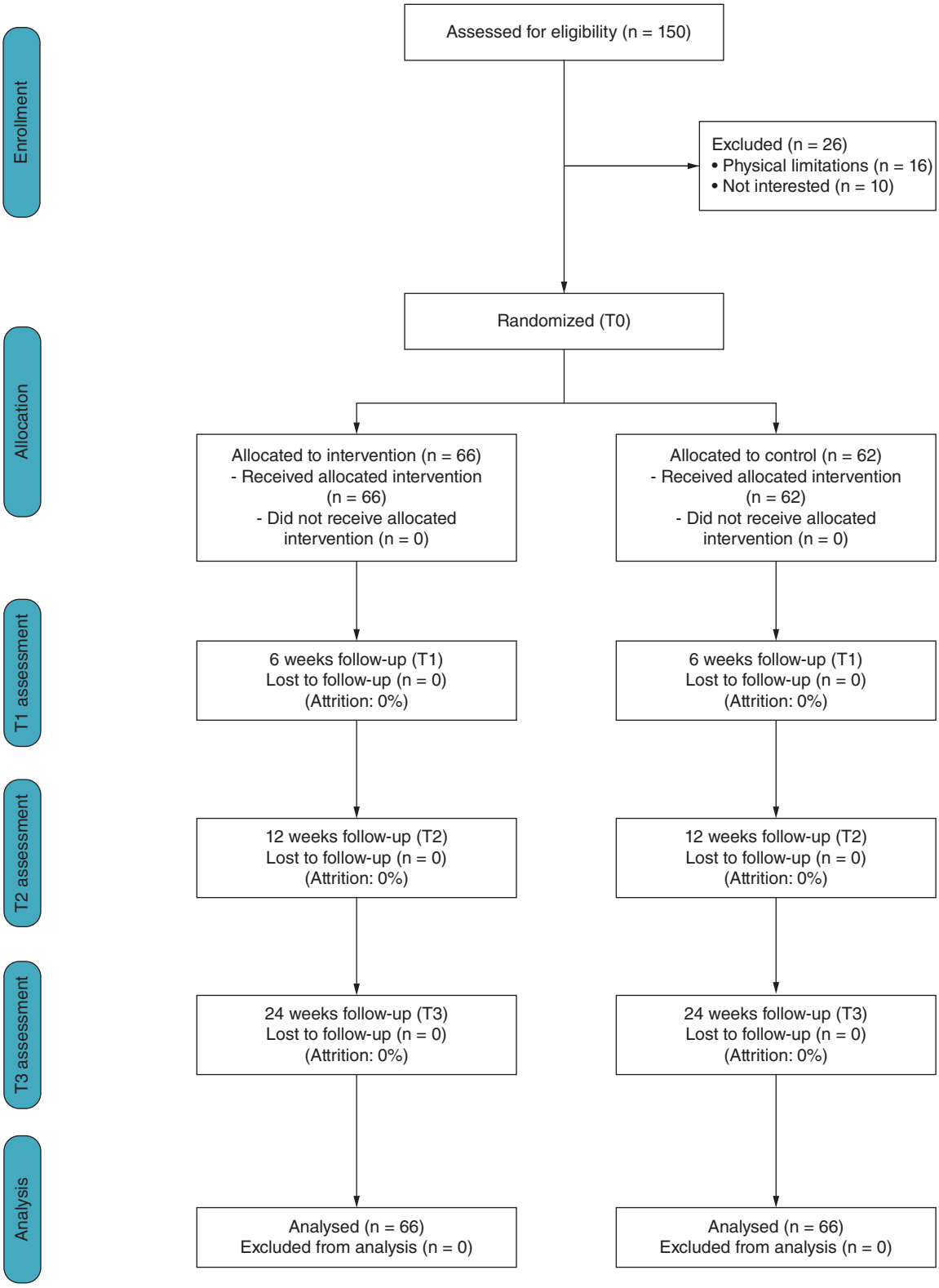

Figure 2. Flow chart.
T: Time.

Table 1. Interventions and Implications for patient improvement in cancer and living meaningfully treatment.

Intervention/action	Mechanism of action	Purpose	Implication	Ref.
Build rapport with patients	Facilitate patients in expressing and managing their emotions while fostering a secure, non-judgmental setting for emotional release	To promote patient confidence and alleviate treatment-related distress	Building rapport with patients can optimize treatment results by cultivating confidence and diminishing treatment-related distress	[22]
Explore adverse impacts of illness and treatment through open communication	Offer emotional support to alleviate anxiety and distress related to illness	Enhance patient coping strategies and improve quality of life	Attending to the adverse effects of illness and treatment can optimize patient outcomes by minimizing distress and fostering effective coping mechanisms	[23]
Implement behavioral intervention utilizing the CALM manual and VR technology	A structured intervention utilizes virtual reality to manage psychological distress and foster adaptive coping strategies	To enhance psychological well-being and alleviate anxiety and depression symptoms	CALM intervention may enhance psychological well-being through immersive VR interventions	
Continue CALM intervention for a maximum of three cycles if the patient is in a state of depression	To ensure patients receive adequate intervention and support for mental health, leading to a sustained reduction in symptoms of depression and improved patient outcomes	Continuing CALM intervention can improve outcomes for patients with depression by ensuring they receive adequate support and treatment	Continuing CALM intervention for up to three cycles can address depressive symptoms, but individual needs should be considered	
Hold weekly group supervision meetings for case development and discussion	Maintaining therapist adherence, competency and skill development leads to improved therapist skills and increased adherence to the intervention protocol	Regular group supervision can improve therapist skills and ensure adherence to the intervention protocol	Weekly supervision meetings provide ongoing support and guidance, improving CALM intervention implementation and outcomes	
Ensure the treatment integrity of the intervention team	To monitor therapists weekly and request case reports to improve treatment outcomes and reduce the risk of intervention drift	Monitoring therapists and ensuring treatment integrity can improve outcomes and reduce the risk of intervention drift	Ensuring treatment integrity maintains fidelity to CALM intervention protocols, increasing internal validity and replicability	
Randomly assign patients to trial after recruitment, and use oncology meeting rooms for CALM interventions	To maintain patient privacy during the intervention, leading to improved patient trust and increased engagement in the treatment process	Ensuring patient privacy can improve trust and engagement in the treatment process	Random assignment and using oncology meeting rooms increase study rigor and feasibility of CALM interventions	
Assess the patient's ability to participate, measure baseline psychological scales	To improve patient selection and treatment outcomes by identifying suitable patients and measuring mental health status before intervention	Assessing patient ability and mental health status can improve patient selection and treatment outcomes	Assessing patients' abilities and measuring psychological scales helps tailor CALM interventions to individual needs	[24]
Adjust CALM intervention into cyclic type	To provide extended and flexible intervention to fit patient's needs better, leading to improved patient engagement and a better-tailored treatment approach	Adjusting CALM intervention can improve patient engagement and provide a better-tailored treatment approach	Cyclic CALM interventions allow for repeated engagement, reinforcing mindfulness practices and potentially increasing effectiveness	
Translate the original CALM handbook into a Chinese study version	To make intervention accessible to a broader range of patients in China, leading to improved patient access to treatment	Translating the CALM handbook can improve patient access to treatment in China	It is improving the accessibility and cultural relevance of CALM interventions for Chinese-speaking populations	
Use VR device as a carrier of CALM Intervention	To enhance patient engagement and provide a more immersive experience, leading to improved patient satisfaction and better treatment outcomes	VR devices can enhance patient engagement and provide a more immersive treatment experience, improving satisfaction and outcomes.	VR devices create an immersive and interactive environment for mindfulness practices and therapy	[25]

CALM: Managing cancer and living meaningfully; VR: Virtual reality.

2.4.3. Emotional navigation

Recognizing the emotional toll of cancer, the CALM intervention incorporated strategies to help patients navigate the complex emotional terrain. This involved acknowledging and validating feelings of despair, fear, guilt and confusion. Therapists guided patients through coping mechanisms and emotional regulation strategies.

2.4.4. Resilience building

A central focus of CALM was fostering resilience. Patients were equipped with tools and techniques to build psychological resilience, enabling them to cope with the challenges of cancer more effectively. This may involve mindfulness practices, cognitive-behavioral strategies and narrative therapies.

2.4.5. Empowerment & control

CALM emphasizes reinstating a sense of control over one's life. Patients were encouraged to actively participate in decisions regarding their treatment, engage in activities that brought joy and fulfillment and identify areas where they could exert influence.

2.4.6. Peer experiences & supportive environment

Drawing from the experiences of others who had faced similar challenges, either through group therapy sessions or shared narratives, was integral to the CALM intervention. Creating a supportive environment where patients felt understood and connected improved their psychological well-being.

2.4.7. Therapeutic alliance

CALM therapists played a pivotal role in facilitating this transformative process. They underwent rigorous training, including formal education and practical exercises, emphasizing empathy, cultural sensitivity and a person-centered approach. Ongoing supervision ensured therapists were adept at addressing the technical aspects of the intervention while remaining attuned to the emotional needs of patients.

2.5. Outcomes

The outcomes assessed in this study included psychological resilience, quality of life, anxiety, depression and perceived social support. These outcomes were measured using the Chinese version of the Connor-Davidson Resilience Scale (CD-RISC), the Functional Assessment of Cancer Therapy-Breast (FACT-B) scale, the Hospital Anxiety and Depression Scale (HADS) and the Perceived Social Support Scale (PSSS), respectively [26–29].

2.6. Sample size

The sample size for this study was determined based on a relevant intervention study [30], with a minimum of 27 cases needed for each group to achieve a power of 90%. Considering the potential losses, 124 breast cancer patients were included in the study to ensure a sufficient sample size.

2.7. Randomization

The random allocation of participants to intervention and control groups was conducted by independent statisticians not involved in the study implementation. Utilizing a computer program, random assignment sequences were generated after baseline assessments. To maintain blinding, assignment lines were printed on cards, sealed in envelopes and opened sequentially as tasks were assigned. Throughout the experiment, the research team remained uninformed about envelope contents.

2.8. Statistical methods

Descriptive statistics were used to summarize the demographic characteristics of the participants and the scores obtained on the measurement scales. Independent t-tests and Chi-square tests were conducted to analyze continuous and categorical variables. Generalized linear mixed models were utilized to examine changes in scores over time. A bootstrap approach was employed to assess the relationship between changes in psychological resilience, perceived social support and quality of life within the intervention and control groups. Statistical analyses were performed using SPSS 26.0, with a significance level of 0.05.

2.9. Ethical considerations

The study was conducted following the principles of the Declaration of Helsinki (World Medical Association, 2013) and approved by the Institutional Review Board of Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (Number of Ethical Approval: 2012088). All participants were informed about the study's purpose, procedure and voluntariness before providing written informed consent. They were made aware of their right to withdraw from the study at any point and avoid answering any questions. Participants signed the informed consent form, indicating they fully understood the study procedure before enrollment. This study was not registered as a clinical trial.

3. Results

A total of 124 breast cancer patients were included in the study, with 62 patients in the intervention group and 62 in the control group. The mean age of participants was 49.85 years, with no significant difference between the two groups. The majority of participants were unemployed (51%) and had secondary or tertiary education (71%). Most were married (121) and the mean time since surgery was 45.01 weeks. Regarding clinical characteristics, modified radical breast surgery was the most common surgery type (98 patients). The disease stages were distributed as follows: Stage I (32 patients), Stage II (52 patients) and Stage III (40 patients). The majority of participants had ever undergone chemotherapy (88 patients) or radiotherapy (32 patients), while targeted therapy and endocrine therapy were current or ever used by 82 and 34 patients respectively. There were no significant differences between the intervention and control groups in terms of socio-demographic or clinical characteristics. Table 2 provides the details.

Table 2. Baseline socio-demographic and clinical characteristics of the patients (n = 124).

Characteristics	All (n = 124)	Intervention group (n = 62)	Control group (n = 62)	*p*-value
Socio-demographics				
Age, years	49.85 ± 9.363	49.26 ± 10.116	50.44 ± 8.586	0.486
Employment status				
Unemployed	51	26	25	0.945
Employed	71	35	36	
Retired	2	1	1	
Education				0.664
Illiterate/Primary	63	31	32	
Secondary	25	11	14	
Tertiary	46	20	16	
Marital status				0.604
Single	2	1	1	
Married	121	61	60	
Separated/divorced/widowed	1	0	1	
Clinical Characteristics				
Time since surgery (week)	45.01 ± 55.251	43.26 ± 43.173	46.76 ± 65.478	0.726
Breast surgery type				0.09
Partial mastectomy	9	8	3	
Modified radical breast surgery	98	43	53	
Simple mastectomy	17	11	6	
Disease stage				0.108
I	32	21	11	
II	52	22	30	
III	40	19	21	
Chemotherapy				
None	2	2	0	0.237
Ever	88	41	47	
Current	34	19	15	
Radiotherapy				0.146
None	68	33	35	
Ever	32	13	19	
Current	24	16	8	
Targeted therapy				0.684
None	39	21	18	
Ever	3	2	1	
Current	82	39	43	
Endocrine therapy				0.150
None	89	40	49	
Ever	1	1	0	
Current	34	21	13	

In the baseline assessment, the mixed linear model indicated that the control group exhibited a mean CD-RISC score of 57.56 (SD = 8.8), while the intervention group had a slightly higher mean of 58 (SD = 9.55), indicating a baseline tendency toward lower resilience levels. Furthermore, baseline assessments showed that the mean FACT-B score was 69.81 (SD = 9.57) in the control group and 71.58 (SD = 9.39) in the intervention group, signifying a nuanced difference in overall quality of life. For baseline depression levels, the control group had a mean HADS-Depression score of 7.29 (SD = 1.85) and the intervention group had a comparable mean of 7.15 (SD = 1.91). Similarly, baseline anxiety levels were identical, with the control group having a mean HADS-Anxiety score of 8.97 (SD = 2.47) and the intervention group having a mean of 8.95 (SD = 2.24). Perceived social support at baseline was measured through the PSSS, showing mean scores of 61.39 (SD = 7.60) for the control group and 62.39 (SD = 6.73) for the intervention group. This finding supports our initial hypothesis that post-breast cancer patients exhibit lower psychological resilience.

Participants in the intervention group demonstrated noteworthy improvements in psychological resilience ($F = 9.059$, $p < 0.01$), quality of life ($F = 3.818$, $p < 0.05$), anxiety ($F = 13.776$, $p < 0.001$), depression ($F = 20.563$, $p < 0.001$) and perceived social support ($F = 67.856$, $p < 0.001$) compared with those in the control group. Furthermore, individuals in the intervention group consistently improved across these measures during the three follow-up assessments. Detailed information and statistical results can be found in Table 3.

Using structural equation modeling in SPSS, we examined the relationship between Change in psychological resilience, change in perceived social support and change in the quality of life in the intervention and control groups (Figure 3A & B). In the control group, the regression coefficient of Change in resilience on Change in perceived

Table 3. Changes within group and comparisons between groups of the CD-RISC, Fact-B, PSSS and HADS.

Scale	T0	T1	Change from T0 (95% CI)	T2	Change from T0 (95% CI)	T3	Change from T0 (95% CI)
CD-RISC							
CG	57.56 ± 8.8	59.53 ± 8.92	1.968 (1.178,2.757)	59.35 ± 9.87	1.79 (0.808,2.772)	61.45 ± 11.11	3.887 (2.401,5.373)
IG	58 ± 9.55	63.6 ± 9.97	5.597 (4.836,6.357)	67.81 ± 9.88	9.806 (8.798,10.815)	69.1 ± 10.34	11.097 (9.917,12.277)
MD (95% CI)	-0.435 (-3.701, 2.83)	-4.065 (-7.429, -0.7)		-8.452 (-11.964, -4.94)		-7.645 (-11.462, -3.828)	
FACT-B							
CG	69.81 ± 9.57	70.29 ± 10.07	0.484 (-0.458, 1.426)	70.35 ± 10.07	0.548 (-0.688, 1.785)	71.52 ± 11.53	1.71 (-0.034, 3.453)
IG	71.58 ± 9.39	72.48 ± 9.8	0.903 (0.053, 1.753)	75.24 ± 9.85	3.661 (2.615, 4.708)	76.27 ± 10.29	4.694 (3.227, 6.16)
MD (95% CI)	-1.774 (-5.145, 1.597)	-2.194 (-5.725, 1.338)		-4.887 (-8.429, -1.345)		-4.758 (-8.644, -0.872)	
HADS-anxiety							
CG	8.97 ± 2.47	8.77 ± 2.65	-0.194 (-0.461, 0.074)	9.24 ± 2.92	0.274 (-0.073, 0.622)	9.84 ± 3.06	0.871 (0.451, 1.291)
IG	8.95 ± 2.24	7.77 ± 2.56	-1.177 (-1.386, -0.969)	6.76 ± 2.84	-2.194 (-2.521, -1.866)	6.34 ± 3.06	-2.613 (-3.04, -2.186)
MD (95% CI)	0.016 (-0.821, 0.854)	1 (0.075, 1.925)		2.484 (1.46, 3.507)		3.5 (2.413, 4.587)	
HADS-Depression							
CG	7.29 ± 1.85	8.08 ± 1.91	0.79 (0.564, 1.016)	7.98 ± 2.11	0.694 (0.39, 0.997)	8 ± 2.3	0.71 (0.338, 1.082)
IG	7.15 ± 1.91	6.55 ± 1.93	-0.597 (-0.794, -0.399)	5.69 ± 2.11	-1.452 (-1.745, -1.158)	5.56 ± 2.41	-1.581 (-1.938, -1.223)
MD (95% CI)	0.145 (-0.523, 0.813)	1.532 (0.849, 2.215)		2.29 (1.541, 3.04)		2.435 (1.597, 3.274)	
PSSS							
CG	61.39 ± 7.60	59.95 ± 5.29	-1.435 (-3.763, 0.893)	61.87 ± 5.32	1.919 (0.033, 3.806)	68.42 ± 4.93	6.548 (4.725, 8.372)
IG	62.39 ± 6.73	64.76 ± 5.68	2.371 (0.157, 4.585)	69.18 ± 5.48	4.419 (2.435, 6.403)	73.66 ± 5.37	4.484 (2.554, 6.413)
MD (95% CI)	1.000 (-1.553., 3.553)	4.806 (2.855, 6.758)		7.306 (5.386, 9.227)		5.242 (3.408, 7.076)	

Sample size of the intervention group: n = 62 (baseline), n = 62 (After 6 weeks), n = 62 (After 12 weeks), n = 62 (After 24 weeks).
Sample size of the control group: n = 62 (baseline), n = 62 (After 6 weeks), n = 62 (After 12 weeks), n = 62 (After 24 weeks).
CD-RISC total score model: (group) $F = 9.059$, $p < 0.01$; (time) $F = 104.759$, $p < 0.001$; (group × time) $F = 44.075$, $p < 0.001$.
FACT-B model: (group) $F = 3.818$, $p < 0.05$; (time) $F = 12.150$, $p < 0.001$; (group × time) $F = 8.096$, $p < 0.001$.
HADS-anxiety model: (group) $F = 13.776$, $p < 0.001$; (time) $F = 25.948$, $p < 0.001$; (group × time) $F = 48.666$, $p < 0.001$.
HADS-Depression model: (group) $F = 20.563$, $p < 0.001$; (time) $F = 15.522$, $p < 0.001$; (group × time) $F = 37.855$, $p < 0.001$.
PSSS model: (group) $F = 67.856$, $p < 0.001$; (time) $F = 158.143$, $p < 0.001$; (group × time) $F = 17.839$, $p < 0.001$.
CD-RISC: Connor-Davidson resilience scale; FACT-B: Functional assessment of cancer therapy; HADS: Hospital anxiety and depression scale; MD: Mean deviation; PSSS: Perceived social support scale; T: Time.

social support was significant ($p < 0.01$, CI: 0.1368, 0.6670), indicating a mediating effect. The partial regression coefficient of Change in perceived social support on Change in quality of life was also significant ($p < 0.01$, CI: 0.1355, 0.6315), supporting a partial mediating effect of Change in perceived social support. The total effect value in the model was 0.5167, with an indirect effect value of 0.1541. The mediating effect share was 0.2982 (CI: 0.0247, 0.3153), indicating a significant indirect effect, confirming the presence of an indirect effect and supporting the partial mediating effect of Change in perceived social support.

In the intervention group, the regression coefficient of change in resilience on change in perceived social support was significant ($p < 0.01$, CI: 0.1711, 0.6507), indicating a positive effect. The partial regression coefficient of Change in perceived social support on Change in quality of life was also significant ($p < 0.05$, CI: 0.1023, 0.7299), suggesting a fully mediating effect of Change in perceived social support. The total effect value in the model was 0.3779, with an indirect effect value of 0.1710. The mediating effect share was 0.4525 (CI: 0.0113, 0.3673), confirming the presence of an indirect effect. These findings support the full mediating effect of Change in perceived social support in the relationship between psychological resilience and quality of life.

4. Discussion

This clinical trial aimed to assess the impact of a CALM intervention on breast cancer patients following surgery. The findings revealed promising results, indicating that

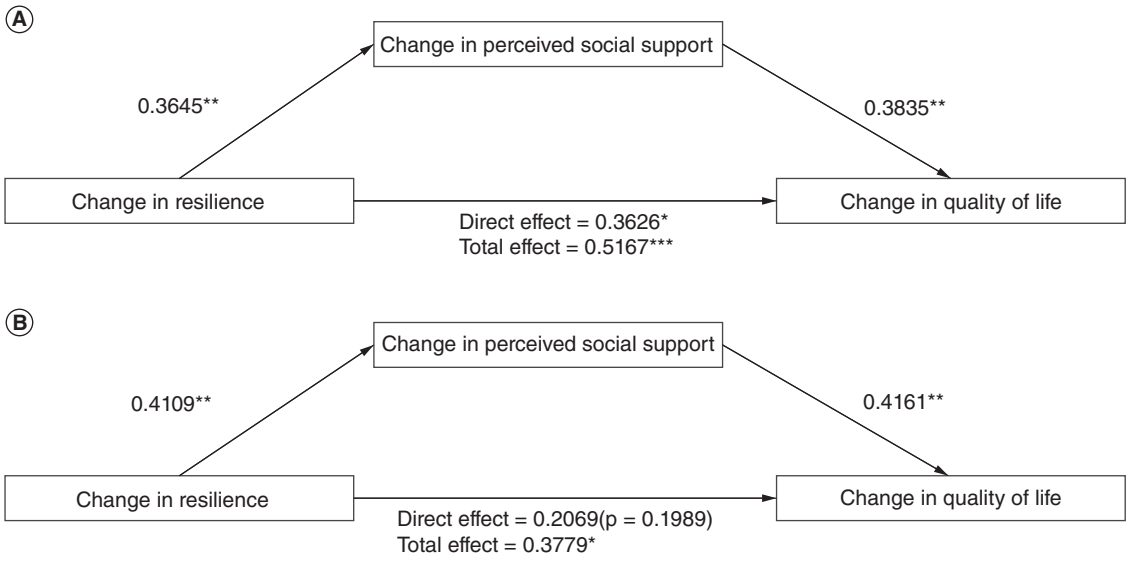

Figure 3. Model of the mediating effect of changes in perceived social support between changes in psychological resilience and changes in quality of life in CG **(A)** and IG **(B)**.
Note: *p-value < 0.05; **p-value < 0.01; ***p-value < 0.001. The path coefficients are regression coefficients.
CG: Control group; IG: Intervention group.

CALM interventions effectively improved psychological resilience, quality of life and perceived social support among breast cancer survivors. The study emphasizes the significance of resilience in managing the disease and highlights the necessity of interventions that facilitate positive outcomes and effective coping strategies for cancer survivors. These findings align with previous research emphasizing the importance of psychosocial interventions in enhancing the well-being of cancer patients, particularly those undergoing mastectomy [31,32].

Furthermore, CALM interventions improved depression and anxiety levels among breast cancer patients. Resilience plays a crucial role in reducing the risk of depression, emphasizing the effectiveness of interventions that target positive emotions and bolster resilience in treating depression [33]. Moreover, CALM interventions led to reduced anxiety levels in breast cancer patients. On the one hand, higher resilience levels were associated with lower anxiety levels [34]. On the other hand, social support plays a vital role in alleviating anxiety among breast cancer patients by offering emotional, informational and tangible assistance, fostering a sense of belonging and acceptance and facilitating social interaction and participation [35]. CALM intervention effectively reduced anxiety levels by providing a platform for therapists and patients to address cancer-related concerns, promoting meaning-making and facilitating social support. Additionally, resilience acted as a protective factor, attenuating the link between stress and symptoms of depression and anxiety in breast cancer patients.

Resilience plays a crucial role in mitigating the risk of depression, even in individuals with a genetic predisposition and interventions targeting resilience have shown efficacy in treating depression [36]. Furthermore, interventions that target patients' resilience and positive emotions rather than solely focusing on psychiatric symptoms have shown efficacy in treating depression [37]. Breast cancer patients face significant stressors that can impact their mental well-being and promoting psychological resilience through interventions like CALM can help alleviate depressive symptoms by enhancing patients' ability to cope with stress. Enhancing resilience is a valuable mechanism for reducing the association between stress and depressive symptoms in breast cancer patients.

Another crucial finding from this study pertains to the mediating effect of perceived social support. Our results indicate that the relationship between psychological resilience and quality of life was partially mediated in the control group. However, in the intervention group, perceived social support fully mediated this relationship.

These findings suggest that CALM interventions can effectively enhance the quality of life in postoperative breast cancer patients by influencing their psychological resilience and perceived social support. Firstly, perceived social support plays a crucial role in improving the overall quality of life by offering emotional solace, practical assistance, empowerment, a sense of belonging and enhanced self-esteem [38,39]. Prior research has demonstrated that tailored social support interventions, accounting for disease severity and treatment status, can substantially enhance the quality of life in breast cancer

survivors [40]. Our mediation analysis further solidifies the link between psychological resilience, perceived social support and quality of life. Specifically, low psychological resilience leads to decreased perceived social support, exacerbating the symptom burden and further diminishing the quality of life. Moreover, earlier studies have highlighted that low psychological resilience in breast cancer patients can impede their ability to recognize, seek and interpret social support, leading to underestimation of the objective social support received and poorer health outcomes [41].

Psychological interventions tailored for breast cancer patients are crucial in addressing their emotional distress, enhancing coping strategies and providing ongoing support throughout their treatment and survivorship journey. The mediation analysis conducted in this study significantly contributes to our understanding of how CALM interventions and psychological resilience influence the quality of life in breast cancer patients. The findings reveal that perceived social support mediates the relationship between psychological resilience and quality of life. This highlights CALM interventions as practical strategies to improve health outcomes and enhance breast cancer patients' overall quality of life. Additionally, the study indicates that individuals who perceive higher levels of social support experience more excellent overall quality of life, suggesting that the intervention plays a pivotal role in enhancing social support, which, in turn, contributes to improved well-being. A similar study also identified social support as a partial mediator in the relationship between resilience and quality of life among breast cancer patients [42]. However, this current study further elucidates the mediating role of perceived social support in the changes observed in psychological resilience and quality of life, emphasizing that psychological interventions can enhance the impact of psychological resilience on quality of life by promoting patients' competent perception of social support. These results underscore the importance of social support as a fundamental factor in fostering psychological resilience and overall well-being among post-mastectomy patients.

Given that the diagnosis and treatment of breast cancer can pose significant emotional challenges, resulting in heightened levels of anxiety, depression and stress among patients, CALM interventions provide the necessary support and tools for effectively managing these emotional burdens. Furthermore, CALM interventions address the psychological repercussions of treatment, including side effects, body image alterations and anxieties surrounding cancer recurrence. CALM interventions enhance patients' overall quality of life by attending to emotional, social and psychological well-being. This intervention creates a safe and supportive environment wherein patients can freely express their emotions, fears and concerns while concurrently fostering the development of adaptive coping strategies. Ultimately, CALM interventions are vital in promoting a multidisciplinary approach to cancer treatment, ensuring that patients receive comprehensive support encompassing their physical and emotional well-being.

The findings of our study bear significant practical implications for the field of psycho-oncology and healthcare practitioners involved in cancer care. Delineating several critical steps in CALM interventions provides a practical roadmap for implementing adequate psychological support for cancer patients. Healthcare professionals can utilize this structured approach to tailor interventions according to the unique emotional needs of individuals facing a cancer diagnosis. By acknowledging and addressing the intricate web of fears, illusions and emotional challenges associated with cancer, practitioners can enhance the overall well-being of patients. Furthermore, the emphasis on therapist expertise in technical aspects and emotional intelligence underscores the importance of comprehensive training programs for mental health professionals in oncology settings. CALM interventions in routine cancer care protocols can improve patient outcomes, foster emotional resilience and contribute to a more holistic and patient-centered approach to cancer treatment. Thus, this paper is a valuable resource for practitioners seeking to enhance the quality of psychosocial care in cancer support.

4.1. Limitations

This study should acknowledge several limitations, including the lack of data on patient perceptions of specific intervention methods, a small sample size from a single center, limited assessment of CALM implementation, and the absence of reliable biomarkers for measuring resilience. Future research should address these limitations by incorporating larger, multicenter designs, gathering physician and patient feedback, employing comprehensive assessment measures and investigating long-term effects. Despite these limitations, the study provides valuable insights into the role of resilience in psychological interventions for breast cancer patients.

5. Conclusion

This study aimed to investigate the impact of CALM interventions on the mental health and overall quality of life of patients following breast cancer surgery, shedding light on the crucial role of resilience in enhancing mental well-being. Additionally, the study examined the mediating effect of perceived social support in the asso-

ciation between psychological resilience changes and quality of life. The findings underscore the significance of enhancing psychotherapeutic interventions for postoperative breast cancer patients, as it amplifies the positive influence of psychological resilience on perceived social support-an essential determinant of quality of life in this population.

6. Declaration of generative AI & AI-assisted technologies in the writing process

During the preparation of this work, the authors consulted chatGPT to assist with language polishing and editing. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Article highlights

- Surgery leads to heightened anxiety, fear, body image issues and reduced quality of life in breast cancer patients.
- Interventions like cancer and living meaningfully (CALM), focusing on resilience, meaning and coping, promise to alleviate distress among cancer patients.
- Social support and resilience are crucial for emotional well-being, coping, life satisfaction and quality of life in breast cancer patients.
- CALM improves resilience, quality of life, anxiety, depression and perceived social support in postoperative breast cancer patients.
- Perceived social support mediates improved resilience and quality of life following CALM intervention.
- Psychological interventions like CALM, enhancing resilience and social support, play a vital role in improving mental health and well-being after breast cancer surgery.
- The CALM intervention significantly improves outcomes for postoperative breast cancer patients.
- Perceived social support is identified as a critical mediator, explaining the link between enhanced resilience and improved quality of life.

Author contributions

S Liu, Y Cai and Senbang Yao contributed equally to this work and shared the first authorship. They were involved in the conceptualization of the research, data collection, analysis, interpretation and manuscript preparation. J Chai and Y Jia participated in the data collection. H Ge, R Huang and A Li were involved in the research and interpretation. H Cheng supervised the entire research process, ensuring the integrity of the work. H Cheng is the corresponding author of the manuscript.

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Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

During the preparation of this work, the authors consulted chatGPT to assist with language polishing and editing. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The study was conducted following the principles of the Declaration of Helsinki (World Medical Association, 2013) and approved by the Institutional Review Board of Research Ethics Committee of the Second Affiliated Hospital of Anhui Medical University (Number of Ethical Approval: 2012088). The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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Understanding mental health in breast cancer from screening to Survivorship: an integrative phasic Model and tool

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ABSTRACT

Integrative models of mental illness and health in psycho-oncology are aimed at all types of cancer, although the patients' experiences and issues may vary. This review summarizes the different theories and models of mental illness and health pertaining to the breast cancer experience and proposes an integrative phasic model applicable to the breast cancer trajectory. Five databases were searched for studies related to breast cancer mental health and illness theories and models. The PRISMA checklist form was used to extract the essential information from the included studies. Eleven theories and models on the experience of breast cancer were found. The integrative model based on these theories and models illustrates that the breast cancer experience is conceptualized as a trajectory with seven landmark '*events*', each associated with a pathogenic '*challenge*' leading to six possible '*symptoms*', 1) psychological distress with anxious features, 2) psychological distress with depressive features, 3) non-specific distress 4) psychological distress with trauma-related features 5) low health-related quality of life, and 6) fear of recurrence. The Breast Cancer Psychological Integrative Phasic Model is supported by a simple clinical tool (BreastCancerPsych – Integrative Clinical Tool) that serves as a valuable resource throughout the care trajectory. These integrative phasic model and clinical tool are designed to help mental health clinicians formulate treatments that are tailored to the needs of their patients, especially for trajectories that are not marked by resilience.

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Introduction

Breast cancer is the most common type of cancer among women, with more than 2 million cases worldwide (Bray et al., 2018). Despite the fact that its incidence has been declining, the number of cases for a given year remains high, with an

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estimated 29 400 breast cancer diagnoses expected in 2023 in Canada (Bray et al., 2018; Canadian Cancer Society, 2022; Jemal et al., 2011). Although the remission rate has surged to 96% in recent years in North America, a good survival rate does not necessarily speak of the mental health *functioning* of a cancer survivor (Bower, 2008).

There is consensus that the breast cancer trajectory includes screening, diagnosis, post-diagnosis/pre-treatment, treatment, post-treatment, and survivorship phases (Brattheim et al., 2017; Iwamitsu et al., 2005; Lam et al., 2010). The recurrence phase can be added as a seventh phase, as it represents a critical period for ongoing patient monitoring (Pedersen et al., 2022). The screening phase detects cancer through a lump or anomaly identified by the individual, a partner, or during an annual mammography, while the diagnosis phase refers to when screening test results are announced (Sitt et al., 2018). Post-diagnosis/pre-treatment covers the time between diagnosis and treatment initiation (Brattheim et al., 2017). The treatment phase includes managing the patient to cure tumors, prevent recurrence or spread, and relieve symptoms (e.g. breast pain, lump, redness, nipple discharge) (Canadian Cancer Society, 2022). The post-treatment phase starts after treatments (Trayes & Cokenakes, 2021). The survivorship phase begins when there are no cancer signs for at least 5 years post-treatment (Miller et al., 2008). Finally, recurrence occurs if breast cancer stem cells return, either at the original site or elsewhere (Fillon, 2022). These phases pose various challenges to patients' mental health.

The emergence of psycho-oncology highlights that cancer affects patients psychologically, not just physically (Holland, 2002, 2018). As survival rates increase, greater attention to the psychological aspects of the disease is necessary. Various theories and models of mental illness and health, building on psycho-oncology, explore psychological responses across the cancer trajectory and the psychological, social, and behavioral factors affecting cancer risk and survival (Holland, 2018; Jacobsen & Andrykowski, 2015; Kangas & Gross, 2020; Lang-Rollin & Berberich, 2018; Stanton & Bower, 2015). Integrating these models into practice allows tailored interventions to address patients' mental health alongside medical treatment, improving coping strategies and quality of life (Rodriguez et al., 2014). However, existing integrative models are generalized for all cancers, though patients' experiences vary by diagnosis (Deshields et al., 2011, 2014; Trudel-Fitzgerald et al., 2013). For example, breast cancer differs in biological traits (e.g. hormone receptor, HER2 status), risk factors (e.g. BRCA mutations), prevention methods, and screening (Sitt et al., 2018; Trayes & Cokenakes, 2021). These factors contribute to distinct mental health challenges, as women with breast cancer report higher distress than those with gastrointestinal or lung cancers (Trudel-Fitzgerald et al., 2013), emphasizing the need for breast cancer-specific models across the care trajectory.

The objective of this review is twofold: Firstly, to summarize the various pathogenic theories and models that have been developed or applied specifically for breast cancer and argue that each of the seven phases presents distinct challenges and may lead to psychological symptoms reaching a pathological level necessitating treatment. Secondly, to develop a conceptual integrative model and clinical tool, based on existing models, which will include the main challenges, various psychological distress symptoms and incorporates the different phases of the care trajectory.

Methods

In order to meet the current objectives, the PRISMA methodology was followed to conduct the review (Liberati et al., 2009; Moher et al., 2009).

Data collection

Five databases were chosen to search for studies related to breast cancer published in peer-reviewed journals: PsycInfo, Web of Science, PubMed, and CINAHL. Keywords were selected with the help of an experienced librarian in the field. We searched for the keywords [breast cancer or cancer breast or breast neoplasm* or neoplasm* breast or breast tumo* or breast carcinoma* or mammary cancer or mammary carcinoma*] AND [illness theory or illness model* or mental health theory or mental health model* or psych* theory or psych* model*] in the databases with no year constraints in June 2023. As the search progresses, more keywords were identified and added as needed. A second round of searching was conducted in January 2024 before the analysis was carried out.

Eligibility criteria

To qualify for inclusion in the sample, the theories/models had to: a) be developed or adapted to breast cancer experience b) address the mental illness or health of patients living with breast cancer during at least one phase of the breast cancer trajectory (screening, diagnosis, post-diagnosis/pre-treatments, treatments, post-treatments and survivorship or recurrence) c) report at least one psychological distress symptom (valid self-report measure or non-self-report): depressive, anxiety, non-specific distress, trauma-related features or quality of life/well-being[1]; d) be available in English or French; and e) be available in hardcopy or downloadable form. Exclusion criteria were studies that presented theories/models that were a) developed or adapted for cancer in general or other cancer type b) empirical studies reporting statistical models. Randomized trials were excluded as they typically focus on testing interventions or treatments rather than developing or integrating theoretical models, which was the goal of this review (Booth et al., 2012; Thomas et al., 2012).Furthermore, no grey literature (e.g. dissertations, policy documents, conference abstracts) was included in the study, as we aimed to ensure the reliability and rigor of our findings by focusing exclusively on peer-reviewed articles from selected databases (Hackenbroich et al., 2022; Hopewell et al., 2007).

Procedure and synthesis

Afterward, articles whose title and abstract fit the inclusion criteria were exported to the Rayyan website (Ouzzani et al., 2016). On this platform, two research team members (double-blinded) [JF; ER] selected the articles that could be part of the final sample based on the abstract. When uncertainties about the eligibility of studies occurred, a third person investigated until 100% agreement was achieved [AB]. The PRISMA checklist form was used to extract the essential information from the remaining articles, and the exclusion criteria were then be applied. Quality appraisal and/or formal risk of bias

assessments were not conducted, as the focus was on synthesizing concepts, theories, and models rather than evaluating the methodological quality of individual studies (Gough et al., 2012). Nevertheless, the strengths and limitations of each theory or model included were evaluated in accordance with review guidelines (Gough et al., 2012). Data was extracted for all studies rated as eligible, including the following fields: authors, year published, study location, sample characteristics, data collection and analysis.

Developing the integrative model and clinical tool

The integrative model was developed through an analysis of selected studies, chosen based on their documented challenges, phases, and psychological symptoms. These studies were systematically categorized according to the phases they addressed and specific aspects relevant to the model described in each. Subsequently, the model served as the foundation for the development of a clinical tool, which incorporates considerations of illness challenges, symptoms, and phases. This tool was presented at the 39th Canadian Association of Psychosocial Oncology (CAPO) conference (https://www.capo.ca/CAPO-2024; Fortin et al., 2024), where it received feedback from psychosocial experts, including researchers, patient partners, and caregivers. This feedback informed revisions aimed at enhancing the tool's potential usability and integration into clinical practice (Domecq et al., 2014).

Results

Theories and models of event-related mental illness and health in breast cancer

We found 11 theories and models on the experience of breast cancer that we will briefly summarize (see Figure 1). The descriptive additional information of each theory and model can be found in Table 1.

Braden et al'.s combined and alternative Model

Braden et al. (1998) posits that the stimuli that allow patients to learn about their disease are the psychological (i.e. depression burden) and physical side effects experienced (e.g. nausea) as part of the cancer diagnosis and treatment. For Badger et al. (2004), who adapted the model to breast cancer population, the perceived severity of illness serves as a trigger for patients living with breast cancer to initiate a learning process (i.e. making sense of their illness experience). Especially during the treatment phase, this learning process can trigger depressive symptoms, which may eventually be overcome by the perception of having the resources to adapt psychologically and physically to cancer (Badger et al., 2004).

Functional Model of counterfactual thinking

Roese's (1994) functional theory of counterfactual thinking argues that receiving a breast cancer diagnosis activates mental representations of past alternatives, producing both positive and negative emotions (Gilbar & Hevroni, 2007; Roese, 1994). The coping strategy employed – whether adaptive (e.g. spirituality, seeking social support) or less adaptive (e.g. avoiding disease information) – influences the experience and evaluation of

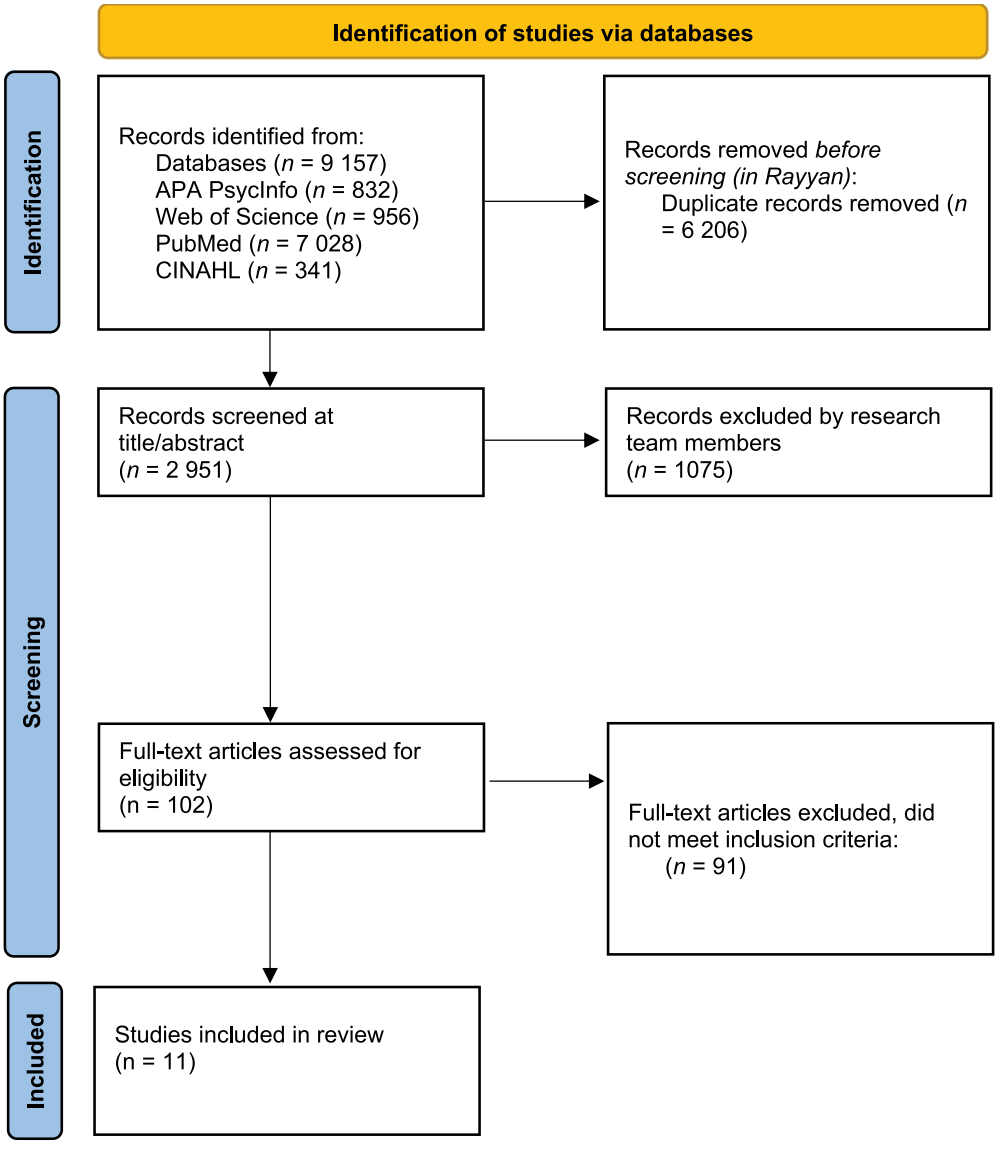


Figure 1. PRISMA flow diagram of study selection process (Page et al., 2021).

having breast cancer (Al-Azri et al., 2009; Cowley et al., 2000). For instance, younger patients using strategies characterized by combative spirit and fewer strategies characterized by hopelessness/impotence, anxiety, and fatalism coped better (Schnoll et al., 1998; W. T. Wang et al., 2013).

Social comparison is a key coping strategy in counterfactual thinking. This strategy can positively or negatively affect psychological adjustment to breast cancer (Wood et al., 1985). Patients without immediate comparison points who look to media 'supercopers' may feel inadequate (Taylor & Lichtman, 2003; Wood et al., 1985). Others may either compare themselves to similar individuals (similarity perspective), which is both adaptive and informative or to those better off (upward comparison perspective), which is usually

Table 1. Descriptive data of the mental health and illness theories and models for breast cancer ($n = 11$).

Mental Health and Illness Theories and Models	Developed (D) or adapted (A)	Specific breast cancer diagnoses covered	Trajectory phases covered	Type of psychological distress symptoms targeted	Health-related quality of life included or not
Braden et al'.s combined model (Badger et al., 2004)	A	Stages I-II and Metastatic	Diagnosis and treatment	Depression	Included
Functional Model of Counterfactual Thinking (Gilbar & Hevroni, 2007)	A	Stages I-IV	Diagnosis	Non-specific distress	Included
Human Response to Illness (HRTI) Model (Pedersen et al. 2010)	A	Not specified	Screening, diagnosis, post-diagnosis/pre-treatment, treatment, post-treatment, and survivorship	Anxiety	Included
Illness Intrusiveness Theoretical framework (Devins et al., 2006)	D	Not specified	Treatment and post-treatment	Non-specific distress	Included
Machine learning-based pipeline theory (Kourou et al., 2021)	A	Stages I-III	Treatment	Depression	Included
Mishel's Uncertainty in Illness Theory (Mishel, 1990)	A	Non specified	Screening, diagnosis, post-diagnosis/pre-treatment, treatment, post-treatment, and survivorship	Anxiety	Not included
Network Model of PTSD (Kangas et al., 2002)	D	Early, mixed and late-stage disease	Diagnosis	TSR	Not included
Recurrence Model 1: Fear of Cancer Recurrence (Lebel et al., 2018)	D	Stages I-III	Survivorship	Anxiety and depression	Not included
Recurrence Model 2: Network Model of Fear of Cancer Recurrence (Yang et al., 2022)	D	Stages I-III	Survivorship	Anxiety and depression	Not included
Recurrence Model 3: Hopelessness Theory of Depression (Brothers & Andersen, 2009)	A	New, consecutive cases with breast cancer recurrence (i.e. previously diagnosed with stages I-III)	Treatments	Depression	Included
Trajectory of Breast Cancer Explanatory Framework (Smit et al., 2019)	D	Not specified	Screening, diagnosis, post-diagnosis/pre-treatment, treatment, post-treatment, and survivorship, recurrence	Non-specific distress	Included

detrimental (Van der Zee et al., 2000; Wood et al., 1985). Downward comparison, comparing oneself to those less fortunate, can boost self-esteem (Van der Zee et al., 2000; Wood et al., 1985). Yet, the most effective strategy appears to be comparing oneself to similar individuals (Van der Zee et al., 2000; Wood et al., 1985).

Human response to illness Model (HRTI)

Mitchell et al. (1991) model describes anxiety as a multidimensional response, manifesting physiologically (e.g. accelerated heart rate), pathophysiologically (e.g. cortisol levels), behaviorally (e.g. aggression, isolation), and emotionally (e.g. introspection, shared meaning). Pedersen et al. (2010) adapted only the physiological dimension for breast cancer, where anxiety is a response to a perceived threat like cancer (Smith & Vale, 2006; Stark & House, 2000). Anxiety triggers physiological responses to reinstate homeostasis (Smith & Vale, 2006; Steimer, 2002), with the central nervous system determining whether an event is threatening (Pedersen et al., 2010). When it is, the sympathetic nervous system and hypothalamic-pituitary-adrenal axis activate (Smith & Vale, 2006; Steimer, 2002), increasing heart rate, blood pressure, and blood vessel dilation (Pedersen et al., 2010), while the adrenal gland releases cortisol (Pedersen et al., 2010). If homeostasis isn't restored, pathological anxiety can arise, leading to more severe health issues or psychiatric comorbidities (Pedersen et al., 2010; Stark & House, 2000).

Illness intrusiveness theoretical framework

Patients' health-related quality of life can fluctuate when one's daily functioning is altered by a life-threatening illness, such as breast cancer (Devins et al., 2006). The Illness Intrusiveness Theoretical framework of Devins (2010) was applied to six common types of cancers, including breast cancer, which provides an understanding that psychosocial (e.g. social support, spirituality), contextual (e.g. level of education, age), and disease/treatment (e.g. severity of illness, side effects) factors modulate the level of health-related quality of life reported by patients in the treatment and post-treatment phases (Devins et al., 2006). In fact, having to commit to a treatment plan (e.g. several chemotherapy appointments) and to live with various treatment side effects means that breast cancer can become an intrusion into the patient's life balance, be perceived as an additional stressor to the daily hassles, and in turn, interfere with various life domains (Avis et al., 2012; Sohl et al., 2014). Altogether, such intrusion may lead to psychological distress, particularly to depressive symptoms (Sohl et al., 2014).

Machine learning-based pipeline theory

This theory was adapted for patients living with breast cancer by Kourou et al. (2021) as they attempted to identify predictors of depressive symptoms that could impede readjustment. Specifically, the model illustrates that the individual's sense of coherence (i.e. sense of control, meaning, and positive expectations), social and cognitive functioning, resilience, and self-efficacy in coping with cancer were statistically related to reported depressive symptoms (Kourou et al., 2021). However, few medical factors (i.e. cancer stage and menopausal status) appeared to be associated with the observed depressive symptoms, which was explained by two possible reasons (Kourou et al., 2021). The first is that the data used to develop the theory were collected early in the cancer trajectory, which probably reflects a period where patients are still in shock

and focus on the overall diagnosis and treatment challenges rather than on specific medical variables (Kourou et al., 2021). The medical variables may be more important in later phases of the disease trajectory (Z. Wang et al., 2020). The second is that patients' reactions are shaped by their understanding of the situation and their ability to manage it, as well as by the symptoms experienced, rather than by specific medical facts, which are just one more piece of information processed as part of the larger self-regulatory mechanism (Kourou et al., 2021). Other authors also suggest that depressive symptoms increase over time and tend to follow anxiety symptoms during the breast cancer trajectory (Else-Quest et al., 2009; Stanton & Bower, 2015; Yang et al., 2022).

Mishel's uncertainty in illness

Mishel's (1990) theory suggests that uncertainty following an event like a cancer diagnosis can impair one's ability to interpret the disease and outcomes. Uncertainty arises when insufficient information prevents categorization of the event, but it's not deemed feared or desired until its implications are clear (e.g. symptom impact on mental health; Mishel, 1990). This vague situation can lead to various conclusions (Mishel, 1990). The theory has been applied to breast cancer patients, from screening to post-diagnosis (Liao et al., 2008). In 134 breast cancer patients, uncertainty at screening correlated with post-mastectomy anxiety (Cho, 2000). Another study showed higher uncertainty and anxiety levels before than after diagnosis in 127 patients (Liao et al., 2008), likely due to the unpredictability of the unknown versus diagnosis details making outcomes clearer (Deane & Degner, 1998). Regardless of the stage, patients with benign tumors reported lower uncertainty and anxiety than those with malignant tumors (Liao et al., 2008), highlighting the importance of tumor type in mental health. The theory also applies to breast cancer survivors in remission (Maheu et al., 2021; Z. Wang et al., 2020), where uncertainty may affect hope, complicating survivorship (Wonghongkul et al., 2000). However, aging survivors report fewer physical symptoms, reducing uncertainty and improving mental health (Maheu et al., 2021), though time/age isn't directly considered in the theory.

The network Model of post-traumatic stress disorder (PTSD)

This theory posits that a cancer diagnosis can trigger pathological stress reactions linked to the severity and uncertainty of the life-threatening disease (Kangas et al., 2002). Cancer is represented as a memory network of interconnected elements, including images (e.g. tumor on mammogram), cognitions (e.g. 'I'm going to die'), emotions (e.g. fear), physiological responses (e.g. shortness of breath), sensory experiences (e.g. dizzy), meanings (e.g. loss of control), and behaviors (e.g. avoidance). Stimulating one element can trigger others, with seemingly unrelated stimuli activating trauma responses. To protect against the threat to survival, many patients engage in denial or avoidance (Kangas et al., 2002). However, avoidance of negative emotions can lead to hypoactivation (e.g. emotional numbness) and hinder recovery by preventing habituation and corrective learning in the cancer fear network (Kangas et al., 2002). Recovery requires activating the fear network and incorporating new, safety-related information to reduce the perceived threat (Kangas et al., 2002).

Recurrence model 1: fear of cancer recurrence

At the survival and recurrence phases of cancer, fear of recurrence can be experienced. Accordingly, some models have been developed in this field and applied to breast cancer specifically. The first is the Fear of Cancer Recurrence model, which puts forward that fear is a multidimensional construct in which external and internal cues (e.g. physician cues and symptom cues) increase patient's perceived risk of recurrence (Lebel et al., 2018; Yang et al., 2022). Fear of recurrence includes, but is not limited to, worries about breast cancer returning or progressing, regret about treatment decisions, memory dysfunction, lack of self-efficacy, and difficulty making plans (Maheu et al., 2021). In relation to the symptomatology associated with PTSD, it has been noted that the fear of recurrence is associated with hypervigilance towards physical symptoms and interpreting these sensations as evidence of recurrence (Yang et al., 2022). Additionally, unrealistic fears and misjudgment of danger are noted in survivors who perceive themselves at high risk of recurrence (Maheu et al., 2021). A potential or existing threat of cancer recurrence may contribute to maintain a cycle of anxiety and relief (Maheu et al., 2021). However, the authors did not comment on the directionality of whether fear of recurrence comes before anxiety symptoms or vice versa.

Recurrence model 2: network Model of fear of recurrence

Another recurrence model is the Network Model of Fear of Cancer Recurrence, which portrays the inter-relationships between the fear of cancer recurrence, anxiety, and depressive symptoms (Yang et al., 2022). The model posits that anxiety symptoms enhance the fear of breast cancer recurrence and depressive symptoms (Yang et al., 2022). Indeed, 'feeling afraid', 'uncontrollable worry', and 'restlessness' are anxiety symptoms that are connected to the fear of cancer recurrence (Mutsaers et al., 2016; Yang et al., 2022). However, the authors did not address the directionality of these variables, which makes it difficult to draw conclusions about which psychological reaction comes before the other.

Recurrence model 3: hopelessness theory of depression

The third model of recurrence is the Hopelessness Theory of Depression, which posits that social support and hopelessness are powerful predictors of depressive symptoms (Brothers & Andersen, 2009) and has been applied to patients living with a recurrent breast cancer diagnosis. Women diagnosed with recurrent breast cancer may feel hopeless, as the trajectory of the disease will likely not lead to survival, but rather to death, and in turn develop depressive symptoms (Brothers & Andersen, 2009; Sarenmalm et al., 2009; Yang et al., 2022). A protective factor that modulates these depressive symptoms would be consistent and positive social support (Brothers & Andersen, 2009). For instance, patients who do not have a romantic partner appear to be more prone to developing depressive symptoms following their diagnosis of recurrent breast cancer (Brothers & Andersen, 2009).

Trajectory of breast cancer explanatory framework

The Trajectory of Breast Cancer (TBC) explanatory framework offers a theoretical synthesis that highlights women's stories of living with breast cancer (Smit et al., 2019). The TBC framework is formed of eight core themes that synthesize key

experiences from screening to survivorship (Smit et al., 2019). For instance, issues associated with breast cancer burden, confrontations over existential issues, illness or symptom appraisal as not being worrisome, sources of available support, belonging to the healthcare system, self versus others, self-image, and survivor identity are elements that patients may struggle with. Patients living with breast cancer may experience these eight core themes in varied ways due to individual emotional differences in facing a given situation. Therefore, they need to put forth strategies to overcome these challenges (Smit et al., 2019). It has been shown that sensitivity from the healthcare professionals and social support may reduce the negative mental health impacts of breast cancer throughout the trajectory (Sacks et al., 2016).

Limitations of existing models and theories

Current models and theories contribute to our comprehension of specific aspects of the care trajectory experience, yet they often lack crucial information. While these models and theories offer valuable insights into individual symptoms of psychological distress (e.g. only focusing on anxiety symptoms), they may fall short in providing a comprehensive understanding of the broader impact on the patient's mental health. Furthermore, these models and theories typically concentrate on one or two phases of the trajectory, primarily focusing on the treatment phase, thereby neglecting mental health challenges that may arise across all stages. Lastly, the recurrence phase, while not universally experienced by all patients, is frequently overlooked in existing models and theories. Recognizing the significance of patients' mental health throughout the entire trajectory underscores the necessity for an integrative model that comprehensively addresses mental health challenges across each breast cancer phase, offering a more holistic and effective approach to care. An important innovation of the integrative model lies in its reliance on theories and models that were originally constructed using either qualitative (e.g. Smit et al., 2019) or quantitative (e.g. Kourou et al., 2021) data. What sets our model apart is its distinctive approach of incorporating both types of data sources, providing a more comprehensive foundation.

A proposed integrative Model and clinical tool

Across the various theories and models of mental illness and health applicable to the breast cancer experience that were presented above, there are patterns of symptoms that can be synthesized into a single overarching, integrative model. To this end, the theory of Séguin et al. (2012) is leveraged, which postulates that the breast cancer trajectory from illness to recovery represents a personal crisis spanning several months to years, and which can be divided into seven phases (Séguin et al., 2012). Each phase is marked by a landmark 'event' with its own specific 'challenge' and in most cases a predominant 'symptom' domain (Séguin et al., 2012). The proposed integrative model considers the full range of theories, models, symptoms of psychological distress, quality of life, fear of recurrence, and the trajectory of the disease (see Figure 2).

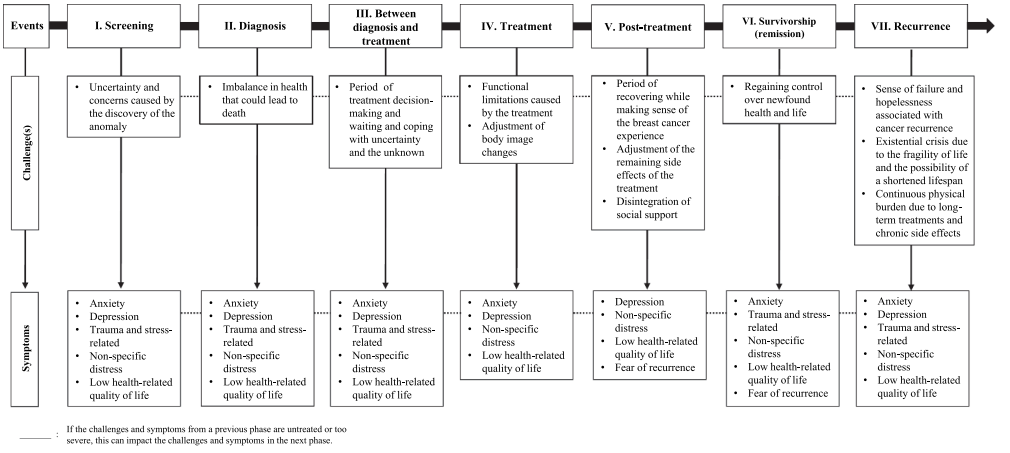


Figure 2. The breast cancer psychological integrative phasic Model.

Breast cancer psychological integrative phasic Model

Screening. The first time a lump is felt in the breast would be considered the first landmark 'event'. Once the abnormality is discovered, it eventually leads the patient to consult a doctor for biopsy (Katapodi et al., 2004). Psychologically, this discovery triggers a personal crisis related to one or more intrapsychic issues (i.e. challenges), which are potentially pathogenic. Physiologically, the fear of undergoing screening tests (e.g. mammograms and biopsies) and possibly receiving a diagnosis can cause stress that manifests itself in psychological (perceived stress) and physiological (cortisol secretion) responses (Lazarus & Folkman, 1984; Poole & Lyne, 2000; Smith & Vale, 2006; Stark & House, 2000; Steimer, 2002). The main 'challenge' experienced during the screening phase is that the discovery of the anomaly creates uncertainty and concerns, as proposed by Mishel's Uncertainty in Illness theory (Mishel, 1990) and the TBC framework (Smit et al., 2019). At this point, the main 'symptom' dimension that emerges is one congruent with anxiety, which can manifest as physiological responses (Gilbar & Hevroni, 2007) and the so-called non-specific or general distress. Patients are in an unknown situation, which may activate a variety of catastrophizing scenarios regarding their daily lives, health, and future (Z. Wang et al., 2020). A common trauma and stressors-related (TSR) and/or anxiety symptom during this phase is avoidance (Smit et al., 2019). Avoidance often stems from a fear of receiving bad news or a reluctance to confront medical issues, which can unfortunately lead to delayed diagnosis and treatment (Smit et al., 2019). Also, quality of life is often compromised (Mokhatri-Hesari, 2020), negatively affecting emotional well-being (e.g. difficulty coping with the possibility of having cancer), social well-being (e.g. not receiving the expected social support), and existential/spiritual (e.g. meaning in life) dimensions (Avis et al., 2012; Mokhatri-Hesari, 2020).

Diagnosis. The communication of the results of the biopsy is considered the landmark 'event' of the diagnostic phase. This event is an unfolding process with different stages, from confirming a cell type to determining the genetic details and hormone sensitivity, which all have implications for treatment. The main 'challenge' in receiving the diagnosis is that patients are faced with an imbalance in their health. In some cases, the cancer

diagnosis can be perceived as life-threatening, since it can sometimes lead to death (Reich et al., 2008; Smit et al., 2019). The announcement of the diagnosis alone can trigger symptoms of psychological distress and predispose patients to psychiatric disorders for the rest of their illness trajectory, as the Human Response to Illness Model (Mitchell et al., 1991) and the Illness Intrusiveness Theoretical Framework propose (Devins, 2010). For other patients, the diagnosis is a form of relief in that they can finally put a name on their so-far unknown condition and regain control of their lives. The 'symptom' developed or accentuated by the diagnostic phase is one of peritraumatic distress (Brunet et al., 2001), exemplified by shock, fear, dissociation, non-specific distress, and the onset of TSR symptoms (Cordova et al., 2007). A strong physiological and/or psychological stress response may also emerge at the time of diagnosis, and this may tend to decrease in the presence of protective factors (e.g. social support) or become chronic (Carlson & Bultz, 2003; Smith & Vale, 2006). The diagnosis phase can also be characterized by specific anxiety symptoms when breast cancer is considered a non-life-threatening danger (Stark & House, 2000). Not surprisingly, anxiety symptoms appear to be lower in patients diagnosed with benign tumors than in those diagnosed with malignant tumors (Liao et al., 2008). Depressive symptoms are predicted to appear later in the trajectory, as the losses become more apparent, so any depressive symptoms at this stage are mainly observed in patients who were experiencing them before the screening phase (Vahdaninia et al., 2010). Quality of life is influenced by the presence of other psychological symptoms, such as TSR symptoms (e.g. denial, hypervigilance), and the extent to which such symptoms interfere with daily life (Stanton & Bower, 2015).

Between diagnosis and treatment. Treatment decision-making and waiting for treatment initiation after being diagnosed with breast cancer is the landmark 'event' of the phase between the diagnosis and the treatment. The main 'challenge' regarding decision-making is that in many cases, patients are given choices between treatment approaches, which requires them to digest complex information about probability and make decisions they may not feel prepared to make (Maheu et al., 2021). Also, the waiting phase is again associated with uncertainty and the unknown, and coping with it represents the second main 'challenge' in this phase. This time, the uncertainty is associated with the treatment(s) and the prognosis of the cancer according to Mishel's Uncertainty in Illness theory (Mishel, 1990). The main 'symptom' dimension of this phase can be characterized by a blend of anxiety, depression, non-specific distress and TSR symptoms. It is also during this phase that patients introspect and evaluate their health status and various issues such as family, social, and professional life, which may lead some to a sense of grief or loss (e.g. loss of health) and develop depressive symptoms, according to the machine learning-based pipeline theory (Kourou et al., 2021). A positive evaluation can lead to a better quality of life, whereas a negative one can cause or exacerbate the development of various symptoms of psychological distress (Mokhatri-Hesari, 2020).

Treatment. The next landmark 'event' of the breast cancer trajectory is when the patient living with breast cancer begins treatments (e.g. radiotherapy, chemotherapy). Two 'challenges' may emerge during this phase. The first one is that many will be affected by new functional limitations (e.g. in their professional or familial roles), mainly because of treatment side effects. This represents a major issue in their self-perception, according

to Braden et al.'s (1998) combined and alternative model. The second challenge is that some patients will develop body image problems, mainly related to the mastectomy, which can accentuate the feeling of loss of control and thus have an impact on self-esteem and quality of life, as per the machine learning-based pipeline theory of Kourou et al. (2021) and the TBC framework of Smit et al. (2019). The treatment phase leads to even more heterogeneous trajectories, and it is difficult to identify a unique predominating 'symptom' dimension. Psychological distress, anxiety, depression, and TSR symptoms are all quite likely. During this phase, the physical side effects (e.g. insomnia, fatigue, nausea, pain) associated with treatments may compound the psychological symptoms (Braden et al., 1998; Deshields et al., 2011). Quality of life can also be seriously affected by the treatments and their side effects in one or several domains, including general health, physical symptoms, sexual functioning, emotional well-being, cognitive impairment, role functioning, social well-being and existential/spiritual issues (Movsas, 2003). Coping style (e.g. seeking social support) at this stage will have a major influence on the mental health of patients, as the TBC framework suggests (Smit et al., 2019). Additionally, patients living with a metastatic breast cancer may experience treatment interruptions without progressing to subsequent phases, intensifying psychological symptoms compared to patients with a higher chance for recovery (e.g. early-stage diagnoses) (Badger et al., 2004).

Post-treatment. The end of the treatment is the next landmark 'event' in the breast cancer trajectory. During this phase, patients attempt to recover and try to make sense of what has happened to them. This represents their main 'challenge'. Yet, another 'challenge' is that although the medical treatments are completed, the side effects of the treatments may continue to persist (e.g. pain, hair loss, fatigue, memory difficulties) and thus influence patients' quality of life, according to Braden et al.'s combined and alternative model (Braden et al., 1998). A third 'challenge' that is empirically documented and clinically reported is the deterioration of social support (Fong et al., 2017; Smit et al., 2019). Follow-up with the medical team becomes rarer from this stage onwards, and declines (e.g. going from several professionals to just one to do follow-up) (Fong et al., 2017). The social support from family and friends can also lessen (i.e. the end of treatment marks the disappearance of the cancer and the impression that the patient no longer needs functional (e.g. going to appointments) and emotional (e.g. less perceived unknown) support. This is reported in the TBC framework (Smit et al., 2019). Moreover, social constraints – social responses that overtly and/or covertly inhibit talking about the cancer experience – may also emerge and lead to increased distress (Adams et al., 2015). The predominant 'symptoms' during this phase are depression-related and those associated with a TSR disorder (e.g. reexperiencing or recalling unpleasant memories) (Kourou et al., 2021). Feelings of loss (e.g. breasts, hair) or grief, associated with depressive symptoms, may resurface. Quality of life domains can all be affected by the post-treatment challenges, especially the emotional and social well-being, but also role functioning (Movsas, 2003).

Survivorship (remission). Once there are no more signs of cancer after the completion of treatment, women are confronted with yet another landmark 'event'. Patients must now adapt their pre-cancer life to their new reality, for example by returning to the workplace.

The survival phase's main 'challenge' can be conceptualized for many patients as regaining control over their newfound health and life, leading to a decrease or disappearance of the various symptoms of psychological distress (Maheu et al., 2021). However, for those whose symptoms are too severe or whose emotional issues have not been properly dealt with, recovery is incomplete, and the symptoms may persist or even worsen. The 'symptoms' of depression and TSR are often prevalent during the survival phase (Britton et al., 2010). Anxiety and non-specific distress are especially present in patients who fear that their cancer will return, which happens more often for patients who conceptualize their cancer as a chronic illness rather than an acute condition (Maheu et al., 2021; Yang et al., 2022). Certain issues (e.g. loss of self-confidence, poor body image) that developed during previous phases may persist into this phase or emerge (Smit et al., 2019).

Recurrence. Traces of cancer may be discovered after treatment has ended, and after a period during which the disease could no longer be detected. This represents that last landmark 'event' in the trajectory. This latest event differs from the previous ones, as it brings the patient back to the beginning of the trajectory (i.e. the screening phase), but with a new perspective. A major 'challenge' associated with cancer recurrence occurs because, despite all efforts to get rid of the cancer, some of its cells have remained. There is a sense of failure and hopelessness to overcome (Brothers & Andersen, 2009). Patients living with a recurrent diagnosis often face another main 'challenge': an existential crisis, grappling with the fragility of life and the possibility of a shortened lifespan. Additionally, they may endure the 'challenge' of a continuous physical burden from long-term treatments and chronic side effects, significantly impacting their quality of life. For patients undergoing screening for a potential recurrent breast cancer diagnosis, hopelessness tends to be the predominant 'symptom', reflecting a more depressive state compared to those with early-stage diagnoses (Brothers & Andersen, 2009). As for the diagnosis phase, learning that the cancer has returned can cause an emotional shock similar to the first breast cancer diagnosis. However, the concerns and uncertainty are experienced differently, as the patient has already been through each event in the trajectory and, by definition, now faces a poorer prognosis. According to the Fear of Cancer Recurrence model (Yang et al., 2022) and the Network Model of Fear of Cancer Recurrence (Yang et al., 2022), the recurrence phase, which is not experienced by all cancer survivors, is associated with many TSR 'symptoms', such as hypervigilance (especially physical symptoms) and fear. Depressive symptoms may also be present in some patients who do not have strong social support or effective coping strategies, as the Hopelessness Theory of Depression states (Brothers & Andersen, 2009).

The integrative model has some limitations. The Trajectory of Male Breast Cancer framework shows that the experience of men living with a breast cancer diagnosis is different from that of women (Rudd et al., 2023), and in that sense, the current model does not necessarily apply to men. In addition, the model does not consider psychiatric disorders that pre-exist in patients living with breast cancer, so the symptoms associated with each phase of the disease trajectory may be experienced differently (Pedersen et al., 2010). Some studies argue that individuals with a psychiatric disorder may be less likely to access primary care services, or their mental illness may overshadow their cancer symptoms, resulting in cancers being diagnosed later with a worse prognosis

(Cunningham et al., 2015). Also, the quality of health care, or the likelihood of receiving appropriate and timely treatment once a diagnosis is made, is reduced in this population, making the issues associated with the disease trajectory distinct from those without prior diagnoses (Cunningham et al., 2015; Kisely et al., 2013). Finally, individual biopsychosocial factors may also modulate psychological responses to breast cancer depending on whether they are identified as risk (e.g. younger age, diagnosis of psychiatric disorder, fatigue, pain, holding minoritized racial/ethnic or sexual/gender identities; Collins et al., 2014; Kisely et al., 2013; Z. Wang et al., 2020) or protective factors (e.g. good social support, being married; Kisely et al., 2013), and therefore, should be considered while using the Breast Cancer Psychological Integrative Phasic Model.

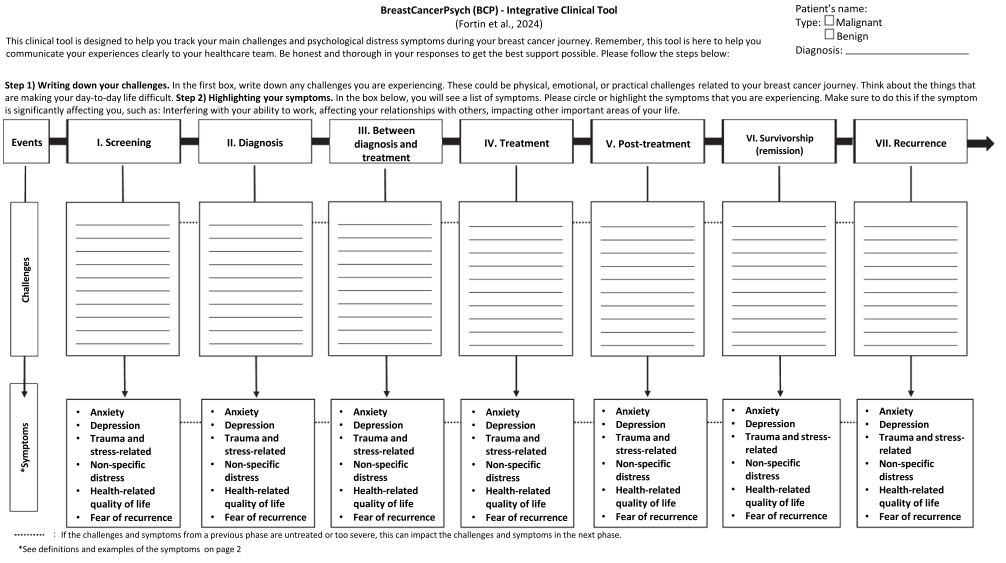
BreastCancerpsych (BPC) - integrative clinical tool

The Breast Cancer Psychological Integrative Phasic Model could be integrated into clinical practice, as it theoretically highlights the main challenges and types of prevalent psychological symptoms associated with each event in the care trajectory. Please refer to Figure 3 for the proposed simple clinical tool (BreastCancerPsych (BCP) – Integrative Clinical Tool) that can be filled by the patient living with breast cancer. This tool serves as a valuable resource, facilitating a more nuanced understanding of the patient's mental health journey, thereby enabling tailored interventions and support throughout the care continuum.

Discussion

The purpose of this paper was to propose an integrative model based on theories and models of mental illness and health applied to breast cancer in women. We introduce the Breast Cancer Psychological Integrative Phasic Model triggered by various stressful and/or traumatic life events that occurred throughout the breast cancer trajectory, inspired by Séguin et al'.s traumatic model (Séguin et al., 2012). Clinically, our proposed model suggests that there are seven 'events' (screening, diagnosis, post-diagnosis but pre-treatment, treatments, remission, survivorship, recurrence) in the breast cancer trajectory. These breast cancer-related events can lead to six possible psychological patterns of symptoms, the most common being 1) psychological distress with anxious features, 2) psychological distress with depressive features, 3) non-specific distress, 4) psychological distress with trauma and stressor related features, 5) low health-related quality of life, and 6) fear of recurrence, thus encompassing all symptoms of psychological distress that are observed in patients living with breast cancer (Casey, 2012). On one hand, the main challenges experienced at each phase of the trajectory are associated with anticipation, uncertainty, fear of suffering or death, which could give rise to anxious, TSR and non-specific distress symptoms (Brunet et al., 2001; Séguin et al., 2012). On the other hand, each event in the trajectory may provoke a sense of real (e.g. breast) or symbolic (e.g. self-image) 'loss', which could elicit depressive and grief symptoms (Séguin et al., 2012).

As the framework of the National Institute of Mental Health's Research Domain Criteria (RDoC) implied, distinguishing psychological symptoms following psychiatric categories like in the DSM-5 is not always efficient when developing treatment theories to clinically help patients (Cuthbert & Insel, 2013). Indeed, the RDoC may complement the DSM-5 by proposing to study the nature of mental health and mental health disorder in



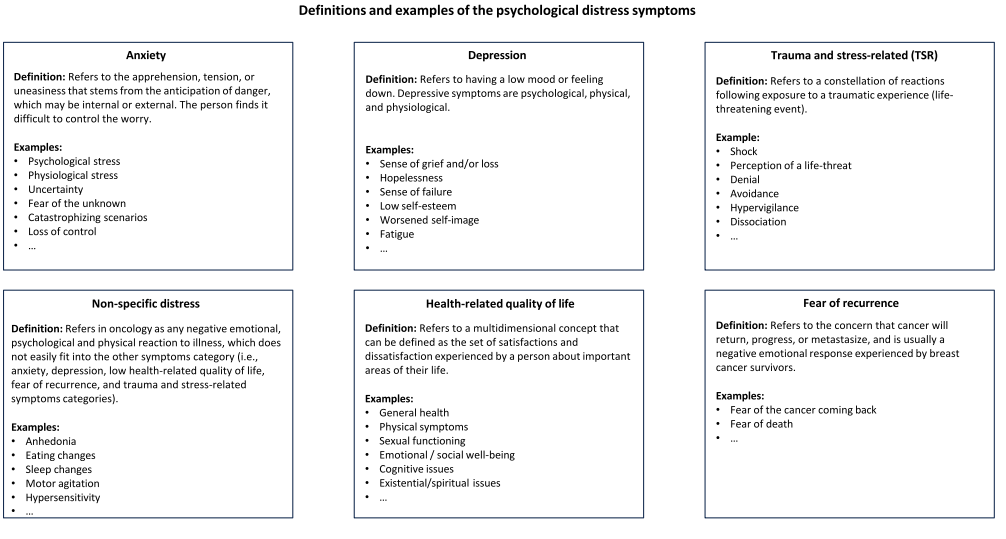


Figure 3. BreastCancerPsych (BPC) - integrative clinical Tool.

terms of varying degrees of dysfunction in general psychological/biological systems (Cuthbert & Insel, 2013). Therefore, the Breast Cancer Psychological Integrative Phasic Model allows visualization of overlapping symptoms of psychological distress (i.e. anxiety, depression, non-specific distress, and TSR symptoms) and their impact on quality of life and fear of recurrence, and this new approach may help identify the areas that are most affected in patients living with breast cancer (Cuthbert & Insel, 2013). The Breast Cancer Psychological Integrative Phasic Model allows for a temporal understanding of the issues that arise from each phase of the trajectory, but also the etiology of each

symptom of psychological distress. Clinicians and medical teams can rely on this model to develop treatments directly related to the experience of patients living with breast cancer. Indeed, the later the interventions are proposed during the breast cancer trajectory, the more the psychological symptoms are likely to become pathological (McGorry et al., 2018). For this reason, it is critical to provide appropriate psychological support to patients in the early stages of their breast cancer trajectory.

Existing evidence suggests that more than one-third of patients living with breast cancer present symptoms of psychological distress requiring attention from healthcare professionals specifically after receiving the cancer diagnosis (Fortin et al., 2021). Despite the challenges posed by limited resources in many health systems/centers, which may hinder screening for psychological distress during the initial phase, current literature indicates that patients are typically evaluated after treatment initiation (Carlson & Bultz, 2003; Riba et al., 2023; Van Amstel et al., 2013). However, the integrative model emphasizes addressing psychological symptoms and main challenges early to optimize patient care and quality of life. In order to support this, the BreastCancerPsych (BCP) – Integrative Clinical Tool was created to allow patients to maintain a private journal of their journey, documenting challenges and symptoms, which can positively impact their mental health (Baikie & Wilhelm, 2005; Kashdan & Rottenberg, 2010). Moreover, for patients requiring external psychosocial support, this tool can provide comprehensive insights into their experiences, enabling psycho-oncology professionals to deliver more personalized care and interventions throughout the trajectory, potentially alleviating the impact of time constraints and resource limitations identified by Butow and Hiller (209). This approach not only enhances treatment adherence but also improves overall quality of life, potentially influencing survival outcomes (Holland et al., 2013; Z. Wang et al., 2020).

Conclusion

The purpose of this article was twofold, namely, to summarize existing theories of mental health that are applicable to the breast cancer experience and create an integrative model based on these theories. The proposed Breast Cancer Psychological Integrative Phasic Model allows for the integration of the different event-related issues that may arise across different phases of the disease trajectory (i.e. screening, diagnosis, post-diagnosis and pre-treatment, treatment, post-treatment, survival (remission) and recurrence), which may trigger psychological distress symptoms, low health-related quality of life and fear of recurrence. For some patients, these event-related issues may also lead to resilience (subclinical). It would therefore be interesting to develop treatment models that consider patients living with breast cancer's experience according to the phase of the trajectory they are in, but also according to the type(s) of psychological symptoms that are present.

Note

1. See Supplemental for definition and rational behind these various psychological distress symptoms.

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Data availability statement

This review synthesized data exclusively from the published literature. A search of PsycInfo, Web of Science, PubMed, and CINAHL databases was conducted to identify relevant studies published that met the predetermined eligibility criteria. All data analyzed in this review are available in the public domain. Please contact the corresponding author to receive the BreastCancerPsych (BCP) – Integrative Clinical Tool or the first author: fortin.justine.2@courrier.uqam.ca.

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REVIEW

Current practices in oncofertility counseling: updated evidence on fertility preservation and post-treatment pregnancies in young women affected by early breast cancer

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ABSTRACT

Introduction: Anticancer treatments have significantly contributed to increasing cure rates of breast cancer in the last years; however, they can also lead to short- and long-term side effects, including gonadotoxicity, and compromised fertility in young women. Oncofertility is a crucial issue for young patients who have not yet completed their family planning at the time of cancer diagnosis.

Areas covered: This review aims to cover all the latest available evidence in the field of oncofertility, including the gonadotoxicity of currently adopted anticancer therapies in the curative breast cancer setting, the available strategies for fertility preservation and the feasibility of achieving a pregnancy following anticancer treatment completion.

Expert opinion: Over the past years, a significant progress has been made in oncofertility care for young women with breast cancer. In the context of the currently available evidence, every young woman with newly diagnosed breast cancer should receive a proper and complete oncofertility counseling before starting any anticancer treatment to increase her chances of future pregnancies.

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1. Introduction

Breast cancer is the most frequent malignancy in young women and the leading cause of cancer-related mortality [1]. Thanks to continuous improvements in treatments, survival rates for early breast cancer are steadily rising, but along with them also short- and long-term adverse events; hence, an increasing focus on survivorship is mandatory [2,3].

Most young patients with early breast cancer are still candidates to receive (neo)adjuvant chemotherapy [4,5], for which gonadotoxicity is certainly one of the main long-term side effect with a severe impact on patients' quality of life (QoL), as it can lead to premature ovarian insufficiency (POI) and its related consequences such as sexual dysfunction, symptoms of early menopause and infertility [6,7].

Approximately half of young patients diagnosed with breast cancer under 40 years of age are concerned about becoming infertile after anticancer treatments [8–10]. However, there are still several limitations in the access to oncofertility counseling (particularly in developing countries) [11]. This is partly due to incomplete information provided at diagnosis to patients, with the consequence that only a minority of young women with newly diagnosed breast cancer decide to access fertility preservation strategies [8,9]. It should be also considered that patients with breast cancer are those with the lowest likelihood to have a subsequent pregnancy as compared to survivors of other types of solid tumors [12].

Hence, to date, guidelines clearly recommend that all women of childbearing age should undergo proper oncofertility counseling prior to treatment start to reduce the risk of developing the negative and irreversible impact that anticancer therapies may have on the reproductive outcomes [6,13,14]. Avoiding to acknowledge the concerns of patients or to address oncofertility issues can lead to negative implications, including non-adherence to adjuvant endocrine therapy (ET) and a negative impact on QoL and long-term prognosis [15].

This review aims to cover all the latest available evidence in the field of oncofertility, including the gonadotoxicity of currently adopted anticancer therapies in the curative breast cancer setting, the available strategies for fertility preservation, and the feasibility of achieving a pregnancy following anticancer treatment completion.

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Article highlights

- Most anticancer regimens administered in the treatment of early breast cancer can impair ovarian reserve and fertility in young women through different mechanisms.
- Still too many patients do not receive proper oncofertility counseling before starting anticancer treatments, with a subsequent risk of permanently compromise their chances of having a future pregnancy.
- Fertility preservation techniques, such as cryopreservation of oocytes/embryos or ovarian tissue, are feasible and safe in almost all young women with early breast cancer patients before treatment initiation.
- Pregnancy following diagnosis and proper treatment can be considered safe for most patients with both hormone receptor-negative and positive breast cancer.
- Optimizing oncofertility care is a crucial component of survivorship with direct positive effect on patients' quality of life, by enabling young women to regain a normal life after breast cancer diagnosis and treatment.

2. Gonadotoxicity of anticancer treatments

As a consequence of improved therapeutic strategies, early breast cancer is increasingly becoming a curable disease through optimal integration of local and systemic therapies [4]. Anthracycline- and/or taxane-based regimens are still the current standard treatment for most patients with early breast cancer who are candidates for chemotherapy. These regimens are currently also combined with other compounds such as anti-HER2 therapy in patients with HER2-positive disease, or platinum salts (which can be combined also with immunotherapy) in triple-negative disease [4]. All these treatments may cause different degrees of gonadal damage by different mechanisms, resulting in POI, fertility-related issues, and potential early menopause [6].

POI is defined as a condition characterized by a reduction in ovarian function in women before the age of 40 years leading to a decreased production of sexual hormones, decreased ovarian reserve, and subsequent infertility [16]. To date, the most widely used marker to assess ovarian reserve in premenopausal patients is the anti-mullerian hormone (AMH) [17]. AMH is produced by granulosa cells of growing follicles and has been widely used as a surrogate for ovarian reserve; more recently, this biomarker has shown promising value as a diagnostic and predictive biomarker of POI also in patients receiving gonadotoxic therapy [17].

2.1. Gonadotoxicity of cytotoxic agents

Standard anticancer therapies for breast cancer can lead to POI through three different coexisting mechanisms: I) directly damaging ovarian follicular cells (by both damaging growing and non-growing follicles); II) accelerating follicular activation and depleting the primordial pool through increased follicle activation and III) damaging the ovarian stroma by altering the ovarian blood supply leading to decreased blood vessels and reduced blood supply to the germ cells [18] (Figure 1).

The main risk factors for this side effect include age at diagnosis (directly connected with the ovarian reserve at the time of treatment initiation) and the type of administered chemotherapy regimen [6,13,19].

In the algorithm of early breast cancer treatment, cyclophosphamide is a crucial (neo)adjuvant therapy, but it is the cytotoxic drug with the highest potential for gonadotoxicity. Treatment protocols incorporating cyclophosphamide significantly increase the risk of POI compared to those that do not include it. Specifically, patients undergoing this treatment face more than double the likelihood of experiencing treatment-induced amenorrhea (Odds Ratio [OR] 2.25, 95% CI 1.26–4.03, $p = 0.006$) [20]. Anthracyclines are also a cornerstone of the (neo)adjuvant treatments of patients with early breast cancer; they are also linked to a notable rise in the risk of

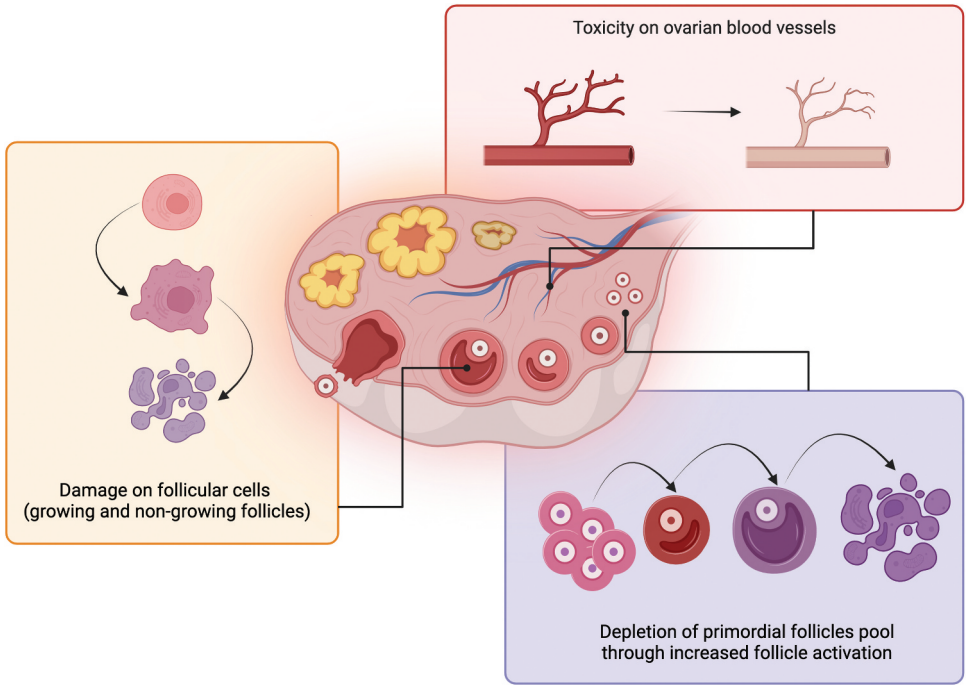

Figure 1. Main mechanisms of gonadotoxicity of cytotoxic agents leading to premature ovarian insufficiency.

chemotherapy-related amenorrhea (OR 1.39, 95% CI 1.15–1.70; $p < 0.001$) [20]. A further increased gonadotoxic risk is also observed with taxanes; women treated with these agents experience a higher rate of chemotherapy-related amenorrhea (OR 0.49, 95% CI 0.30–0.80; $p = 0.004$) [21]. Using a taxane following anthracycline- plus cyclophosphamide-based regimens was shown to significantly lower serum AMH levels one year after treatment completion (0.22 vs 0.04 µg/L, $p < 0.001$). Similar rates of chemotherapy-related amenorrhea are anticipated with the combination of cyclophosphamide plus a taxane or the sequential administration of anthracycline plus cyclophosphamide followed by a taxane, with 81% and 80% of patients reporting cessation of menses after chemotherapy, respectively [22].

Use of a platinum agent combined with a neoadjuvant anthracycline- and taxane-based regimen is associated with improved rates of pathological complete response and event-free survival in triple-negative breast cancer [23,24]. However, specific data on the ovarian toxicity of platinum salts in breast cancer are limited to date [25].

In premenopausal women with breast cancer, persistence of chemotherapy-related amenorrhea is common after the end of treatments and is associated with worse long-term QoL [26]. In a recent analysis, among 1,636 women treated with chemotherapy for early breast cancer, 1,242 (83.0%) women reported chemotherapy-related amenorrhea after 1 year from the end of treatments and 599 (66.1%) of 906 women reported it after 4 years; in the QoL analysis, persistent chemotherapy-related amenorrhea was associated with worse insomnia, systemic therapy-related adverse effects, and worsened sexual functioning even after 4 years from the end of the treatments [26].

2.2. Gonadotoxicity of targeted agents

In recent years, several targeted therapies have moved or are currently entering clinical practice, drastically changing the history of early breast cancer. Among them, the most important are anti-HER2 agents in early HER2-positive disease [27], Cyclin-Dependent Kinases 4/6-inhibitors (CDK4/6i) in the adjuvant setting of high-risk hormone receptor-positive disease [28,29], immune checkpoint-inhibitors (ICI) in the neoadjuvant treatment of triple-negative breast cancer [30], and Poly (ADP-ribose) polymerase-inhibitors (PARPi) for the adjuvant treatment of patients harboring germline *BRCA* (g*BRCA*) pathogenic variants (PVs) at high-risk of recurrence [31]. Few data are currently available on the ovarian toxicity of these new agents [32].

2.2.1. Anti-HER2 agents

Some evidence exists on the gonadal safety of anti-HER2 targeted agents; however, notably, these drugs are rarely used as single-agent strategy in the early breast cancer settings but are commonly combined with chemotherapy [4].

Anti-HER2 monoclonal antibodies (i.e. trastuzumab and pertuzumab) are now routinely administered in both the neoadjuvant and adjuvant settings. However, no data exist on their combination on possible effects on ovarian function and fertility. In the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial comparing between trastuzumab, lapatinib, their combination or sequence, menopausal status was assessed at random assignment and during study follow-up for all premenopausal patients [33]. The amenorrhea rate was 72.6% with trastuzumab alone, 74.0% with lapatinib alone, and 74.8% and 72.1% with combined and sequential use of trastuzumab and lapatinib, respectively ($p = 0.64$). It should be considered that all patients received prior chemotherapy and there was no control arm without anti-HER2 agents. However, in the combination arm with trastuzumab and lapatinib, no signals of increased risk of gonadotoxicity was observed [33].

In the adjuvant paclitaxel and trastuzumab (APT) trial, a single-arm study evaluating weekly paclitaxel treatment with trastuzumab for 3 months (followed by trastuzumab for up to 1 year) as a strategy to de-escalate adjuvant chemotherapy in patients at lower risk of relapse, an overall low rate of amenorrhea (28%, 95% CI 18–41%) after 18 months was reported among premenopausal patients [34]. Recently, an analysis of the NeoALTTO trial provided further insights on the short-term impact of anti-HER2 therapy (alone and combined with weekly paclitaxel) on the ovarian reserve of premenopausal women with HER2-positive early breast cancer. In this trial, patients received a 2-week course of anti-HER2 therapy alone with trastuzumab, lapatinib or their combination; afterward, the treatment was combined with weekly paclitaxel for 12 cycles combined with the same anti-HER2 therapy used in the first 2 weeks. This analysis showed only a small reduction in AMH levels during the 2 weeks of anti-HER2 treatment alone (irrespective of the type of anti-HER2 administered) and then a profound decline of AMH levels in most patients after completing weekly paclitaxel. As expected, the factors that had a major impact on the acute risk of treatment-induced gonadotoxicity were age and pretreatment ovarian reserve (assessed by AMH levels) [35]. These data suggest the apparent gonadal safety of anti-HER2 therapy but they raise attention on the potential ovarian damage with chemotherapy regimens, even those not including anthracyclines or cyclophosphamide.

Regarding antibody-drug conjugates (ADCs), the first approved anti-HER2 ADC in the early breast cancer setting is Trastuzumab Emtansine (T-DM1) for patients with HER2-positive disease and residual disease at surgery after neoadjuvant chemotherapy plus anti-HER2 treatment [36]. There are few data on the impact of T-DM1 on ovarian reserve and fertility. In the ATEMPT trial, amenorrhea after treatment was assessed in 123 premenopausal women that received T-DM1 (compared to paclitaxel in combination with trastuzumab). Amenorrhea at 18 months was less common in the T-DM1 arm (24%) as compared to the control arm of paclitaxel and trastuzumab (50%) ($p = 0.045$) [34]. Trastuzumab Deruxtecan (T-DXd) is another HER2-directed ADC that has more recently demonstrated impressive results in the treatment of HER2-positive [37] and HER2-low [38] metastatic breast cancer. Considering the efficacy in the advanced setting, several studies are examining the value of T-DXd in the treatment of early breast cancer. No specific data so far are available on the impact of T-DXd on patients' ovarian reserve and fertility.

2.2.2. CDK 4/6i

CDK4/6i in association with ET have demonstrated to be an effective combination in the advanced setting and have also

been explored as adjuvant treatment in high-risk hormone receptor-positive/HER2-negative early breast cancer [28,29,39,40]. Two adjuvant trials demonstrated a significant improvement in terms of invasive disease-free survival (iDFS) with the addition of a CDK4/6i to ET [28,29]. The monarchE trial investigated the addition of 2-year abemaciclib to standard adjuvant ET, while the NATALEE trial adopted a 3-year treatment with ribociclib [29]. Currently, the only CDK4/6i approved for early-stage treatment is abemaciclib for hormone receptor-positive/HER2-negative high-risk early breast cancer [41].

Cyclins and cyclin-dependent kinases are key regulators of cell cycles, with a crucial role in cancer in controlling proliferation, senescence, migration, apoptosis, and angiogenesis [42]. In the ovary, consecutive activation of several CDKs leads granulosa cells of primordial follicles to switch from a quiescent state to reentering the cell cycle. Therefore, the use of CDK4/6i may have an impact on ovarian primordial follicles with subsequent potential gonadotoxic effect [43]. Due to their inclusion in the treatment algorithm of early breast cancer and considering that about 15–20% of patients are potential candidates for abemaciclib [44,45] and about 50% candidates for ribociclib [46], investigating the potential gonadotoxicity of CDK4/6i is highly relevant [32]. It should also be considered that more than 90% of the high-risk patients included in both monarchE and NATALEE studies have previously received chemotherapy, which its known impact on ovarian function andreserve. However, despite 43.5% of patients included in monarchE trial and 44% of patients included in NATALEE trial were premenopausal, no data have been reported so far on the incidence of post-treatment amenorrhea nor on ovarian reserve.

In preclinical studies, only data on palbociclib are available and results are conflicting on the potential damaging role of CDK4/6 exogenous inhibition in the ovary and specifically in granulosa cells [43,47]. Notably, there is also evidence of a possible protective role of palbociclib in ovarian cells [43]. Among clinical studies in the adjuvant setting, only a subanalysis of the PenelopeB study reported the potential gonadotoxicity of palbociclib [48]. Results from this biomarker analysis showed that 1-year palbociclib did not significantly affect estradiol and FSH levels when added to adjuvant ET after chemotherapy, suggesting the potential gonadal safety of this option. Evidence on the gonadotoxicity of 2-year abemaciclib and 3-year ribociclib are urgently needed.

2.2.3. PARPi

PARPi are administered in patients harboring germline PVs in the *BRCA*1/2 genes. Following the approval of PARPi in the treatment of advanced disease with olaparib and talazoparib [49,50], data from the OlympiA study have led to the approval of adjuvant olaparib in *BRCA* carriers with early breast cancer at high-risk of relapse [31]. In the OlympiA trial, all patients had received previous (neo)adjuvant chemotherapy before starting PARPi [49]. The only existing data on the gonadotoxicity of PARPi are reported in mouse models. The study conducted by Winship et al. evaluated the influence of classical anticancer agents (i.e. cyclophosphamide, doxorubicin, carboplatin, or paclitaxel) administered alone or in combination with olaparib in *BRCA* wild-type female mice. Primordial follicles treated with chemotherapy in association with PARPi were drastically reduced by 36% compared to the control arm without PARPi ($p < 0.05$) [51], while all other follicular cells, ovulations and AMH levels showed no significant changes. No data in women are available to date.

2.2.4. Immunotherapy

Immune checkpoint inhibitors (ICIs) are changing the treatment paradigm in breast cancer also in the early-stage setting. Results from Keynote-522 and IMpassion031 showed an improved pCR rate with the addition of pembrolizumab (anti-PD1) and atezolizumab (anti-PDL1), respectively [30,52]. More recently, two studies have shown efficacy in using ICIs (Pembrolizumab in Keynote-756 [53] and Nivolumab in Checkmate-7FL [54]) also in patients with hormone receptor-positive early breast cancer. None of these studies have yet reported specific data on gonadotoxicity or pregnancy after treatment. It should be remembered that ICIs are combined with chemotherapy during neoadjuvant treatment.

In preclinical studies, ICIs have been shown to enhance the infiltration of immune cells and the expression of tumor necrosis factor-α in the ovary. This process reduces the ovarian follicular reserve and adversely affects oocyte maturation and ovulation. These findings indicate that ICIs may negatively impact both present and future fertility, highlighting the need for increased research in women receiving ICIs [55]. Assessing how fertility may be affected by immunotherapy is crucial, since these drugs will increasingly be used in the early stages for many young patients with several solid tumors. In addition, ICIs can affect almost all endocrine pathways, including those involved in fertility and reproduction [56].

3. Fertility preservation strategies in young patients with early breast cancer

Due to the gonadotoxicity of anticancer treatments, increasing attention should be paid to fertility and ovarian function preservation techniques. The different fertility preservation techniques available for patients with breast cancer are cryopreservation of gametes (oocytes and/or embryos) and ovarian tissue. Moreover, it is important to discuss the strategies currently available to protect ovarian function before and during anticancer treatments. Special considerations in fertility preservation techniques should be paid in patients harboring g*BRCA* PVs.

3.1. Fertility preservation techinques

The two main techniques that can be employed prior to the start of anticancer treatments to preserve fertility are: I) Controlled ovarian stimulation (COS) for oocyte/embryo cryopreservation and II) Ovarian tissue cryopreservation [6] (Figure 2).

3.1.1. Oocyte/embryo cryopreservation

COS for oocyte/embryo cryopreservation is the technique recommended as the first choice by international guidelines

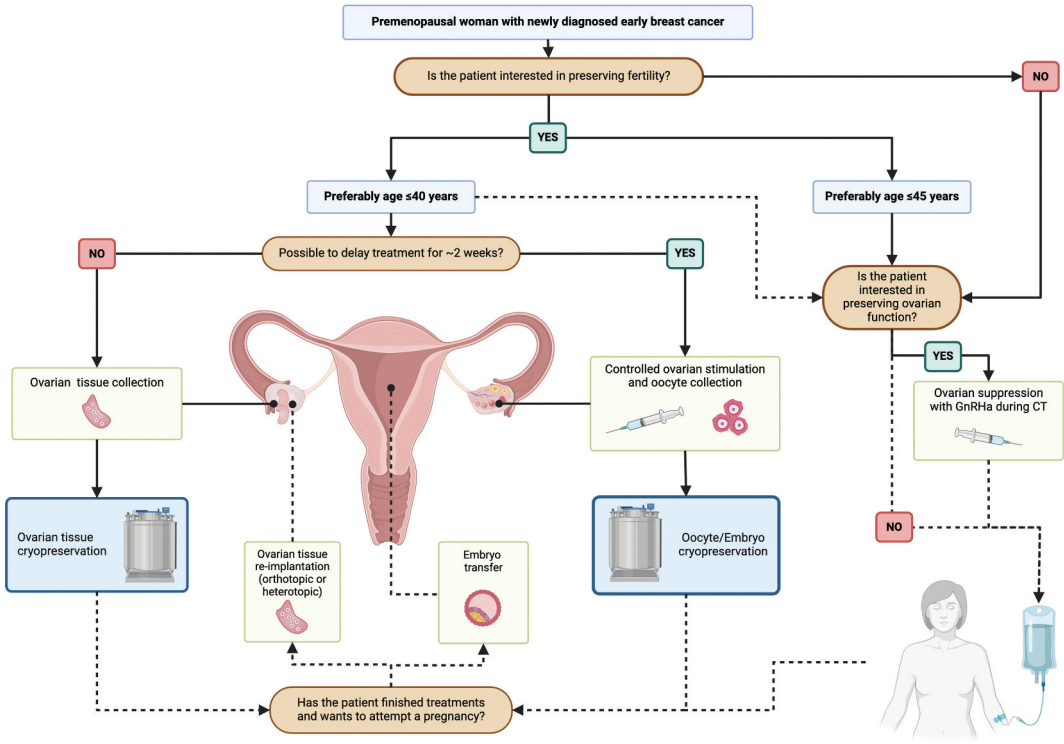

Figure 2. Proposed decision-making algorithm for premenopausal women with early breast cancer who wish to preserve fertility and/or ovarian function before starting anticancer treatments.

Abbreviations: GnRHa, gonadotropin releasing-hormone analogues; CT, chemotherapy.

in all patients wishing to preserve fertility before starting anticancer treatments [6,13]. This technique is indicated particularly for post-pubertal patients (preferably younger than 40 years of age at diagnosis) and whenever there is enough time available before the start of anticancer treatments, considering that two weeks are needed for COS to allow proper oocyte collection [6,13,57]. This procedure requires COS aiming to stimulate ovarian follicles. This process requires careful monitoring through ultrasound scans and serial blood hormone measurements to adjust the dose of the drugs and avoid complications. Once the follicles reach the desired size, oocyte maturation is induced [58]. The ovarian response to stimulation varies based on the patient's age and ovarian reserve [59].

Historically, different concerns have been raised about this procedure; firstly, hormone stimulation may raise doubts in endocrine-sensitive disease like breast cancer [60]. To minimize the peaks of estradiol levels during COS, one of the potential solutions is to use an aromatase inhibitor during COS, minimizing estradiol level produced during this phase [61]. A meta-analysis based on 11 studies and 2,121 patients, of whom 990 underwent COS with letrozole and 1,131 COS without letrozole, showed that the addition of letrozole to COS did not have any negative effect on the number of collected mature oocytes, maturation rates and fertilization rate; at the same time, COS with letrozole was associated with significantly decreased peak estradiol levels, also in studies evaluating only patients with breast cancer (mean ratio 0.28, 95% CI 0.24–0.32; $p < 0.001$) [62].

Another hormonal strategy applied to reduce the possible side-effects of the transient increase in estrogen during COS is to include tamoxifen as part of COS protocol. In a prospective study by Meirow and colleagues, 70 patients with breast cancer received 76 fertility preservation cycles with COS for oocyte retrieval for IVF and embryo cryopreservation. Of the 76 cycles reported, 48 were performed with COS cotreatment with tamoxifen while 28 received COS without tamoxifen supplementation. Coadministration of tamoxifen during COS did not appear to impair fertility-preservation outcomes in terms of number of oocytes collected, fertilization rate, or number of stored embryos. After a long follow-up ranging between 3 to up to 10 years, there was no difference in survival outcomes between patients who received the tamoxifen protocols and those treated without tamoxifen [63].

A recent meta-analysis compared different COS strategies (i.e. COS with tamoxifen, COS with gonadotropins and letrozole, or COS with gonadotropin only), for fertility preservation in patients with breast cancer [64]. This work included four studies with 348 patients; no significant differences were reported among the total number of retrieved oocytes between COS with tamoxifen and COS with letrozole or between COS with tamoxifen and COS with gonadotropin only. However statistically significant decrease was observed in the total levels of estrogens during COS with letrozole compared with tamoxifen alone (mean difference 3,184.4 pg/mL; 95% CI 1,414.4–4,953.7 pg/mL) [64].

In terms of long-term safety, in a recent meta-analysis, 11 studies with 3,980 patients assessed survival outcomes in women who underwent COS for fertility preservation before starting (neo)adjuvant chemotherapy. Compared to 2,386, women who did not receive fertility preservation at diagnosis, the 1,594 patients who underwent COS had a reduced risk of

recurrence (RR 0.58, 95% CI 0.46–0.73) and mortality (RR 0.54, 95% CI 0.38–0.76). Similar trends of better outcomes were also observed in women with hormone receptor-positive disease who underwent COS (HR 0.36, 95% CI 0.20–0.65) or in those patients undergoing COS before neoadjuvant chemotherapy (RR 0.22, 95% CI 0.06–0.80) [65].

A further concern arises from the fact that at least 2 weeks of COS are required before oocyte collection and treatment start [66]. This concern is becoming more prominent to date, as neoadjuvant treatment is increasingly becoming the strategy of choice for all breast cancer subtypes [4]. However, this technique only delays the starting of treatment by about 6 days, and this is also thanks to the random-start COS protocols, which allow stimulation to be started during any period of the ovarian cycle [65]. Nowadays, the random-start strategy has shown to be effective as the standard protocol [67], with similar numbers of retrieved oocytes [68].

When comparing the pregnancy outcomes of cancer survivors to those of women who underwent elective fertility preservation, the success rate was similar [69]. The cumulative pregnancy rate per transfer and cumulative live birth rate per transfer was similar between the cancer survivors compared to those of patients with other kind of infertility (37% vs. 43%; $p = 0.49$, and 30% vs. 32%; $p = 0.85$, respectively) [70].

3.1.2. Ovarian tissue cryopreservation (OTC)

OTC is a fertility preservation method performed without the need for COS. According to international guidelines, this method is not the first choice, but reserved for certain special situations, such as for prepubertal girls or pre-menarche adolescents diagnosed with malignancy, or for patients, generally younger than 35 years, who are unable to undergo COS due to an oncological urgency that prevents delayed treatment (a situation that is more frequent for hematological malignancies and rarer in the case of early breast cancer) [6,13] (Figure 2).

The process consists of laparoscopically retrieving ovarian tissue, treating it with cryoprotectant, and storing it in liquid nitrogen using either a slow-freezing or vitrification technique. At the end of the oncological treatments, if the patient is interested in getting pregnant and did not succeed spontaneously, ovarian tissue is thawed and placed either back into a site within the pelvic cavity (orthotopic transplantation) or in another site (heterotopic transplantation) such as the abdominal wall or forearm [6].

The pregnancy rate following transplantation of cryopreserved ovarian tissue is 37% (95% CI 32–43%) in terms of pregnancy rate and 28% (95% CI 24–34%) in terms of live birth rates, including both women who conceived naturally and those who conceived through in-vitro fertilization (IVF) procedures [71].

Unlike the previous method, this technique allows also to restore ovarian function. It has been shown that transplanted ovary began to function after 1–5 months, and the grafted tissue can maintain its viability and function for a median of 2.5 years (interquartile range: 1.4–3.4 years) [71]. Through this method, over 200 live births have been reported to date [72]. In terms of safety concerns, the fear that some tumor cells might be transferred back with the ovarian tissue should be considered. Fleury and colleagues studied reported outcomes from cryopreserved ovarian tissue and tumor cells were not found in 272 breast cancer patients across seven studies where their ovarian tissues were cryopreserved [73]. Another concern for this technique arises in patients carrying PVs in genes associated with a high risk of ovarian cancer (e.g. g*BRCA carriers*) [74].

3.2. Ovarian function preservation

The possibility of temporarily inhibiting during chemotherapy the normal ovarian cycle through a pharmacologically-induced menopause with a gonadotropin releasing hormone agonist (GnRHa) is the rationale behind the development of ovarian function preservation techniques [75,76].

GnRHa act by temporally blocking the activity of the hypothalamus, which leads to decreased levels of FSH and LH in the body; this blockage of the hypothalamic-pituitary-ovarian axis reduces ovarian activity and slows down cell metabolism within ovarian follicles. Consequently, during chemotherapy, ovarian follicles may be less sensitive to chemotherapy-induced damage and may be preserved in a temporarily dormant state. In addition, GnRHa may also reduce blood flow to the ovaries, thereby reducing the uptake of chemotherapy drugs further protecting ovarian follicles from toxicity [77]. A potential direct anti-apoptotic effect on cumulus cells have also been described as a possible protective mechanism [78].

In the last 15 years, several trials investigated the role of GnRHa in preserving ovarian function during chemotherapy [79–83]. In all these studies, GnRHa (i.e. goserelin 3.6 mg or triptorelin 3.75 mg) were used concomitantly with chemotherapy regimens starting 1–2 weeks before the initiation of chemotherapy and then for up to 4 weeks after chemotherapy. A large meta-analysis including 12 randomized trials and a total of 1,231 premenopausal women showed that adding GnRHa to chemotherapy was effective in reducing the risk of POI (OR 0.36, 95% CI 0.23–0.57; $p < 0.001$) [84]. Only 5 trials reported post-treatment pregnancies: a total of 33 among 359 women treated with chemotherapy plus GnRHa became pregnant following treatment completion compared with 19 among 347 patients who received cytotoxic treatment alone (OR 1.83; 95% CI, 1.02–3.28; $p = 0.041$) [84]. Another meta-analysis based on individual patient-level data supports these prior results: five randomized trials were included for a total of 873 premenopausal patients, of whom 436 were assigned to the GnRHa group during chemotherapy, while 437 to the control group that received chemotherapy alone. The incidence of POI was 14.1% in the GnRHa group and 30.9% in the control group (OR 0.38, 95% CI, 0.26–0.57; $p < 0.001$) [85]. In the GnRHa group, 37 of 359 (10.3%) patients achieved a post-treatment pregnancy compared with 20 of 367 (5.5%) patients in the control group (IRR 1.83; 95% CI 1.06–3.15; $p = 0.03$) [85].

Despite the results in post-treatment pregnancies were statistically significantly positive in both meta-analyses favoring the GnRHa group, numbers remain small to support an effect of this strategy in terms of fertility preservation

potential. Hence, GnRHa therapy is recommended by international guidelines as a strategy to preserve ovarian function in young patients with breast cancer [6,13,86].

In terms of safety concerns, recent data have clarified the safety of concomitant use of GnRHa during chemotherapy in all breast cancer subtypes, including among patients with hormone receptor-positive disease [85,87–89].

3.3. Fertility preservation in young patients harboring germline BRCA pathogenic variants

In the oncofertility counseling of patients harboring g*BRCA* PVs, some additional factors should be considered including a potential increased ovarian aging and reduced ovarian reserve as well as the need to undergo risk-reducing gynecological surgery at a young age due to the risk of developing ovarian cancer [90].

Preclinical and clinical studies have shown that g*BRCA* PVs can lead to increased follicular apoptosis, POI, and early menopause or accelerated ovarian aging [91,92]; similar findings were observed in the studies investigating AMH as a biomarker of ovarian reserve [93–95]. Based on the available literature, it seems plausible that g*BRCA* PVs may adversely affect fertility through the accumulation of DNA damage secondary to inadequate DNA repair resulting in cell apoptosis and accelerated ovarian aging [92,96]. Furthermore, due to the primary function of *BRCA* tumor suppressor genes, it has been hypothesized that the impact of gonadotoxic therapies on the ovarian reserve of women with g*BRCA* PVs could be more severe, further increasing the risk of gonadotoxicity and subsequent infertility [97].

In addition to the presumed direct effects of g*BRCA* PVs on women's fertility potential, the recommendation to undergo risk-reducing removal of the ovaries and fallopian tubes between the age of 35 and 40 years in *gBRCA*1 carriers and 40–45 years in *gBRCA2* carriers or as soon as family planning is complete is another issue that indirectly influences fertility [60]. Notably, cancers in g*BRCA* PVs carriers tend to arise at a younger age than in sporadic cases [98].

While fertility and ovarian function preservation strategies described for patients affected by sporadic disease are the same also for *gBRCA* carriers, some special considerations should be considered in this specific population.

Oocyte/embryo cryopreservation is the first strategy to be offered to patients interested in fertility preservation, including those harboring g*BRCA* PVs [6,14]. The technique has been shown to be safe, with no adverse effect on mortality and/or breast cancer recurrence [65], even for this specific population [99,100]. In line with the growing body of preclinical evidence, some studies have shown that g*BRCA* PVs carriers have a lower number of retrieved oocytes than non-carriers [95,101–103]. One of the most recent papers on this topic, involving 57 g*BRCA* PVs carriers and 254 patients with sporadic disease, found a statistically significant difference in the median number of mature oocytes retrieved between g*BRCA* PVs carriers with breast cancer and controls (7 oocytes vs. 9 oocytes, $p = 0.05$) [104]. However, other studies on the topic have not found similar results [105–107].

Despite the putative possibility that g*BRCA* may have a reduced ovarian performance, COS and oocyte cryopreservation are considered the standard of care for fertility preservation in post-pubertal g*BRCA* PVs carriers. This technique has important implications for patients harboring g*BRCA* PVs which can be concerned about transferring PVs to their offspring: in fact, this technique offers the possibility of performing pre-implantation genetic testing [108].

To avoid the transmission of the germline pathogenic variant to the offspring, pre-implantation genetic testing for monogenic/single-gene disorders (PGT-M) can be proposed to *gBRCA* carriers. This technique aims to detect the presence of specific genetic alteration in the early stages of embryonic development [109]. While this technique reduces the risk of transmitting genetic diseases offering to parents the possibility of making informed choices regarding the health of their children, it also opens to several issues, including on ethical and economical aspects: in fact, this technique implies additional costs compared to traditional IVF, requires advanced technology and specialized personnel, and does not always guarantee a successful pregnancy [108]. Furthermore, there may be ethical concerns regarding embryo selection considering that carrying a *BRCA* pathogenic variant does not cause malformations to the child, but increases the risk of developing *BRCA*-related cancers. Therefore, specific counseling and psychological support to the couples are needed to minimize decisional conflict or regret and adequate psychological support should be offered during and after PGT-M [108,109].

Regarding OTC, there is concern about the safety of this approach in patients with hereditary cancer syndromes associated with an increased risk of ovarian cancer such as in women harboring g*BRCA* PVs [90]. Despite this technique has proven to be successful also in patients carrying g*BRCA* PVs [110], it should be considered only in selected cases following strict criteria for transplantation procedure and also following the indications for risk-reducing surgery after the achievement of a pregnancy [74].

Ovarian protection during chemotherapy with the use of GnRHa can be considered in g*BRCA* PVs carriers diagnosed several years before the recommended age of risk reducing surgery [13,60]; however, very limited evidence exists on the efficacy of this approach in g*BRCA* PVs carriers [87].

4. Pregnancy after breast cancer treatments

Different doubts have concerned physicians and patients for several years regarding the feasibility and safety of having a pregnancy after breast cancer. However, in recent years, an increasing amount of evidence has provided safety evidence on pregnancy after sporadic breast cancer (both in case of hormone receptor-positive and negative disease) as well as in patients harboring g*BRCA* PVs (Figure 2).

4.1. Pregnancy after hormone receptor-negative and HER2-positive breast cancer

A large meta-analysis included 112,840 patients with early breast cancer, of whom 7,505 had a pregnancy following anticancer therapy [111]. Overall, as compared to patients

with BC without subsequent pregnancy, those with a post-treatment pregnancy showed better DFS (HR 0.68, 95% CI 0.51–0.91) and OS (HR 0.53, 95% CI 0.42–0.67) also when adjusted for the potential guarantee-time bias. In a subgroup analysis assessing maternal safety according to hormone receptor status, there was no detrimental prognostic effect of pregnancy after hormone receptor-negative breast cancer in terms of DFS (HR 0.72, 95% CI 0.55–0.95) [111].

In patients with HER2-positive disease, an exploratory analysis of the HERceptin Adjuvant (HERA) trial reported that 33 patients who conceived after a trastuzumab-free interval of 5–70 months achieved overall 45 pregnancies. Seven (16%) patients had a spontaneous abortion, four (9%) had an induced abortion and one live birth (3%) with congenital anomalies was described [112]. No data on patients' survival outcomes have been reported. A combined analysis of the NeoALTTO and ALTTO trials including 92 patients with a pregnancy occurring following discontinuation of adjuvant Trastuzumab and/or Lapatinib showed that 10 patients (12.5%) had an induced abortion, 10 (13.5%) a spontaneous abortion, and one live birth (3%) was reported with congenital anomalies. This analysis revealed also that pregnancy in young patients previously treated for HER2-positive disease had no detrimental prognostic effect in terms of DFS (10.6% in pregnant patients vs. 19.4% in 1,307 non-pregnant patients) after a median follow-up of 6.23 years [113].

4.2. Pregnancy after hormone receptor-positive breast cancer

Concerns on the safety of pregnancy in patients with hormone receptor-positive early breast cancer are mainly due to the hormonal-driven disease and the indication to receive at least 5 years of adjuvant endocrine treatment after surgery [4]. However, in recent years, reassuring data have shown the safety of pregnancy in this population.

A recent meta-analysis specifically addressed this issue, including 3,805 patients with hormone receptor-positive early breast cancer, of whom 1,285 became pregnant after treatment. During the follow-up period that ranged from 4.3 years to 15.8 years, no increased risk in terms of DFS (HR 0.96, 95% CI 0.75–1.24; $p = 0.781$) nor OS (HR 0.46, 95% CI 0.27–0.77; $p < 0.05$) was reported in patients affected by early breast cancer with a subsequent pregnancy compared to those patients without a pregnancy [114].

The POSITIVE trial (NCT02308085) has been designed specifically to evaluate the possibility of temporarily interrupting adjuvant ET to try to achieve a pregnancy after early breast cancer [115]. In the POSITIVE study, which included 518 young women aged ≤42 years at inclusion, ET could be temporarily interrupted between 18 and 30 months after starting the treatment. The maximum time of discontinuation was 24 months before going back to complete the 5–10 years of recommended adjuvant ET. After a median follow-up of 41 months, no higher risk of breast cancer events was found in the treatment-interruption group, with 8.9% (95% CI 6.3% to 11.6%) of events compared to the 9.2% (95% CI 7.6% to 10.8%) events in control group derived from the Suppression of Ovarian Function Trial (SOFT) and Tamoxifen and Exemestane Trial (TEXT) combined analysis. Notably, >90% of patients included in the POSITIVE trial had stage I-II breast cancer and only 4.5% of the patients had >4 positive axillary nodes; in the small subgroup analysis including patients with high-risk node-positive disease, 5 out of 23 patients relapsed [115]. Further follow-up from this trial is awaited to have a more robust answer; nevertheless, the first results of the POSITIVE trial are reassuring and allow to improve our counseling patients with lower risk of relapse (i.e. stage I and II disease) who want to consider a temporary interruption adjuvant ET to try to achieve a pregnancy [116].

4.3. Pregnancy after breast cancer in patients harboring germline BRCA PVs

In patients carrying PVs in g*BRCA* genes, a study of Valentini et al. identified 128 gBRCA PVs carriers who were diagnosed with breast cancer while pregnant or who became pregnant after a diagnosis of breast cancer and matched them with 269 gBRCA PVs carriers who did not become pregnant after breast cancer. The 15-year survival rate was 91.5% in pregnant cohort and 88.6% for those in non-pregnant cohort (adjusted HR 0.76, 95% CI 0.31–1.91; $p = 0.56$) [117]. A retrospective study by Lambertini et al. investigated specifically the safety of pregnancy after early breast cancer. Out of 1,252 g*BRCA* PVs carriers with breast cancer included in the study, 195 had a pregnancy after breast cancer. No detrimental maternal or fetal outcomes were described in these patients [118].

More recently, this study has been enlarged by including 4,732 young g*BRCA* PVs carriers from 78 centers worldwide [119]. Patients included were all younger than 40 years of age at the time of breast cancer diagnosis. At a median follow-up of 7.8 years, 659 women had at least one pregnancy following breast cancer, while 4,073 patients had no pregnancy and served as controls. Overall, the cumulative incidence of pregnancy at 10 years was 22%, being 18% for patients with hormone receptor-positive disease and 26% for those with hormone receptor-negative disease. In total, 517 patients (79.7%) carried at least one pregnancy to term, 406 (91.0%) patients delivered at term (≥37 weeks), and congenital abnormalities were documented in <1% of newborns. No significant association was demonstrated between having a pregnancy and the occurrence of DFS events with an adjusted HR of 0.99 (95% CI 0.81–1.20; $p = 0.90$). In subgroup analyses, a significant interaction was observed between having a pregnancy and *BRCA* genes, with adjusted HR for *BRCA*1 of 0.80 (95% CI 0.63–1.01) and adjusted HR for *BRCA*2 of 1.55 (95% CI 1.12–2.16; $p = 0.007$ for interaction). Moreover, a significant interaction was also observed between having a pregnancy and hormone receptor status, with adjusted HR for hormone receptor-positive disease of 1.30, (95% CI 0.67–1.08; $p = 0.90$) and adjusted HR for hormone receptor-negative disease of 0.76 (95% CI, 0.60–0.95; $p = 0.009$ for interaction). The occurrence of pregnancy was associated with improved breast cancer-specific survival (BCSS: adjusted HR 0.60; 95% CI 0.40–0.88; $p = 0.009$), and OS (adjusted HR 0.58, 95% CI, 0.40–0.85; $p = 0.005$). No significant interaction was observed between occurrence of pregnancy and any variable in the subgroup analyses.

Therefore, according to these increasingly strong evidence, data allow to conclude that pregnancy is safe in this group of patients and can be considered advisable, always considering each patient's risk of recurrence after treatments.

5. Discussion

Oncofertility has gained an increasingly important value for young patients affected by early breast cancer who are candidates to anticancer treatments associated with a potential risk of infertility [120]. Every physician involved in the treatment of early breast cancer in premenopausal patients should be aware of the potential gonadotoxicity of anticancer treatments. Based on patient's wishes and in collaboration with fertility specialists, the best strategies to preserve ovarian function and fertility should be discussed before treatment start. Moreover, patients wishing to become pregnant at the end of treatment should be clearly counseled on the feasibility of this approach and the best timing for conceiving [121].

It is crucial that physicians and patients place the highest priority on the life-saving treatments at every stage of the disease; however, it is equally crucial to inform all women as early as possible about their fertility preservation options, enabling them to make informed and autonomous decisions about their treatments [122].

It is essential that physicians fulfill their legal, ethical, and moral responsibility to ensure the physical and psychological well-being of patients with cancer [121]. To achieve this purpose with the highest quality and to ensure the highest standard of care for young patients, the oncofertility counseling should be managed in a multidisciplinary team involving medical oncologists together with different professional figures such as breast surgeons, gynecologists specialized in fertility preservation techniques, reproductive endocrinologists, embryologists, psychologists, as well as genetic counselors [123].

The strong collaboration and trusting relationship between the woman and the multidisciplinary team of reproductive medicine specialists and oncologists can minimize the risks for the patient and maximize the chances of a successful subsequent pregnancy. To date there is no ideal time to attempt a pregnancy after breast cancer and each patient must follow a personalized pathway; the combination of data on the disease and the patient's specific reproductive potential should be considered before attempting a pregnancy, which must be as safe and effective as possible for the patient and for the child [124].

Thanks to the continuous progress of research in this field and the numerous studies published in this area in recent years, patients with different types of malignancy and who received different treatments can be adequately advised on the best way to achieve a pregnancy [116], including the possibility of trying to conceive spontaneously or through the use of reproductive technologies or their cryopreserved material [125].

The healthcare team should fully manage all the challenges and peculiarities of the oncofertility program and to also alleviate the psychosocial distress of the women involved [123,126].

Notably, lack of awareness on oncofertility or underestimating its importance, both before and after anticancer treatment, can severely impact on patients' QoL and also on adherence to treatments and prognosis [15,123].

Continuity of care can enable women to make more informed choices about how and when to attempt pregnancy at the end of treatments, supporting a broader role of the oncofertility unit beyond access to fertility preservation strategies at diagnosis [125]. Hence, the role of the oncofertility unit is gradually changing from acute management of infertility risk to long-term counseling and care that should also be offered to women for whom fertility-preserving procedures are not possible or not required [6,13].

6. Expert opinion

6.1. Steps for a proper oncofertility counselling

Different factors need to be evaluated to determine the most suitable approach for preserving fertility and/or ovarian function [120]. Several aspects should be considered, including the patient's age at diagnosis, the stage of disease, the urgency of starting anticancer treatments, the type of recommended therapy, previous pregnancies, and the desire for a future pregnancy.

The oncofertility counseling can be divided into two steps: I) before the start of anticancer treatments, to enable the proper preservation of ovarian function and/or fertility, and II) after the end of treatments, to assess the possibility of having a pregnancy.

6.2. Oncofertility counselling before anticancer treatments

Current international guidelines recommend performing a complete oncofertility counseling for all patients with cancer diagnosed at reproductive age, before starting any anticancer systemic treatment [6,13]. During the oncofertility counseling, the discussion should encompass their current or anticipated family desires, their health and prognosis, the potential implications of the disease, the impact of proposed anticancer treatments on fertility and gonadal function, interest for future conception, and considerations regarding effective contraception [122,127].

If the patient has pregnancy desire, fertility preservation techniques should be offered before starting any gonadotoxic treatment. To perform COS and oocyte/embryo cryopreservation, the use of a GnRH antagonist protocol may be preferred for its feasibility in urgent situations, short time, decreased risk of ovarian hyperstimulation syndrome (OHSS), and safety reasons [128]. The entire procedure lasts around 2 weeks in clinical practice, with a delay from the start of treatments of around 6 days [65]. An optimal organization between oncology and fertility units is critical to ensure timely referral [125]. If there is no enough time to access this technique or there are contraindications, OTC

becomes the preferred strategy, but it should be performed in highly specialized centers [6,13].

In patients who are not interested in fertility preservation but are concerned in developing POI, GnRHa can be used for protecting ovarian function during chemotherapy [75]. In patients interested in fertility preservation, GnRHa during chemotherapy should not be regarded as a replacement for cryopreservation procedures, but it should be considered as a supplementary option or when COS and/or OTC are not accessible/feasible [75,84] (Figure 2).

6.3. Oncofertility counselling after anticancer treatments

Oncofertility counseling plays also a crucial role in the post-treatment period to discuss feasibility and safety of pregnancy after early breast cancer. Hormone receptor expression and the need to receive adjuvant ET are crucial factors that should be considered in counseling patients (Figure 3).

In patients with hormone receptor-negative disease (who may have been affected by triple-negative or HER2-positive disease), (neo)adjuvant treatments should be completed before attempting pregnancy. Having a pregnancy after breast cancer does not pose an increased risk of tumor recurrence. The most prevalent complications include prematurity, low birth weight, elective and emergency cesarean section, assisted vaginal delivery, and postpartum hemorrhage [129]. Hence, it is advisable to closely monitor pregnancies occurring after treatment and wait at least 1 year following the completion of chemotherapy in cancer survivors before attempting pregnancy [130].

In patients with hormone receptor-positive disease, the discussion is slightly more complex, as they are candidates to receive adjuvant ET for at least 5 years, with the risk of further reducing the biological window for pregnancy. Recent data from the POSITIVE trial showed the safety of discontinuing adjuvant ET for a period not exceeding 2 years in patients at relatively low risk of recurrence which have already received at least 18 months of prior ET. The importance to resume adjuvant ET for the time remaining at the end of the pregnancy or the 24 months allowed as per the POSITIVE protocol should be highlighted with the patients. A 3-month wash-out period from completion of endocrine treatment is recommended before attempting pregnancy, particularly in those patients receiving tamoxifen [131].

In patients that completed adjuvant ET before attempting pregnancy, conceiving seems safe and feasible, without increasing the risk of recurrence (Figure 3).

6.4. Viewpoint

With the growing availability of targeted treatments, future research efforts should provide evidence on their gonadotoxicity and impact on the possibility and safety of becoming pregnant following their completion. Changes in treatment algorithms are continuing to improve the rates of cures for patients with early breast cancer; however, it is imperative to ensure a return to a normal life following treatment completion, with a major focus on patients' survivorship issue including the possibility to have a pregnancy following completion of breast cancer treatments.

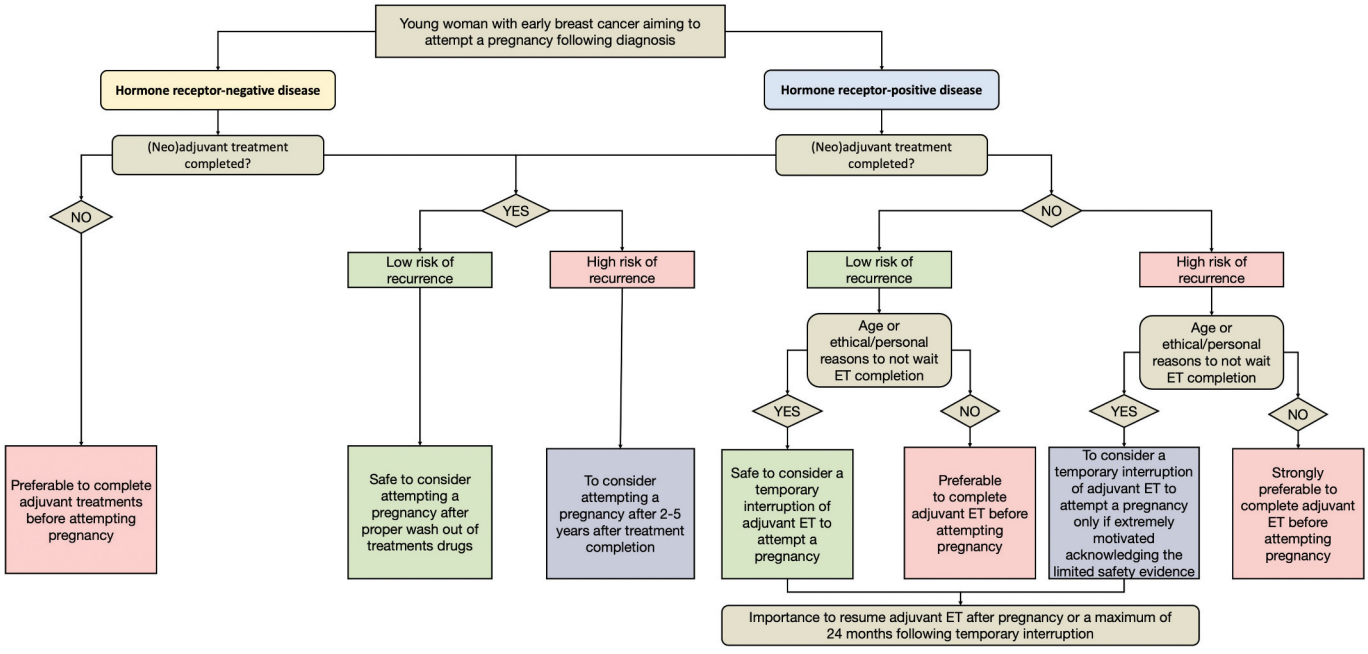

Figure 3. Proposed decision-making algorithm for premenopausal women with early breast cancer who wish to conceive following diagnosis.
Abbreviations: ET, endocrine therapy.

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REVIEW

Fertility preservation options at cancer diagnosis; classifying use and decision-making in the United States

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ABSTRACT

Introduction: Incidence rates for cancer among adolescent and young adults (AYA) have increased 30% since 1970. Declines in mortality underscore the importance of discussing fertility preservation (FP) options prior to receiving gonadotoxic treatments. National guidelines outline FP options including oocyte (OC), embryo (EC), and ovarian tissue cryopreservation (OTC) for female AYA patients. Significant progress has led to changes in FP practices, initially limited to EC. Subsequently, OC was deemed non-experimental in 2013, followed by OTC in 2020. Despite these advancements and guideline recommendations, the availability and utilization of FP services vary.

Areas Covered: Rapid review methodologies were employed to classify trends in female AYAs utilization of FP cryopreservation options following guideline updates. FP options reviewed include OC, EC, and OTC. Additionally, the review examined if aspects of the decision-making process relevant to FP were present.

Expert Opinion: Ten articles met inclusion criteria. Results suggest that the declassification of OTC has not necessarily increased its use and OC and EC appear to be most frequently used. The factors associated with decision making appear to have remained consistent with financial constraints having the most impact, followed by partner status and concerns about recurrence.

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1. Introduction

Cancer among adolescents and young adults (AYAs), defined as ages 15–39 years continues to present significant clinical challenges [1]. In 2024, an estimated 84,100 new cases will be diagnosed among AYAs in the United States, with approximately 8,890 cancer-related deaths in this age group. This incidence reflects nearly a 30% increase in rates compared to the late 1970s [2,3]. Increase in incidence rates for early-onset cancers can partially be attributed to improved detection of cancer through screening programs. Additional evidence suggests that changes in risk factor exposures (e.g. lifestyle, diet, environment, etc.) in early life and young adulthood are also associated with increased incidence rates [4,5]. For example, recent data suggest that this upsurge may be in part due to rising obesity rates and obesity-related cancers in the AYA population [3]. Despite increasing incidence, advances in cancer treatments have contributed to a steady decline in mortality rates, decreasing by an average of 0.9% annually from 2013 to 2022 with a 5-year survival rate of 85.9% among AYAs [2,6]. This, in combination with individuals continuing to defer parenthood to later stages of life [7,8], underscores the growing population of individuals who will be diagnosed with cancer before or during family-building years. Consequently, addressing the impact of cancer treatment on future fertility and offering fertility preservation (FP) options is a crucial element of the multidisciplinary approach to providing high-quality cancer care in female AYAs diagnosed during reproductive ages.

Organizations such as the American Society of Clinical Oncology (ASCO), American Society for Reproductive Medicine (ASRM), and National Comprehensive Cancer Network (NCCN) have established clinical practice guidelines for male adults, female adults, and pediatric cancer patients to engage in timely discussion with oncology care clinicians regarding threats to fertility and the presentation of available FP options. Despite the existence of such guidelines, discussion of these topics with patients remains inconsistent [9]. This variability highlights the need for standardized counseling approaches and shared decision-making processes.

For female adults facing fertility-threatening cancer treatments, guideline-concordant FP options available include cryopreservation of unfertilized oocytes, embryo cryopreservation, and ovarian tissue cryopreservation [9]. Significant strides have been made in the field of FP over the last two decades, marked by the removal of experimental labels and updates to clinical guidelines. Initially limited to embryo cryopreservation as the sole non-experimental method, the landscape shifted

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Article highlights

- All 10 articles included participants who underwent either OC and/or EC.
- Half of the articles included participants who chose OTC with three of these published after 2020 when OTC was declassified as experimental.
- Specific to the removal of experimental labels, one article retrospectively assessed the type of FP chosen between 2005-2013 and 2014-2019. This article found that the percentage of OC increased from 23.7% from 2005-2013 to 42% between 2014-2019.
- For OTC, the percentage decreased from 31.6% in 2005-2013 to 19.1% in 2014-2019.
- Most articles found patients preferred EC, specifically when they had a partner.
- Compared to females who did not undergo FP, there was often a delay to cancer treatment in females who underwent FP prior to cancer treatment.
- One article found 35% of patients who initiated FP returned to use cryopreserved specimens.
- Findings on whether FP discussions occurred prior to treatment were inconsistent.
- Concerns about fertility significantly affected treatment decisions, many women described the hardship of navigating cancer treatment and decisions about FP at the same time.
- Common reasons for decline FP included: financial barriers, concerns about delaying cancer treatment, being unaware of FP options, and no follow-up

with oocyte cryopreservation being declassified as experimental in 2013, followed by ovarian tissue cryopreservation gaining non-experimental status in 2020 [10,11]. Despite these advancements broadening choices for females in the United States, the associated financial costs of these procedures remain substantial [12]. While legislative strides have been made in mandating insurance coverage for FP in cancer patients in several states, financial constraints persist as a key barrier for many individuals seeking these services [13]. Other barriers include the emotional response to cancer diagnosis, poor counseling, and time needed to coordinate FP care prior to treatment [8,12–14].

This review aimed to classify trends regarding female AYA utilization of FP options in the United States within published manuscripts following updates to guidelines declassifying some options as experimental [10,11]. FP options considered for this review included oocyte cryopreservation (OC), embryo cryopreservation (EC), and ovarian tissue cryopreservation (OTC). Additionally, the review examined if aspects of the decision-making process about the use of FP or the choice of FP options were present within the publication. By synthesizing findings from recent studies, this review aims to provide clinicians and researchers with updated insights into the evolving landscape of FP practices and supporting informed decision-making by patients facing fertility-threatening treatments.

2. Methods

A rapid narrative review [15,16] was conducted to synthesize evidence and present a critical analysis of the usage of FP options and decision process among female AYAs diagnosed with cancer. To enhance the rigor of a traditional narrative review, a rapid review search methodology was also utilized. Rapid reviews are gaining popularity as a valid form of knowledge synthesis in which components of the systematic review process are simplified [15,16]. Therefore, the preparation of this manuscript was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRSMA) guidelines and reporting checklist [17].

2.1. Search strategy

A literature search was conducted in PubMed for articles published between January 2013 (to account for the declassification of OC as experimental) to May 2024. Medical Subject Headings (MeSH) terms for cancer [18], fertility preservation, Oncofertility, and female were utilized for the search (Supplemental Table S1). The inclusion criteria for articles were: (1) participants were post-pubertal female AYAs aged 15–39; (2) FP cryopreservation services (OC, EC, OTC) were utilized at cancer diagnosis prior to receiving cancer treatment; (3) articles in which more than one form of FP preservation was noted; (4) articles were in English; and (5) research was conducted in the United States. This review focuses on the United States due to the predominantly private healthcare system, variability in insurance coverage and affordability, and sociocultural factors that shape FP practices and accessibility that differ significantly from other countries [19]. Articles were excluded if they: included non-human models, focused on patients under age 15 (due to the definition of AYA as aged 15–39), focused exclusively on males, patients did not utilize FP cryopreservation services prior to cancer treatment, did not report on multiple forms of FP, or were published as conference abstracts, protocols, editorials, or reviews.

2.2. Study Inclusion

Covidence©, a web-based collaboration software platform, was used to organize and manage the review database [20]. The initial search yielded 2,868 publications, of which 2,866 were unique titles. One independent coder (SP) reviewed all titles and abstracts to identify articles for full-text review. Articles that did not meet basic inclusion criteria were excluded (n = 2,832), and 34 full texts were screened. An additional 24 articles were excluded at this stage, resulting in 10 articles to be included in this review. Three coders (SP, PV, MB) completed data abstraction on full-text articles.

2.3. Data Extraction

The population, intervention, comparator, outcomes, timeframe, and study design (PICOTS) framework [21] was used to select which study characteristics were extracted. General study characteristics included study design, years studied, cancer types, sample size, and general patient characteristics including mean patient age, relationship status, parity, etc. When reporting on FP cryopreservation services utilized, this review identified which FP services were included in each article. We additionally quantified how many patients used each FP option to classify the usage of different FP services observed over time. Among the articles meeting inclusion

criteria, we additionally documented factors influencing patient decision-making if they were present in the manuscript.

3. Findings

3.1. Study characteristics

Descriptions of the articles included in this review can be found in Table 1. All 10 articles were published between 2013 to 2023. Most articles employed a retrospective study design in which patient medical records were reviewed to describe FP service-related outcomes for female AYA patients with cancer [22–28]. One study was qualitative [29], one utilized a prospective cohort study design [30], and one conducted a cross-sectional survey [31]. Articles assessed data from 2001 to 2021 with study sample sizes ranging from 4 to 68 female AYA patients who pursued FP cryopreservation services. While the majority of studies included participants with varying cancer types, breast cancer was the most common. Approximately half of the participants across studies had a partner, and less than half in most studies reported a prior live birth at the time of diagnosis. Education levels and race/ethnicity were not consistently reported. However, when reported, participants were overwhelmingly White or Caucasian and highly educated.

3.2. Classifying the utilization of FP options prior to cancer treatment

All 10 articles included participants who underwent either OC and/or EC. Half of the articles included participants who chose OTC [22,25–28], with three of these being published after 2020 when OTC was declassified [26–28]. Specific to the removal of experimental labels, one article retrospectively assessed the type of FP chosen between 2005–2013 and 2014–2019. This article found that the percentage of OC increased from 23.7% from 2005–2013 to 42% between 2014–2019. For OTC, the percentage decreased from 31.6% in 2005–2013 to 19.1% in 2014–2019 [27]. Additionally, most articles found that patients preferred EC, specifically when they had a partner [25,28].

When compared to participants who did not undergo FP, there was often a delay in cancer treatment for participants who underwent FP prior to cancer treatment [26,28]. Despite delaying cancer treatments to preserve fertility, one article found that only 35% of patients who initiated FP returned to use cryopreserved specimens [26]. In general, this review found that female AYA patients often had high success rates for achieving pregnancy and having a live birth after FP treatment. For example, one article found participants had a pregnancy rate of at least 66% and a 45% live birth rate after FP in their sample [26].

3.3. Elements of decision-making associated with FP cryopreservation service use among AYA females

Of the ten articles, nine reported on factors associated with decision-making for FP [23–31]. One article developed a theoretical framework representing the foundations of the decision-making process for FP. This framework included four phases: Identify (cancer diagnosis and the potential impact on fertility), contemplate (by actively deliberating to form opinions about FP), resolve (to decide on whether to undergo FP or not), and engage (by taking appropriate actions to carry out FP decisions) [29]. Most articles documented patients receiving FP counseling, which was found to be associated with undergoing FP. One article found that 60% of participants who received fertility counseling proceeded with FP [24]. Findings on whether FP discussions occurred prior to treatment were inconsistent in this review. One article found that 27% had documented fertility counseling within 72 hours of a diagnosis and treatment discussion [25]. However, another found over half the participants discussed fertility concerns with a healthcare professional prior to starting treatment [30].

More than half of the participants in one article (52%) felt that concerns about fertility significantly affected their treatment decisions, with several opting for less aggressive therapies due to these concerns [30]. Another article highlighted the difficult process of having these discussions, regardless of whether the participant accepted or declined FP; however, not all participants described hardship as they navigated the process and formulated a decision [29]. When FP was pursued, cancer type, cancer severity, partner status, and desire for future children often dictated what type of FP was chosen [28,31]. Commonly noted reasons for declining FP across all articles included: financial barriers [26,27,32], concerns about delaying cancer treatment [25,26,31], unawareness of FP options [31], no follow-up with a patient navigator to discuss next steps [26], and logistical challenges such as living too far [26].

3.4. Limitations

Despite these findings, this review is not without limitations. Our search strategy and inclusion criteria may have limited the studies and thus did not identify all relevant studies. There may be publication bias as we only included published, peer-reviewed manuscripts. This may have resulted in missing important data from unpublished studies, non-peer-reviewed sources, or manuscripts that were not accepted for publication. Further, there is a possibility that more female AYA patients used FP options in settings where data are not collected for publication. We also recognize that the AYA population within the United States represents a limitation of this study. While this scope was intentional, given the unique healthcare and sociocultural contexts in the United States, it may restrict the generalizability of the findings to other populations and international healthcare systems.

4. Conclusion

Ethical considerations in fertility preservation for patients with cancer require ensuring informed decision-making. This includes discussing the impact of cancer treatments on fertility, outlining available preservation options, and coordinating these with cancer treatment timelines. Additional topics, such as financial and emotional costs, expected success rates,

Table 1. Study characteristics*.

Article	Primary Objective	Study Design	Years Studied	Cancer Type	Patient Characteristics	Outcomes of Interest for This Review
Articles Published After OC Declassification in 2013						
Hershberger et al [30]	Describe the decision-making process that women diagnosed with cancer experience when considering whether to undergo FP	Qualitative	NR	Breast, Hodgkin's lymphoma, Ovarian, Leukemia, Non-Hodgkin's lymphoma, Renal	Mean age 28.7 years, over half had partners ($n = 14$), most were White ($n = 21$), had a graduate or professional degrees ($n = 12$), and did not have children at the time of diagnosis ($n = 23$)	**Sample Size:** 27, with 13 who underwent FP cryopreservation **FP**:** OC: 6, EC: 6, Both OC and EC: 1, OTC: n/a **Decision-Making:** Developed a theoretical framework representing the foundations of the decision-making process for FP including four phases: Identify (learn/acknowledge cancer diagnosis and impact on fertility), contemplate (actively deliberate to form a decision about FP), resolve (make the decision on whether to undergo FP or not), and engage (take appropriate actions/behaviors to carry out decisions) Findings highlight a difficult process regardless of whether the woman accepted or declined FP; however, not all the women described hardship as they navigated the process and formulated a decision
Ruddy et al [31]	Explore the burden of concerns about fertility, how fertility concerns affect treatment decisions, and FP strategies used by women newly diagnosed with breast cancer	Prospective cohort	2006–2012	Early-stage breast	Mean age 37 years (with 37% < than 35 years), most were married (76%), were White (88%), had a college education (84%), and over half had children at the time of diagnosis (66%)	**Sample Size**: 620, with 53 who underwent FP cryopreservation **FP**:** OC: 7, EC: 46, OTC: n/a The majority of those who used FP techniques reported undergoing EC **Decision-Making:** Over half the participants discussed fertility issues with their physicians prior to starting treatment (68%) Greater concern about fertility was associated with younger age, nonwhite race, not having children, and receipt of chemotherapy When making decisions, 48 participants were very concerned about fertility at time of decision-making about treatment and several opted out of therapies due to these concerns, 52 participants felt that concerns about fertility affected treatment decisions a lot
Senapati et al [23]	Identify factors influencing the utilization of FP in patients with hematological disorders who present for FP consultation and to compare FP treatment choices and ovarian stimulation parameters between patients who present before or after exposure to chemotherapy	Retrospective cohort	2006–2011	Lymphoma, leukemia, myelodysplastic syndrome, aplastic anemia	Mean age 25.9 years, approximately half had a partner (56.7%), most were White (79.1%), education levels NR, most had no children (nulligravid 73.1%, 88.1% nulliparous)	**Sample Size**: 67, with 12 who underwent FP cryopreservation prior to treatment **FP**:** OC/EC: 10, OTC: 2 After FP counseling, 7% of patients opted for OC, 25% for EC, and 3% for OTC **Decision-Making:** No elements of decision-making were explicitly discussed

(*Continued*)

Table 1. (Continued).

Article	Primary Objective	Study Design	Years Studied	Cancer Type	Patient Characteristics	Outcomes of Interest for This Review
McCray et al [24]	Evaluate documented fertility discussion prior to therapy, what FP options were chosen, and if pregnancy was achieved	Retrospective chart review	2006–2014	Breast	Mean age 35.1 years, over half were married (67%), most were White (83%), education levels NR, specific number of children at diagnosis NR	**Sample Size**: 303, with 17 who underwent FP cryopreservation **FP**:** OC/EC: 17, OTC: n/a Of patients who had both a GnRH agonist prescribed for ovarian protection during chemotherapy and an IVF consultation, 4/5 (80%) underwent OC/EC, 1 (25%) became pregnant spontaneously, and 2 (50%) became pregnant through embryo transfer Of patients who only had an IVF consultation, 13/50 (26%) pursued OC/EC, 22 (7%) became pregnant spontaneously, 3/13 (23%) became pregnant through embryo transfer **Decision-Making:** Majority of patients who had documented fertility counseling by a physician underwent FP 26% of patients had documented fertility counseling. Having fertility counseling was associated with younger patient age and having fewer children at the time of diagnosis
Nurudeen et al [25]	Evaluate FP decisions and compare ART outcomes between newly diagnosed cancer patients and age-matched healthy controls	Retrospective cohort	2005–2012	Breast, Hematologic, Ovarian, GI/ Colorectal, Uterine, Brain/Spinal, Cervical, Sarcoma, Thyroid, other	Mean age 33.6 years, 35% married, approximately half were White (54%), education levels NR, and less than half reported a prior live birth (41%)	**Sample Size**: 82, with 49 who underwent FP cryopreservation **FP**:** OC: 11, EC: 38, OTC: n/a **Decision-Making:** 60% of women who received fertility counseling chose to undergo FP Single women began FP in half the time of married women (10.4 vs. 22.9 d) All 21 married women chose EC, whereas 17 of the 28 (61%) single women chose EC over OC

(*Continued*)

Table 1. (Continued).

Article	Primary Objective	Study Design	Years Studied	Cancer Type	Patient Characteristics	Outcomes of Interest for This Review
Higgins et al [26]	Assess the rate of fertility counseling provided and document the utilization of FP techniques and relevant outcomes	Retrospective cohort	2001–2017	Hematologic conditions requiring allogenic hematopoietic cell transplantation (11% were benign disorders)	Median age 31 years, partner status NR, race/ethnicity NR, education levels NR, 42% were nulligravid	**Sample Size**: 128, with 28 who underwent FP cryopreservation **FP**:** OC: 9, EC: 4, OTC: 9 31 (30%) were referred to a reproductive endocrinologist, of whom 13 (10%) underwent FP, of these, 9 procedures yielded successful cryopreserved tissue **Decision-Making:** Of 177 patients, only 34 women (27%) had documented fertility counseling within 72 hours of diagnosis and 61 (48%) received fertility counseling prior to hematopoietic cell transplantation 13/38 patients who underwent REI consultation pursued FP Reasons for not pursing FP: disease severity (68%) with perceived urgency of therapy or concern for complications, financial barriers (20%) secondary to lack of insurance, and low antral follicle count during initial work-up (12%) OC was chosen when the woman did not have a stable partner and chose not to use a sperm donor
Articles Published After OTC Declassification in 2020						
Akel et al [27]	Measure the delay to cancer treatment experienced by patients who underwent FP, pregnancy rates after FP treatment, and examine barriers cited for why patients decline FP	Retrospective cohort	2007–2017	Gynecologic (ovarian, endometrial, uterine, cervical, multiple)	Median age for those who proceeded with FP 32.96, partner status NR, race/ethnicity NR, education levels NR, children at time of diagnosis NR	**Sample Size**: 90 with 32 who underwent FP cryopreservation **FP**:** OC/EC: 32, OTC: 18 Of the 32 patients who initiated FP, 35% returned to use cryopreserved specimens (8 embryos, 3 oocytes), with 6 successfully giving birth, 2 current pregnancies, and 6 births via gestational carriers This study found a high success rate after FP treatment, with a 45% live birth rate and a pregnancy rate of at least 66% Compared with patients who did not elect FP, patients with cancer who elected FP had an approximately 2-week delay to initiation of cancer treatment (not statistically significant) **Decision-Making:** Noted reasons for declining FP included: Patient not undergoing gonadotoxic treatment (*n*-2), previously frozen embryos (n = 1), medically ineligible (n = 2), lived elsewhere (n = 3), FP cost-prohibitive (*n*-3), no follow-up with patient navigator (n = 7), not enough time for FP (n = 6), and not interested (n = 5)

(*Continued*)

Table 1. (Continued).

Article	Primary Objective	Study Design	Years Studied	Cancer Type	Patient Characteristics	Outcomes of Interest for This Review
Mgboji et al [28]	Characterize the female AYA population seen for FP, and to identify demographic and clinical factors influencing FP decision-making	Retrospective chart review	2005–2019	Medical conditions requiring gonadotoxic therapy including hematologic malignancies, gynecologic malignancies, other malignancies, nonmalignant hematologic diseases, and nonmalignant conditions	Median age 17 years, partner status NR, most were White (66%), education levels NR, children at time of diagnosis NR	**Sample Size**: 106 with 51 aged 18–21 **FP**:** OC: 38, EC: n/a, OTC: 25 64% of the study population ($n = 68$, 42.6% were > 18) pursued FP treatments; Of the participants who pursued FP, 36.8% ($n = 38$) pursued OC and 36.8% ($n = 25$) pursued OTC The type of FP chosen between 2005–2013 and 2014–2019 due to the removal of experimental labels was assessed. The percentage of OC increased from 23.7% from 2005–2013 to 42% between 2014–2019. For OTC, the percentage decreased from 31.6% in 2005–2013 to 19.1% in 2014–2019 Patients aged 18–21 chose OC (43.1%, $n = 22$) over OTC (7.8%, $n = 4$). Post-menarche patients often underwent OC (40.7%, $n = 37$) vs OTC (16.5%, $n = 15$) **Decision-Making:** This study evaluated whether specific demographic and/or clinical factors affected the decision to pursue FP, but did not explicitly assess other elements of decision-making
Kappy et al [29]	Explore whether FP in patients with cancer diagnoses prolongs the time to treatment initiation and identify factors influencing FP decision-making	Historical retrospective cohort	2012–2019	Breast (most common), lymphoma/leukemia, ovarian, GI, rhabdomyosarcoma, other	In the FP group, the mean age at the time of FP consult was 30.5 ± 6.7, approximately 67% reported having a partner at the time of consult, many women identified as Hispanic (33.3%), education levels NR, (70%) were nulliparous	**Sample Size**: 51, with 25 who underwent FP cryopreservation **FP**:** OC: 10, EC: 11, Both OC and EC: 2, OTC: 2 Most women who underwent FP chose EC (36.7%), followed by OC (33.3%) Of the 20 patients with partners who underwent FP, 13 (65%) underwent EC. Of the 12 women who underwent OC, 50% had a partner There was a statistically significant difference in interval from first FP consultation to cancer treatment between women who received FP treatment versus those who did not, often longer intervals in those who underwent FP cryopreservation **Decision-Making:** Cancer type and partner-status dictated what type of FP was chosen

(*Continued*)

Table 1. (Continued).

Article	Primary Objective	Study Design	Years Studied	Cancer Type	Patient Characteristics	Outcomes of Interest for This Review
Sauerbrun-Cutler et al [32]	Determine the proportion of AYA women that engage in FP discussions and REI consultations, identify characteristics among those who did and did not have a FP discussion, and assess barriers to FP	Cross-sectional survey	2019–2021	Breast	Most were aged 35–42 years (70%), 56 (89%) were partnered, most identified as White (86%), education levels NR, and majority of women had children at the time of diagnosis ($n = 46$, 73%)	**Sample Size**: 63, with 4 who underwent FP cryopreservation **FP**:** OC/EC: 4, OTC: n/a Of the 4 participants who pursued FP, 1 had a successful live birth utilizing a frozen embryo, 3 conceived spontaneously without the use of previously frozen gametes There was a higher proportion of FP discussions and REI consultations for the 29 participants who desired future children in the 2013–2016 time compared to the 2005–2012 time, all 4 women who pursued FP procedures were in the 2013–2016 time period **Decision-Making:** Those who had FP discussions were more likely to desire future children, and were more likely to be younger than those that did not have FP discussions Most common reasons for declining FP REI referrals or procedures included: having desired number of children ($n = 24$, 41%), financial barriers ($n = 8$, 14%), concern about delaying cancer treatment or cancer recurrence ($n = 7$, 12%), and unaware of FP options ($n = 6$, 10%)

Articles are listed in chronological order.
*NR: Not reported.
**Numbers indicate patients, not quantity of gametes.

future family planning, and post-treatment options, must be addressed while respecting patient autonomy and fostering shared decision-making [32,33].

The recent increase in awareness of FP technologies has somewhat contributed to higher rates of FP counseling and utilization [34,35]. While further advancements in FP technologies are on the horizon, it is unlikely that any significant breakthrough will alter clinical practices for female patients with cancer in the next five years [12]. However, improvements in data collection, particularly those accounting for cancer status, could significantly impact patient care and decision-making. Currently, the Society for Assisted Reproductive Technology (SART), the United States entity that reports national data on assisted reproduction technologies (ART) outcomes, does not collect reasons for cryopreservation [36]. The lack of information on reasons for use of ART, greatly limits our understanding of FP success rates specific to patients with cancer [37]. Although individual fertility centers report outcomes for those using ART, available data primarily reflects general population use, creating a critical gap in evidence for cancer patients. The lack of cancer-specific success rates has considerable ethical implications for informed consent, as patients cannot make truly informed decisions without reliable and relevant data on success rates.

Financial barriers remain a significant factor limiting access to FP services [14,38,39]. Patients often face minimal or no insurance coverage for these procedures, leaving the financial burden on them and their families, alongside other cancer-related expenses. While financial assistance programs exist, decisions about pursuing FP are often driven by cost rather than the desire for biological parenthood. Moreover, certain FP options may delay cancer treatment, adding complexity to decision-making. These barriers and unique challenges exacerbate inequities in care and limit informed decision-making. Expanding accessibility and education is vital to promote equitable FP care [40].

Furthermore, the changing political and legal landscape in the United States adds an additional layer of complexity to FP care. The overturning of *Roe v. Wade* and the subsequent *Dobbs* decision in June 2022 had a ripple effect of political and religious implications being intertwined with medical care [41]. These new legal and ethical challenges have created heated debates on whether 'life' begins at conception thus making embryos 'children' and preventing the disposition of unhealthy or surplus embryos [42]. A recent event involved two couples whose embryos were accidentally destroyed, being awarded loss compensation in an Alabama court, effectively further confirming that state of Alabama's conferment of personhood to embryos [43]. Moreover, some states mandating insurance companies to cover FP for those with oncologic conditions have prohibited the creation of embryos, limiting options for patients.

At this juncture, FP options for female patients, whether facing a cancer diagnosis, treatment, or survivorship, are constrained not only by financial, technological, and accessibility limitations, but also by political and ethical controversies [44,45]. Ethical dilemmas often arise when balancing the urgency of cancer treatment with the pursuit of FP, as delays in treatment may adversely impact disease outcomes, while forgoing fertility options can cause emotional distress. These discussions should incorporate individual factors such as age, cultural and religious beliefs, financial constraints, and the stage of treatment, and should be supported by clear policies for embryo or gamete storage. A multidisciplinary, patient-centered approach that integrates oncology, reproductive counseling, psychosocial support, and cultural competence is essential to navigate these ethical complexities effectively, preserve fertility, and safeguard patients' future quality of life and mental health [33,46]. Addressing these challenges requires enhanced collaboration across healthcare, policy, and advocacy stakeholders to ensure equitable access and comprehensive care for all patients. Future research should prioritize efforts to close data gaps, evaluate FP outcomes specific to cancer patients from diverse populations and across international settings, and assess the broader implications of political developments on FP access and decision-making.

5. Expert opinion

The landscape of FP options for female AYA patients facing a cancer diagnosis has evolved significantly, yet challenges persist in counseling, decision-making, uptake, and implementation. Findings from this review have several implications for clinical practice and patient care in the realm of FP.

Shifts in FP Utilization: Technological advancements have expanded the options of FP services available, notably with OC gaining widespread acceptance following its declassification as experimental in 2013. With the limited numbers of publications meeting criteria, it is challenging to make definitive statements about trends in the use of FP types. Our findings indicate that as the experimental label of OC was removed it became used more often. However, EC is still the most utilized option. Patients, particularly those with partners, showed a strong preference for EC among the studies in this review. This preference may reflect perceived reproductive security and partnership dynamics influencing decision-making around FP options. Prior to lifting the experimental label, this review found that OTC was used sparingly during the experimental phase. Despite the potential advantages in feasibility and cost-effectiveness of OTC compared to OC and EC, the declassification of this option as experimental appeared to increase use only minimally after 2020. This suggests that while advancements in technology and regulatory changes broaden options, clinical uptake may be influenced by factors beyond technical feasibility.

In light of the evolving political landscape in the United States and the emergence of personhood legislation, OTC may be a preferable option for female AYA patients with cancer. A common concern with OTC is the potential risk of reintroducing cancerous cells during transplantation. To minimize the risk of reintroducing malignant cells, OTC should be carefully evaluated by a multidisciplinary team and performed at specialized clinics. While generally uncommon, autotransplantation carries higher risks for hematologic cancers like leukemia, often making it unsuitable for such cases. Promising alternatives, such as in vitro maturation of oocytes, are under development. However, treatments like chemotherapy prior to OTC

may compromise ovarian reserve, highlighting the need to balance safety and fertility preservation [47–50].

Unlike OC and EC, which may have varying legal restrictions and ethical considerations in different states or regions, OTC involves the removal and freezing of ovarian tissue, which is then stored for potential future use. This method might be less contentious from a legal and regulatory standpoint as it does not involve the creation of embryos. OTC thereby avoids some of the ethical dilemmas associated with EC, such as the disposition of unused embryos or religious and ethical objections to freezing embryos. OTC may also be more accessible to patients as the surgical removal and freezing of ovarian tissue may be performed with other medical procedures. This can be particularly beneficial for patients who need to undergo immediate cancer treatment and do not have time for ovarian stimulation. As the field progresses, it will be imperative to continue to monitor the outcomes for FP cryopreservation services to determine the most feasible, and cost-effective options.

Implications for counseling and support: The choice of which type of FP option to use is based on a myriad of sociodemographic (partner status, parity, finances), medical (type of cancer, type of treatment), and personal factors (desire for children, perceived severity of threat of infertility). It is additionally a very personal decision. From the manuscripts in which the decision process for choice of FP was described, it was noted that the loss of fertility was of great concern to the majority of patients. Younger females diagnosed with cancer who did not have any children at the time were somewhat more likely to use FP if they had a consultation about options with a reproductive endocrinologist. Given the complexities and varied outcomes associated with FP, comprehensive counseling, and support services are crucial. This includes discussing the implications of different FP options, addressing potential delays in cancer treatment, managing expectations regarding success rates, and providing guidance on decision-making around the use of cryopreserved specimens.

Despite undergoing FP, a significant proportion of patients from studies included in this review did not return to use their cryopreserved specimens, which raises ethical and practical considerations regarding long-term storage, patient counseling, and informed decision-making about FP. The literature suggests a variety of reasons why people do not return to use their stored gametes. Primarily, patients have found a partner and do not wish to be a single parent. Some patients may also conceive spontaneously [51–53]. When cryopreserved materials were used, positive outcomes in terms of pregnancy and live birth rates following FP were noted. This highlights the efficacy and importance of these interventions in preserving fertility, FP services being part standard of care, and supporting reproductive goals post-cancer treatment. We must also consider the importance of counseling for circumstances in which there is no fertility to preserve and when successful egg/embryo creation does not result in a child. These findings reinforce the value of FP as an integral part of comprehensive cancer care for AYA females.

Barriers to use: It is well established that the threat of infertility is often as equally distressing as the cancer diagnosis itself [54–56]. Despite the availability of options, there are multiple barriers that can prevent uptake. These barriers include limited time to pursue options prior to treatment, the need for navigation in the process of managing cancer treatment and the use of FP, and decisional factors such as the desire for children but concerns about cancer recurrence or the need for partner or donor sperm if embryos are created. There is a dearth of FP navigators, which contributes to the low uptake of FP, despite counseling and multiple guidelines suggesting their use. Decisional regret is often cited in the literature among survivors who chose not to pursue FP prior to treatment. However, navigators appear to help improve the process by having discussions and supporting patients, resulting in a reduction of regret even if FP is not pursued. The FP procedures for females are invasive, and unlike sperm cryopreservation, typically require anesthesia for oocyte retrieval or ovarian tissue retrieval. Without navigators to help females explore and utilize FP options and financial resources, the burden may be too great while also navigating cancer care [14]. While the need to inform patients of potential infertility and available FP options is suggested in multiple guidelines from national entities such as ASCO, ASRM, NCCN, it does not occur as often as it should [35].

It is well established in the literature that several disparities exist in access to and utilization of fertility services [57]. As demonstrated in previous literature, our review found that the majority of patients included in the research studies and therefore those utilizing FP in the published literature were White. This phenomenon could be the result of FP not being culturally acceptable to all patients [58]. However, literature has found that the odds of FP referral are approximately two times higher for White women [14,59]. In alignment with previous findings [60], one article in our review found that non-White individuals were significantly more concerned about infertility, indicating that these disparities are not due to a lack of interest [30]. Socioeconomic disparities were additionally found in this review with several articles citing financial barriers as reasons to not pursue FP. In the United States, c fcfmedical care typically requires insurance and FP is not always covered by insurance. Two studies in this review took place in states where insurance coverage was mandated for FP. Despite this, participants still reported concerns regarding financial burdens [26,28]. Patients from lower socioeconomic backgrounds may be uninsured or reliant on public insurance, which restricts their accessibility to FP services [57]. While the literature is rich with information on the economic disparities in fertility preservation among female AYA patients with cancer, there is little action being taken to address these issues.

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