Universidade de Aveiro Departamento de Educação e Psicologia
2020

ANA CLÁUDIA PEREIRA BÁRTOLO

MATERNIDADE APÓS O CANCRO: COMPREENDER AS PREOCUPAÇÕES COM A FERTILIDADE E O IMPACTO PSICOSSOCIAL DA DOENÇA E SEUS TRATAMENTOS

MOTHERHOOD AFTER CANCER: A BROAD APPROACH TO UNDERSTANDING FERTILITY CONCERNS AND PSYCHOSOCIAL IMPACT OF THE DISEASE AND TREATMENT

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Tese apresentada à Universidade de Aveiro para cumprimento dos requisitos necessários à obtenção do grau de Doutor em Psicologia, realizada sob a orientação científica da Doutora Sara Otília Marques Monteiro, Professora Auxiliar Convidada do Departamento de Educação e Psicologia da Universidade de Aveiro, e da Doutora Isabel Maria Barbas dos Santos, Professora Auxiliar do Departamento de Educação e Psicologia da Universidade de Aveiro.

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Dedico este trabalho a todas as mulheres jovens diagnosticadas com cancro em Portugal. Especialmente às jovens que colaboraram neste projeto de investigação, o meu MUITO OBRIGADA!

SÍSIFO

Recomeça...
Se puderes
Sem angústia
E sem pressa.
E os passos que deres,
Nesse caminho duro
Do futuro
Dá-os em liberdade […]

[…] *És homem, não te esqueças!*
Só é tua a loucura
Onde, com lucidez, te reconheças...

Miguel Torga

o júri

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agradecimentos
(1/2)

Eis o momento tão desejado de agradecer…
São tantas as recordações que levo comigo, os desafios, as conquistas…
Mas, acima de tudo, as amizades que fiz neste percurso…

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agradecimentos
(2/2)

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palavras-chave preocupações reprodutivas, fertilidade, maternidade, cancro da mama, mulheres, jovem adulta, qualidade de vida, viés atencional

resumo

Um cancro diagnosticado em idade jovem ameaça a fertilidade e pode ter consequências imediatas ou a longo-prazo nos projetos de construção familiar e bem-estar psicológico. Diretrizes nacionais e internacionais advogam a necessidade de aconselhamento acerca da fertilidade. No entanto, mulheres jovens diagnosticadas com cancro reportam preocupações reprodutivas e dificuldades de adaptação à incapacidade (ou potencial incapacidade) de satisfazer a tarefa desenvolvimental de ser mãe, que prevalecem ao longo da sobrevivência. Neste contexto, os principais objetivos do presente trabalho foram: (i) examinar preocupações relacionadas com a saúde reprodutiva e indicadores de ajustamento psicossocial (e.g. ansiedade, depressão e qualidade de vida relacionada com a saúde) entre mulheres jovens sobreviventes de cancro (18-40 anos de idade), com um foco sobre o cancro da mama; e (ii) explorar a influência de processos cognitivos implícitos - processos atencionais - nas preocupações com a fertilidade e no ajustamento psicossocial. Este trabalho incluiu dois estudos de revisão, um estudo de validação de uma medida multidimensional para avaliar preocupações reprodutivas e quatro estudos empíricos transversais. As participantes foram recrutadas em diferentes instituições hospitalares. A maioria das sobreviventes reportaram preocupações relacionadas com a fertilidade e com o risco que o cancro representava para a saúde dos filhos. As preocupações reprodutivas mostraram ser um mediador da relação entre a importância da parentalidade e a qualidade de vida relacionada com a saúde. Além disso, os dados sugeriram que a experiência de mulheres jovens diagnosticadas com cancro da mama, que enfrentam incerteza sobre a fertilidade, parece espelhar a resposta de mulheres inférteis sem história de cancro, em termos de preocupações com a fertilidade e morbilidade psicológica. Adicionalmente, o recurso a métodos de avaliação complementares, medidas de autorrelato e abordagens metodológicas de natureza *quasi*-experimental (e.g. tarefas de Stroop emocional e *dot-probe*), permitiu suportar a hipótese de que existe um enviesamento atencional para pistas relacionadas com a reprodução em mulheres jovens. Esse enviesamento associou-se positivamente com preocupações relacionadas com a comunicação do estado de fertilidade ao parceiro e com a sintomatologia depressiva reportada em sobreviventes de cancro da mama. Os resultados deste trabalho sugerem a necessidade de providenciar suporte psicoeducacional para minimizar as preocupações de mulheres em idade reprodutiva; e de desenvolver programas dirigidos à flexibilidade atencional e auto-regulação.

keywords

reproductive concerns, fertility, motherhood, breast cancer, women, young adult, quality of life, attentional bias

abstract

Cancer diagnosed at a young age threatens fertility and may have immediate or long-term consequences for family building projects and psychological well-being. International and national guidelines advocate the need for fertility counseling. However, female cancer survivors report reproductive concerns and difficulties in adapting to the (potential) inability to fulfill the developmental task of becoming a mother, which prevail throughout survival. In this context, the main objectives of this work were: (i) to examine reproductive health concerns and psychosocial outcomes (e.g. anxiety, depression, health-related quality of life [HRQoL]) among young adult cancer survivors (18-40 years), with a focus on breast cancer; and (ii) to explore the influence of selective information processing biases on fertility-related concerns and psychosocial adjustment. This work involved two systematic reviews, a validation study of a multidimensional instrument to assess reproductive concerns and four cross-sectional studies. Participants were recruited from different public hospital institutions. Most cancer survivors reported concerns related to fertility and to the children's health risk. Reproductive concerns showed to be a mediator in the relationship between the importance of parenthood and HRQoL among breast cancer survivors. Moreover, data suggested that the experience of young women diagnosed with breast cancer facing uncertainty about fertility seems to mirror the response of non-cancer infertile women in terms of fertility concerns and morbidity. Additionally, a complementarity between self-report measures and *quasi*-experimental methodological approaches (e.g. emotional Stroop and dot-probe tasks) supported the hypothesis that there is an attentional bias toward reproduction-related cues among young women. This enhanced attention was positively associated with concerns related to partner disclosure and depressive symptoms in breast cancer. The findings of this research work suggest the need for providing psycho-educational support to minimize concerns in reproductive-age women; and develop programs focused on attentional flexibility and self-regulation.

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LIST OF ABBREVIATIONS

ATLAS	Adjuvant Tamoxifen: Longer Against Shorter
aTTom	Adjuvant tamoxifen—to offer more?
ASCO	American Society of Clinical Oncology
ANOVA	Analysis of variance
ART	Assisted Reproduction Technology
BCTRI	Breast Cancer Treatment Response Inventory
BSI	Brief Symptoms Inventory
CES-D	Centre for Epidemiological Studies Depression Scale
χ^2	Chi-square test
CENTRAL	Cochrane Central Register of Controlled Trials
CFI	Comparative fit index
EEG	Electroencephalography
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30
ESMO	European Society of Medical Oncologists
ERPs	Evoked-related potentials
EFA	Exploratory factor analysis
FC	Fertility care
FPI	Fertility Problem Inventory
Fex-Can	Fertility and Sexuality following Cancer
FACT-G	Functional Assessment of Cancer Therapy-General
GnRH	Gonatrophin releasing hormone
HRQoL	Health-related quality of life
HADS	Hospital Anxiety and Depression Scale
HPV	Human papillomavirus
JBI	Joanna Briggs Institute
MANCOVAs	Multivariate analyses of covariance
OASIS	Open Affective Standardized Image Set
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols

POMS	Profile of Mood States
QoL	Quality of life
IBCSG	Quality of Life Office at the International Breast Cancer Study Group
RCTs	Randomized controlled trials
RCACS	Reproductive Concerns After Cancer Scale
RCS	Reproductive Concerns Scale
RT	Response times
RRSO	Risk-reducing salpingo-oophorectomy
RMSEA	Root mean square error of approximation
SAM	Self-Assessment Manikin
SRMR	Standardized root mean residual
UV	Ultraviolet
WLSMV	Weighted least squares with the mean and variance adjustment

INTRODUCTORY NOTE

Cancer is a global health burden, and for younger women in particular, certain challenges and concerns are unique. This diagnosis may represent a threat to fertility and to the creation or continuation of a young family due to the gonadotoxicity of some anticancer treatments. Based on this, fertility and motherhood-related anxieties during survivorship have gained increasing attention in recent years. Previous studies have investigated main reproduction-related concerns (Logan et al., 2019) after diagnosis and psychosocial outcomes based on disrupted fertility (e.g. Canada & Schover, 2012; Penrose et al., 2013). However, there is a need to continue to invest in the assessment of fertility and parenthood concerns (a relatively neglected area in Portugal) and the psychological impact of uncertainty regarding fertility in cancer survivors. Furthermore, new intervention challenges should also be explored.

Thus, the main purposes of this work were to: (1) provide a valid measure to evaluate reproductive concerns among female cancer survivors in Portugal; (2) understand how reproductive concerns can hinder the process of adaptation in survivorship; (3) explore new intervention routes in two ways: (i) examine the effectiveness of psychoeducational programs using a distance approach to alleviate concerns and maladjustment; (ii) examine how attentional biases to reproduction-related stimuli can interfere with morbidity and, therefore, should be targeted for intervention. To achieve the latter goal, an innovative methodology including *quasi*-experimental approaches was used. Breast cancer is among the types of cancer whose systematic therapies have been well established as a direct or indirect factor increasing infertility risks (e.g. Paluch-Shimon et al., 2020; Poorvu et al., 2019). For that reason, breast cancer was highlighted in this work. In addition, with an increasing number of young breast cancer survivors, the need to promote adaptation becomes even greater (Ferlay et al., 2018).

This thesis is organized in four chapters, briefly described as follows:

Chapter I | Theoretical Background presents an overview of the current literature supporting the studies conducted and their rationale. First, a better understanding of the role of specific anticancer treatments in fertility was provided. Then, reproductive concerns and psychosocial variables of young women experiencing uncertainty about fertility were address. Still in this section, we briefly propose a rationale to justify the need to consider attentional processes in the assessment.

Chapter II | Objectives and General Method comprises a summary of the methodologies used in the review and empirical studies included in this research work. In order to carry out the empirical studies, there were two main moments of data collection, which took place in different hospital institutions. This chapter illustrates the inclusion criteria, data collection procedures, instruments/materials and statistical methods considering each of the research phases.

Chapter III | Systematic reviews and Empirical studies includes seven original studies, reported in the format of scientific papers, that were conducted to achieve the general objectives described above. These papers followed the guidelines of the journals in which they were published/submitted. Five of these papers are already published in international peer-reviewed journals and two are submitted and currently under review. Studies 2, 3 and 4 pertain to research phase 1, including only self-report measurements. Studies 6 and 7 pertain to research phase 2, where there is complementarity between self-report measures and *quasi*-experimental methodological approaches. The remaining studies, 1 and 5, are systematic reviews.

Finally, **Chapter IV | General discussion** presents the synthesis and general discussion of the main findings and methodological limitations. Furthermore, this section offers an integration of the main clinical implications of the work. We conclude by outlining brief recommendations to guide professionals and institutions working on fertility and motherhood issues with women in their reproductive years.

CHAPTER I

Theoretical Background

1. CANCER EPIDEMIOLOGY: A FOCUS ON YOUNG WOMEN

Cancer is a public health problem that affects individuals' quality of life, occurring at different stages of the life cycle. This group of diseases can start almost anywhere in the human body and is characterized by the uncontrollable division of abnormal cells, which can invade nearby tissues and/or other organs (generating metastasing) (NCI, 2020; WHO, 2020). There has been an increase in the incidence of cancer diagnoses in recent years (Bray et al., 2018; DGS, 2015), but also in life expectancy due to scientific and technological advances in early detection and treatment. Epidemiological data estimated an incidence of 18 078 957 new cases of cancer in 2018 worldwide, and identified 58 199 new cases in Portugal (Ferlay et al., 2018).

Global patterns suggest that the incidence of this malignancy is strongly related to age, with a lower rate for individuals under 40. However, there is a growing interest in better understanding the risk factors and challenges of cancer in younger patients. Gene mutations, smoking, drinking, exposure to ultraviolet (UV) radiation, infections with some types of human papillomavirus (HPV), diet and hypertension are some of the factors that can affect the occurrence of cancer in this age-group (American Cancer Society, 2019; Merten et al., 2017).

Breast cancer, thyroid and female genital tract, more specifically cervix uteri, are the top three cancer types in terms of 5-year prevalence in young women (20 to 39 years). Worldwide, the number of young adult women who are alive 5 years after cancer diagnosis is approximately twice the number of men. Most recent data estimated a proportion of 176.8/100 000 cases (Ferlay et al., 2018). Thus, quality of life issues among young female cancer patients are attracting more attention since successful survivorship also includes maintaining a high quality of life and personal projects after diagnosis.

One of the distinguishing features of young women is that family planning may not yet be complete. Therefore, reproductive impacts of treatments are a current focus of attention. Studies are consensual in demonstrating that future fertility is at risk due to anticancer treatments (Duffy & Allen, 2009; Poorvu et al., 2019; Waimey et al., 2015). Fertility-related risks vary based on the treatments employed and age at diagnosis (Poorvu et al., 2019). These risks are especially relevant in developed countries, where parenthood is increasingly delayed (Schmidt et al., 2012). Portugal is no exception. The mother's age at the birth of her first child was 30.4 years in 2018, an increase of 5 years since the 1960s (PORDATA, 2019). Therefore, this medical condition can reduce the fecundity of women who still hope to start or complete their family.

2. UNDERSTANDING CANCER TREATMENT-RELATED INFERTILITY

Cancer treatments may affect female fertility permanently or transiently. The pregnancy rate among cancer patients is significantly lower than in age-matched peers (Magelssen et al., 2008; Stensheim et al., 2011). Overall, as suggested by Waimey et al. (2015), disruptions in the neuroendocrine axis, immature ovarian follicles or significant reduction in the follicle number and other damage to the reproductive organs necessary to carry a pregnancy to term may arise as a consequence of anticancer treatments. The type of treatment chosen depends on several factors, namely tumor type, stage of disease, and response to therapies (Anchan & Ginsburg, 2010). Typically, standard surgical treatments used in gynecological cancers (e.g. ovarian and advanced cervical cancer) involve total abdominal hysterectomy with oophorectomy, leading to permanent infertility (Duffy & Allen, 2009). Even procedures that include only partial removal of the fallopian tubes, uterus, vagina, or cervix or that affect the bladder, large intestine, and rectum may also impair the ability to conceive (Waimey et al., 2015). Moreover, various reports have documented the gonadotoxic action of radiotherapy and chemotherapeutic agents (e.g. Maltaris et al., 2007; Poorvu et al., 2019; Suhag et al., 2015; Waimey et al., 2015) in a variety of tumor types.

Research indicates that total body irradiation and abdominal and directed pelvic radiation may impair the ovarian reserve (Ducan et al., 2016; Waimey et al., 2015) and/or cause uterine dysfunction (Suhag et al, 2015) (e.g. reduce uterine volume and elasticity, endometrial injury) also leading to a higher risk of pregnancy-related complications such as miscarriages, preterm birth and placental abnormalities (Wo & Viswanathan, 2009). For example, in treatment of cervical and rectal cancer and hematological malignancies (e.g. Hodgkin’s disease), the ovaries are at risk of substantial exposure to significant doses of radiation (Maltaris et al., 2007). Also, cranial irradiation for a variety of central nervous system tumors may result in premature ovarian failure, depending on the disruption of hypothalamic-pituitary-gonadal axis (Marci et al., 2018; Suhag et al, 2015; Wallace et al., 2005).

The newest protocols have replaced high-dose radiotherapy with multimodal treatment that combines multiagent chemotherapy and radiotherapy (as little as possible) (Overbeek et al., 2017). However, chemotherapy drugs may also be toxic to the ovaries, despite great variation in the risk of gonadal dysfunction from different regimens (Ruddy et al., 2012). Since most treatments are given as multidrug regimens, the relative contribution of each drug can be difficult to determine (Wallace et al., 2005). It is widely known that certain classes of chemotherapy agents are more toxic, such as alkylating agents, which include cyclophosphamide, ifosfamide, busulfan (Salama & Woodruff, 2017) and procarbazine (Overbeek et al., 2017). A systematic review reported that the prevalence of amenorrhea ranged from 40% to 80% among breast cancer survivors who received cyclophosphamide-containing regimens (Overbeek et al., 2017).

Chemotherapy-related amenorrhea is an imperfect surrogate marker of infertility and may be transient. Despite this, women who remain amenorrheic for 24 months after completing treatment will not regain ovarian function (Sukumvanich et al., 2010). According to a retrospective survey by Letourneau et al. (2012), even among young women who continued to menstruate after chemotherapy alone (e.g. without pelvic radiation or pelvic surgery), percentages of 12-month infertility (defined here by trying to get pregnant with unprotected intercourse for at least one year without success) ranging from 15% to 27% were found for non-Hodgkin lymphoma and for breast cancer, respectively. Ovarian failure is primarily dependent on the patient’s age (Amir et al., 2010; Letourneau et al., 2012; Jacobson et al., 2016), with older women at diagnosis demonstrating greater damage than younger ones. This may in part reflect that younger patients’ ovaries are more resistant to chemotherapy (Anchan & Ginsburg, 2010), probably due to the larger primordial follicle reserve (Maltaris et al., 2007).

Therefore, young female cancer survivors have a significantly narrower window of opportunity to try to satisfy their family building projects. Cancer-related infertility risks can be a major concern, leading to long-term distress and impaired quality-of-life, especially for those who receive insufficient information about these issues (Suhag et al, 2015).

2.1. Unique aspects of breast cancer

Young women diagnosed with breast carcinoma form a unique population. While the principles of breast cancer management in women under 40 are the same as in older women, these younger women usually have tumors of more aggressive phenotypes (Paluch-Shimon et al., 2017), an increased risk of local recurrence associated with breast-conserving surgery (Kasum et al., 2014) and special psychosocial concerns related to fertility risks and genetic predisposition to cancer and risk of transmission to offspring (Ferzoco & Ruddy, 2015). The premature menopause and impaired fertility have far-reaching physiological and psychological impacts recognized by international guidelines (Paluch-Shimon et al., 2017; 2020). This is the cancer type with most robust data regarding disruption of menstrual function and loss of reproductive potential after anticancer treatments (Poorvu et al., 2019; Snyder et al., 2010). Stensheim et al. (2011), in a study involving 27 556 cancer survivors, suggested that breast cancer survivors have the lowest probability of a post-cancer pregnancy among other survivors, compared to those from the general population.

A majority of breast neoplasms are classified as invasive ductal type [70%-75%] (Cardoso et al., 2019), which can spread to surrounding normal tissue and through the blood and lymph systems to other parts of the body (NCI, 2020). Hence, younger women with invasive carcinoma typically undergo a multimodal treatment involving surgery, adjuvant radiotherapy and chemotherapy (Anchan & Ginsburg, 2010). These treatments may cause significant damage to the reproductive organs of these patients.

Although infertility resulting from breast cancer surgery is highly unlikely, in a diagnosis of BRCA 1/2 mutation (most frequently mutated genes) the extent of the surgical approach is a topic discussed with patients (Suter & Pagani, 2018). Risk-reducing salpingo-oophorectomy (RRSO) should be proposed to all women from the age of 35 (Paluch-Shimon et al., 2017; 2020; Suter & Pagani, 2018). This procedure could obviously make the patient infertile. Moreover, radiotherapy plays an important role in treatment due to higher risk of local recurrence of this malignancy (Ferzoco & Ruddy, 2015). This treatment modality for breast neoplasms is localized and directed above the diaphragm (Anchan & Ginsburg, 2010), with only an indirect effect on the ovaries through internal radiation scatter (Dow & Kuhn, 2004). The dose of radiation and effect of this therapeutic is relatively small (Maltaris et al., 2007) and the ovaries are often spared significant toxicity (Hulvat & Jeruss, 2009). In turn, chemotherapy can cause infertility by direct gonadotoxicity. Most premenopausal women diagnosed with breast cancer will have experienced some degree of alkylating agent exposure (Anchan & Ginsburg, 2010), which causes the greatest potential risk to future fertility (Christinat et al., 2012).

Particularly in younger pre-menopausal women with hormone receptor-positive tumors, endocrine therapy including ovarian function suppression/ablation with gonadotrophin releasing hormone (GnRH) analogs and tamoxifen is well established and is considered a legitimate complement to conventional adjuvant chemotherapy (Cardoso et al., 2019; Paluch-Shimon et al., 2017). The recommended duration of tamoxifen treatments for women with early breast cancer ranges from 5 to 10 years (Cardoso et al. 2019). Based on two clinical trials [Adjuvant Tamoxifen: Longer Against Shorter (ATLAS) and [Adjuvant tamoxifen—to offer more? (aTTom)] (Davies et al., 2013; Gray et al., 2013), continuation of tamoxifen for up to 10 years demonstrates further reductions in recurrence compared to stopping after 5 years. This selective estrogen receptor modulator has not generally been associated with cessation of ovulation (Hulvat & Jeruss, 2009), but its extent can affect fertility indirectly. These women are prohibited from becoming pregnant during therapy due to the teratogenic risks of treatment (Braems et al., 2011; Suter & Pagani, 2018). Thus, a delay of 5 to 10 years in conception can lead to natural ovarian aging (decline in ovarian reserve) (Lambertini et al., 2016). Clearly, adherence to endocrine therapy can be a problem in survivorship care (Benedict et al., 2017). It is likely that the desire to have a (or another) child after cancer might influence the decision to decline initiation or discontinue this type of treatment, as shown in the study by Llarena et al. (2015) involving 515 premenopausal patients aged <45.

Proactive counselling should be provided for younger women diagnosed with breast cancer, but pregnancy after diagnosis should not be discouraged. Studies have even suggested a protective effect of pregnancy in breast cancer patients (Lopresti et al., 2018). A meta-analysis including fourteen studies (1244 cases and 18,145 controls) found that the risk of death was reduced by 41% in young women who became pregnant after diagnosis compared to those who did not become pregnant (Azim et al., 2011). Currently, a prospective study (POSITIVE trial -IBCSG 48-14/BIG 8-13) with endocrine responsive early breast cancer patients is being carried out to assess the risk of relapse if therapy is interrupted for up to 2 years to get pregnant (Pagani et al., 2019). However, feasibility and optimal timing of pregnancy remain concerns for this population (Sella & Partridge, 2020).

2.2. Fertility counselling: Guidelines and barriers

Various practice guidelines advocate fertility counseling, highlighting the importance of clinicians discussing with their patients of reproductive age the potential impact of anticancer treatments on fertility soon after diagnosis, as well as providing comprehensive information on fertility preservation options to optimize decision-making (e.g. Almeida-Santos et al., 2016; Cardoso et al., 2019; Lambertini et al., 2016; Oktay et al., 2018; Peccatori et al., 2013; Yasmin et al., 2018). According to the recently updated recommendations on fertility preservation of the American Society of Clinical Oncology (ASCO) (Oktay et al., 2018) and to the European Society of Medical Oncologists (ESMO) guidelines (Paluch-Shimon et al., 2020; Peccatori et al., 2013), all patients with potential interest in preserving their fertility (or those who are ambivalent) should be referred to reproductive specialists. However, this does not rule out the need for collaborative care between oncology and fertility units (Deshpande et al., 2015; Lambertini et al., 2013), allowing for the proper determination of individual risk of infertility and promoting the possibility of becoming pregnant in the future (Lambertini et al., 2016).

Established methods of female fertility preservation include embryo cryopreservation or cryopreservation of unfertilized oocytes, conservative gynecologic surgery in the treatment of gynecologic malignancies (e.g., radical trachelectomy, which consists of removing the uterine cervix) and transposition of the ovaries prior to radiation therapy (oophoropexy), shielding the ovaries (Lavery et al., 2014; Logan & Anazodo, 2019; Oktay et al., 2018). More specifically, ovarian suppression during chemotherapy with GnRH analogues has been available as a strategy to preserve ovarian function at least in breast cancer patients, although there is some discussion around this option (Lambertini et al., 2016; Lavery et al., 2014; terWelle-Butalid, 2019).

Unfortunately, despite clear indications that fertility is a major issue in the cancer setting, this topic is not routinely discussed (Quinn et al., 2015). Marked sex differences regarding provided information about the impact of treatment on fertility were found, with men being given more information (Armuand et al., 2012). Further, based on the region where guidelines are used, there may be differences related to health-care systems, the availability of resources, and responsibility for providing information, which consequently influence the degree of priority given to fertility counselling (Logan & Anazodo, 2019). There is great variability in the rate of female patients who received information about infertility risks and fertility preservation options (van den Berg et al., 2019). Ruddy et al. (2014), in their study involving women ≤ 40 years of age diagnosed with early-stage breast cancer in the United States, showed that only 68% had discussed fertility issues with their physicians before treatment. On the other hand, in a more recent study carried out in the Netherlands, 79% of physicians reported always or regularly discussing these issues with their female patients, but only 54% often refer them to a reproductive specialist (Louwé et al., 2018). Also, in Portugal, considering a sample of 111 clinicians, only 59.3% reported informing their female cancer patients about fertility preservation options very often or always (Melo et al., 2018). This reflects a serious problem, because some female patients desiring pregnancy will have no other choice than becoming mothers through alternative routes such as third-party reproduction (donor eggs, embryo donation and surrogacy) or adoption (Salama & Woodruff, 2017; Snyder et al., 2010).

Numerous studies have explored barriers to practices regarding fertility issues that seem to be independent of contextual specificities. Over more than 10 years, lack of knowledge about fertility preservation strategies and resources or referrals and lack of training (Quinn et al., 2007; 2009; van den Berg et al., 2019) have been reported as factors that may impact on communication efforts. Additionally, international and national literature has consistently pointed to other professional barriers including the lack of time in the first appointment, when the focus is on diagnosis and treatment (Melo et al., 2018; Quinn et al., 2007; van den Berg et al., 2019).

Specific guidelines on how to conduct the best fertility counseling are also unavailable (Logan & Anazodo, 2019). For this reason, professionals reported disagreement between departments on who is responsible for infertility discussions and this topic is not routinely addressed in multidisciplinary meetings (van den Berg et al., 2019). Moreover, this can lead to the marginalization of some patients, since doctors' decisions to discuss these risks with some patients and not with others are subjective and can be based on patient-related characteristics, for example (e.g. age, having children, cancer prognosis) (Melo et al., 2018; van den Berg et al., 2019). Nevertheless, within current guidelines, only one-third point to the relevance of the mental health clinician working collaboratively in the context of fertility counselling. Indeed, a multidisciplinary approach could promote the possibility of patients having optimal care (Logan & Anazodo, 2019). The presence of a dedicated psychologist proved to be a facilitator in the expression of doubts, fears and emotions, when information on fertility care is provided (Razzano et al., 2014).

Recognized gaps can maintain or exacerbate reproductive health concerns. A systematic search showed that lack of fertility support and patients' knowledge are consistently associated with experiences of uncertainty and concern (Logan et al., 2019). Despite this, data suggest that no attention is paid to these concerns after cancer treatments (van den Berg et al., 2019). Even women who underwent fertility counseling prior to anticancer treatments do not see their concerns related to fertility potential, becoming pregnant and personal health adequately addressed during the survivorship period. Nor does there seem to be a modification of fertility counseling in the case of exposure to treatments that increase infertility risks (Young et al., 2019). Perception of the infertility risk varies from person to person (Lambertini et al., 2016). Therefore, to optimize the fertility care of younger women with cancer and ameliorate the patient-provider relationship, interventions should explore and address the unique concerns of this population (Deshpande et al., 2015).

3. IMPORTANCE OF FERTILITY AND PARENTHOOD

Young women diagnosed with cancer seem to experience greater psychological instability and worse functioning than their older counterparts (Champion et al., 2014), with premature menopause and infertility among the most troubling issues they face (Howard-Anderson et al., 2012). About 29.1%-73.5% of female cancer patients under 45 years wish to have children post-diagnosis (e.g. Geue et al., 2014; Gorman et al., 2014; Peate et al., 2011; Villarreal-Garza et al., 2017). The experience of cancer may affect patients' reproductive intentions (Schmidt et al., 2016). However, a study conducted by Geue et al. (2014) involving young German cancer survivors, indicated that the intensity of the desire for children increased from pre-to-post treatment in childless women. Even patients without a desire for children at diagnosis may change their mind about wanting children 3–7 years later (Armuand et al., 2014). Among the incentives to have children after cancer are the importance of parenthood for survivors, achieving normality and the desire to focus on something positive (Schmidt et al., 2016).

Importantly, the desire to have a child (or another) is a likely predictor of post-treatment fertility-related distress among young women with breast or gynaecological cancer, regardless of whether they already have children (Sobota & Ozakinci, 2018). Patient-physician communication plays a relevant role if preventive measures are desired (Dryden et al., 2014). Despite this, fertility preservation options are very complex and engaging, requiring women to weigh up their desire to have children against the potential risk of the preservation methods (Duffy & Allen, 2009). Moreover, the urgent need for treatment may hinder access to standard strategies (oocytes/embryos cryopreservation) (Lambertini et al., 2016; Yee et al., 2012).

More specifically, qualitative evidence suggests that women with breast cancer have more factors of uncertainty than certainty in the decision-making process about fertility, making difficult decisions in stressful situations without sufficient support (Komatsu et al., 2018). Perhaps also for this reason, fertility and parenthood concerns exist and are mostly reported in international studies exclusively focused on breast cancer patients (e.g. Adams et al., 2011; Peate et al., 2019; Schmidt et al., 2016).

3.1. Reproductive health concerns

Given the threat to family planning, female cancer survivors of reproductive age report a wide range of reproductive concerns. This concept involves worries relating to fertility (Logan & Anazodo, 2019; Wenzel et al., 2005), to the health of the potential child, their own health and survival after conception, or partner issues (Gorman et al., 2012; 2014; Schmidt et al., 2016). These concerns are constant and persistent from early to late survivorship (Logan et al., 2019) and their intensity may differ based on patient age (Partridge et al., 2004; Ruddy et al., 2014), prior number of pregnancies (Partridge et al., 2004) and previous anticancer treatments (Ljungman et al. 2018; Ruddy et al., 2014), with younger women at diagnosis, with fewer prior pregnancies and previously undergoing chemotherapy reporting higher concerns.

A literature review focused on general findings on reproductive issues found that most self-reported concerns were referred to the children, involving patients' worries about the cancer risk to their offspring mainly in breast neoplasms (Schmidt et al., 2016), where there is an increased risk of genealogical transmission of BRCA variants (Pilato et al., 2011). Fertility concerns are also prominent and cross-cutting (Howard-Anderson et al., 2012; Murphy et al., 2015; Sobota & Ozakinci, 2014) and significantly higher than in controls without a history of invasive cancer (Ruddy et al., 2011). Young women face the lack of control and choice regarding development of the task of being a mother. Hence, these specific concerns were primarily associated with the desire to have children (Ljungman et al., 2018; Partridge et al., 2004; Ruddy et al., 2011; Villarreal-Garza et al., 2017), but also with their identity as women (Penrose et al., 2012). Even women treated conservatively (e.g. primary ovarian cancer; radical trachelectomy) reported a fear of losing reproductive potential (Carter et al., 2007; 2010b; Sait, 2011).

Of particular importance is the fact that menopause symptoms seem to concern cancer survivors, and some women after breast cancer fail to understand whether their symptoms are transitory or are permanent effects of acute treatments (Anderson et al., 2011). Evidence suggests that women with breast cancer tend to overestimate their likelihood of cancer treatment-related infertility (Partridge et al., 2004). Indeed, it is important to provide appropriate information that includes accurate estimates of risk of fertility loss. Due to reproductive concerns, some patients chose not to receive chemotherapy and/or endocrine therapy (Llarena et al., 2015; Ruddy et al., 2014). The failure to adhere to adjuvant therapy may have important consequences for survival following breast cancer (e.g. Davies et al., 2013; Gray et al., 2013).

More specifically, Portuguese women with breast cancer seem to be more dissatisfied with their physician's explanations about fertility, for example, compared to survivors in the United States, and are less likely to undergo fertility care (Gonçalves et al., 2018), although these techniques are available free of charge (Almeida-Santos et al., 2016). For this reason, these women may be at risk of experiencing more reproductive concerns. It is noteworthy that greater concerns are associated with greater decisional conflict regarding fertility preservation (Benedict et al., 2016b; Kim et al., 2016), which may explain less adherence to procedures.

Within a cancer population, reproductive concerns are disruptive and this has been linked to depression not specific to fertility (Gorman et al., 2010; 2015), significantly lower quality of life (Benedict et al., 2018; Cândido et al., 2016; Wenzel et al., 2005) and lower satisfaction with sex-life (Ljungman et al., 2018) in oncological heterogenous samples involving breast and colorectal cancer, hematological malignancies and others. However, previous studies fail to test pathways of influence to better understand the mechanisms involved in the maladjustment.

3.2. Psychosocial impact of (in)fertility issues

It is not surprising that disrupted fertility is a negative experience and has a deleterious effect on quality of life (Chachamovich et al., 2010). Among cancer survivors, potential infertility can result in a sense of loss (Duffy & Allen, 2019) and distress (Penrose et al., 2012), even in women who did not plan to have children. These patients are forced to compromise their reproductive potential in favor of life-saving oncological treatments (Penrose et al., 2013; Yee et al., 2012) and this can create biographical disruption (Ussher et al., 2018).

For some younger female cancer survivors, motherhood is understood as a taken-for-granted component of femininity (Dryden et al., 2014). Therefore, these women feel inadequate because of their potential inability to undergo this life course transition (Dryden et al., 2014; Loftus & Andriot, 2012). Encounters with other women in their peer group may reinforce the lack of connection and feelings of exclusion due to the inability to participate in conversations about common experiences of pregnancy and motherhood (Halliday et al., 2014; Loftus & Andriot, 2012). The risks of infertility after cancer still lead some women to consider themselves unwanted regarding romantic relationships (Dryden et al., 2014).

The literature suggests that a woman diagnosed with cancer in reproductive age with an unfulfilled desire for children may report lower long-term mental health than another who sees her family building projects completed (Armuand et al., 2014). Young adults unable to have a desired biological child experienced more infertility-related traumatic symptoms (e.g. intrusive thoughts), more concerns about fertility and less sexual satisfaction than their peers, even 5–10 years post-treatment (Canada & Schover, 2012). Some women resort to avoidance to deal with the pain associated with the impact on reproductive potential. Avoiding thoughts about fertility problems and planning to address such issues in the future can be protective for some women (Benedict et al., 2016a), but in the long term, it can contribute to maladjustment (Canada & Schover, 2012).

The experience of infertile cancer survivors appears to be similar to that of infertile women in the general population, although the former face additional difficulties related to the demands of aggressive anticancer treatments (Penrose et al., 2013). In Carter et al. (2010a), gynecologic cancer survivors and leukemia/lymphoma/sarcoma cancer survivors (N=122) with cancer-related infertility showed identical reproductive concerns, depression and distress levels and worse physical quality of life compared to an infertile group without a history of cancer.

Some patients need to consider a potential infertility diagnosis without knowing for sure. There is evidence that uncertainty experienced as a reaction to the cancer diagnosis is itself linked to emotional distress and impaired quality of life (Shaha et al., 2008). This reinforces the need for exploration into how uncertainties arising from reproductive capacity after cancer can also be disturbing, in the same way as confirmed infertility. A recent review by Logan et al. (2019) draws attention to fertility-related psychological distress as a consequence of objective reproductive function, but also of the perception of fertility status. Clinically significant depression has been consistently presented by patients experiencing fertility preservation treatments as a preventative measure (Lawson et al., 2014) and/or as a result of their concerns (Gorman et al., 2015).

3.3. Psycho-educational support: innovative strategies

Information and support may facilitate management of concerns and distress and renegotiation of identify among cancer patients facing potential infertility (Ussher et al., 2018). As mentioned above, despite these evidence-based recommendations, gaps in counselling are recognized and improvement strategies highlight the involvement of specialized oncology nurses in fertility care (van den Berg et al., 2019). While these healthcare professionals need to be able to provide basic information about fertility issues, this intervention is also limited by the burden on their routine practice with time constraints and communication difficulties (Keim-Malpasse et al., 2018), which results in feelings of loneliness regarding the experience of potential fertility loss among cancer patients (Goossens et al., 2015). Furthermore, psychosocial aspects of fertility disruption may not be addressed. In response to this issue, innovative strategies involving the development of information materials and structured interventions have been signaled as a new path to fulfilling this responsibility (Canada & Schover et al., 2005).

Psycho-educational approaches may be an effective adjunct to clinical practice (Lukens & McFarlane, 2004), especially if they involve online access and computerized media being potentially more cost-effective. More specifically, the effectiveness of Internet interventions within the field of reproductive health has been demonstrated (Aarts et al., 2012). Previous work with female infertility patients showed that online psycho-educational support that includes information about fertility problems, but also encourages active coping and self-efficacy, has a meaningful impact on specific aspects of fertility-related distress (e.g. concerns around relationships with family and friends in the face of infertility) (Cousineau et al., 2008). Based on the idea that the experience of infertile cancer survivors seems to mirror the emotional response of non-cancer infertile women (Penrose et al., 2013), this could be an appropriate intervention modality.

Meneses et al. (2010a; 2010b) developed the Fertility and Cancer Project specifically focused on young breast cancer survivors and including education and support services electronically delivered to meet reproduction-related needs. Preliminary evidence from this approach, involving educational modules, message forums, and interaction with researchers, indicated significant positive effects of participation in knowledge about cancer-related factors (Meneses et al., 2010b), which could influence fertility, vigor and vitality and mental and social functioning from the baseline to a 6-month follow-up (Meneses et al., 2010a). However, to the best of our knowledge, investigations designed for this group have not been widely pursued. More recently, Winterling et al. (2016) developed a web-based psycho-educational intervention, Fex-Can (Fertility and Sexuality following Cancer), to alleviate sexual problems, but also fertility-related distress including concerns among young cancer patients. This intervention proposal included educational and behavioral change content, involving a balance between problem solving (change) and acceptance. A protocol describing the randomized clinical trial has been published, but there is still no data on the effect of this intervention on primary and secondary outcomes such as health-related quality of life, anxiety, depression, fertility knowledge and self-efficacy related to fertility (Lampic et al., 2019).

In the context of distance approaches, more interactive and dynamic elements, which minimize the lack of face-to-face interaction, may be a key component for the success of the intervention (Aarts et al., 2012). However, these modalities are not exempt from limitations. For example, as suggested by Aarts et al. (2012), the implementation of eHealth technologies requires that the Internet be widely and freely accessible to citizens, which is not the case in countries with few resources. Additionally, access to computerized media may be of a selective nature, reflecting increased levels of education (Andersson & Titov, 2014).

4. ATTENTIONAL BIAS: TOWARDS AN UNDERSTANDING OF REPRODUCTION-RELATED COGNITIVE PROCESSING

In addition to exploring innovative strategies to improve support for female cancer patients regarding fertility issues, new routes of intervention can be provided through the understanding of the implicit cognitive processes that can maintain the burden of reproductive concerns and maladjustments. Attentional processes were implicated as central in individuals' emotional responses (McLeod & Hangan, 1992; William et al., 1996). They have evolved to enable organisms to rapidly detect and focus on biologically relevant stimuli in the environment (Mogg & Bradley, 2004), considering that the ability to process information is limited (Norman et al., 1968). The phenomenon of hyper-attention to stimuli with enhanced saliency or relevance is known as attentional bias (e.g. Fadardi et al., 2016; Muris & Merckelbach, 1998;).

Evidence supports the role of motivational influences in attention allocation and preparation for action (Mogg & Bradley, 2004). Appetitive and defensive motivational systems are activated in contexts of promoting sustenance (e.g. nutrition, procreation) or threats to life (e.g. illness, injury), respectively, inducing similar heightened attention and arousal for the selection of an action (approach or avoidance) (Bradley et al., 2001; Lang & Bradley, 2013). For instance, when defensively motivated through aversive cues, an individual shows enhanced attention, even if these cues are not substantive, but instead representations using, for example, pictures (Lang & Bradley, 2013). These systems are designed to be evolutionarily adaptative, while imbalances in attention to certain stimuli may be maladaptive based on individual characteristics (Derryberry & Tucker, 2006).

Biased cognition in clinical anxiety disorders has been widely studied (e.g. generalized anxiety disorder, specific phobias, social phobia and panic disorder). Although there are several models around the nature and mechanisms involved in attentional bias (see Cisler & Koster, 2010), one more generalist view is that threat-related bias is a core anxiety component, which is transversal to all disorders (Bar-Haim et al., 2007). Attentional bias has been theorized to be present in a variety of other clinical conditions, including cancer (Custers et al., 2015; Lam et al., 2018), asthma (Jessop et al., 2004), even in children (Lowther et al., 2016), chronic pain (Fashler et al., 2016; Todd et al., 2018), and chronic fatigue (Hou et al., 2008). More specifically, those past studies suggest that people become sensitized to stimuli related to health-threat information. Concretely, individuals tend to direct their attention toward cues that are linked to their clinical condition (e.g. Custers et al., 2015; Lowther et al., 2016) during the early, automatic stages of processing. Even in the face of ambiguity and uncertainty about a certain diagnosis (e.g. family history of breast cancer), stimuli associated with the stress source may interfere with cognition (e.g. Erblich et al., 2003). Consistently with assumptions of cognitive theories (Mathews & McLeod, 2005), the adoption of a hypervigilant mode may have unintended negative consequences, leading to concern about illness and emotional distress.

Taken together, previous research instigates to explore whether “Can increased awareness or focus on reproduction-related stimuli contribute to morbidity, when a threat to fertility exists? Figure 1 presents the rational to answer this question. Presumably, these stimuli may activate the appetitive motivational system, mobilizing attention due to the connection with survival, in addition to involving social sensitivities (e.g. unrelated families) (Bradley et al., 2001). However, for young women diagnosed with cancer, they simultaneously represent a potentially threatened life goal, that is, there is a co-occurrence of an aversive state. Therefore, prioritization of reproduction-related cues at the cost of other information can contribute to increased feelings of lack of connection and inadequacy (e.g. Dryden et al., 2014; Halliday et al., 2014; Loftus & Andriot, 2012), preventing adjustment of the meaning of the potential limitation by pursuing other life goals. This potential bias may also justify increasing or maintaining reproductive concerns throughout treatment, even when fertility counseling is provided (Young et al., 2019). On the other hand, to avoid anticipated pain, some younger women may activate withdrawal mechanims, reducing their natural focus on reproduction-related information (Higgins, 1997). This regulatory strategy can occur with or without awareness of the intention to regulate the emotion (McLeod & Bucks, 2011).

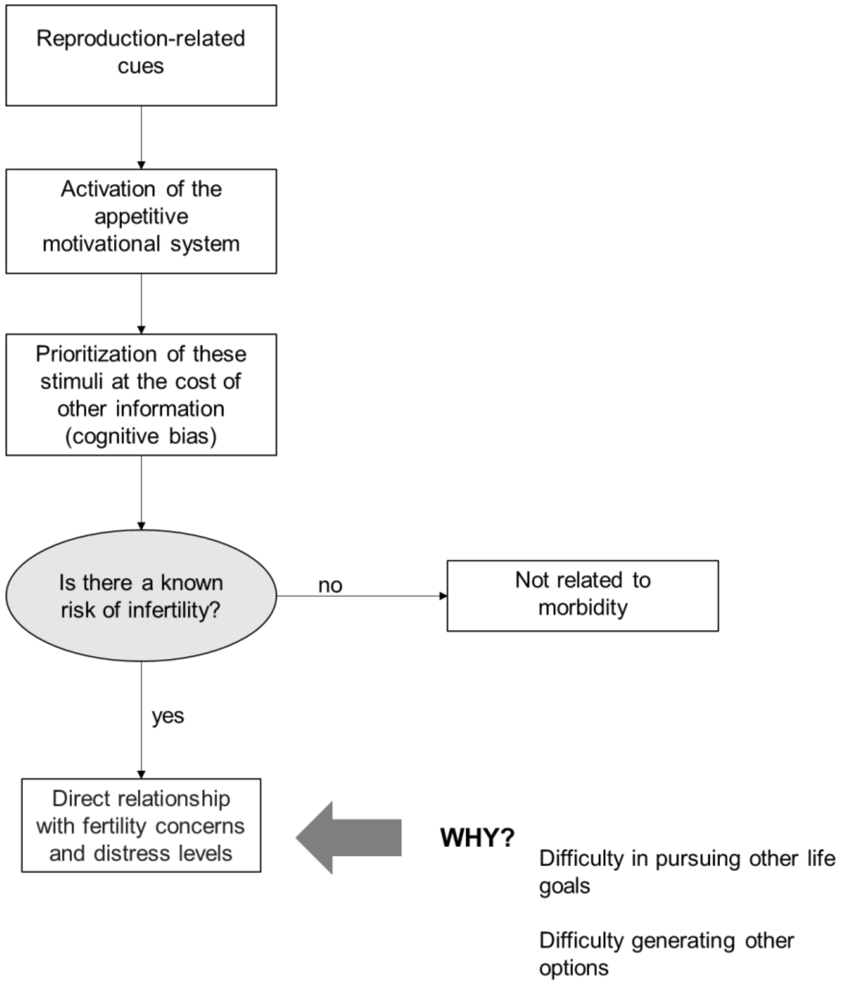

Figure 1. Rationale for supporting the assessment of attentional processes.

Attention is difficult to isolate from other cognitive processes. The use of response time paradigms has provided an indirect measure traditionally used to assess selective attention. The experimental paradigms most commonly used by researchers to examine the mechanisms involved in attentional biases have been the emotional variation of the classic Stroop task (Stroop, 1935) and visual probe tasks (MacLeod et al., 1986). However, results may differ regarding the nature of the specific attentional processes.

In an emotional Stroop task, participants are instructed to read the color of a word, ignoring its semantic content. This task requires the inhibition of an automatic act, with longer latencies being indicative of more attention. However, with this paradigm, it is not possible to evaluate the facilitated attention or the difficulty to disengage attention, being only an indicator of automatic or strategic processing (Cisler et al., 2009). Instead, a typical version of the visual probe task allows examination of whether the stimulus of interest is attracts attention or is avoided (Rooijen et al., 2017). This methodology involves exposing the participant to pairs of stimuli that appear simultaneously on a computer screen, after which one of the stimuli is replaced by a probe. The objective is to demonstrate whether the participant is quicker to detect probes that replace the target stimuli, which would be indicative of cognitive bias. Both experimental procedures have been developed and applied in the cancer setting and can be used to explore the potential attentional bias to reproduction-related information.

CHAPTER II

Objectives and General Method

This work involved two systematic reviews, a validation study and four cross-sectional studies, which are presented in the format of scientific articles (see Chapter III). Together, these studies allowed better understanding the role of reproduction-related issues in the concerns and psychosocial adjustment of young adult female cancer survivors, mainly breast cancer survivors. Furthermore, they provided an opportunity to assess the cognitive mechanisms that underpin vulnerability in this setting, involving *quasi*-experimental approaches focusing on cognitive processing. In this chapter, we summarize the purpose of each study and the methodological options underlying both review studies and empirical studies. The data collection was divided in two phases: (1) the study of reproductive concerns, psychological morbidity and health-related quality of life (HRQoL) using self-report measures; (2) the study of selective information processing biases using behavioral measures (see Figure 1).

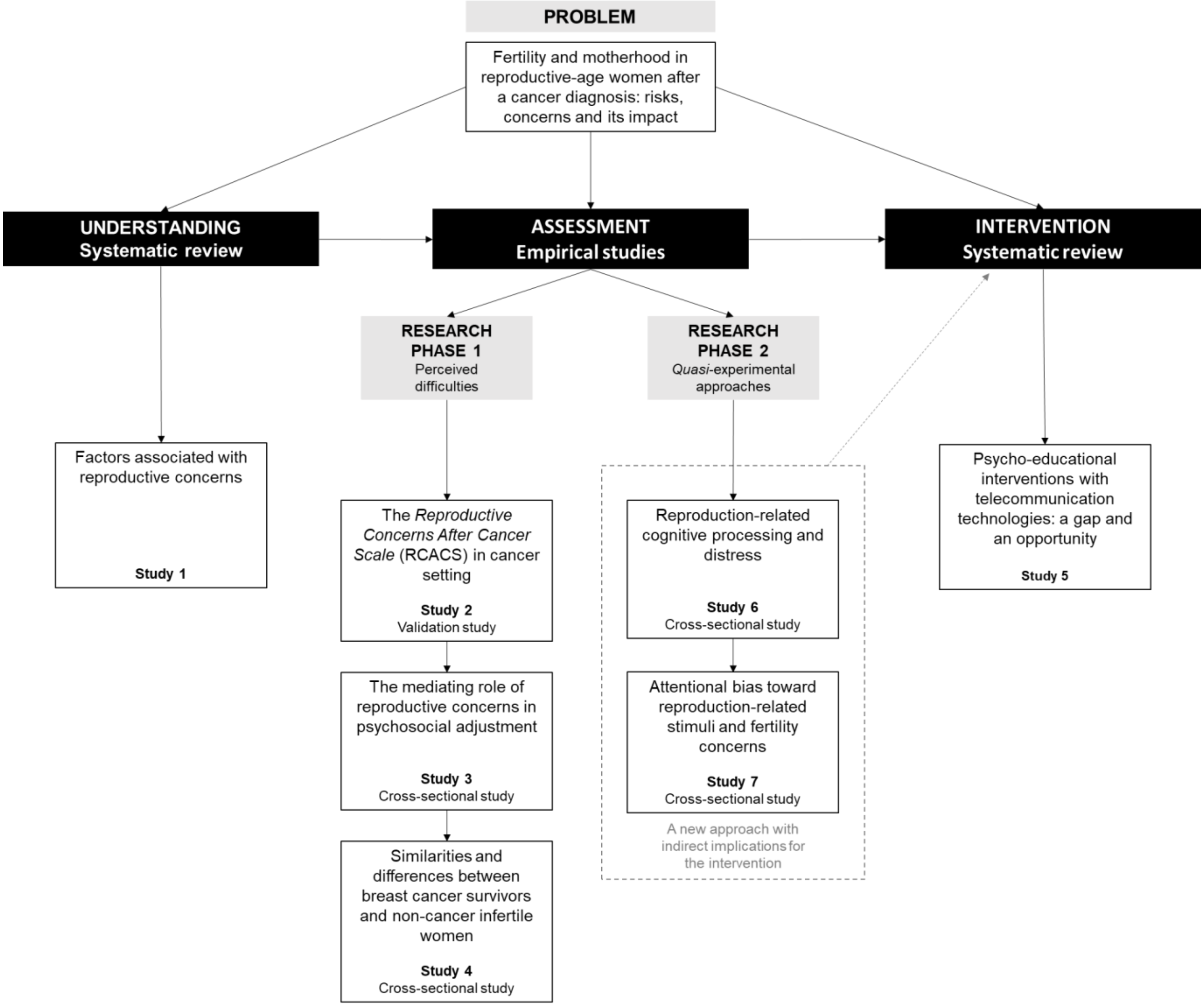

Figure 1. Overview of the studies conducted.

1. RESEARCH AIMS

This work address some of the gaps identified in the literature on the topic of fertility, parenthood and cancer (see Chapter I), namely: (i) provide a validated instrument to assess reproductive concerns among Portuguese female cancer survivors; (ii) identify mechanisms involved in adjustment of breast cancer survivors at a reproductive age; (iii) introduce analysis of more cost-effective interventions that minimize gaps in fertility counseling; and (iv) investigate how implicit cognitive processes can be a distress factor and, simultaneously, a target for intervention regarding infertility risks after a breast cancer diagnosis. Based on this, the specific aims of this work were to:

1) Systematically review the dimensions of subjective reproductive concerns and their relationship with sociodemographic, clinical, and psychosocial variables in reproductive-aged women (Study 1).
2) Validate the European Portuguese version of the *Reproductive Concerns After Cancer Scale* (RCACS) among young adult females diagnosed with cancer, exploring its factor structure, internal consistency and convergent and discriminant validity (Study 2).
3) Examine the association between the importance of parenthood, reproductive concerns and depression and HRQoL in young breast cancer survivors (Study 3);
4) Compare the fertility-related concerns, psychological distress and HRQoL of breast cancer survivors with uncertain fertility, non-cancer women with infertility history and healthy women (Study 4).
5) Systematically review the effectiveness of psycho-educational interventions using telecommunication technologies on emotional distress and quality of life in general in adult cancer patients (Study 5);
6) Examine reproduction-related cognitive processing (using visual and verbal stimuli), and explore the relationship between potential attentional biases and fertility concerns and distress among breast cancer survivors (Studies 6 and 7).

2. STUDIES AND METHODOLOGIES

2.1. Systematic reviews: Search strategy and procedures

Both systematic reviews (Study 1 and Study 5) included in this work followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al., 2009). The protocols of these review studies were registered on PROSPERO (Moher et al., 2015) and are available in full on the NIHRHTA program website: https://www.crd.york.ac.uk/prospero/.

Data collection involved database searches, namely Scopus, Web of Science (science and social science citation indices), PubMed, ProQuest, and Psychology & Behavioral Sciences Collection (through EBSCOhost). As a supplement to the search, the reference lists of included articles were also screened. The key terms and eligibility criteria were defined in accordance with the aims of each review. In order to improve the understanding about reproductive concerns among cancer survivors in reproductive age (a central theme of this work), Study 1 included only records involving women aged 15 to 49. In Study 5, with a more exploratory perspective of drawing attention to the effectiveness of distance approaches and the need to consider them in the intervention in young women with cancer, the inclusion criteria were more comprehensive involving cancer patients more than 18 years old (more details about each study are described in the appropriate section in Chapter III).

In the first phase of the data extraction process, the potentially eligible articles were selected based on their titles and abstracts. Then, the full texts were analyzed, and doubts were discussed and resolved by the review team. Importantly, the studies included in each systematic review were critically assessed using the Joanna Briggs Institute (JBI) Statistics Assessment and Review Instruments critical appraisal checklists (e.g. Moola et al., 2017; Tufanaru et al., 2017). Unfortunately, the heterogeneity of the data regarding study design, cancer type and instruments used did not allow meta-analyses to be performed.

2.2. Empirical studies: Sample and data collection procedures

2.2.1. Research phase 1: Perceived difficulties

This phase involved an assessment of the subjective perception of reproductive concerns and psychosocial outcomes such as distress, HRQoL, need for parenthood and rejection of a childfree lifestyle among female cancer survivors aged 18 to 40 years. Participants with a cancer history were mostly recruited from three hospital institutions, namely: Gynecology and Obstetrics Department of Centro Hospitalar de São João, in Porto; Breast Clinic of Instituto Português de Oncologia Francisco Gentil, in Porto; and the Gynecology Department of the Instituto Português de Oncologia Francisco Gentil, in Coimbra.

Studies 2, 3, and 4 of this research work were carried out based on the data obtained in this recruitment phase. Table 3 illustrates the sample size and the inclusion criteria associated with each study, which differed according to the objectives foreseen for each one of them (see Research aims section). None of the studies included young women who were pregnant at the time of enrollment. Paper-and-pencil questionnaires and interviewing was the preferred data-collection method adopted in all studies. Cancer patients were invited to participate on the day of the medical appointment, avoiding additional travel costs.

Table 1. Characteristics of the empirical studies carried out in research phase 1.

Study	Sample size (N)	Data collection (paper-and-pencil/online)	Cancer type	Age at enrollment (criterion)	Eligibility criteria	Comparator
2	192	Paper-and-pencil and online	Hetero geneous	18-40y	Women diagnosed with cancer at least 1 year prior to participation	Not applicable
3	104	Paper-and-pencil	Breast cancer	18-40y	Women over the age of 18 diagnosed with early stage cancer (IIIA) who received chemotherapy	Not applicable
4	43	Paper-and-pencil	Breast cancer	18-40y	Women with a history of early cancer (IIIA), disease-free and who wish to have a biological child	Non-cancer infertile group (n=56) Control group (n=37)

First, we conducted the validation study of the RCACS using a heterogeneous sample involving breast cancer, gynecologic cancers, hematological malignancies and others. Here, exceptionally, data collection was complemented with a web-based survey disseminated through newsletters, mailing lists and social networks. In turn, cross-sectional studies (3 and 4) involved only breast neoplasms diagnosed in young adulthood (> age 18). Specifically, Study 4, exploring whether the experience of uncertainty about fertility after breast cancer mirrors the emotional response of infertile young women, implied recruiting comparison groups. Hence, we collected a non-cancer infertile group, which had not yet started their Assisted Reproduction Technology (ART) treatment cycle, from the Reproductive Medicine Unit of the Centro Hospitalar Universitário de São João. A control group without cancer or infertility diagnosis in the past was also involved and recruited from public and private institutions (e.g. daycare centers, hairdressers).

2.2.2. Research phase 2: *Quasi*-experimental approaches

In the empirical studies of research phase 2, there was a convergence of complementary investigative techniques (see Table 2). *Quasi*-experimental methodological approaches were included to understand attentional processes. We conducted two studies, which involved the development and administration of two different experimental paradigms (a Stroop task [Study 6] and a dot-probe paradigm [Study 7]).

In this phase, disease-free breast cancer survivors aged 18 to 40 years, who had a history of early-stage breast cancer (≤ IIIA) without recurrence, were recruited. None of the participants underwent hysterectomy, prophylactic oophorectomy or tubal ligation procedures. In Study 6, only native Portuguese speakers were included. All participants were collected at the Breast Center of the Centro Hospitalar Universitário de São João. Eligible breast cancer survivors were referred by medical staff and contacted via phone (by the Ph.D. student). In addition, a control group was recruited for comparison. Young women were included in this group if they had no cancer diagnosis or known fertility problems. This recruitment process involved an online call disseminated by e-mail through the University of Aveiro population, including the pre-selection questionnaire. Eligible participants were contacted via e-mail and/or phone after registration online, to schedule face-to-face data collection.

The evaluation protocol was administered individually. All participants were seated comfortably in front of a computer screen in a quiet room. The procedure started with the administration of the experimental tasks, followed by filling in the self-report questionnaires. This option was taken so that the self-report measures did not influence the salience of the stimuli used in tasks. Participants did not receive feedback on their performance in any of the tasks. Both tasks were run on a 15.4-inch monitor using E-Prime 2.0 Professional (Psychology Software Tools, Inc.).

2.3. Empirical studies: Materials and data analysis

2.3.1. Self-report measures

The selection of the self-report questionnaires used to operationalize the constructs of interest in this work were based on their robust psychometric properties in previous studies, assessed dimensions, preferring multidimensional measures and a shorter length. Except for the RCACS, all instruments were validated for European Portuguese. A brief description of each instrument can be found below. More details are provided in the scientific articles included in Chapter III. Table 2 presents a checklist of the instruments used in each study according to their purposes.

Sociodemographic and clinical questionnaire: This questionnaire was developed by the research team specifically for this work and administered both in phase 1 and phase 2 of the data collection process. Information about age, marital status, level of education and nulliparity was collected. Regarding the clinical aspects, when oncological samples were recruited, this questionnaire included variables such as cancer type, age at diagnosis, diagnosis duration, previous anticancer treatments and previous fertility care.

18-item Reproductive Concerns After Cancer Scale [RCACS]: This scale was a suitable measure for assessing reproductive concerns in young female cancer survivors who were 18–35 years and younger than 45, according to studies by Gorman et al. (2014; 2019). Furthermore, the original instrument incorporated multiple dimensions related to fertility and parenthood concerns assessed through 18 items, namely: fertility potential, partner disclosure, child's health, personal health, acceptance and becoming pregnant.

These features justified its inclusion in this work. For each item, participants are asked to identify their level of agreement with each statement using 5-point Likert scales ranging from 1 (strongly disagree) to 5 (strongly agree). A total score for the full scale (18-90 points) and a mean score for each subscale are obtained, with higher values indicating more concerns. As previously mentioned, we validated the Portuguese version of the RCACS, which was translated and adapted by the Quality of Life Office at the International Breast Cancer Study Group (IBCSG) (Study 2). The original factor structure was not maintained. Thus, the items in the Portuguese version were grouped only in five dimensions that we designate as follows: (1) fertility potential, (2) children's health risk and future life, (3) partner disclosure, (4) barriers to getting pregnant/having children and (5) acceptance. Following this result, the subsequent studies considered this configuration of the European Portuguese version. Although the RCACS was developed for women with a cancer history, three of its subscales (fertility potential, partner disclosure and acceptance) were administered to “non-cancer” participants (e.g. infertile group and healthy controls) because they include items that involve general concerns which can be reported by any woman of reproductive age (e.g. “I am afraid I won’t be able to have any (more) children”; “I am concerned that my (potential) spouse/partner will be disappointed if I can’t get pregnant”). Hence, we only used these dimensions and not the complete scale in Studies 4, 6 and 7.

14-item Hospital Anxiety and Depression Scale (HADS) [Portuguese version: Pais-Ribeiro et al., 2007]: This is a brief self-report questionnaire specifically designed to assess anxiety and depression symptoms in a general hospital setting. However, the HADS has been widely used in different clinical and community settings. This instrument consists of two distinct subscales: depression subscale and anxiety subscale. Both were used in this research work. Each subscale includes 7 items and participants respond using a 4-point Likert scale. The total score for each subscale is obtained through the sum of its item responses and ranges from 0 to 21, with higher scores indicating more symptoms.

European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) [Portuguese version: Pais-Ribeiro et al., 2008]: This questionnaire was designed to assess HRQoL in adult cancer populations, involving a multidimensional structure. It is also a self-report measure often used to compare the HRQoL of cancer patients and population-based controls without a history of cancer (e.g. Arndt et al., 2017; Doege et al., 2019). In total, the EORTC QLQ-C30 presents 30 items, including five functional subscales, a global health status/quality of life subscale, three symptom subscales and single-item measures. For the purpose of this work, only physical, role, emotional, cognitive and social functioning and global health status/quality of life were evaluated and used in data analyses. For each item, participants are invited to respond using a 4-point Likert scale ranging from “not at all” to “very much”, with the exception of two items from the global health/QoL subscale, which use a 7-point scale. Separate scores are calculated for each dimension (range 0-100), with higher scores indicating better perceived functioning.

Fertility Problem Inventory (FPI) [Portuguese version: Moura-Ramos et al., 2012]: We chose to include this questionnaire in our data collection due to the fact that it includes a dimension of global infertility stress related to representations about the importance of parenthood and children in one’s life. This dimension involves two subscales, namely need for parenthood (10 items) and rejection of a child-free lifestyle (8 items), which were administered in this research. Participants are asked to answer the items on a 6-point Likert scale (e.g. from “Strongly disagree” to “Strongly agree”). Separate scores for each subscale can be computed by summing up the respective items. Furthermore, the sum of the items of these two subscales yields an importance of parenthood global index, with higher values indicating greater importance of parenthood.

Table 2. Instruments used in each empirical study.

	EMPIRICAL STUDIES				
	RESEARCH PHASE 1			RESEARCH PHASE 2	
Materials	**Study 2**	**Study 3**	**Study 4**	**Study 6**	**Study 7**
Sociodemographic and clinical questionnaire	✓	✓	✓	✓	✓
Self-report measures					
18-item Reproductive Concerns After Cancer Scale [RCACS] (full scale)	✓	✓			
Fertility potential	✓		✓	✓	✓
Children's health risk and future life	✓				
Partner disclosure	✓		✓	✓	✓
Barriers to getting pregnant/having children	✓				
Acceptance	✓		✓	✓	✓
14-item Hospital Anxiety and Depression Scale (HADS)					
Anxiety	✓		✓	✓	✓
Depression	✓	✓	✓	✓	✓
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30)					
Global health status/quality of life scale	✓				
Physical functioning	✓	✓	✓		
Role functioning	✓	✓	✓		
Cognitive functioning	✓	✓			
Emotional functioning	✓	✓	✓		
Social functioning	✓	✓	✓		
Fertility Problem Inventory (FPI) – Importance of parenthood index		✓			
Need for parenthood	✓				
Child-free lifestyle subscale	✓				
Experimental Tasks					
Emotional Stroop Task				✓	
Visual Dot-probe Task					✓

2.3.2. Experimental tasks

This is the first research to examine reproduction-related cognitive processing, and for this reason, the experimental tasks used were designed specifically by our team. The emotional Stroop task used word stimuli. However, previous studies indicate that verbal cues may have less potential to elicit attentional bias than pictorial stimuli (e.g. Moritz et al., 2008). For this reason, a visual dot-probe task involving images was also administered. Furthermore, the use of these two paradigms ensures that the potential attentional bias to reproduction-related information is not an artifact of particular experimental procedures. Reaction times and accuracy were recorded in both tasks, although the main focus of analyses in Studies 6 and 7 are the results in terms of response times. A brief description of each task is presented below.

Emotional Stroop Task: A variation of the emotional Stroop paradigm was applied consisting of four 20-word lists (one reproduction-related and three unrelated ones, involving positive, negative and neutral content). The details of developing and implementing this task are described in Study 6 (see Chapter III). Generically, two data collection steps prior to the main study were required: a face-to-face collection to generate a pool of reproduction-related words, which involved 14 healthy women aged 26 to 40 years recruited from the general population; and a subsequent web survey to evaluate the 50 most frequently reported words, according to the affective dimensions of valence and arousal and relation to reproduction. This last step involved a new sample consisting of 33 women aged 25 to 40 years (15 cancer survivors and 18 controls without cancer history). Then, the top 20 selected words scoring higher in their relation with reproduction entered the main study, generating a reproduction-related Stroop list. In turn, the three non-reproduction related comparison lists were extracted from the Affective Norms for English Words (ANEW) database for European Portuguese (Soares et al., 2012), based on affective ratings and their equivalence (e.g. mean word length, number of syllables) with reproduction-related stimuli. In the Stroop task, words were presented in random order in 1 of 3 colors (red, green or blue). Participants were instructed to indicate the color of each word that appeared on the computer screen by pressing designated keys (“f”, “j” and “k”) as quickly as possible. Longer Stroop color-naming times in reproduction-related words, compared to other words, were indicative of biased attention.

Visual Dot-probe Task: This task included pictures obtained from the Open Affective Standardized Image Set (OASIS) (Kurdi et al., 2017): a set of images with reproduction-related content (e.g. family interactions, pregnancy) (n=20); a set with content unrelated to reproduction, but also displaying people interacting (n=20); and a set of control images including inanimate objects (non-human stimuli) (n=10). Firstly, the research team selected images of scenes potentially related to reproduction. This was followed by a preliminary study using 31 young women aged 18 to 40 years (14 cancer survivors and 17 healthy women) who assessed each image individually. Based on the results of this study, the twenty pictures with highest ratings in relation to reproduction were selected for the dot-probe task. The set of images with content not specifically related to reproduction were matched with reproduction-related stimuli in terms of emotional valence and arousal. The control condition included images with low arousal. Luminance differences were controlled between the three sets of images. Each trial consisted of the following sequence: (i) a fixation cross was displayed in the center of the computer screen; (ii) a pair of images consisting of a reproduction-related stimulus and a picture with unrelated content was displayed on the right and left of the screen (positions counterbalanced across trials); and (iii) the images disappeared and a small asterisk (probe) appeared in the position occupied by one of the images. The control images were presented side by side in some of the trials, obtaining a baseline condition. Participants were instructed to indicate the position of the asterisk (left or right) by pressing one of the designated keys (Z or M) as quickly as possible. A quicker detection of probes when they substituted reproduction-related images suggested an attentional bias towards these cues (more details are provided in Study 7, Chapter III).

2.3.3. Data analysis

The statistical options employed to respond to the specific objectives of the empirical studies are described in the methodology sections of the papers (see Chapter III). Overall, all studies involved descriptive statistics to characterize the samples in terms of sociodemographic, clinical and psychosocial variables. Regarding inferential statistics, the following more advanced analyses are highlighted: (i) in Study 2, we conducted exploratory factor analysis (EFA) using weighted least squares with the mean and variance adjustment (WLSMV) estimator through MPlus, version 6.12 (Muthén & Muthén, Los Angeles, USA), to explore the fit of alternative factor models for the Portuguese version of RCACS; (ii) in Study 3, a path model was tested through IBM Amos software, version 24, for better understanding the indirect effect of the importance of parenthood in women’s lives on depression and HRQoL through reproductive concerns; (iii) in Study 4, multivariate analyses of covariance (MANCOVAs) using IBM SPSS, version 24 (SPSS Inc., Chicago) were performed, allowing comparisons between the breast cancer survivor group, non-cancer infertile women and the control group regarding combined variables; and (iv) finally, in Studies 6 and 7, response time differences using two distinct experimental paradigms were analyzed using a mixed-design analysis of variance (ANOVA) including the group (breast cancer survivors vs. non-cancer controls) as the between-subjects factor and trial type as the within-subjects factor.

2.4. Ethical considerations

The protocols of the empirical studies carried out in each of the research phases were approved by the Ethics Committee of all institutions involved (e.g. Instituto Português de Oncologia Francisco Gentil in Porto and Coimbra, Centro Hospitalar Universitário de São João, and Universidade de Aveiro). All studies were performed in accordance with the Declaration of Helsinki from the World Medical Association, and informed consent (written or online) was obtained from all participants before starting the data collection. Furthermore, all procedures adopted in conceiving and implementing this work considered the principles of the deontological code of the Portuguese Psychologists' Association. Importantly, in research phase 2, the specific objectives of the experimental tasks could not be revealed before the evaluation in order to not influence performance. For this reason, participants were informed that the aims would be presented at the end of the session. Therefore, debriefing was provided at the end and all questions were answered.

3. PUBLICATION AND DISSEMINATION

The aims and results of this research work were continually disseminated to scientific and non-scientific communities. In an initial phase of the work., the project was presented at service meetings of hospital institutions to inform health professionals about the objectives of the participant recruitment and data collections that would take place. Moreover, a website was created (**http://psycho-oncologyresearch.web.ua.pt/**) to disseminate several studies in progress, and later, associated findings that could inform the academic community and also the general population. This website was publicized through newsletters and social networks.

The systematic reviews and empirical studies (7 studies) resulting from this work were submitted/published along with statements regarding the sources of funding. At the date of submission of this thesis, 5 articles (see Chapter III) have been published in international journals with scientific arbitration. The work was also presented at scientific events. It is noteworthy that the Ph.D. student was co-organizer of the 1st National Congress of Scientific Research in Psychosocial Oncology (**http://congressonacionalicop.web.ua.pt/**) held at the University of Aveiro (March 13-15, 2019) and which involved the participation of breast cancer survivors through painting and photography exhibitions.

CHAPTER III

Systematic reviews and Empirical studies

STUDY 1

Towards an understanding of the factors associated with reproductive concerns in younger female cancer patients: Evidence from the literature

Publication

Bártolo, A., Santos, I.M., & Monteiro, S. (in press a). Towards an understanding of the factors associated with reproductive concerns in younger female cancer patients: evidence from the literature. *Cancer Nursing*. https:/doi.org/10.1097/NCC.0000000000000822
SCImago/Scopus© SJR 2019: 0.78/Q2; ISI JCR® Impact factor (2019): 1.850

Communications at scientific events

Bártolo, A., Monteiro, S., & Santos, I.M. (2018). Understanding the Reproductive Concerns of Young Female Cancer Patients: Evidence from the Literature. Oral communication presented at the 4th Portuguese Order of Psychologists Congress, Braga, Portugal.

Monteiro, S., Bártolo, A., & Santos, I. M. (2018). The role of reproductive concerns in psychosocial adjustment of cancer survivors. Oral communication presented at the 12th National Congress of Health Psychology, Lisbon, Portugal.

Bártolo, A., Santos, I.M., & Monteiro, S. (2017). Reproductive concerns and psychosocial adjustment in young adult female cancer. Oral communication presented at the UnderInvestigation: Psychology & Education@UA, Aveiro, Portugal.

Abstract

Background: Cancer treatments may compromise fertility and family building in reproductive-age women. Previous research has shown that younger women with cancer experienced several reproductive health concerns.

Objective: The aim of this study was to conduct a focused review of existing research about the subjective perceptions of reproductive concerns among young women with cancer (aged 15-49 years) and identify their potential predictors and outcomes.

Methods: A systematic synthesis of mixed-methods research was conducted including peer-reviewed articles in English. Relevant studies were identified through the electronic databases of Scopus, Web of Science, PubMed, ProQuest and Psychology & Behavioral Sciences Collection (through EBSCOhost).

Results: A total of 22 reports met the eligibility criteria (8 qualitative and 14 quantitative). Research showed that younger women reported concerns related to their fertility status and/or own health after conception, their children's health and their dyadic relationships. Redefinition of the motherhood role and the family future were also a source of concern. However, there is variance among women in concerns and experiences based on life stages and expectations.

Conclusions: Reproductive concerns seem to be affected by personal circumstances and previous therapeutics. These concerns constitute a potential risk factor, simultaneously, for psychosocial maladjustment and adherence to endocrine therapy and fertility care.

Implications for Practice: This article proposes a conceptual framework to understand the dimensions and potential predictors and outcomes of perceived concerns among reproductive-age cancer patients. Our data allow us to look at these concerns from a multifactorial perspective, identifying areas to be addressed in providing clinical care, namely, by nurses accompanying patients over an extended period.

Keywords: reproduction, younger, women, fertility care, oncological.

Background

The occurrence and diagnosis of cancer are a public health problem with immediate and long-lasting side-effects that worry patients. Epidemiological data estimated an incidence of 152 new cases of cancer per 100.000 young women aged 15-49 years in 2018 in the United States of America. In European countries, the incidence rate of cancer in this age group ranged from 97.1/100.000 to 150.7/100.000 for Albania and the United Kingdom, respectively[1]. For some premenopausal women, the disease presents additional reproduction-related challenges.

Considering that pregnancy later in life has become increasingly common, mainly in developed countries[2], some women who are faced with a cancer diagnosis have not yet started or completed their motherhood plans. It has been widely acknowledged, however, that cancer treatment may cause gonadal function damage[3]. The effects may be directly due to gynaecological surgeries, irradiation and cytotoxic chemotherapy or mediated by hormonal alterations[4]. Thus, most young women undergoing cancer treatments face uncertainty about their reproductive ability[5].

Research has highlighted the need for professionals to be alert to the future expectations and life planning of young adults at any stage of cancer diagnosis[6]. Despite this, discussions about fertility with reproductive-age cancer patients seem to be at a suboptimal level[7]. Oncologists' lack of communication skills and lack of time with patients emerged as the main barriers to the discussion of this topic during care[8]. Thus, patients interested in maintaining future fertility may initiate cancer treatment with unsatisfied information needs and without the opportunity to discuss their concerns with professionals.

There is increasing interest in exploring perceived concerns about reproduction in younger women diagnosed with cancer. Over the past decade, qualitative syntheses have been published in this field. Previous reviews mainly report concerns related with menstrual changes, potential infertility risk and successful conception among younger women. Howard-Anderson and colleagues[9] reviewed relevant outcomes in breast cancer among premenopausal women and/or those aged <51 years, identifying worries about entering the menopause, treatment-induced infertility and reproductive options. Sobota and Ozakinci[10] predominantly found worries about pregnancy complications among young female cancer patients. According to their review[10], a positive effect of fertility-related interventions (e.g. counselling, online support and fertility preservation) on the well-being of female cancer patients was reported. However, due to their broad scope, neither review provides clear evidence regarding the current understanding on the subjective perceptions of reproductive concerns and their impact. In addition, most studies included in these reviews were conducted between 2003 and 2007 not including more recent studies developed in the last decade. Other reviews concentrating on breast cancer also pointed to concerns about future fertility[11,12] involving research dating from 1994 to 2006.

Nevertheless, reproductive health is a multifactorial concept[13], which is not restricted to reproductive ability but also includes aspects related to relationships and developmental tasks. Murphy and colleagues'[13] systematic review examined the understanding of adolescents and young adults' priorities regarding reproductive health. This overview identified the side effects of treatment on body image (e.g. hair loss) and fertility, and their relation with forming and maintaining romantic partnerships at this stage of life. Data from this study draw attention to survivors' fear of rejection and to difficulties in disclosing the history of cancer and its consequences to partners. However, once again, because of its broad focus, this review did not delve into the subjective concerns reported by younger women with cancer or the factors that influence them. For example, concerns related to the mother's role after cancer and family building alternatives have not been addressed in previous discussions.

Therefore, it is important to provide systematic information that contributes to an overall understanding of what is currently known about reproduction-related concerns from a multidimensional perspective that goes beyond the ability to conceive. Moreover, the risk factors that contribute to these specific concerns should be detailed to minimize marginalization of cancer patients in discussing reproductive issues during clinical care. To advance research on this topic, our purpose was to conduct a focused review of existing literature about the reproductive concerns inclusive of mixed methods research, which was not limited to studies with breast cancer patients. Specifically, we aimed to highlight and understand the dimensions of subjective reproductive concerns among women of reproductive age and their relationship with socio-demographic, clinical and psychosocial variables.

Methods

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines[14]. According to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 statement[15], the protocol was registered on PROSPERO (CRD42018086391) and is available in full on the NIHR HTA program website (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018086391).

Eligibility criteria

Studies were included in the systematic overview if they (i) involved reproductive-age female cancer patients (15-49 years at enrolment) at the active stage or disease-free survivors; (ii) identified the reproductive concerns reported by patients and factors associated with their concerns; (iii) were written in English; and (iv) were published in a peer-reviewed journal over the last 10 years. The review involved all studies in which female-only results are reported, irrespective of whether male participants were included as well. Literature/systematic reviews, validation studies, book chapters, unpublished articles, commentaries and conference abstracts were excluded. Also excluded were studies that focused on describing reproductive characteristics but without capturing the patient's subjective concerns.

Literature search

The systematic search was performed using Scopus, Web of Science (science and social science citation indices), PubMed, ProQuest and Psychology & Behavioral Sciences Collection (through EBSCOhost). The following key terms were used: cancer, women/female, younger, concerns, reproduction, fertility, reproductive health, menopause, pregnancy, parenthood, contraception, child, family, partner/dating/marriage. The search was adapted for the 5 databases and OR and AND functions were used to combine the above terms. Specific filters related to publication date, language and document type were used whenever possible. Searches in these databases were supplemented by a manual search of the reference lists of included articles. Attempts were made to find unavailable articles by contacting authors.

Extraction and synthesis strategy

The selection process was conducted by the first author considering the review team's pre-established inclusion and exclusion criteria. Then, the author independently reviewed the titles and abstracts, and produced a list of studies for full-text examination. All documents raising any doubts were discussed and resolved by consensus between all the co-authors. To provide a systematic synthesis of mixed-methods research, data were extracted from the qualitative and quantitative studies and reported separately. Main information was gathered, such as: (i) basic demographic information (e.g. country, sample size, age, cancer type); (ii) main reproductive-related concerns; and (iii) their relationship with socio-demographic, clinical and psychosocial variables. Because of the substantial heterogeneity of studies concerning their objectives, it was not possible to determine a summarized effect size regarding the main outcomes. Moreover, incomplete statistical data in articles also prevented determination of the standardized effect size measures for each study.

Quality Appraisal

The quality of the retrieved articles was critically appraised by the review team using the Joanna Briggs Institute (JBI) Statistics Assessment and Review Instruments (JBI-MAStARI) critical appraisal checklists for qualitative research, analytical cross-sectional studies and cohort studies[16-18]. A substantial number of the checklist criteria should be filled to include each study in the review, that is, at least 50% of the JBI criteria. Any disagreements between the revisions were resolved by discussion between all the co-authors.

Results

Study characteristics

A flowchart of the literature search is presented in Figure 1. As shown, a total of 352 studies were identified. From these, 48 duplicate articles were removed before the selection process based upon title and abstract. Most studies were excluded because they did not examine concerns in young female cancer patients. Thus, only 68 full texts were retrieved for assessment of eligibility. Of these, 46 did not meet the inclusion criteria. Most of the excluded articles involved samples including women over 50 years at the time of recruitment. In some cases, the age range was not reported. Two articles presented preliminary data of larger quantitative studies already published at the time of this review and, for this reason, were excluded[19,20], while the final studies presenting the definitive data were included. Additionally, two studies reported secondary analyses based on data from partial samples that had already been used in previous studies[21,22]. However, these reports presented distinct research questions and, for this reason, were included in results analysis. No studies were excluded on the basis of quality appraisal.

Twenty-two reports were included in the systematic review, 8 with a qualitative design and 14 with a quantitative design. Data for the qualitative research were collected using mainly interviews (n=5) and focus groups (n=2). Two out of 14 quantitative studies also used qualitative items to explore reproductive concerns. Evidence from these items was extracted and, based on this, the qualitative synthesis of this review included 10 studies (see Table 1). Thirteen articles were included in the quantitative synthesis because, according to the purpose of the review, quantitative data from the study by Carter et al.[23] were not relevant. Thus, only the exploratory qualitative item of the article was used in the synthesis. There was a wide variety of data collection methods used in the quantitative studies, namely, in person, by telephone, by post, through a web-based survey and by e-mail. Of the included studies, 81.8% used a cross-sectional design. In general, studies from the United States were over-represented (55%). However, there were studies carried out in other countries such as Australia (n=3), the United Kingdom (n=1), Mexico (n=1), Sweden (n=1), Portugal (n=1) and Brazil (n=1). The baseline sample size ranged from 6[24,25] to 34[26] for exclusively qualitative studies (M=15.4; SD=10.1), and from 20[27] to 620[28] young female cancer patients for studies using a quantitative approach (M=234.6; SD=186.8).

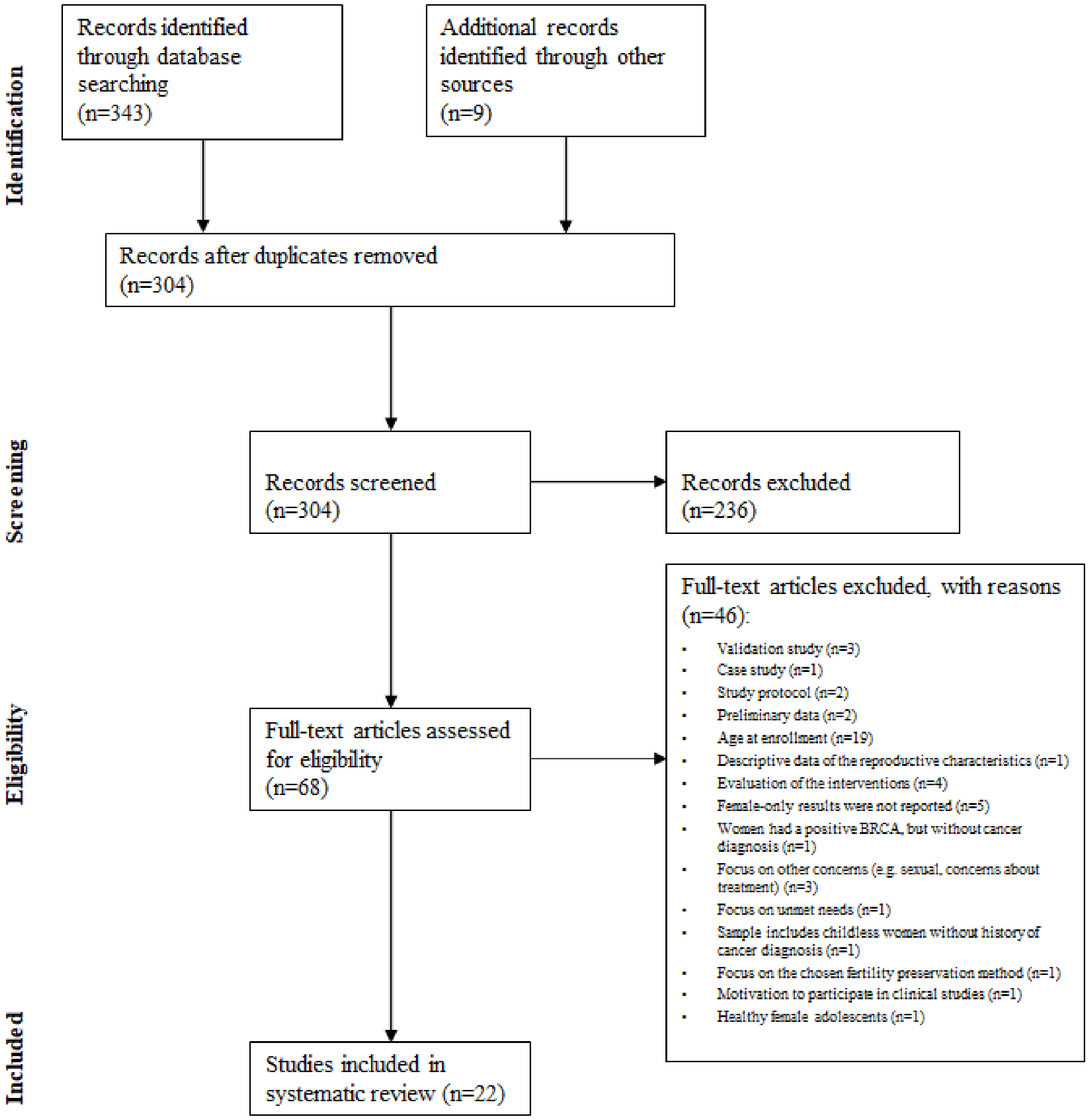

Figure 1. Flowchart of literature search. Adapted from: Moher et al.[14].

Concerning the participants' characteristics, the age criterion varied among studies as shown in Tables 1 and 2. Most of the reports involved young adults aged 18 years or over and under 45 at the time of enrolment. One study included women over 45 years[29].

Table 1. Summary of the studies included in qualitative evidence.

First author name, year	**Country**	**Sample size (N)**	**Cancer type**	**Age at enrollment** (criterion)	**Age at diagnosis** [mean or range]	**Description of target population**	**Key Concerns**
Anderson et al., 2011[24]	Australia	6 (younger women)	Breast	34-36 years	<40 years (criterion)	Women who would complete the acute treatment (surgery, radiology, chemotherapy) within 2 years and reported at least one target menopausal symptom (moderate to severe)	▪ Menopausal symptoms and their impact
Assi et al., 2018[26]	Brazil	34	Heterogeneous	23-39 years	–	Female cancer patients who underwent fertility preservation	▪ Fertility preservation
Carter et al., 2010[23]	United States	71	Cervical	18-45 years	–	Women undergoing radical trachelectomy (RT) vs radical hysterectomy (RH)	In RH condition: ▪ Cancer spread ▪ Menopause prevention In RT condition: ▪ Ability to conceive
Carter et al., 2010[29]	United States	122	Gynecologic and Leukemia/lymphoma/sarcoma	18-49 years	21-46 years; 4-45 years	Female cancer patients without evidence of disease for at least 1 year (Gynecologic cancer survivors vs Leukemia/lymphoma/sarcoma cancer survivors treated by Bone Marrow/Stem Cell Transplant)	▪ Effect of diagnosis and treatment on offspring ▪ To adopt as cancer survivor

Table 1 (continued)

First author name, year	**Country**	**Sample size (N)**	**Cancer type**	**Age at enrollment** (criterion)	**Age at diagnosis** [mean or range]	**Description of target population**	**Key Concerns**
Corney et al., 2014[34]	United Kingdom	19	Breast	30-44 years	27-41 years	Childless women with first episode cancer diagnosed at least 6 months before	▪ Fertility ▪ Little time to find a partner and have a child ▪ Conception as a trigger of recurrence ▪ Child's health (abnormality) ▪ Child's genetic risk
Coyne et al., 2008[25]	Australia	6	Breast	<50 years (29-43)	–	Women diagnosed in the last 12 months	▪ Children's needs at each step of the treatment
Dryden et al., 2014[35]	Australia	8	Heterogeneous	<30 years (18-26)	–	Childless women who had received a cancer diagnosis	▪ Fear of rejection by partners (or potential partners) ▪ Child's health
Fisher et al., 2012[38]	Australia	8	Breast	<50 years (≥31, ≤49)	31-42 years	Cancer patients who had dependent children	▪ Impact of cancer diagnosis on the mothering role
Gorman et al., 2011[36]	United States	20	Breast	26-38 years	≤40 (criterion)	Women diagnosed with early stage breast cancer (I or II)	▪ Fertility concerns varying from women to women
Gorman et al., 2012[30]	United States	22	Heterogeneous	18-34 years	6 months to 30 years	Female cancer survivors	▪ Ability to conceive ▪ Negative impact of the fertility problems on the partner ▪ Impact of the pregnancy on one's own health ▪ Child's genetic risk and family history ▪ Cost of becoming a mother

Age at the time of diagnosis was not reported in 41% of the studies. Six reports involved young women diagnosed at different stages of life including childhood, adolescence, and adulthood[26,29-33]. The studies included mostly white women, with a college degree and married or living in cohabitation. Two of the qualitative studies included only childless women[34,35].

Regarding clinical information, 50% of the studies involved samples including young women diagnosed with breast cancer. Reproductive concerns were also assessed using heterogeneous samples (e.g. gynaecological, lymphoma, leukemia and thyroid). Some reports failed to provide details of participants' treatment. However, in 8 studies, more than 80% of cancer patients underwent chemotherapy.

Study quality

Descriptions of the critical appraisal are shown in Table 3. Regarding exclusively qualitative studies, a rigorous procedure was adopted in the coding and interpretation process. However, most research did not discuss the potential influence of the researcher during the data collection process. Of 8 studies, 1 used a researcher triangulation method to minimize the bias[24]. Additionally, 50% of studies fail to provide information about cultural aspects and the theoretical orientation of the study. Beliefs and values and their influence on the concerns experienced are little addressed. In turn, the majority of quantitative studies met the JBI criteria. The most common reasons for bias in the results of qualitative evidence were related to a small sample size and lack of control of confounding factors. The self-report measures used in the reports included were shown to be valid tools in previous research. Nevertheless, the internal consistency for the samples under study should have been reported in all articles.

Qualitative evidence

Research has suggested that young female cancer patients experience reproductive concerns either in an active phase of the disease or during survival. While fertility has not been widely viewed as the major concern for all reproductive-age female cancer patients[36], the studies showed that most of these women were worried about their fertility status, that is, whether the treatments reduced their ability to conceive[23,29,30,34]. This finding was replicated among young women diagnosed with breast cancer, gynaecological cancer, leukaemia/lymphoma/sarcoma and using heterogeneous samples for cancer type. However, Carter and colleagues[23] found that in young women with cervical cancer treated with radical trachelectomy, an alternative oncological surgery which preserves fertility, concerns related to future conception seemed to decline over 2 years post-surgery.

The menopause, as a consequence of therapeutics, is also one of the factors that worried cancer patients[23,24]. These young women faced uncertainties about whether their periods would return after treatment[24] and this can exacerbate fertility status concerns, mainly for those who wanted to have a child or more children. Some young women even express the feeling of losing their future projects, especially family building, due to the menopause.

Fertility preservation enhances the opportunity to satisfy biological motherhood, but it can also be a factor of concern for female cancer patients both at the time of the procedure and afterwards[26]. This is a physically invasive procedure and, although the literature does not point to ovarian stimulating drugs with standard treatment protocols as a risk factor for increasing cancer development[37], this concern may prevail in some patients. Nevertheless, fertility preservation also presented challenges related to the high costs of the procedure and time. Early initiation of anticancer treatments becomes a priority, but preserving fertility may imply the decision to postpone the starting of chemo-radiotherapy[26,34]. This decision must be taken by the patients and there is a need to improve information regarding infertility-related treatments and fertility preservation options. The literature indicates that not discussing these issues prior to treatment can lead to a major concern in the future[29].

Of 10 studies including only childless women, 2 drew attention to specific concerns related to partners (or potential partners)[34,35]. Mostly in their 30s, these women felt pressure to find a partner or give the partner a child, and in some cases, reported fear of rejection because of the potential inability to conceive. The changes in appearance and potential loss of fertility seem to hinder a sustainable relationship and this is a source of vulnerability for patients[34]. Some younger women feel undesirable and limited in romantic relationships[35]. In turn, the potential negative impact of fertility problems on partners was also a reported concern in the state-of-the-art. Young women were worried about the need to involve their partner in a complex medical process to become pregnant[30].

Furthermore, other concerns related to personal health and children's health (or potential) were found after cancer diagnosis and were identified as an emotional obstacle to parenthood[30]. Among them, it was verified that patients were worried about how conception could trigger cancer recurrence[34]. Concerns related to potential complications during pregnancy and anomalies, medical problems and/or passing on a genetic risk of cancer to the child[30,34,35] were also observed (see Table 1). More specifically, we verified that younger women with breast cancer considered donated eggs or adoption as an option if they had a genetic mutation linked to hereditary cancer[34]. Nevertheless, adopting as a cancer survivor was also a concern among cancer patients. Issues related to discrimination during the adoption process due to illness seemed to concern gynaecological and leukaemia/lymphoma/sarcoma cancer survivors[29].

Lastly, cancer patients face the inability to meet the physical, emotional and social needs of their offspring. Thus, the (re)construction of identity as a mother is also a challenge of living with cancer, although many young women do not feel this role recognized by health professionals[38]. Studies showed that women diagnosed with breast cancer who had dependent children presented concerns related to child-rearing responsibilities[25] and future planning if the disease became terminal[38]. For this reason, women reported planning and organizing roles and responsibilities for their partners and children in the future, addressing, for example, financial issues. Living with cancer also raises concerns about communicating with their children about the disease. These patients need to deal with uncertainties about what and when to talk to their child about this issue[38].

Quantitative evidence

How to assess reproductive concerns?

The scores for cancer patients' reproductive concerns in each study were determined using a variety of assessment forms. The most widely used method was administration of one of the following self-report measures: the 14-item Reproductive Concerns Scale (RCS) developed by Wenzel et al.[39][α range=.81-.91]; or the18-item Reproductive Concerns After

Cancer (RCAC), a multidimensional scale developed by Gorman et al.[40][α range=.82-.83], which were used in 7 out of 13 studies, including subscales about fertility potential, partner disclosure, child's health, personal health, acceptance and becoming pregnant. The other studies used items adapted from the Fertility Issues Survey[41] (n=3) or generated one single item related to the desire for future fertility at diagnosis (n=1), this being interpreted as an indicator of the presence of fertility concerns. Table 2 illustrates the different assessment tools for each study.

Factors affecting the reproductive concerns experienced

In the literature, reproductive concerns reported by young female cancer patients were compared to the following groups: (1) young women without history of cancer or invasive cancer (n=2) and (2) non-cancer, infertile young women (n=1). Data showed that young women previously diagnosed with early-stage breast or gynaecological cancer presented higher reproductive concerns than control groups[27,42]. One study[35] found no group differences when comparing the infertile gynaecological or leukemia/lymphoma/sarcoma cancer survivors (but eligible for third-party reproductive options) with non-cancer, infertile women. Descriptive analysis of the quantitative studies reinforces the findings obtained in the qualitative studies, reporting mainly concerns about potential fertility problems in young female cancer patients[31,43]. More specifically, Benedict and colleagues[31] verified that 64% of the young women were concerned about their ability to conceive. Among studies, the prevalence rates of concerns related to the risks of cancer for children's health ranged from 38%[44] to 61%[29] for young women with breast cancer and leukemia/lymphoma/sarcoma cancer survivors treated by Bone Marrow/ Stem Cell Transplant, respectively. More recent research[33] showed that concerns related to a transmissible genetic mutation seem to be independent of the type of cancer (breast, ovarian and colorectal cancer vs other diagnosis). Gorman et al.[21] also observed that 41% of female cancer survivors reported concerns about potential adoption, that is, not being assessed as a good candidate after cancer. Additional concerns, related to a desire to physically experience a pregnancy and not being emotionally stable enough to be a mother, have emerged from descriptive data[21].

Table 2. Summary of the studies included in quantitative evidence.

First Author, year	Study Design	Country	Sample size (N)	Cancer type	Age at enrollment [criterion]	Age at diagnosis [mean or range]	Description of target population	Reproductive concerns measure	Data analysis	Main variables
Benedict et al., 2016[31]	Cross-sectional study	United States	346 (N=179 in subgroup)	Heterogeneous	18-35 years	23.4 (n=19 age < 15 years)	Female survivors who had successfully completed treatment at least 1 year before and were disease free	18-item Reproductive Concerns After Cancer (RCAC) scale	Regression coefficients	▪ Decisional conflict regarding future fertility preservation
Benedict et al., 2018[22]	Cross-sectional study	United States	314	Heterogeneous	18-35 years	23.5	Premenopausal females who had completed treatment at least 1 year before and were disease free	18-item Reproductive Concerns After Cancer (RCAC) scale	Regression coefficients	▪ Quality of life
Cândido et al., 2016[42]	Cross-sectional study	Portugal	52 (+ N=43 in control group)	Breast or gynecologic	18-40 years	–	Women previously diagnosed with early-stage (0-III) cancer	14-item Reproductive Concerns Scale (RCS)	Path model	▪ Cancer diagnosis ▪ Non-specific distress symptoms ▪ Quality of life
Carter et al., 2010[29]	Cross-sectional study	United States	122 (+ N=50 non-cancer infertile)	Gynecologic cancer survivors or Leukemia/lymphoma/sarcoma	18-49 years	21-46 years; 4-45 years	Female cancer patients without evidence of disease for at least 1 year and non-cancer infertile women	14-item Reproductive Concerns Scale (RCS)	Mean scores	▪ Cancer diagnosis

Table 2 (continued)

First Author, year	**Study Design**	**Country**	**Sample size (N)**	**Cancer type**	**Age at enrollment** [criterion]	**Age at diagnosis** [mean or range]	**Description of target population**	**Reproductive concerns measure**	**Data analysis**	**Main variables**
Gorman et al., 2015[45]	Cross-sectional study	United States	200	Heterogeneous	18-35 years	–	Female cancer survivors at least 1 year after diagnosis	18-item Reproductive Concerns After Cancer (RCAC) scale	Odds ratio for depression	▪ Depression
Gorman et al., 2017[21]	Cross-sectional study	United States	163	Heterogeneous	18-35 years	–	Female cancer survivors at least 1 year after diagnosis who wanted to have a (another) child in future	18-item Reproductive Concerns After Cancer (RCAC) scale	Mean scores	▪ To consider adoption
Kim et al., 2016[32]	Cross-sectional study	United States	204	Heterogeneous	18-35 years	22.9 (n=5; age ≤14 years)	Female cancer survivors diagnosed at least 1 year before, not currently pregnant	18-item Reproductive Concerns After Cancer (RCAC) scale	Odds ratio for use of fertility care services	▪ Use of fertility care services after cancer treatment
Ljungman et al., 2018[44]	Cross-sectional study	Sweden	181	Breast	23-42 years	18-39 years (criterion)	Women diagnosed with invasive cancer	18-item Reproductive Concerns After Cancer (RCAC) scale	Correlation coefficients Odds ratio for reproductive concerns	▪ Sexual function ▪ Desire to have children ▪ Previous chemotherapy
Llarena et al., 2015[46]	Prospective cohort study	United States	515	Breast	25-45 years	–	Women diagnosed with stage 0-III, estrogen receptor-positive and/or progesterone receptor-positive breast cancer	Women expressing a desire for future fertility at diagnosis	Odds ratio for non-initiation and hazard ratio for early discontinuation	▪ Non-initiation or early discontinuation

Table 2 (continued)

First Author, year	**Study Design**	**Country**	**Sample size (N)**	**Cancer type**	**Age at enrollment** [criterion]	**Age at diagnosis** [mean or range]	**Description of target population**	**Reproductive concerns measure**	**Data analysis**	**Main variables** ▪
Raghunathan et al., 2018[33]	Cross-sectional study	United States	187	Heterogeneous	18-35 years	0-34 years	Female cancer survivors who had completed treatment and were disease free	3-item Child's Health Subscale of the 18-item Reproductive Concerns After Cancer (RCAC) scale	Mean scores	▪ Transmissible genetic mutation
Ruddy et al., 2011[27]	Cross-sectional study	United States	20 (+ N=20 in control group)	Breast	≤43 years (31-43 years)	<40 years (criteria)	Women diagnosed with early-stage (I-IIIa) breast cancer at least 1 year from diagnosis with history of chemotherapy without evidence of recurrence and who remained premenopausal	A refined Fertility Issues Survey	Mean scores	▪ Cancer diagnosis ▪ Desire to have children
Ruddy et al., 2014[28]	Prospective multicenter cohort study	United States	620	Breast	≤40 years (17-40 years)	–	Women newly diagnosed with early-stage (0-III) breast cancer less than 6 months ago at enrollment	A modified Fertility Issues Survey 4-point Likert scale ranging from a lot of concern to no concern	Odds ratio for fertility concerns	▪ Undergoing chemotherapy ▪ Age < 35 years ▪ Non-Caucasian ▪ Not already having children
Villarreal-Garza et al., 2017[43]	Cross-sectional study	Mexico	134	Breast	19-40 years	≤40 years (criterion)	Women newly or previously diagnosed with breast cancer	25 items adapted from the Fertility Issues Survey	Regression coefficients	▪ Desire to have children

Data from quantitative studies have indicated that overall reproductive concern scores are affected by several other aspects. Age younger than 35 years and being nonwhite were associated with a greater likelihood of fertility concerns in one of the studies[28]. Previous chemotherapy in treatment of breast cancer was also a significant predictor of reproductive concerns, revealing some patients' awareness of the impact of this therapeutic method on gonadal function[28,44]. Reproductive characteristics, such as not already having children[30] and the wish for (more) children in the future[27,43,44], were also associated with higher levels of reproductive concerns among younger breast cancer patients. More specifically, the desire to have children prior to diagnosis was shown to be a positive predictor of experienced reproductive concerns[43] (see details in Table 2). Heterogeneous samples of female cancer survivors suggested that women who considered the adoption option, as an alternative to childbirth, were less worried about their personal health than those who did not consider this option[21].

Reproductive concerns as a potential predictor

Of 13 studies, 7 examined the association of the reproductive concerns reported by young female cancer patients with psychosocial variables and treatment options. Regarding statistical procedures, five studies used regression analysis (see Table 2). Psychosocial variables included depression (n=1)[45], non-specific distress symptoms, quality of life [QoL] (n=2)[22,42]and sexual function[44]. Data pointed to reproductive concerns as a significant predictor of the depressive symptoms of female cancer survivors. Gorman et al.[45] found an association between experiencing reproductive concerns and a greater likelihood of moderate to severe depression, controlling for variables such as education, duration of survivorship and social support. Non-specific distress symptoms were significantly associated with these specific concerns in samples of early-stage breast or gynaecological cancer patients[42]. QoL also seems to be affected by reproduction-related concerns among oncological samples. Here, the literature points to direct[22] and indirect effects[42] of these concerns on the impairment of QoL. Benedict et al.[22], observed that, besides the association between increased reproductive concerns and lower QoL, young adult female cancer survivors with lower QoL reported higher levels of concerns about fertility and greater difficulty in accepting these problems, higher concerns about becoming pregnant and partner disclosure compared with a group experiencing higher QoL levels. In turn, an exploratory study suggested a potential mediator effect of distress on the negative relation between reproductive concerns and QoL[42]. Regarding the association between dimensions of reproductive concerns and sexual function, only small effects were found. A higher effect was found for the negative relation between satisfaction with sex-life and concerns about personal health[44].

A study by Llarena et al.[46] showed that, in addition to the role of psychosocial aspects, reproductive concerns may also influence the choice of initiating or maintaining specific therapeutics. In that study with young women diagnosed with early-stage estrogen receptor-positive and/or progesterone receptor-positive breast cancer, fertility concerns were associated with non-initiation and early discontinuation of tamoxifen. Descriptive statistics of studies involving also breast cancer patients reinforce these findings. Some participants mentioned that their treatment decisions were affected by fertility concerns, namely decisions related to receiving chemotherapy and endocrine therapy[28,43].

Lastly, 2 cross-sectional studies showed an association of reproduction-related concerns with resorting to fertility care (FC) by young adult female cancer survivors. On one hand, higher concerns were associated with having higher decisional conflict (uncertainty in making a decision) concerning future fertility preservation post-treatment[32]. On the other hand, greater reproductive concerns specifically related to personal health in young survivors decreased the likelihood of these women having FC after cancer treatment[32].

Table 3. Summary of the critical appraisal criteria according to the Joanna Briggs Institute (JBI) Statistics Assessment and Review Instruments (JBI-MAStARI)

Qualitative research	**n out of N**
Congruity of the study regarding the stated philosophical perspective and the research methodology	8 out of 8
Congruity of the study regarding the research methodology and collection data methods, analysis and interpretation of results	8 out of 8
Cultural and theoretical location	4 out of 8
Reciprocal influences researcher - research	1 out of 8

Table 3. (continued)

Qualitative research	**n out of N**
Voices of the participants adequately represented	7 out of 8
Ethical Approval	7 out of 8
Conclusions based on the analysis or interpretation of the data	8 out of 8
Analytical cross-sectional studies/cohort studies	
Inclusion criteria clearly defined	14 out of 14
Detailed description of subjects and setting	14 out of 14
Objective criteria for measurement of the condition	13 out of 14
Confounding factors identified	14 out of 14
Strategies for dealing with confounders	11 out of 14
Valid and reliable measures	8 out of 14
Appropriate statistical analysis	11 out of 14

Discussion

The aim of this study was to review the subjective perceptions of reproductive concerns among younger female cancer patients and their relationships with socio-demographic, clinical and psychosocial aspects. This study involved mostly women aged between 18 and 40 years-old, including samples of breast cancer patients, gynaecological cancer patients or more heterogeneous samples (e.g. lymphoma and leukemia), who showed, not surprisingly, the presence of reproductive concerns. Overall, these women seemed aware of the effects of oncological treatments on reproductive health, and reported concerns about their fertility status[23,30,31,34, 43], their own health after conception[30,34], their children's health[33-35] or about their partners (or potential partners) and their romantic relationships after cancer[30,34,35]. These results are consistent with previous reviews[9,10,11,12,13], but our systematic synthesis of mixed-methods research revealed a variance across women regarding concerns. For example, redefining the motherhood role, while considering the limitations of cancer diagnosis, is something that worries patients with dependent children. For these women, it is important that their responsibilities as mothers are recognized by healthcare professionals[38]. In turn, childless women feel the pressure of passing time to find a partner and have children. In these patients, the fear of rejection in marital relations becomes more evident and there are feelings of inadequacy[35]. Therefore, when providing interventions, medical staff should examine the individual characteristics and expectations of female cancer patients.

Quantitative research also shows that women who are younger than 35 years, are non-white[28] and previously undergoing chemotherapy[28,44] are at greater risk of experiencing higher reproductive concerns. Also, the desire to have children is one relevant predictor of concerns about reproductive health[43], reinforcing the idea already underlined in other research that life planning should be considered in the course of the disease[6]. Furthermore, considering adoption may be a factor protecting against distress in this context, which should be discussed with patients. However, it is important to recognize that this is simultaneously an aspect of concern for some younger women due to the fear of stigmatization by adoption agencies[21].

Data from this review suggested that the subjective perceptions of the reproductive consequences of cancer diagnosis also impacts on younger women's well-being and decisions. Reproductive concerns have a predictive role in psychosocial adjustment [22,42,45], and treatment options related to therapeutics in cancer and resorting to FC[31,32]. The studies reviewed indicated that these specific concerns represent a risk factor for increased depressive symptomatology, lower QoL, and in the case of breast cancer, non-initiation or early discontinuation of hormone therapy. This latest finding is in line with the perspective of Benedict et al.[47], who suggest the prioritization of fertility and concern about the side-effects of treatment as factors affecting adherence to adjuvant endocrine therapy. In turn, regarding FC, studies indicated that concerns about one's health after potential conception may also contribute to less likely use of FC[32] post-treatment among female cancer survivors.

Despite this evidence, a considerable gap exists in addressing reproductive concerns. Clinical guidelines advocate fertility counselling, aiming to improve the knowledge and well-being of women with cancer. However, recent findings have shown that fertility counselling is not given to most female cancer patients and, when given, does not seem to lessen their concerns[48]. Thus, Figure 2 illustrates a conceptual framework for understanding of concerns among reproductive-age cancer patients. This framework shows the main dimensions of concern emerging from the literature. Moreover, risk factors and outcomes of reproductive concerns were identified and directions of influence have been presented to contribute to improving the assessment and consequent response to these specific concerns of women with cancer.

Limitations and future directions

Perceptions of reproductive concerns in the context of oncological disease seem to be a subject widely studied in the United States, but little explored, for example, in European countries or among minority groups. We also found methodological limitations in the studies, which reduce the strength of the evidence and should be noted. First, research tends to be too broad in scope including heterogeneous samples regarding types of cancer and/or associated treatment. Second, some studies included childhood, adolescent and adult survivors in the same sample, which may have led to bias in the conclusions. Besides, age at diagnosis was not reported in many studies. For these reasons, differences were not highlighted considering the developmental stage at which the diagnosis arose. Future studies should concentrate on understanding reproductive concerns considering the underlying variability of these factors. Third, concerning quantitative studies, many had a cross-sectional design, which prevented identifying the patterns of change along the various stages of diagnosis and treatment. Clearly, there is a need to develop further studies involving longitudinal data collected over time, particularly to explore the trajectories of reproductive concerns. A minor point is the descriptive data of the studies, with some records not providing details of participants' treatment and their reproductive characteristics (e.g. menopausal status, number of children at diagnosis). Also, the internal consistency of the self-report measures was not reported in all studies.

No studies explored specific concerns related to the effect of aging on the reproductive system and the risks of having children in later life. This issue is especially relevant in the context of female breast cancer. Considering the benefits of extending endocrine therapy in young women (5 vs 10 years)[49], at the end of the treatment some women are already 40 years or older. Thus, more research is needed, focusing on the concerns and attitudes of women facing this challenge. Areas related to reproductive health, such as contraception, have also not been explored in this context, although decisions related to contraceptive methods after diagnosis can be a cause for concern.

Despite the limitations noted, the evidence showed that the reproductive concerns of young women should continue to be examined and be a target of attention for healthcare professionals. To improve understanding of these specific concerns, more sophisticated data analysis to test pathways of influence, based on the conceptual framework proposed, could be the focus of future research. We emphasize, however, that this review only included peer-reviewed articles in English, so studies in other languages or unpublished at the time of the selection process may be missing.

Clinical Implications

Based on the findings of this review, dedicated programmes for younger women at risk should incorporate discussion of fertility, transmissible genetic mutation, family-building and expectations and the motherhood role and future plans. Cancer nursing plays an important role in addressing reproductive health concerns as these nurses maintain continuous contact with patients over an extended period. Inter-professional collaboration between nurses, oncologists, fertility teams[50], genetic counsellors, social workers and other health care providers is needed for more effective counselling. Nurses in this scenario can establish referral paths to support more specific problems reported by younger patients. Additionally, there is a need to develop psychological interventions that focus on beliefs associated with reproduction and the reproductive role, strengthening the strategies to deal with the consequences of treatment either individually or as a couple. Finally, valid and more effective measures to assess reproductive concerns should be included in care provision for better understanding of the concerns and to reduce the under-identification of this distress factor by medical staff.

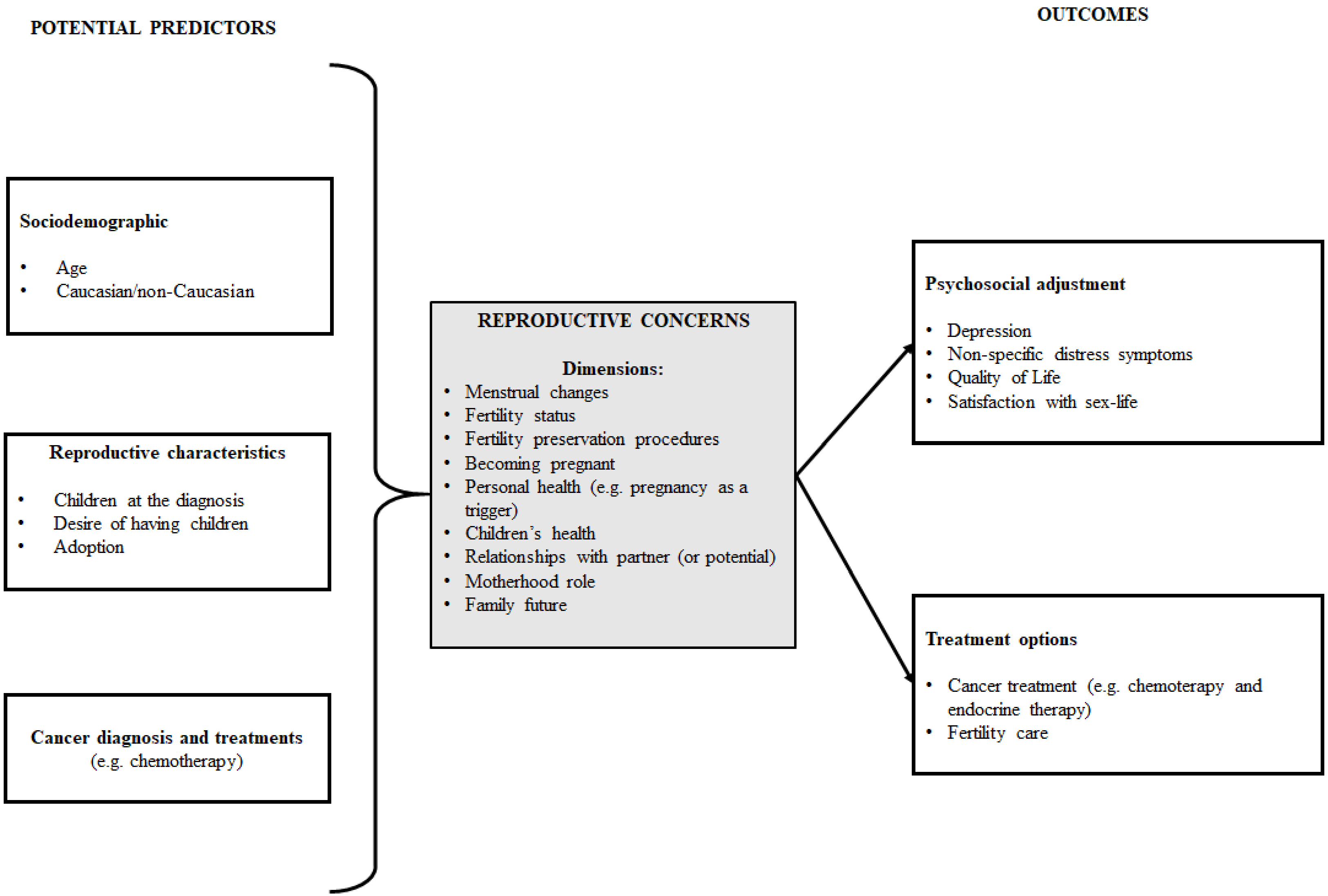

Figure 2. Conceptual framework to understand factors associated with reproductive concerns of female cancer patients in reproductive-age at enrolment (aged 17-49 years). *Note:* This framework is based on previous studies included in this overview. Dimensions of reproductive concerns are shown in the figure.

Conclusion

To the best of our knowledge, this is the first review exclusively focused on the subjective perceptions of reproductive concerns among younger women diagnosed with cancer, synthesizing simultaneously their potential predictors and outcomes. Reproductive health concerns emerged as a potential target for intervention with young women both in the active phase of the disease and during survival. Our findings suggest that some socio-demographic and reproductive characteristics and cancer-related factors affect the concerns experienced and should be considered in care provision (see Figure 2). Additionally, these concerns seem to be a potential predictor of certain maladjustment outcomes and have influenced decisions regarding oncological treatments and use of FC. The results of this study may encourage medical staff, and more specifically nurses, to make early assessment of, explore, and address reproductive concerns by recognizing their risk factors and consequences for younger women.

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STUDY 2

The European Portuguese version of the Reproductive Concerns After Cancer Scale (RCACS): A psychometric validation for young adult female cancer survivors

Publication

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Highlights

- Evidence suggest that young women diagnosed with cancer report reproduction-related concerns.
- The Reproductive Concerns After Cancer Scale (RCACS) is a reliable and valid self-report measure.
- Results from the Portuguese version of RCACS demonstrated a five-factor structure.
- An early identification of concerns may reduce the marginalization of patients.

Abstract

Purpose: The purpose of this study was to evaluate the psychometric properties of the Portuguese version of the 18-item Reproductive Concerns After Cancer Scale (RCACS) among young adult female cancer survivors.

Methods: The psychometric validation was conducted based on a convenience sample of 192 cancer survivors aged between 18 to 40 years. An exploratory factor analysis (EFA) was used to test the factor structure of the Portuguese version of RCACS and reliabilities were examined. Convergent and discriminant validity was also used to assess the construct validity. The Hospital Anxiety and Depression Scale (HADS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORT QLQ-C30) and the need for parenthood and rejection of child-free lifestyle subscales of the Fertility Problem Inventory (FPI) were used as convergent measures.

Results: A five-factor model was obtained with acceptable fit indexes and internal consistencies ($.72<\alpha<.89$): (1) fertility potential, (2) children's health risk and future life, (3) partner disclosure, (4) barriers to getting pregnant/having children and (5) acceptance. Overall, convergent and discriminant validities were confirmed. Levels of anxiety and depression symptoms as well as health-related quality of life (QoL) had weak-to-moderate associations with reproductive concerns. Women who had a child or did not want a biological child were less concerned.

Conclusion: This scale proved to be a reliable and valid measure of reproductive concerns for the Portuguese population with potential relevance for application in clinical practice.

Keywords: motherhood, psycho-oncology, reproduction, women, younger.

Introduction

Anticancer treatments can cause fertility loss, threatening biological motherhood. In women under 40 years of age, exposition of the ovaries to alkylating chemotherapy or radiotherapy to the pelvis and abdomen or cranial and total body irradiation induce gonadotoxicity (Salama and Woodruff, 2017). More specifically, women with hormone receptor-positive breast cancer undergoing prolonged adjuvant hormonal therapy to reduce recurrence and mortality (Davies et al., 2013) have an increased risk of infertility with the induced aging of the reproductive system. This unwanted side effect can be distressing to the youngest survivors who have unfinished family building projects. Some of these women are faced with the fear of losing their motherhood dreams and their feminine identity (Assi et al., 2018).

Research has identified several concerns in women who have been diagnosed with cancer in reproductive age, which go beyond the ability to conceive. They report concerns related with a possible transmission of cancer risk to the child, malformations in the child, cancer recurrence after a potential pregnancy, complications during pregnancy (Sobota and Ozakinci, 2014), child-rearing responsibilities and future in the potential absence of the maternal figure (Coyne and Borbasi, 2008) and disclosure of infertility as a side effect of cancer in romantic relationships (Murphy et al., 2015). Consequently, these concerns seem to impair the psychosocial adjustment of young women (Benedict et al., 2018; Gorman et al., 2010; 2015) and, in some cases, lead to the refusal to initiate or discontinuation of cancer therapies (Llarena et al., 2015; Villarreal-Graza et al., 2017).

To our knowledge, in Portugal, there are no validated scales to assess the subjective perception of reproductive concerns after cancer among young adult female cancer survivors. However, epidemiological data estimated that there were approximately 96 new cases of cancer per 100.000 Portuguese young adult females (20-39 years) in 2018, being the European country with the 12th highest incidence rate in this age range (Ferlay et al., 2019).

Despite international guidelines recommending fertility counseling for these young women (e.g. Oktay et al., 2018; National Comprehensive Cancer Network, 2019), barriers to discussing these issues with patients are still identified by Portuguese oncologists, namely related to lack of time, communication skills and patient-related characteristics (e.g. prognostic, status of marital relationship, high probability of fertility not being affected) (Melo, Fonseca, Silva, Almeida-Santos, & Canavarro, 2018). Thus, the needs of patients worried about their reproductive future may be neglected. For this reason, early identification of reproductive concerns through a reliable measure is a significant step towards being able to provide appropriate counseling and reducing the marginalization of patients in this country.

Overall, few scales identify the fertility and parenthood concerns of young women in reproductive age. Three measures have been most commonly used in the literature to assess reproductive concerns, these being the Reproductive Concerns Scale [RCS] (Wenzel et al., 2005), the Reproductive Concerns After Cancer Scale [RCACS] (Gorman et al., 2014; 2019) and items adapted from the Fertility Issues Survey (Partridge et al., 2004).

The Reproductive Concerns After Cancer Scale (RCACS) seems to be one of the most promising self-report instruments to evaluate these specific concerns, incorporating multiple dimensions such as fertility, pregnancy, children’s health, disclosure and acceptance. This scale was originally developed in English (Gorman et al., 2014) and has been translated and adapted to Mandarin (Qiao et al., 2016) and Swedish (Ljungman et al., 2018). The validation studies of the English and Chinese versions including large samples of young women diagnosed with cancer for at least one year showed strong psychometric qualities (Gorman et al., 2014; Qiao et al., 2016).

Therefore, the aim of this study was to evaluate the psychometric properties of the European Portuguese version of the RCACS among young adult females. The factor structure and internal consistency of this version were explored considering cultural differences. Furthermore, the relationship between the RCACS and theoretically related constructs was examined to determine the convergent validity of the measure, and discriminant validity was also investigated.

Methods

Participants

Young female cancer survivors aged between 18 and 40 who had been diagnosed at least one year prior to participation in the study, without a cognitive and physical inability to independently reply to the self-report measures, were eligible. Cancer survivors were excluded if they were currently pregnant or did not read and understand European Portuguese. Following these criteria, a total of 192 participants were recruited.

Procedure

Paper-and-pencil questionnaires and interviewing was the main data-collection method adopted in this study. A convenience sample of young women was recruited from the Gynecology and Obstetrics Department of Centro Hospitalar de São João, Porto, the Breast Clinic of Instituto Português de Oncologia Francisco Gentil in Porto and the Gynecology Department of the Instituto Português de Oncologia Francisco Gentil in Coimbra, between October 2017 and July 2018. This study has been carried out in accordance with Declaration of Helsinki and informed consent was obtained from all participants. The entire protocol was also available via the online server of the University of Aveiro to increase the sample size since there is extensive evidence that the two forms of collection are equivalent (Gwaltney et al., 2008). The link to the survey was disseminated through newsletters, mailing lists and social networks. Of the 192 young women included, 144 participants completed the paper version of the questionnaire and 48 participants completed the online questionnaire.

Instruments

Socio-demographic and clinical questionnaire

A questionnaire assessing sociodemographic and clinical variables was administered. The patient’s age, marital status, level of education and employment status were assessed. Participants’ medical situation questions included variables such as cancer type, age at diagnosis, disease duration and previous treatments. Their reproductive history was also assessed, including the number of children, the desire to have more children, previous miscarriage and previous fertility care.

18-item Reproductive Concerns After Cancer Scale (RCACS)

The RCACS is a self-report measure that contains 18 items assessing the fertility and parenthood concerns of young adult female cancer survivors. The original version of this scale (Gorman et al., 2014) measures six dimensions of reproductive concerns: fertility potential, partner disclosure, child’s health, personal health, acceptance and becoming pregnant. For each item, participants are asked to indicate their level of agreement with each statement using a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). A mean score can be calculated for each dimension and total scores range from 18 to 90 points, with higher scores representing a higher level of concern. The English version of the RCACS has shown good reliability among samples of female survivors who were 18 to 35 years [alpha coefficient, $.78 \leq \alpha \leq .91$] (Gorman et al., 2014) and younger than age 45 [omega coefficient, $.66 \leq \Omega \leq .87$] (Gorman et al., 2019). The process of translation into European Portuguese was coordinated by the Quality of Life Office at the International Breast Cancer Study Group (IBCSG) involving the forward (English - Portuguese) and backward (Portuguese – English) technique and proof reading by three different translation agencies (see Figure 1).

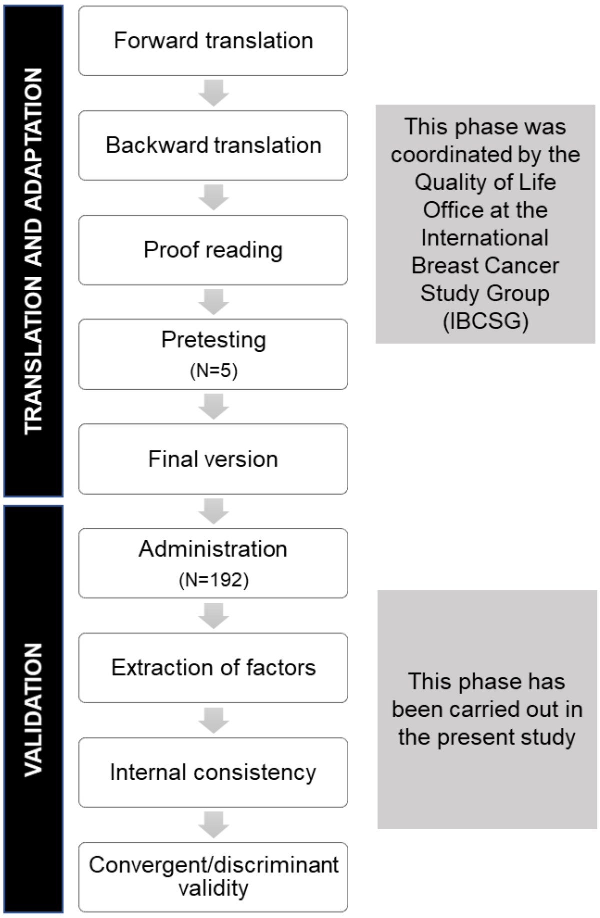

Figure 1. An overview of the phases and steps of cross-cultural adaptation and validation of the European Portuguese version of the Reproductive Concerns After Cancer Scale (RCACS).

The final version was pre-tested with five breast cancer patients at the Cancer Center in Lisbon (Fundação D. Anna Sommer Champalimaud & Dr. Carlos Montez Champalimaud Centro de Investigação da Fundação Champalimaud). The version provided by the IBCSG was used in a previous study (Pagani et al., 2019). In the present study, we examined its psychometric properties.

Comparative measures

The14-item Hospital Anxiety and Depression Scale (HADS) was used to assess the severity of anxiety and depression symptoms among cancer survivors [Portuguese version by Pais-Ribeiro et al. (2007)]. It is composed of two subscales including seven items evaluating anxiety (HADS-A) and seven items evaluating depression (HADS-D). Participants respond using a 4-point Likert scale and each domain obtains a total score ranging from 0 to 21. Higher scores indicate a higher level of anxiety or depressive symptoms. We found good reliability in this sample ($\alpha_{\text{HADS-A}} = .88$, $\alpha_{\text{HADS-D}} = .85$).

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30) [validated by Pais-Ribeiro et al. (2008)] is a thirty-item tool developed to assess health-related quality of life (QoL). This scale includes five functional scales, a global health status/QoL scale, three symptom scales and single-item measures. Participants are invited to respond using a 4-point Likert scale ranging from "not at all" to "very much". In this study, we only used the functional scales assessing physical, role, emotional, cognitive and social functioning and global health status/QoL scale. The scores for each subscale range from 0 to 100, with higher scores indicating better functioning of young adult female cancer survivors. Alpha coefficients were good in this sample ($.72 \leq \alpha \leq .92$).

Two subscales of the Portuguese version of the Fertility Problem Inventory (FPI; Moura-Ramos et al., 2012), associated with representations of the importance of parenthood, were also used as comparative measures. The need for parenthood subscale assesses the perception of parenthood as a main goal in life. In turn, the rejection of a child-free lifestyle subscale assesses the negative view of life without a child and how happiness can depend on it (Moura-Ramos et al., 2012). Participants are asked to rate how much they agree/disagree with each statement on a 6-point Likert scale, ranging from "Strongly disagree” to “Strongly agree”. Both subscales showed good reliability (α=82, α=.83) for the need for parenthood and child-free lifestyle subscales, respectively.

Statistical analysis

Statistical analysis was performed with Statistical Package for Social Sciences, version 24 (SPSS Inc., Chicago) and MPlus, version 6.12 (Muthén & Muthén, Los Angeles, USA). The characteristics of the young adult female cancer survivors were analyzed using descriptive statistics. We used an exploratory factor analysis (EFA) based on cultural and language differences. Furthermore, only two studies confirmed the original factor structure of the RCACS (Gorman et al., 2019; Qiao et al., 2016) and the most recent study showed that the six-factor model did not fit well statistically (Gorman et al., 2019). Given the ordinal nature of the RCACS, an EFA using weighted least squares with the mean and variance adjustment (WLSMV) estimator was conducted through MPlus (DiStefano and Morgan, 2014). This EFA approach allowed us to test the fit of alternative factor models. Based on the structure observed in the studies of Gorman et al. (2014; 2019), the upper limit of the number of factors to be extracted was six. We used oblique rotation (Oblimin) allowing correlations between factors. The scree-plot and the eigenvalues one were the criteria used to identify the maximum number of factors to retain. Items that loaded above .4 on one of the factors were considered. The chi-square test (χ^2), the root mean square error of approximation (RMSEA) and the Comparative fit index (CFI) evaluated the model’s fit. An acceptable-fit model via an EFA should present a non-significant χ^2, RMSEA≤.08 and CFI>.90 (Kline, 2005). According to Nunnally (1978), one rule of thumb regarding sample size to perform an EFA is that the subject to item ratio should be at least 10 to 1. Based on this, the achieved sample size was enough to ensure stability of a factor solution. The internal consistency of the RCACS total scale and its factors was calculated using the Cronbach alpha coefficient. Values between .70 and .95 were considered acceptable (Terwee et al., 2007). For all statistical tests, the alpha level was 5% (two-tailed).

Construct validity: Hypotheses

Convergent validity was evaluated by examining Spearman’s rank correlations between the RCACS and other validated scales. Following the guidelines presented by Ratner (2009), the correlations were classified as weak (0-0.3), moderate (0.3-0.7) and strong (>0.7-1.0). Based on previous literature, it was hypothesized that there would be positive associations between the subjective perception of reproductive concerns and depression and anxiety symptoms (Cândido et al., 2016; Gorman et al., 2010; 2015) and a weak-to-moderate negative correlation between these specific concerns and QoL (Benedict et al., 2018). These constructs were represented by measures such as HADS and EORTC QLQ-C30. We also hypothesized that the need for parenthood and the rejection of a child-free lifestyle measured by FPI subscales were conceptually distinct constructs, but correlated positively with the reproductive concerns reported by young women. Mann-Whitney nonparametric tests were also performed to assess differences in RCACS scores across groups. The predictions to identify discriminant validity were based on previous research. Thus, we hypothesized that participants aged <35 years (Ruddy et al., 2014) and who had self-reported a greater desire to have (more) biological children (Ljungman et al., 2018; Ruddy et al., 2011, Villarreal-Garza et al., 2017) would have higher rates of reproductive concerns. Additionally, childless women would also have higher concerns related to partners (or potential partners) and the ability to conceive (Corney and Swinglehurst, 2014; Dryden et al., 2014). Based on the original validation study (Gorman et al., 2014), comparisons were made between young women married or living in cohabitation with those who were not, hypothesizing that the former would have lower mean scores in the global scale.

Results

Sample characteristics

Cancer survivors were 18 to 40 years-old and mean age was 35.92 years (SD=3.96). Most participants were married/cohabiting (70.3%), had a university degree (51.5%) and were employed (86.9%). The most frequently reported diagnosis was breast cancer (81.3%) and mean age at cancer diagnosis was 32.20 (SD=4.80) years. More than 80% of participants had received chemotherapy and 60.4% were still undergoing treatment, namely endocrine adjuvant therapy. At the time of participating, 30% of the young women were being followed by a psychologist or psychiatrist. Concerning their reproductive history, about 57.8% of the young women had one or more children. The majority (83.3%) had received information about implications of the oncological treatments on fertility and 17.2% had previously undergone fertility care, for example, oocyte cryopreservation and oophoropexy. Among young adult female cancer survivors, 12.5% had had a previous miscarriage and more than 50% of participants wanted to have a (or another) biological child. The socio-demographic and clinical characteristics are presented in Table 1.

Table 1. Socio-demographic and clinical characteristics of the young female cancer survivors (n=192).

Characteristic	**N**	**%**
Age in years (M±SD, range)	35.92±3.96, 18-40	
Marital status		
Married/cohabiting	135	70.3
Single	42	21.9
Divorced/separated	15	7.8
Education		
Primary school	3	1.6
Middle school	32	16.7
High school	58	30.2
University	99	51.5
Employment status		
Employed/Self-employed	167	86.9
Unemployed	16	8.3
Student	4	2.1
Disability pension	4	2.1
Number of children		
No children	81	42.2
1 child or more	111	57.8

Table 1. (continued)

Characteristic	**N**	**%**
Cancer type		
Breast cancer	156	81.3
Cervical cancer	6	3.1
Ovarian cancer	12	6.3
Endometrial cancer	1	.5
Leukemia	4	2.1
Hodgkin lymphoma	4	2.1
Non-hodgkin lymphoma	2	1.0
Thyroid	4	2.1
Sarcoma	3	1.5
Time since initial diagnosis in months (M±SD, range)	45.50±30.75, 12-180	
Age at diagnosis in years (M±SD, range)	32.20±4.80, 9-40	
Cancer treatment		
Chemotherapy	159	82.8
Radiotherapy	135	70.3
Current stage of the cancer treatment		
Undergoing treatment	116	60.4
Follow-up	75	39.1
Use of mental health services		
Yes	30	15.6
No	162	84.4
Previous miscarriage		
Yes	24	12.5
No	166	86.5
Information about fertility-related implications		
Yes	160	83.3
No	32	16.7
Previous fertility care		
Yes	33	17.2
No	156	81.3
Wants a (or another) biological child		
Yes	99	51.6
No	86	44.8

Factor validity

According to the scree-plot, a factor structure including a maximum of five factors was suggested. Examining the fit measures, the 5-factor solution, conceptually justified, presented an acceptable fit (RMSEA=.07, 90% CI [.05, .09]; CFI=.98). A significant χ^2 was found, but due to the large sample size this test may be misleading [$\chi^2(73)=143.82$, $p<.001$] (Ulman and Bentler, 2003). There were no items with negative residual variance. The factor-item loadings ranged from .511 to .970. The original six-factor model was not found, but two dimensions were replicated in our data, namely *partner disclosure of fertility status* (factor 3, 3 items; M=2.25; SD=1.13) and *acceptance* (factor 5, 3 items; M=2.49; SD=.98). Factor 1 observed in the new structure involved four items assessing concerns related to the ability/desire to have (more) children and getting pregnant (M=2.79, SD=1.13). Factor 2 included items related to children's health risk and future life (4 items; M=3.97; SD=1.07). Factor 4 contained four items relating to concerns about implications/barriers to getting pregnant or having children for one's own health and future (4 items; M=2.86, SD=.98). Table 2 presents mean scores for each item and factor loadings.

Table 2. Items' mean scores, factor loadings and reliability of the identified factors of the RCACS.

		Fertility potential	Children's health risk and future life	Partner Disclosure	Barriers to getting pregnant/ having children	Acceptance
Item No.	M±SD	Factor 1 **(α=.873)**	Factor 2 **(α=.857)**	Factor 3 **(α=.888)**	Factor 4 **(α=.732)**	Factor 5 **(α=.718)**
1	3.19±1.40	**.847**	.066	.009	.014	-.132
2	3.81±1.36	.075	**.850**	-.006	-.077	-.098
3	2.39±1.30	.078	.003	**.773**	.086	.008
4	4.23±1.11	.024	**.695**	-.125	.261	-.118
5	2.37±1.18	-.010	.019	.008	-.024	**.727**
6	2.42±1.26	**.647**	-.023	.087	.040	.149
7	2.22±1.26	.104	.028	**.845**	-.062	-.088
8	2.69±1.33	**.893**	-.067	-.014	.039	.086

Table 2. (continued)

		Fertility potential	Children's health risk and future life	Partner Disclosure	Barriers to getting pregnant/ having children	Acceptance
Item No.	M±SD	Factor 1 **(α=.873)**	Factor 2 **(α=.857)**	Factor 3 **(α=.888)**	Factor 4 **(α=.732)**	Factor 5 **(α=.718)**
9	3.81±1.34	-.074	**.869**	.122	.051	.205
10	2.24±1.20	.094	-.011	.042	-.018	**.569**
11	3.04±1.38	.014	.076	.088	**.649**	-.155
12	2.72±1.32	-.088	-.093	.145	**.676**	-.036
13	3.08±1.36	.088	.292	-.098	**.629**	-.055
14	2.54±1.21	.198	-.101	.080	**.618**	.166
15	2.87±1.30	.280	.145	.028	-.108	**.511**
16	2.13±1.19	-.043	.019	**.970**	.037	.049
17	2.84±1.35	**.806**	-.016	.122	-.028	.024
18	4.02±1.27	-.038	**.918**	.003	-.041	-.007

Internal consistency

The total scale presented a Cronbach alpha coefficient of .84, indicating good internal consistency of the measure. Most of the item-to-total scale correlations were above .40. Even when we delete an item the alpha coefficient remained good (>.80) (see Table 2). Cronbach alpha coefficients for each of the five factors were acceptable, ranging from .72 to .89.

Convergent validity

As expected, the RCACS total scores were positively associated with anxiety and depressive symptoms and negatively associated with QoL sub-dimensions, except for role functioning. The need for parenthood was the variable most strongly associated with the RCACS index and, more specifically, with dimensions such as fertility potential, partner disclosure and acceptance. Lower acceptance of the fertility status was moderately correlated with higher scores in the rejection of a child-free lifestyle subscale. The children’s health risk and future life domain presented weak-to-moderate correlations with all the other scales. Higher concerns related to the barriers to getting pregnant/having children were more strongly associated with higher anxiety symptoms, but were not associated with representations about the importance of parenthood (see Table 3).

Discriminant validity

Overall, participants who had not yet had children or who wanted to have a (another) biological child presented significantly higher RCACS total scores, compared to their counterparts who did not want (more) children. Concerning the domains of this scale, differences in scores across groups considering sociodemographic characteristics were also found. Women under the age of 35 had significantly higher mean levels of concerns related with fertility potential and lower acceptance compared to older women. We observed lower scores in the partner disclosure dimension for young women who were married or lived in cohabitation than for those who were not. However, these women reported higher concerns with potential fertility and children’s health risk and future life. As hypothesized, childless women presented higher scores in dimensions such as fertility potential, partner disclosure and acceptance of fertility status than women who already had children. Table 4 shows that discriminant validity was obtained.

Table 3. Convergent validity: correlations between subjective perception of reproductive concerns (RCACS) and distress (HADS-D and HADS-A), Quality of Life sub-dimensions and representations about the importance of parenthood.

Factor	HADS-D	HADS-A	PF	RF	EF	CF	SF	Global health status/QoL	Need for parenthood	Rejection of child-free lifestyle
Fertility potential	.089	.033	.037	-.070	-.064	-.078	-.040	.090	.411***	.192**
Children's health risk and future life	.287***	.352***	-.358***	-.219**	-.292***	-.272***	-.319***	.235**	.266***	.283***
Partner Disclosure	.153*	.125	-.001	.056	-.066	-.005	-.070	.037	.301***	.207**
Barriers to getting pregnant/ having children	.191**	.289***	-.199**	-.092	-.201**	-.081	-.227**	.087	-.017	-.002
Acceptance	.257***	.176*	-.024	-.088	-.129	-.161*	-.092	.138	.453***	.347***
RCACS total score	.255***	.280***	-.162**	-.121	-.229**	-.158*	-.241***	.187*	.416***	.265***

Note: HADS-D = Depression; HADS-A = Anxiety; PF = Physical functioning; RF= Role functioning; EF= Emotional functioning; CF= Cognitive functioning; SF= Social functioning; *** p<.001; **p<.01; * p<.05.

Table 4. Discriminant validity: differences in RCACS scores across groups using the Mann-Whitney test.

	Fertility potential			**Children's health risk and future life**			**Partner Disclosure**			**Barriers to getting pregnant/ having children**			**Acceptance**			**RCACS total score**		
	M	**SD**	**Statistic**	**M**	**SD**	**Statistic**	**M**	**SD**	**Statistic**	**M**	**SD**	**Statistic**	**M**	**SD**	**Statistic**	**M**	**SD**	**Statistic**
Age																		
<35 years	**3.13**	1.04	2743**	3.86	1.03	3335	2.48	1.21	3209	2.75	1.04	3392	**2.73**	1.07	2829***	55.33	11.39	2831.5
≥35 years	2.65	1.15		4.01	1.08		2.15	1.08		2.88	.96		2.40	.93		51.69	11.97	
Married/ cohabiting																		
Yes	2.73	1.12	3367.5	**4.09**	1.03	3008.5*	2.01	.99	2461.5***	2.86	1.01	3627.5	2.44	.95	3209.5	52.04	13.30	3044
No	2.92	1.16		3.69	1.12		**2.80**	1.24		2.82	.93		2.62	1.05		54.37	13.30	
Already having children																		
Yes	2.47	1.03	2739.5***	**4.27**	.87	2849***	1.93	.85	3088.5***	2.84	1.01	4310	2.35	.90	3342*	51.13	10.05	3297.5*
No	**3.21**	1.14		3.56	1.17		**2.67**	1.32		2.86	.95		**2.69**	1.06		**54.91**	13.78	
Desire to have children																		
Yes	**3.36**	.93	1453***	4.05	.96	4126	**2.53**	1.15	2881.5***	2.91	.91	3694.5	**2.77**	.91	2414***	**57.30**	10.24	1852.5***
No	2.10	.94		3.91	1.15		1.91	.98		2.74	1.05		2.18	.99		47.08	10.57	

Note: M=Mean; SD=Standard deviation; *** p<.001; **p<.001; * p<.05.

Discussion

In this study we performed the validation study of the European Portuguese version of the RCACS by allowing the availability of the measure to assess the reproductive concerns of young adult female cancer survivors in a multifactorial perspective.

Contrary to expectations, the EFA of the scale data did not reveal the six-factor model confirmed by the English and Chinese versions (Gorman et al., 2019; Qiao et al., 2016). All items remained, but a different structure consisting of only five factors was obtained: (i) fertility potential, (ii) children’s health risk and future life, (iii) partner disclosure, (iv) barriers to getting pregnant/having children and (v) acceptance. The dimensions related with disclosure and acceptance of the fertility status were composed of the same items as the original framework. However, the personal health and becoming pregnant domains of the American English version were not replicated here (Gorman et al. 2014). The items included in those subscales loaded on three different factors. Item 6 loaded on the fertility potential dimension being also related with ability to conceive. Item 4 loaded on the children’s health risk and future life dimension that goes beyond health issues to involve concerns about the future of children also reported in the literature (Coyne and Borbasi, 2008). Lastly, items 11, 12, 13 and 14 loaded on the independent factor. This factor grouped concerns about how getting pregnant / having children can be a trigger for cancer recurrence, anxiety and routine changes. Based on these results, concerns related with barriers to motherhood showed to aggregate into a single dimension of the measure.

The acceptable fit indexes and loadings (>.50) show that all items measuring the factors support the five-factor model. The meaning and interpretation of the RCACS items are relevant aspects for the construction of the measure. There may have been some nuances in the participants' interpretation and response due to cultural and language differences that explain the new factorial structure found in our data. Overall, young adult women included in this validation study showed similarities in terms of sociodemographic characteristics compared to samples used in other studies that confirmed the original factor structure. Nevertheless, breast and gynecologic cancers accounted for the majority of cases differing from the recent study by Gorman et al. (2019) involving mostly women diagnosed with breast cancer and lymphoma. The mean time since diagnosed cancer was four years. In turn, the Chinese version (Qiao et al., 2016) validation study included a sample, on average, diagnosed no more than two years ago. These and other clinical features can also contribute to differences in the results. In this regard, future work should (re) examine the fit of the RCACS factorial model and its invariance considering the two alternative solutions.

Cronbach alpha coefficients between .72 and .89 for the domains obtained revealed that the Portuguese version presented good internal consistency among young adult female cancer survivors. The coefficient of .84 for the entire scale was similar to that reported for the English version (Gorman et al., 2014) and higher than the Mandarin one (Qiao et al., 2016).

Similar to the other versions of the RCACS, evidence of convergent validity was confirmed by correlations of this scale with theoretically related constructs such as anxiety and depressive symptoms (Cândido et al., 2016; Gorman et al., 2010; 2015), QoL (Benedict et al., 2018) and representations of the importance of parenthood, as hypothesized. Among them, the need for parenthood subscale involving items related to the desire to be a mother was the variable showing the strongest associations with recalled reproductive concerns. This finding is consistent with previous studies that identified the wish for children as a positive predictor of these concerns (Villarreal-Graza et al., 2017). We also highlight that the children's health risk and future life domain of the RCACS had significant correlations with all other external scales. This result suggests that these specific concerns have an impact on the psychological adjustment and functionality of the participants, in line with the literature presenting the child's health concerns as a primary emotional barrier to biological motherhood (Gorman et al., 2012).

In terms of discriminant validity, our hypotheses were partially supported. Young women who had children and who did not wish to have biological children in the future had lower RCACS total scores than their counterparts who had not yet had children and who wanted to have a (another) child, confirming previous findings (Ljungman et al., 2018; Ruddy et al., 2011; 2014; Villarreal-Graza et al., 2017). Additionally, it was possible to distinguish specific concerns among women who wanted and did not want to have (other) children. Women who did not report a desire to have a (another) biological child were less worried about potential fertility and disclosure issues, but had similar scores regarding concerns related to children's health risk and future life and barriers to getting pregnant/having children. Also, according to our predictions, childless women presented higher concerns about their fertility status and disclosure to their partners. Research had suggested these women felt that uncertainty about their fertility made future planning difficult (Corney and Swinglehurst, 2014) and, in some cases, they report fear of rejection by partners (Dryden et al., 2014).

In turn, differences between the groups of married or cohabiting survivors and those who were not were replicated at the global scale level. However, women who were not married or in a committed relationship presented higher scores in the partner disclosure dimension. This is not surprising since the disclosure of cancer history and the potential loss of fertility can be particularly difficult for young women who do not yet have a marital relationship but imagine having a partner in the future or who have not yet made the decision to form a family as a couple. Living with the partner in same household can also allow their greater involvement during the diagnosis and treatment process, minimizing the barriers to discussing the fertility status. Furthermore, younger women (< 35 years old) reported higher concerns related with fertility, as previously shown (Ruddy et al., 2014), and lower acceptance of the potential infertility status, but differences were not found for other subscales. Qualitative data had already shown that women in their 30s felt the time to start a family was running out, reporting pressure to find a partner and try to have a child (Corney and Swinglehurst, 2014).

Despite the encouraging findings, this study reveals limitations that should be noted. First, the homogeneity of the cancer type; the majority of the participants (81.3%) had breast cancer while the instrument has been developed for samples with diverse characteristics including different cancer types. Second, there was no assessment of the reproducibility/repeatability as in the Chinese version (Qiao et al., 2016). Third, the infertility risk depends on multiple factors but differences in reproduction-related concerns according to cancer type, surgery type and therapies with high or lower risk could not be determined. Further studies should consider these characteristics to investigate discriminant validity, as suggested by Gorman et al. (2014). However, strengths should also be pointed out. This study involved participants from the north, south and center of Portugal, including women with and without the desire for biological motherhood.

Conclusion

This study contributes to a growing body of evidence about the psychometric properties of the RCACS, which has only been translated and validated for two countries. Our results suggest that the European Portuguese version of the RCACS scale seems to be a reliable and valid measure to assess the multiple dimensions of reproductive concerns among young adult female cancer survivors. However, a new five-factor structure has been proposed, which may provide relevant implications for future research. A return to examining the dimensional structure of the RCACS is instigated. Furthermore, to our knowledge, this is the first validated measure to assess reproductive concerns in Portugal. Therefore, using this measure in clinical practice may contribute to reducing counseling inequalities by facilitating appropriate assessment and discussion of patient concerns. The RCACS is simple to administer and can be used in routine appointments to assess younger women.

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STUDY 3

Depression and health-related quality of life among young adult breast cancer patients: The mediating role of reproductive concerns

Publication

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Bártolo, A., Santos, I.M., Valério, E., Raposo, S., & Monteiro, S. (2019). Reproductive concerns in young women undergoing adjuvant endocrine therapy for breast cancer. Poster presented at the National Science Summit, Lisbon, Portugal.

Abstract

Biological motherhood plays an important role in the lives of many young women facing breast cancer and threats to reproduction may be disruptive. In this study, we explored the indirect effects of the importance of parenthood and childlessness on depression and health-related quality of life (HRQoL) among cancer patients aged 18-40 years (n=104) through reported reproductive concerns. These specific concerns fully mediated the relationship between the importance of parenthood in women's lives and HRQoL. Greater importance of parenthood was directly associated with higher depression symptoms. Interventions should address the reproductive needs and concerns of patients to improve their HRQoL.

Keywords: parenthood, women, childless, distress, oncology, younger.

Introduction

Current estimates indicate that breast cancer in young adult women (20-39 years) has incidence rates in European countries ranging from 12.6/100.000 to 41.0/100.000, for Moldova and Italy, respectively[1]. This malignancy is known to influence the reproductive ability through cytotoxic effects of chemotherapy and radiotherapy treatments. Most chemotherapeutic regimes used in breast cancer treatments can induce the damage of germinal tissue in the gonads and lead to premature ovarian failure[2]. The aging of the reproductive system is another factor affecting the ovarian reserve of those who are nearer to the latter end of young adulthood, when anticancer treatments are completed (e.g. prolonged adjuvant hormonal therapy[3]). Therefore, the desire for biological motherhood and potential lack of choice in family building projects may represent additional challenges in the course of the disease.

Specific guidelines have been developed to improve fertility counseling, but some women still report limited conversations, which only focused on warnings not to become pregnant during chemotherapy[4], and report a lack of information regarding the early-menopause and infertility risk and options to assess and preserve their fertility[5]. Previous research has identified professional and organizational barriers to discussion of oncofertility care with cancer patients. Most professionals point to lack of time, awareness and knowledge as barriers to dealing with fertility issues and report disagreement between departments on who is responsible for discussing this topic[6]. Nevertheless, some patients have not yet completed their families at the time of diagnosis and desire to have children after treatment[7].

An unfulfilled desire for parenthood seemed to be associated with impaired mental health[8]. Distress caused by an interrupted desire for childbearing can persist even 5 to 10 years post-treatment[9]. Moreover, the wish for children in the future has been identified as a significant positive predictor of the reproductive concerns among women with breast cancer[9,10]. Menstrual changes, potential treatment-related fertility loss and fertility options have been consistently indicated as major concerns among younger women[11,12]. However, other issues related to their own health after a potential pregnancy and the genetic risk to their offspring also worry cancer patients[13]. These unique concerns reflect a serious problem, since they have been shown to increase the risk of depression[14,15] and a poorer quality of life[16].

Our aim was to provide a better understanding of the mechanisms involved in the maladjustment of young adult women faced with a reproduction-threatening disease. In general, although the desire for children and childlessness are a burden and a worrying factor, it is unclear how much the meaning of motherhood influences psychosocial outcomes among cancer patients. Thus, we explored the association between the representation of the importance of parenthood, fertility and parenthood concerns and depression and health-related quality of life (HRQoL). Furthermore, based on the emergent literature, we hypothesized that the relation between these variables is likely to be complex, that is, greater importance of parenthood in women's lives may be associated with higher depression symptoms and lower HRQoL through reproductive concerns.

Materials and Methods

Participants and Procedure

This cross-sectional study included breast cancer patients who were recruited from a hospital in the North of Portugal. Women aged 18 to 40 years, diagnosed over the age of 18 with early-stage breast cancer (≤ IIIA) who received chemotherapy were eligible to participate in the study. The researcher invited 170 patients to participate on the day of the medical appointment. Of these, 104 were included in this analysis. We excluded patients for the following reasons: having undergone hysterectomy, prophylactic oophorectomy or tubal ligation procedures, or being currently pregnant. The protocol for this research was approval by the Hospital Ethical Committee and participants gave their consent before enrolment. Sociodemographic and clinical information was assessed by standard questions.

Measures

Reproductive concerns. Fertility and parenthood concerns were assessed with the 18-item Reproductive Concerns After Cancer Scale (RCACS)[17]. The psychometrically validated Portuguese version of the scale presents five dimensions: fertility potential, children's health risk and future life, partner disclosure, barriers to getting pregnant/having children and acceptance of the fertility status[18]. For each item, participants are asked to rate how much they agree/disagree with each statement on a 5-point Likert-scale. The global index ranges from 18 to 90 with higher scores indicating higher levels of reproductive concerns. In this study, the Cronbach alpha coefficient was .836.

Importance of parenthood. Representations of the importance of parenthood were measured using two subscales of the Portuguese version of the Fertility Problem Inventory (FPI). Based on the approach proposed by Moura-Ramos and colleagues[19], the importance of parenthood global index was obtained from the need for parenthood and rejection of a childfree lifestyle subscales, involving questions related to perceiving parenthood as a main goal in life and the negative view of life without a child. Participants respond using a 6-point Likert scale from “Strongly disagree” to “Strongly agree”. A higher score represents greater importance of parenthood in women’s lives. The alpha coefficient was good in this sample (α=.859).

Depression. Depression symptoms were assessed through the depression subscale of the 14-item Hospital Anxiety and Depression Scale (HADS)[20]. This subscale is composed of seven items and participants are invited to respond using a 4-point Likert scale. The total score ranges from 0 to 21, with higher scores indicating a higher level of depressive symptoms. A Cronbach alpha of .847 was obtained in the present sample.

Health-related quality of life. The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30)[21] is a thirty-item questionnaire used to measure HRQoL, including five functional scales, a global health status/QoL scale, three symptom scales and single-item measures. In this study, only the functional scales assessing physical, role, emotional, cognitive and social functioning were used. Items are rated on a 4-point Likert scale ranging from “not at all” to “very much”. The scores range from 0 to 100, with higher scores indicating better functioning. Cronbach alpha coefficients were acceptable (ranging from .605 to .920 for cognitive and social functioning, respectively).

Statistical analysis

Data analysis was performed with IBM SPSS software, version 24 and IBM Amos software, version 24. Pearson's correlations were used to evaluate the bivariate relations between importance of parenthood, reproductive concerns and psychosocial aspects. The correlations were classified as weak (0-0.3), moderate (0.3-0.7) and strong (>0.7-1.0)[22]. In order to test the mediating effect of reproductive concerns, a path analysis was conducted using AMOS. The importance of parenthood was defined as an exogenous variable and depression and HRQoL as endogenous variables. Bootstrap procedures using 5000 samples were used to obtain the confidence intervals and significance of the indirect effects[23]. The bias-corrected 95% bootstrap confidence intervals that do not include zero determined a significant mediation effect. To assess overall model fit, the chi-square statistics (χ^2), comparative fit index (CFI), standardized root mean residual (SRMR) and root mean square error of approximation (RMSEA) were used. Non-significant χ^2 values and CFI equal to or greater than .95, SRMR value below .08 and RMSEA below .06 were required for a good-fitting model[24].

Results

Descriptive statistics: sociodemographic, clinical and reproductive characteristics and concerns

Participants had an average age of 36.61 years (SD=3.03). Of the 104 respondents, 71.2% were married or lived in a cohabitation relationship and more than 50% had received college education. Most participants had received radiotherapy and 67.3% were undergoing endocrine therapy. The mean length of survival was 36.14 months (SD= 24.51). Forty percent of the young women did not have a biological child and 43.3% reported they wanted a (another) child. At the time of enrolment in the study, 14 (13.5%) participants had a history of miscarriage or abortion. Ninety-two women (88.5%) had received information about the implications of diagnosis/treatments for fertility, but only 19.2% reported having undergone fertility preservation before treatment. Women presented higher mean scores for concerns related to children's health risk and future life

(M=3.90; SD=1.12) and to barriers to getting pregnant/having a child (M=2.76: SD=.95) compared to other concern RCACS dimensions. Based on the cut-off criteria defined by Gorman et al.[15], 35.6% of this sample presented moderate to high overall reproductive concerns. In addition, there is no relation between partnership status and reproduction-related concerns [*r*=-1.78, *p*=.071]. Sociodemographic, clinical and reproductive characteristics are presented in Table 1.

Table 1. Patient socio-demographic, clinical and reproductive characteristics (n=104).

Characteristics	**N**	**%**	**Mean**	**SD**
Age at enrolment, in years			36.61	3.03
Age at diagnosis, in years			33.44	4.23
Relationship status				
Married/cohabiting	74	71.2		
Single/other	30	28.8		
College educated				
Yes	54	51.9		
No	50	48.1		
Employment status				
Employed	89	85.6		
Unemployed	13	12.5		
Student	1	1.0		
Length of survival, in months			36.14	24.51
Cancer treatment				
Surgery	89	85.6		
Radiotherapy	78	75.0		
Endocrine Therapy	70	67.3		
History of miscarriages/abortions				
Yes	14	13.5		
No	89	85.6		
Number of biological children				
No children	42	40.4		
One child or more	62	59.6		

Table 1. (continued)

Characteristics	**N**	**%**	**Mean**	**SD**
Received information about fertility-related implications				
Yes	92	88.5		
No	12	11.5		
Underwent fertility care before treatment				
Yes	20	19.2		
No	83	79.8		
Wants a (or another) biological child				
Yes	45	43.3		
No	52	50.0		
Overall reproductive concerns				
Low[a]	67	64.4		
Moderate to High[b]	37	35.6		
Dimensions of concern				
Fertility potential			2.46	1.05
Children's health risk and future life			3.90	1.12
Partner disclosure			2.05	.98
Barriers to getting pregnant/having children			2.76	.95
Acceptance			2.31	.90

[a]Mean scores in the RCACS < 3; [b]Mean scores in the RCACS > 3 to 5.

Relationship between importance of parenthood, reproductive concerns and psychosocial outcomes

There was a moderate positive correlation between importance of parenthood and self-reported reproductive concerns. Reproduction-related concerns were also positively associated with depression symptoms and negatively associated with physical, emotional and social functioning. In turn, higher importance of parenthood was associated with higher levels of depression. Moderate negative correlations were found between depression and all functional scales of HRQoL (Table 2).

Table 2. Pearson correlations between importance of parenthood, reproductive concerns and psychosocial outcomes.

Variables	Mean±SD	1	2	3	4	5	6	7	8
1. Reproductive concerns	49.38±11.35	1							
2. Importance of parenthood	58.36±15.30	.419***	1						
3. Depression	3.42±3.42	.207*	.343***	1					
4. Physical functioning	82.58±14.54	-.228*	-0.043	-.546***	1				
5. Role functioning	82.37±20.88	-.110	0.013	-.341***	.523***	1			
6. Emotional functioning	71.37±26.34	-.193*	-0.137	-.486***	.381***	.267**	1		
7. Cognitive functioning	79.01±21.66	-.179	-0.034	-.432***	.508***	.450***	.547***	1	
8. Social functioning	78.37±26.57	-.255**	-.176	-.663***	.429***	.283**	.513***	.370***	1

Note. **p*<.05. ***p*<.01. ****p*<.001

Path analysis: the role of reproductive concerns

A path model examining the indirect effect of the importance of parenthood on depression and HRQoL through reproductive concerns was conducted as shown in Figure 1. The importance of parenthood, overall reproductive concerns and depression index were represented by single indicators. In turn, physical, emotional and social functioning were specified as indicators of a single latent variable (unobserved) designated HRQoL. Based on correlations analysis, cognitive and role functioning were not included in the model since these variables were unrelated to reproductive concerns. Direct paths were controlled and dependent errors were correlated. The fit indexes indicated the good fit of the model ($\chi^2_{(6)}$=5.83, *p*=.443; CFI =1.00, SRMR=.027, RMSEA=.000). As hypothesized, the effect of the importance of parenthood on HRQoL assessed through physical, emotional and social functioning was fully mediated by reproductive concerns [-.133 BC 95% CI -.274, -.034, *p*=.013], that is, greater importance of parenthood in women's lives was associated with increased reproductive concerns and, consequently, they reported a poorer quality of life. Additionally, there was a positive direct effect of the importance of parenthood on depression. However, no significant indirect effect was found in this relationship [.032 BC 95% CI -.050, .122, *p*=.349].

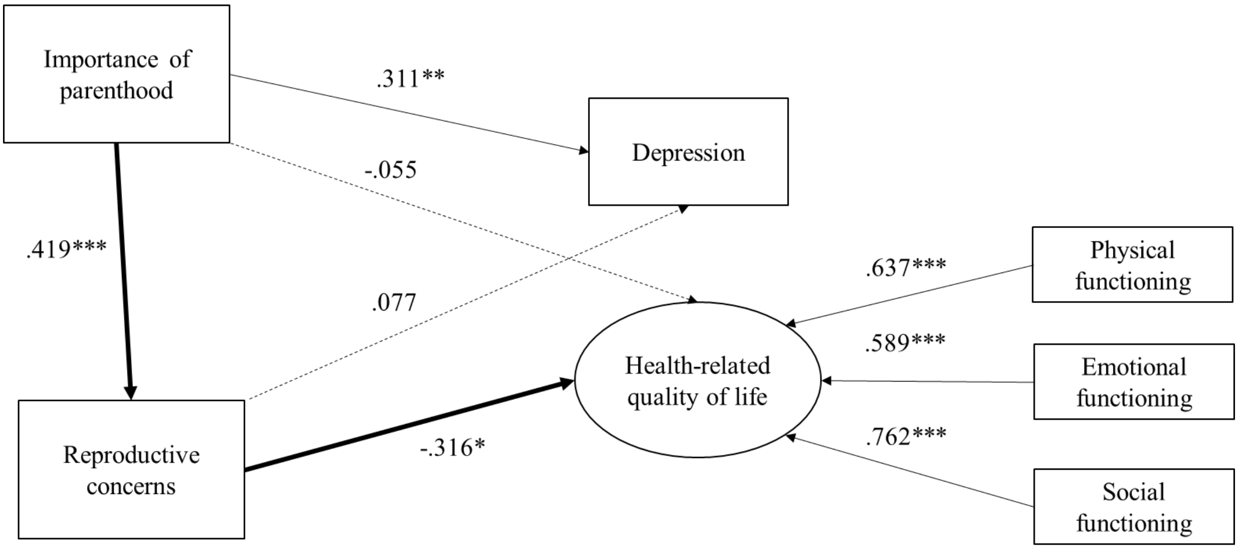

Figure 1. Path model examining the mediating role of reproductive concerns.

Note: ***p<.001; **p<.01; *p<.05; Thick lines illustrate the mediation effect.

Discussion

To our knowledge, this is the first study providing preliminary evidence about the indirect effect of the meaning of parenthood on breast cancer patients' HRQoL, through reproductive concerns. These findings demonstrate the need to improve HRQoL, namely the physical, emotional and social functioning of women who attach great importance to motherhood in their lives, by addressing reproductive concerns during health care provision.

In line with the results of Ljungman and collaborators[9], the most common areas of concern among these young adult women were children's health risk and future life and the barriers to getting pregnant/having a child, involving issues related to their own health and future. Therefore, in addition to discussions about the effects of exposure to gonadotoxic therapy on the reproductive potential, concerns about perceptions of genetic risk and pregnancy as a trigger to recurrence should be addressed. As suggested in recent research[25], it is important to clarify misconceptions and to address preimplantation genetic diagnosis as an option for patients with a heritable syndrome. More specifically, the literature has shown that women with *BRCA* mutation have unique concerns related to childbearing and feel pressure to make decisions about future motherhood[26]. Special attention should be given to these issues, even when there is no personal history of cancer yet, but a germline mutation is present.

Our data suggested that young adult with breast cancer who reported more need to start or complete their family and a more negative view of a childless life had a higher risk of experiencing depressive symptoms, regardless of their reproductive concerns. Although there is a gap in the literature regarding representations of the importance of parenthood and its impact on women with cancer, this direct effect is not completely surprising and similar results have been found in infertile women[27]. These women have to deal with the uncertainty about their reproductive capacity and potential interruption or discontinuation of their family building projects. Particularly, when biological motherhood is a major goal in life, young adult women may find it more difficult to adjust their expectations, with acceptance and reorganization of a childless future resulting in more emotional difficulties. Interrupted desired childbearing is recognized as a distress factor, and even long term survivors[6] and some breast cancer patients, in the case of a hormone-sensitive disease, discontinue endocrine therapy due to their desire for future fertility[28]. Based on this, it is imperative to fill the gaps in counselling about options to preserve fertility and alternative family-building options[5], decreasing psychological morbidity and increasing the empowerment of these young adult women in their decision-making processes.

The major contribution of this study is to show the psychosocial impact of the importance of parenthood on the life of women faced with a reproduction-threatening disease. This study provided a better understanding of the psychological mechanisms involved in responding to the challenges of an oncological disease at a reproductive age, highlighting the mediating role of reproductive concerns. Future research should include larger samples and prospective longitudinal studies replacing cross-sectional designs, which do not reveal the trajectory of the meaning of parenthood and childlessness and its direct and indirect impact on psychosocial outcomes. A mixed-methods approach incorporating the voices of young adult women may also help explain the results of our path analysis. Additionally, the length of survival and the use of fertility care should be considered in more complex pathway models.

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****Note:** Reference list formatted according to the National Library of Medicine (NLM) style based on Journal of Adolescent and Young Adult Oncology guidelines*

STUDY 4

Fertility under uncertainty: Exploring differences in fertility-related concerns and psychosocial aspects between breast cancer survivors and non-cancer infertile women

Publication

Bártolo, A., Santos, I., & Monteiro, S (in press b). Fertility under uncertainty: exploring differences in fertility-related concerns and psychosocial aspects between breast cancer survivors and non-cancer infertile women. *Breast Cancer*.
http://dx.doi.org/10.1007/s12282-020-01124-w
SCImago/Scopus© SJR 2019: 0.91/Q1; ISI JCR® Impact factor (2019): 2.695

Communications at scientific events

Neves, M., Carvalho, B., Bártolo, A., & Monteiro, S. (2020). Reproductive concerns in cancer survivors and infertile women. Oral communication presented at the 13th National Congress of Health Psychology, Covilhã, Portugal.

Abstract

Background: The threat to fertility due to anticancer treatments can be distressing to women who wish to complete their family. The current study assessed the fertility-related concerns, psychological distress and health-related quality of life (HRQoL) of breast cancer survivors in comparison to non-cancer women with infertility history and to healthy controls from the general population.

Methods: We surveyed young adult women aged 18 to 40 who wished to have a (or another) biological child. Participants completed self-report measures assessing fertility concerns, anxiety, depression and physical, emotional, role and social functioning. Group differences were assessed using multivariate comparisons as well as univariate tests and discriminant analysis for individual measures.

Results: A total of 136 women were recruited, of whom 43 were breast cancer survivors, 56 non-cancer infertile women and 37 healthy controls. Considering the female cancer survivors as the focus of the analysis, data suggested that these women presented identical concerns to the non-cancer infertile group and higher than the healthy women with regard to fertility potential ($p<0.01$). However, women diagnosed with cancer reported worse HRQoL than their counterparts, showing lower scores in physical functioning ($p<0.05$) than infertile women and lower role ($p<0.05$) and social HRQoL ($p<0.01$) than the controls. Anxiety and depressive symptoms did not differ between the three groups.

Conclusions: The results suggest that living with uncertainty about reproductive potential after cancer can be a disruptive experience. Breast cancer survivors and infertile women are at risk of future emotional maladjustments, given the reported level of fertility concern.

Keywords: oncology, reproductive concerns, infertility, women, uncertainty, quality of life.

Introduction

Despite advances in cancer diagnosis and treatment, the biology of breast tumors in young women requires multimodal care. These women present more aggressive subtypes, in more advanced stages, higher risk of carrying a hereditary allele and face varying demands related to the physical and mental side-effects of anticancer treatments [1-3]. This cancer type is currently the most incident cancer diagnosis among female adolescents and young adults worldwide (15-39 years: 15.2/100.000 [4]) registering a rapid increase during the third and fourth decades of life [2]. Living with breast cancer at a young age may disrupt the normal life-course and brings challenges related to menopause symptoms, contraception and potential loss of fertility [5-7].

Adverse effects of anticancer treatments on the reproductive system are known. Young breast cancer survivors are at risk of reduced ovarian function, especially those treated with alkylating agents (e.g. procarbazine) and those who are older at the time of treatment [8]. A recent systematic review showed that there is, on average, a 20% risk of current regimens of chemotherapy-induced permanent ovary function failure among breast cancer patients under 40 years of age [9]. Moreover, pregnancy is not recommended during active cancer therapies due to the teratogenic risks [10] leading to postponing the attempt to satisfy biological motherhood. Hormone receptor-positive breast cancer requires the use of adjuvant endocrine therapy which, in cases of a high risk of replacement, may be prescribed for 10 years [3, 11]. Therefore, the desire to have a child (or another one) may lead these patients to decide to discontinue their treatment [12].

The changed fertility status and unfulfilled desire for a child (or another one) seems to be considerably upsetting for cancer patients and may result in distress [13, 14] and feelings of inadequacy as a woman and partner [15]. This is not surprising since infertility, even among women from the general population, is a burden factor causing clinically relevant anxiety and depressive symptoms [16], reproductive concerns, and affects mental quality of life [17]. The benefits of fertility counseling interventions available to young women with cancer are not yet clear. Unfortunately, the information received during cancer care is still limited and unsatisfactory [15] and has not alleviated patients’ concerns [18]. Data has indicated that discussion of fertility in consultations may increase anxiety [14] and it is worth focusing on concerns, fertility options and their risks, to help in decision-making, as well as consulting a fertility preservation counselor and have access to specialized psychological support [19].

Carter and collaborators [20] explored if infertile cancer survivors demonstrated a “double trauma” response to loss of the ability to conceive and/or carry a pregnancy after a cancer diagnosis. To this end, the researchers compared women with cancer-related infertility (e.g. without uterus or without ovarian function) and non-cancer infertile women on a wait-list for oocyte donation using measurements of mood, reproductive concerns and quality of life. However, they found that maladjustment occurred but was independent of the etiology of infertility. Notably, other studies seem to indicated that most women did not receive a definitive diagnosis about their reproductive ability and needed to deal with ambiguity regarding future fertility and motherhood from diagnosis through to survivorship [21]. The threat to fertility can be equally distressing. Lawson et al. [22] evaluating pre-menopausal cancer females preserving fertility as a preventive measure and infertile patients, at the onset of controlled ovarian hyperstimulation treatment, revealed that the cancer group (68.3% diagnosed with breast cancer) reported higher levels of anxiety and depressive symptoms than infertile women and comparable distress throughout the course of fertility care. To our knowledge, no comparative studies currently exist about the concerns and psychosocial outcomes involving disease-free women facing an uncertain trajectory of reproductive challenges after breast cancer and infertile women.

Building on existing literature, the main purpose of this study was to assess the similarities and differences between young adult female breast cancer survivors, who do not know their fertility status and wish to have children, and non-cancer women with infertility diagnosis, in comparison with a healthy control group, regarding their fertility-related concerns, psychological distress and health-related quality of life (HRQoL). Young female cancer survivors experience unique vulnerabilities related to the fear of cancer recurrence after conception, germline mutation and risk to their offspring [23-25], changes in body image [26] and communicating their health status to children [27]. Partner relationships and childbearing are also important issues [23] common to women diagnosed with cancer facing uncertain damage to fertility and non-cancer infertile women. Studies even showed that young cancer survivors are primarily worried about their ability to conceive, compared to other concerns related to child health and interpersonal difficulties (e.g. Benedict et al. [28]).

Following previous findings, our first hypothesis was that breast cancer survivors and non-cancer infertile women would report comparable levels of fertility-related concerns, but higher concerns than healthy controls. We also hypothesized that there would be differences in anxiety and depression symptoms and health-related quality of life among the groups. More specifically, the cancer and infertile group would present higher psychological distress than the control group based on the (potential) impairment of biological motherhood as a developmental task. In addition, cancer survivors would be the group with the worst HRQoL, due to the sequelae of anticancer treatments.

Materials and Methods

Participants and Procedure

All participants in this cross-sectional study were between 18 and 40 years old and wished to have a biological child (or another one) in the future. Cancer survivors were recruited from the Breast Clinic of Instituto Português de Oncologia Francisco Gentil in Porto and the eligibility criteria were i) history of early-stage cancer (≤ IIIA), ii) undergoing adjuvant or neoadjuvant therapies, iii) no recurrence/other cancer history; iv) no current evidence of disease; v) did not undergo hysterectomy or prophylactic oophorectomy; and vi) did not become pregnant after anticancer treatments. An infertile group were recruited at the Reproductive Medicine Unit of the Centro Hospitalar Universitário de São João. For this study, infertility diagnosis was defined as a disease characterized by the failure in the capacity to reproduce after 12 months of regular, unprotected sexual intercourse [29]. Infertile women were included if they had no cancer history, had a history of female, combined or idiopathic infertility and had not yet started their Assisted Reproduction Technology (ART) treatment cycle. Women who met the main inclusion criteria were identified by medical staff on the day of the appointment. Finally, a control group was recruited from the general population, involving women without cancer or infertility diagnosis in the past. The study was released to public and private institutions (e.g. daycare centers, hairdressers) and eligible women who agreed to participate were included. In this group, participants were excluded if they were currently pregnant. Ethical approval was obtained from the hospitals' Ethics Committees. Informed consent was signed by all participants.

Measures

Young adult women completed a sociodemographic and clinical questionnaire that collected information about age, partnership status, level of education, employment status and nulliparity. Clinical information obtained from the breast cancer survivor group also included questions related to age at diagnosis, disease duration and previous anticancer treatments. In turn, the infertility history was evaluated among non-cancer infertile women.

The Reproductive Concerns After Cancer Scale [RCACS] [30-32] has been administered to investigate the fertility-related concerns experienced by women of reproductive age. Three subscales of the Portuguese version [32] comprising 10 items were used in this study: fertility potential, partner disclosure of the fertility status and acceptance of the possibility of not having children. Participants respond using a 4-point Likert scale from “Strongly disagree” to “Strongly agree”. Higher scores on the subscales reflect higher levels of fertility concerns and lower acceptance. In the current study, Cronbach alpha coefficients for the dimensions included ranged from .661 to .805 for the cancer group, .688 to .814 for the non-cancer infertile group and .844 to .870 for the control group.

Psychological distress was assessed using the 14-item Hospital Anxiety and Depression Scale [HADS] [33]. This self-report measure consists of two subscales, both with seven items, which evaluate the severity of anxiety and depression symptoms. Participants are asked to give their answers on a 4-point scale. Each HADS subscale yields a total score ranging from 0 to 21. The clinical cut-offs are: normal (0 to 7 points), mild (8 to 10 points), moderate (11 to 14 points) and severe levels of anxiety or depression (15 to 21 points). In the present work, the Cronbach alpha for the three groups ranged from .715 to .865 for the anxiety subscale and .688 to .833 for the depression subscale.

Finally, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 [EORTC QLQ-C30] [34] was used with the three groups to measure HRQoL. This is a 30-item multidimensional scale including five functional scales, namely physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning, a global health status/QoL scale, three symptom scales and single-item measures. In this study, only the functional scales were administered. Participants are invited to respond on a 4-point scale ranging from “not at all” to “very much”. A higher score represents better functioning. Based on the low internal consistency scores ($\alpha<.60$ [35]), the cognitive functioning scale was not used in the analysis ($\alpha=.55$ for the cancer group). The Cronbach alpha coefficients for the remaining subscales ranged from .671 to .915 for the cancer group, .652 to .886 for the non-cancer infertile group and .654 to .949 for the control group.

Data analysis

Statistical analyses were performed using SPSS Version 24.0 (IBM Corp. Released 2017). Descriptive statistics (means, standard deviation, frequencies) were used to summarize the sociodemographic and clinical information of the participants included in the three groups. One-way analysis of variance (ANOVA) and Chi-square tests were used to determine the group differences considering continuous and categorial variables, respectively. Multivariate Analyses of Covariance (MANCOVAs) using Pillai's trace criterion for handling unequal sample sizes [36] were conducted to provide comparisons between the cancer group, infertile women and the control group regarding three combined variables designated by fertility-related concerns, psychological distress and HRQoL. To test the hypotheses, age (continuous), partnership status (2 levels), and nulliparity (2 levels) were inserted as covariates in all analyses. These analyses were followed by both univariate tests and discriminant analysis. Post hoc power analysis revealed that the sample size was sufficient to detect medium to large effects regarding group differences [$f = .30$, $p < .05$, power = .90, G*Power 3.1.94] at a significance level of .05.

Results

Sociodemographic and clinical characteristics

Overall, 136 Caucasian women completed the protocol. The sample included 43 female breast cancer survivors, 56 non-cancer infertile women and 37 women without cancer or infertility diagnosis in the past (control group) [see Figure 1].

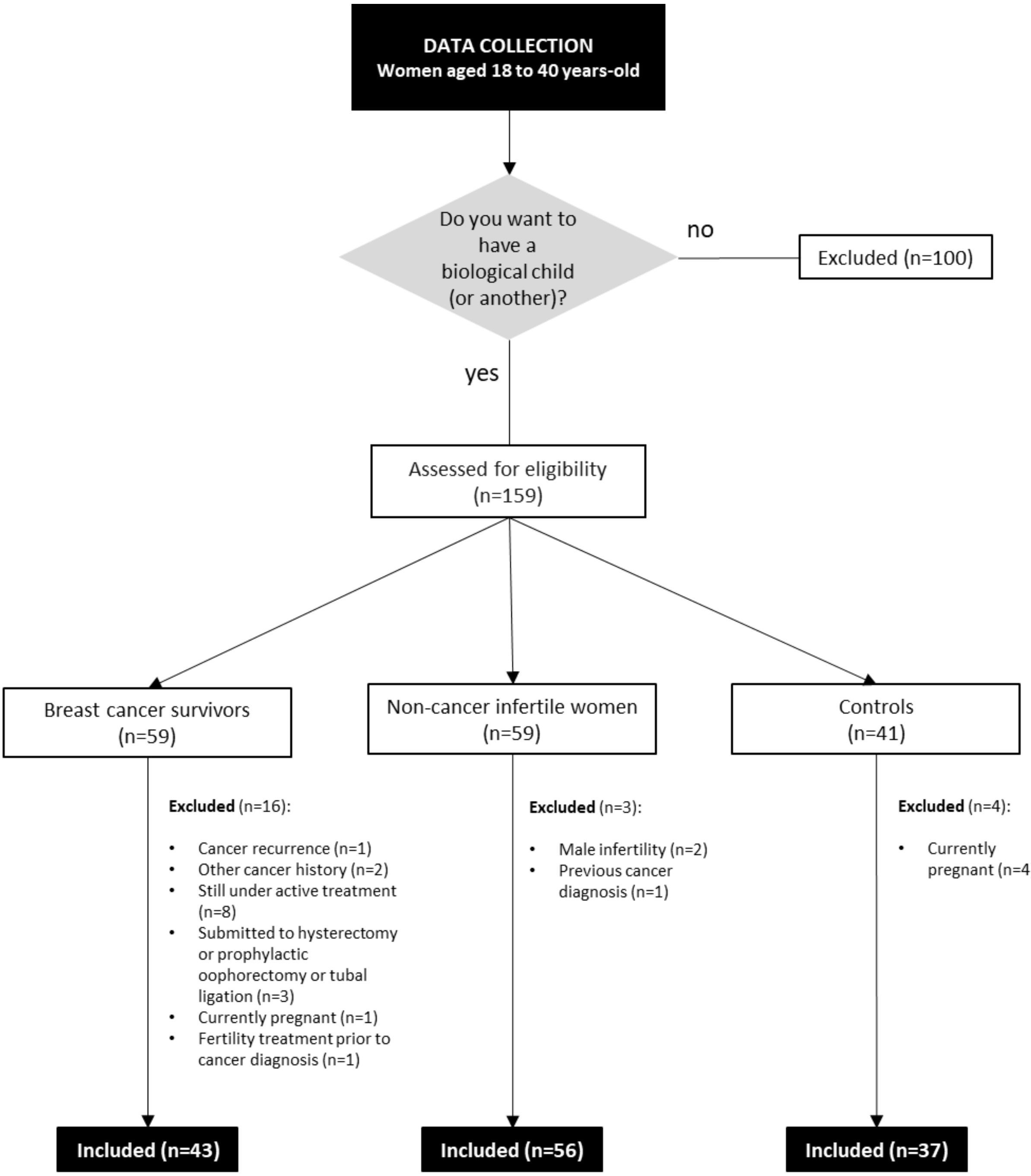

Figure 1. Study flow diagram.

Table 1 presents comparisons between female breast cancer survivors, non-cancer infertile women and controls regarding sociodemographic characteristics. No differences were found between groups when analyzing level of education, employment status and previous use of mental health care. The average age at enrollment of women included in the control group was significantly lower than in the cancer and (p<.001) non-cancer infertile (p=.001) groups. The majority of women in the three groups were married or lived in cohabitation. Fewer non-cancer infertile women (8.9%) have a biological child compared to breast cancer survivors and controls.

In the cancer group, mean age at breast cancer diagnosis was 33.40 (SD=3.81) years. Most of these patients received chemotherapy (88.4%) and radiotherapy (86.0%) and 72.09% were currently undergoing endocrine therapy. Most were informed about the potential effects of their cancer treatment on their reproductive potential even before treatment (90.7%). The mean length of survival was three years. Regarding the infertile women without cancer diagnosis, 50% of the participants had infertility with a female cause, reporting problems related to ovulation, endometriosis and damage to fallopian tubes. At the time of data collection, 30.4% of the infertile women reported having some previous miscarriage. On average, these women had been trying to get pregnant spontaneously for four years and 64.3% had undergone at least one ART cycle.

Table 1. Sample characteristics.

		Breast cancer survivors (n=43)	**Non-cancer infertile women (n=56)**	**Controls (n=37)**	**F/χ^2, *p***
Age at enrolment (years)	Mean(SD); Range	36.16(3.11), 26-40	35.02(3.37), 27-39	32.41(3.87), 25-40	**12.39, <.001**
Married/cohabiting					
Yes	n (%)	31(72.1)	55(98.2)	25(67.6)	**17.75, <.001**
No	n (%)	12(27.9)	1(1.8)	12(32.4)	
Education					
Middle school	n (%)	8(18.6)	5(8.9)	6(16.2)	4.69, .329
High school	n (%)	9(20.9)	21(37.5)	9(24.3)	
University	n (%)	24(55.8)	29(51.8)	22(59.5)	
Employed, full or part time					
Yes	n (%)	33(76.7)	50(89.3)	35(94.6)	4.90, .087
No	n (%)	9(20.9)	6(10.7)	2(5.4)	
Had at least 1 biological child					
Yes	n (%)	20(46.5)	5(8.9)	25(67.6)	**35.52, <.001**
No	n (%)	23(53.5)	51(91.1)	12(32.4)	
Current use of mental health services					
Yes	n (%)	8(18.6)	4(7.1)	4(10.8)	2.88, .227
No	n (%)	35(81.4)	51(91.1)	33(89.2)	

Comparisons of breast cancer survivors, non-cancer infertile women and controls

Subjective perception of fertility concerns

A multivariate group effect was observed, that is, the MANCOVA model found a significant effect of group (cancer group, non-cancer infertile group or controls) on a combined dependent variable called fertility-related concerns (V= .187, F(6,258)=4.44, p<.001, ηp^2=.094). When we examined the univariate main effects and marginal means of each of the three variables included, we found that groups did not differ significantly in terms of partner disclosure and acceptance difficulties regarding the possibility of not having children, after we controlled for age, partnership status and nulliparity (see Table 2). On the other hand, breast cancer survivors and infertile women without cancer history reported higher scores than the control group in the fertility potential dimension (p=.021 and p=.001, respectively). Not surprisingly, women diagnosed with cancer had fertility potential concern levels comparable to the non-cancer infertile women (p=.217).

Psychological distress

Concerning psychological distress, no differences were found between female breast cancer survivors, non-cancer infertile women and women without cancer or infertility diagnosis in the past (V=.026, F(4,260)=.847, p=.497, ηp^2=.013). Differences in group distributions by severity categories were tested, but no significant results were also found ($\chi^2_{(2)}$=1.34, p=.553 and $\chi^2_{(2)}$=1.11, p=.683 for anxiety and depression, respectively). In the cancer and control groups, 25.6% and 27% of women reported moderate to severe anxiety symptoms, respectively. Most participants had minimal depressive symptoms (score<11) in all groups. Only 2.3% of cancer survivors and 1.8% of infertile women revealed moderate to severe depression (see Table 3).

Table 2. Descriptive statistics, multivariate and univariate analysis: a comparative analysis between breast cancer survivors, non-cancer infertile women and healthy controls.

	Breast cancer survivors (n=43)			**Non-cancer infertile women (n=56)**			**Controls (n=37)**			**F, *p***	η_p^2
	M	**SE**	**95% CI**	**M**	**SE**	**95% CI**	**M**	**SE**	**95% CI**		
Fertility concerns											
Fertility potential	3.32	.141	(3.04-3.60)	3.71	.144	(3.42-3.99)	2.70	.179	(2.35-3.06)	**7.31, .001**	**.101**
Partner disclosure	2.39	.168	(2.06-2.72)	2.85	.171	(2.51-3.19)	2.64	.213	(2.22-3.06)	1.72, .182	.026
Acceptance	2.75	.134	(2.49-3.02)	3.02	.137	(2.75-3.29)	2.97	.170	(2.64-3.31)	1.12, .329	.017
Psychological distress											
Anxiety	7.02	.636	(5.77-8.28)	8.13	.650	(6.85-9.42)	6.91	.807	(5.31-8.51)	.766, .467	.012
Depression	2.97	.492	(2.00-3.94)	3.82	.504	(2.83-4.82)	3.73	.625	(2.50-4.97)	.899, .410	.014

SE= Standard Errors; *Note:* Estimated marginal means were used; Post hoc analysis using Bonferroni approach. [a]Using Pilai's Trace.

Table 2. (continued)

	Breast cancer survivors (n=43)			**Non-cancer infertile women (n=56)**			**Controls (n=37)**			**F, *p***	**η_p^2**
	M	**SE**	**95% CI**	**M**	**SE**	**95% CI**	**M**	**SE**	**95% CI**		
Health-related quality of life											
Physical functioning	84.46	2.05	(80.42-88.51)	92.24	2.09	(88.10-96.38)	91.97	2.60	(86.83-97.10)	**4.59 .012**	**.066**
Role functioning	82.70	3.36	(76.08-89.36)	83.77	3.44	(76.98-88.02)	96.44	4.26	(88.02-104.88)	**3.45, .035**	**.050**
Emotional functioning	71.31	3.79	(63.82-78.80)	69.09	3.88	(61.43-76.76)	73.66	4.81	(64.15-83.17)	.208.,812	.003
Social functioning	80.25	2.95	(74.42-86.09)	90.02	3.02	(84.05-96.00)	94.36	3.75	(84.05-86.95)	**5.54, .005**	**.079**

SE= Standard Errors; *Note:* Estimated marginal means were used; Post hoc analysis using Bonferroni approach. [a]Using Pilai's Trace.

Health-related quality of life

There was a significant group main effect with regard to HRQoL (*V*= .154, *F*(8, 256)=2.67 *p*=.008, $^{\eta}p^{2}$=.077). Results from the univariate ANOVAS and estimated marginal means showed that cancer survivors had significantly worse physical functioning than non-cancer infertile women (*p*=.039). Furthermore, young adult women in the cancer group also had worse role (*p*=.033) and social functioning (*p*=.009) than the control group. Other comparisons between groups showed no significant differences.

Table 3. Description of psychological distress of breast cancer survivors, non-cancer infertile women and controls, considering the severity of symptoms.

		Breast cancer survivors (n=43)	**Non-cancer infertile women (n=56)**	**Controls (n=37)**
Anxiety				
Minimal $^{(<11\ \text{points})}$	n (%)	32 (74.4)	46 (82.1)	27 (73.0)
Moderate to Severe $^{(11\text{-}21\ \text{points})}$	n (%)	11 (25.6)	10 (17.9)	10 (27.0)
Depression				
Minimal $^{(<11\ \text{points})}$	n (%)	42 (97.7)	55 (98.2)	35 (94.6)
Moderate to Severe $^{(11\text{-}21\ \text{points})}$	n (%)	1 (2.3)	1 (1.8)	2 (5.4)

Discriminant analysis

The MANCOVAs were followed up with a discriminant analysis involving only the variables that presented main effects of group, that is, fertility potential and physical, role and social HRQoL. Two discriminant functions were found: the first explained 79.8% of the variance and the second 20.2%. In combination, these discriminant functions differentiated the groups significantly, Λ=.44, $\chi 2_{(12)}$ = 107.80, *p*<.001. The correlations between variables and the discriminant functions revealed that the fertility potential dimension loaded on the first function (*r*=.535). In turn, physical, role and social functioning loaded on the second function (*r*=.671; *r*=.408; *r*=.640, respectively). The discriminant function plot showed that the fertility potential concerns discriminated cancer survivors and infertile women from the controls and functionality contributed to distinguishing women with previous cancer diagnosis from infertile women and the control group (see Fig. 2).

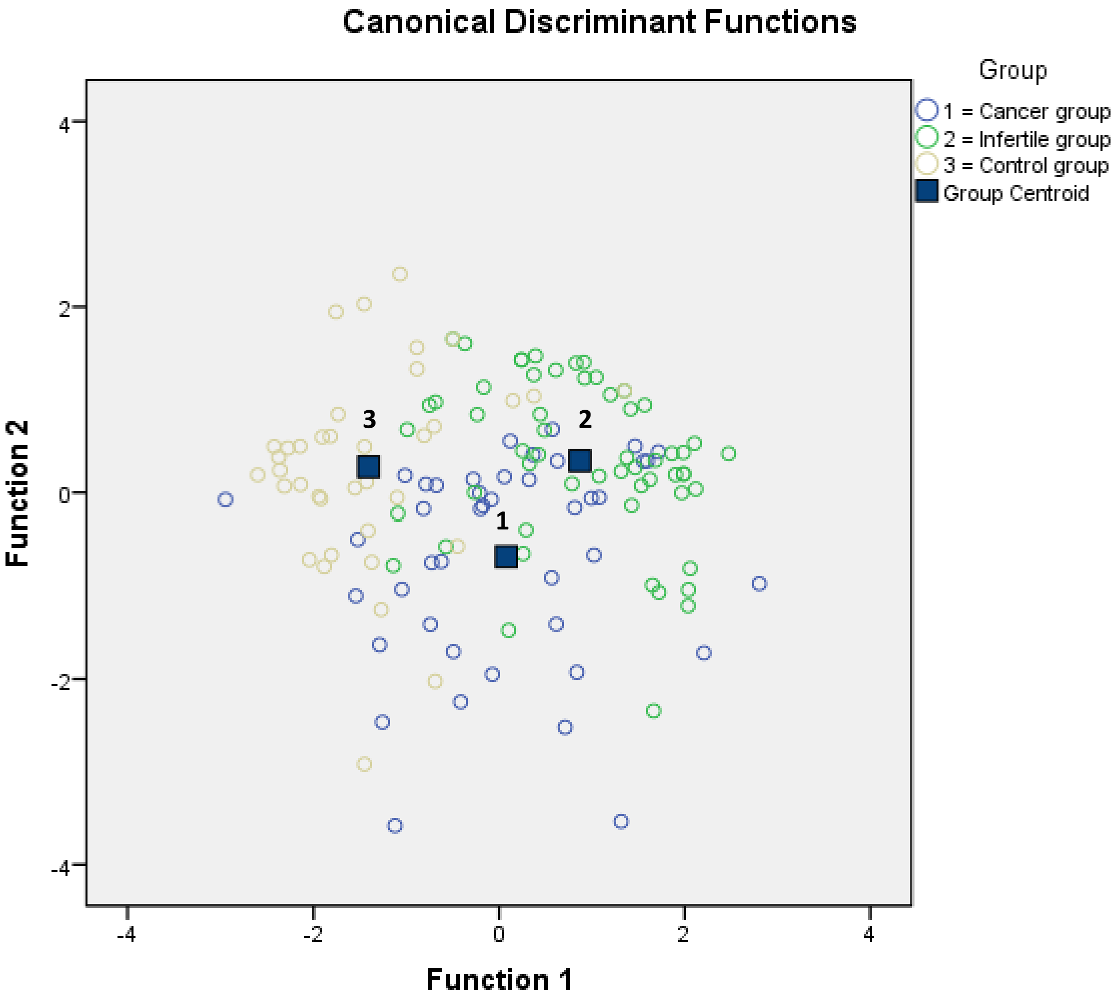

Figure 2. - Discriminant function plot.

Discussion

This study described the fertility-related concerns, psychological distress and HRQoL of young female breast cancer survivors compared to non-cancer infertile women and female healthy controls. Overall, the findings of this study show that the threat to fertility is disturbing. There are more similarities than differences between cancer survivors who do not know their fertility status and infertile patients. Standing out from other studies published for its design, our data support the theory that the experience of breast cancer survivors, who deal with a potential risk of loss of fertility, seems to mirror the emotional response of non-cancer infertile young women waiting for the ART cycle.

As hypothesized, the results suggest that relevant levels of concern about fertility potential are present in young adult survivors who face ambiguity and uncertainty concerning their reproductive potential. These concerns were comparable to those of the non-cancer infertile group and were higher than those of younger women in the general population without cancer or infertility history. Current research data seem consistent with the previous literature, demonstrating that breast cancer survivors without an infertility diagnosis expressed greater fertility concerns than age-matched healthy controls who wished to have children [37]. For survivors, motherhood can be a way to anchor their lives representing the sense of normality [24] and a real or subjective threat to this possibility becomes worrying.

When comparing the groups with regard to psychological distress, no differences were found, contradicting our second hypothesis. Most participants presented minimal anxiety and depressive symptoms in the three groups. The lack of clinical relevance of the reported symptoms may therefore be a function of the adaptive response to fertility risks. According to Mennings' model [38], infertility (or potential infertility) triggers a state of crisis that can lead to maladaptive behavioral changes, just as there is a real chance for positive growth. At-risk fertility participants may have adjusted the meaning of their limitation (or potential limitation) by pursuing other life goals (e.g. Verhaak et al. [39]). However, the high incidence of concerns related to potential fertility in cancer and infertility groups may increase the long-term risk of these patients experiencing psychological morbidity. Studies using quantitative methods have identified reproductive concerns as a significant predictor of depressive symptoms among young cancer survivors [40, 41] and fertility counseling does not seem to minimize this problem [18].

Furthermore, breast cancer survivors reveal lower HRQoL than their infertile and presumed fertile counterparts without cancer history, confirming our initial hypothesis. The impaired quality of life of these patients is known. Women of 50 and under with breast cancer appear to have even worse outcomes in terms of HRQoL than older patients with the same diagnosis [6]. When studying the functionality of cancer survivors, Quinten et al.

[42] found worse role and social functioning in these patients compared to the general population. In the current study, the findings were similar, with these variables discriminating the groups. Univariate analysis showed that young adult cancer survivors reported worse scores in role and social HRQoL than healthy controls. This is not surprising and may reflect the sequelae of anticancer treatment.

Although similarities were found between survivors and women living with a diagnosis of infertility, the HRQoL domain scores in the infertility group were close to controls. Additionally, cancer survivors presented lower physical HRQoL than non-cancer infertile women, whereas the results did not significantly differ from the control group. Following the argument of Carter et al. [20], infertile women can invest more in optimizing their physical functionality in order to enhance the chances of becoming pregnant and, therefore, have better physical HRQoL. This issue is particularly relevant considering the sample of this study, as all women included would undergo fertility treatments. It should be noted that women suffering from fertility problems may later see their physical QoL diminished by the effects of medical procedures of ART treatments (e.g. hormonal stimulation) [35].

Despite the results obtained, the power to detect small differences between groups is limited due to the sample size. Another limitation lies in the fact that all infertile women included in the study were candidates for ART treatment and were about to begin their treatment cycle. These women may see treatment as a new hope of achieving biological motherhood, and therefore, have better psychosocial outcomes. Ideally, the infertile cancer-free comparison sample should have included women with no plans for future ART treatment. In addition, the majority of cancer survivors are currently undergoing endocrine therapy, and as such, prevented from satisfying family building projects by the teratogenic effects of therapy. A different emotional response may be detected in survivors who terminate or discontinue their therapy to become pregnant. In this regard, in order to understand the trajectory of concerns, distress and HRQoL among younger women seeking to fulfill the developmental task of being a mother after cancer, it is important to conduct prospective longitudinal studies.

A major strength of this study was the use of two comparison groups, namely non-cancer infertile women and controls. To our knowledge, previous studies did not include a control group and thus did not identify the real differences between fertility-at-risk groups and presumably fertile women [20, 22]. While the women with cancer or infertility have a comparable emotional adjustment to controls at enrolment, these patients are at greater risk of experiencing distress in future because they show more fertility concerns. This becomes more relevant when there is a previous cancer diagnosis and potential infertility and associated concerns emerge as a double burden factor [43], which may also affect their quality of life [44], already limited by treatment.

Health professionals working in hospitals should be aware of their cancer patients' projects, particularly regarding maternity. Our preliminary data indicate that, whether or not there is a high probability that fertility will be affected, concerns about potential fertility should not be overlooked. There are still numerous professional and organizational barriers to effective fertility counseling. Berg et al [45], in their study, indicate that most oncology professionals reported disagreement on who is responsible for discussing fertility issues with patients. Moreover, priority is given to the large amount of information on the diagnosis of cancer. For this reason, another direction of routine practice could be to assess reproductive concerns in younger women who should be referred to other services/departments. Specialized oncology nurses should have an important role in this referral process due to the continuous contact with cancer survivors, preventing these issues from becoming another burden factor in the future. Specific information resources can also be provided, such as booklets and internet-based programs, involving text and/or video and guided self-navigation. Finally, based on our findings, future studies should also explore how current support programs for infertile women without cancer awaiting treatment are effective in reducing their fertility concerns.

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***Note:** Reference list formatting style based on Breast Cancer guidelines*

STUDY 5

Effectiveness of psycho-educational interventions with telecommunication technologies on emotional distress and quality of life of adult cancer patients: A systematic review

Publication

Bártolo, A., Emelda, P., Rodrigues, F., Pereira, A., Monteiro, S., & Santos, I. M. (2019). Effectiveness of psycho-educational interventions with telecommunication technologies on emotional distress and quality of life of adult cancer patients: a systematic review. *Disability and Rehabilitation*, *41*(8), 870-878.

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Implications for rehabilitation

- Rehabilitation professionals working in the field of oncology should invest in the development of psycho-educational interventions responding the patients' educational needs and promoting their stress control skills.
- Programs using telecommunications technologies may reduce disparities in service delivery within this setting, minimizing geographic and socio-economic barriers to engagement in the interventions.
- With the current technological development, it is possible to perform more interactive interventions that stimulate therapist-patient interactions. However, available protocols in this field still employ basic resources (e.g. websites, e-mail and videos).
- Young adult cancer patients are exposed to additional requirements related to fertility and parenthood. New intervention approaches should consider their informational needs.

Abstract

Purpose of the article: To provide a comprehensive review of psycho-educational interventions using telecommunication technologies developed for adult cancer patients, assessing their effectiveness in reducing emotional distress and improving quality of life (QoL).

Materials and Methods: A narrative approach was used for extraction and synthesis of the data. Relevant studies were identified through the electronic databases PubMed, Scopus, Web of Science, ProQuest, Psychology & Behavioral Sciences Collection (through EBSCOhost) and CENTRAL.

Results: Eight studies involving 1016 participants met inclusion criteria. The majority of the studies included (n=6) used a randomized design and were published between 2007 and 2016. Interventions used a variety of delivery resources, such as telephone, e-mail and websites, but all were aiming to respond to information needs and develop stress control skills. A trend towards reducing distress and improving quality of life was found, but estimated effect sizes were typically small ($d<0.5$). Telephonically delivered psycho-educational interventions presented the highest between-group effects on these outcomes during survival, but were limited by sample size.

Conclusions: The efficacy of interventions using distance approaches in the cancer setting is still not well-established. Further research should be conducted through well-designed studies with more interactive features that minimize the lack of face-to-face interaction.

Keywords: psychoeducation; oncology; functioning, depression; anxiety; survivor.

Introduction

Cancer diagnosis is emotionally demanding, resulting in high rates of distress that are not limited to the early stage of the disease, but also continue in advanced stages [1]. Even when surviving, there is a potential for cancer survivors to experience distress through facing physical, social, psychological and existential stressors [2]. A diminished quality of life (QoL) is common, mainly among long-term survivors. The belief that the disease has lasting harmful effects and the lack of meaning in life are related with poor results [3].

Length of survival has improved due to technological advances in early detection and oncological treatments [4]. Therefore, it is increasingly important to meet cancer patients' needs in continuum from early diagnosis to survival. These patients report many unmet needs in psychological, information, physical and daily life domains [5].

Psycho-educational interventions are evidence-based practices that are well established as adjunctive treatment in the cancer setting [6], responding to patients' educational needs about the disease and its physical and psychological consequences/responses. However, psycho-education goes beyond the transmission of knowledge, involving active cooperation with exercises focused on promoting adherence to treatment and management or stress control skills [7].

Specific psychosocial interventions have shown acceptability and efficacy in reducing anxiety and depression and in improving the QoL of cancer patients and survivors [8], and some combine multiple delivery approaches [9,10]. Previous reviews and meta-analyses confirmed the effectiveness of psycho-educational interventions on the reduction of specific distress symptoms and improvement of the functionality of these populations, but were limited to in-person psycho-educational interventions [11] and had a disproportionate focus on females [12,13,14]. Considering that delivery of mental health services using telecommunication technologies has gained popularity in recent years, there is a need to provide an overview of distance approaches.

Clinical practice guidelines have already been proposed for the use of distance approaches, defining the concept of *telepsychology* as the provision of psychological services using resources such as telephone, e-mail and Internet [15]. This new vision of service delivery, extended to psycho-educational interventions, allows the education of patients in a cost-effective way, decreasing the burden on healthcare professionals [16] and, ultimately, is easily disseminated and reduces disparities in health [17]. It is mainly geographical diversity and socioeconomic status that increase the disparities in care delivery [18]. More specifically, for rural inhabitants, psycho-educational support using distance approaches can be an alternative that decreases logistical barriers to intervention. Preliminary results of a longitudinal study with rural breast cancer survivors supported this solution, showing a sustained improvement in QoL over time [10].

Thus, a systematic review approach was used for the first time to explore psycho-educational interventions using telecommunication technologies as delivery resources, targeting adult cancer patients in an active phase of the disease and disease-free survivors. Due to the substantial heterogeneity of the studies reported in the literature, in terms of methodologies, measures employed and sample size, it was not possible to synthesize the data quantitatively in a meta-analysis. In order to conduct the systematic review, the following specific objectives were defined: (i) comprehensively review the available psycho-educational interventions designed over the past decade; and (ii) examine their effectiveness on the reduction of the emotional distress and improvement of the QoL of these patients, analyzing the evidence from the literature.

Methods

The study was performed with the aim of identifying psycho-educational interventions at a distance, designed for adult cancer patients, in the last decade, and their effectiveness. The methods used in this study are in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [19]. Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocols (PRISMA-P) 2015 statement [20], the protocol for this systematic review was registered on PROSPERO (CRD42017064351) and is available in full on the NIHR HTA programme website (www.hta.ac.uk/2283).

Search strategy and eligibility criteria

A systematic search of the published literature was made using six electronic databases: PubMed, Scopus, Web of Science (Science and Social Science Citation Index), ProQuest, Psychology & Behavioral Sciences Collection (through EBSCOhost) and, more specifically, Cochrane Central Register of Controlled Trials (CENTRAL) to locate randomized controlled trials (RCTs) on psycho-educational interventions for cancer. The searches were made between April and May 2017 with keywords including “psycho-educational intervention”/“psycho-education”, “cancer”, “depression”, “anxiety”, “distress” and “quality of life”. Additional searches using terms such as “telephone”, “web-based” or “internet-based” and “e-mail” were also considered, but the results were not improved regarding the number of records identified. OR and AND functions and database-specific filters were used where these were available. The reference lists of included articles were screened manually to identify additional studies associated with the aim of the review. Studies were eligible for final inclusion in the systematic review if they met the following criteria: (i) published between 2007 and 2017; (ii) written in English; (iii) employing a quantitative design; (iv) involving cancer patients ≥ age 18; (v) developing and evaluating a psycho-educational intervention program using telecommunication technologies aiming to respond to the needs of cancer patients and survivors; and (vi) reporting emotional distress and/or QOL measures as an intervention outcome. Interventions had to be performed by a healthcare professional or trained paraprofessional.

Data extraction process

The search identified potential eligible records. After removing duplicate records, titles and abstracts were screened by two of the co-authors. The pair of raters independently extracted relevant full papers, and unsuitable studies, based on inclusion criteria, were removed. The discrepancies between the two main reviewers concerning the eligibility of extracted full texts (n=6) were resolved through discussion with a third co-author and a final list of studies for examination was produced. For each study, information was gathered within the following categories: (i) basic demographic information such as country, sample size, age, sex and cancer type; and (ii) characterization of the available interventions including study design, resource, conceptual framework, type of focus and main findings.

Assessment quality

The included studies were critically assessed by the two co-authors to ascertain their validity. Firstly, the Cochrane Collaboration “Risk bias” tool was proposed, in a registered protocol, to check the quality of the RCTs. However, considering that the systematic review included heterogeneous types of study, the review team performed an appraisal of quantitative studies based on the Joanna Briggs Institute (JBI) Statistics Assessment and Review Instruments (JBI-MAStARI) critical appraisal checklist for RCTs and quasi-experimental studies (non-randomized experimental studies) [21,22]. Additionally, the quality of the intervention design and reporting was also assessed to check that studies fulfilled the following criteria: (i) described rationale; (ii) detail of the program protocol; and (iii) intervention dissemination.

Data synthesis

A narrative synthesis of the studies included in the systematic review was conducted due to heterogeneity of the data regarding design, cancer type, measures used to assess psychosocial outcomes and follow-up periods. When possible, effect sizes were reported for outcomes included in each study measuring differences between groups or between baseline and follow-up times. Three studies used a *t* test to detect differences, but did not calculate the effect sizes. Thus, Cohen’s *d* was determined using the formulas below for independent and paired samples [23].

$$ds = \frac{\overline{X1} - \overline{X2}}{\sqrt{\frac{(n1-1)SD1^2 + (n2-1)SD2^2}{n1+n2-2}}} \quad or \quad ds = t\sqrt{\frac{1}{n1}} + \sqrt{\frac{1}{n2}} \quad and \quad dz = \frac{Mdiff}{\sqrt{\frac{\sum(Xdiff - Mdiff)^2}{N-1}}}$$

Based on benchmarks suggested by Cohen [24], interpretation of the effect sizes was as follows: small (*d* = 0.2), medium (*d* = 0.5), and large (*d* = 0.8).

Results

A flow diagram depicting the selection process can be found in Figure 1. As shown, a total of the 2846 studies were identified through database searching and an additional 6 were identified by back citation. After removing 232 duplicate records, 2620 studies were screened based upon title and abstract, but 2590 did not meet the eligibility criteria. The full text was retrieved for 29 studies of which 21 were excluded. Among records eliminated, 23.8% of studies provided an intervention protocol (n=2) [25,26] or development of a program [27–29] (n=3) in the last five years, but did not report their effectiveness on psychosocial outcomes defined in the eligibility criteria. All these interventions proposed internet-based programs and 3/5 were specific to breast cancer. One of the 21 studies removed tested a predominantly educational program focusing on the decision-making process using prostate cancer patients who had not made a treatment decision, but none of the psychosocial outcomes were assessed at post-intervention [30]. The 8 studies included in the review were published between 2007 and 2016.

Demographic characteristics

This review covered a total of 1016 patients with cancer in an active phase (N=778) and survivors (N=238). The number of participants enrolled in each study ranged from 36 [31] to 273 [32] (SD=99.48) and half of the studies were conducted in the United States. Most participants were married, with a high level of education and the mean age reported in six studies ranged from 47 [33] to 56 [34] (M=52.93; SD=3.05). Of the 8 studies included in the review, five studies dealt only with women who had been diagnosed with breast cancer [33–37]; and three focused on cancer patients with multiple cancer diagnoses [31,32,38] such as lung and colorectal cancer common between samples. The records included newly diagnosed patients with early stage disease (n=2), heterogeneous samples with early and advanced stages (n=2) and patients who had been disease-free for 1-6 years (n=2) focusing on survival. One study developed in South Korea involved cancer patients after their primary treatment [32]; and two focused on the first surgery [35] or the first day of chemotherapy [31] (Table 1).

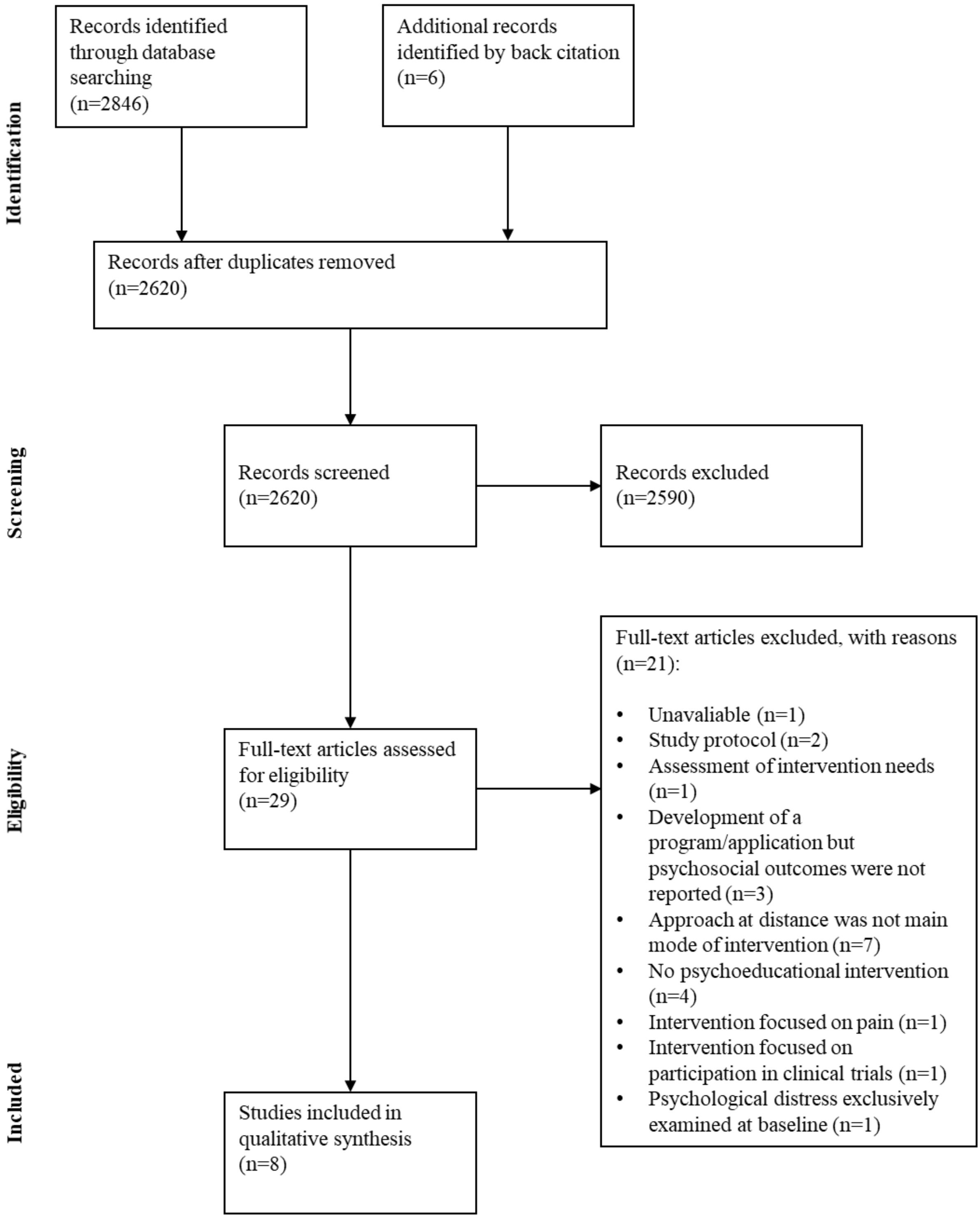

Figure 1. Flow diagram depicting the selection process of studies for inclusion in systematic review. Note: Adapted from: Moher et al. [19].

Table 1. Summary of the cancer patient's characteristics.

Author	Country	Sample Size	Mean Age	% Female	Cancer Type	Description of target population
Allard [35]	Canada	117	53.6	100% female	Breast	French-speaking women with primary cancer or suspected who underwent the first surgery (a day surgery)
Ashing and Miller [34]	United States	39	55.5	100% female	Breast	African American cancer survivors disease free within 1-6 years reporting moderate HRQL concerns
Ashing and Rosales [36]	United States	199	52.9	100% female	Breast	Latina cancer survivors disease free within 1-6 years with at least moderate distress and burden levels
David et al. [33]	Germany	65	47.0	100% female	Breast	Cancer patients registered for psychosocial counseling via e-mail
Lee et al. [31]	South Korea	36	_	55.6% female	Lung, Breast, Colorectal, Gastric, Lymphoma and Others	Cancer patients who arrived to chemotherapy unit (first day) for a cycle reporting significant levels of distress
Northouse et al. [38]	Midwestern United States	38	54.8	57.9% female	Lung, Breast, Colorectal and Prostate	Cancer patients diagnosed with early or advanced stage disease (2-12 months prior to enrollment) + family caregivers
Sherman et al. [37]	United States	249	53.8	100% female	Breast	Cancer patients diagnosed with early-stage disease without previous history of cancer
Yun et al. [32]	South Korea	273	_	72.9% female	Breast, Stomach, Colon, Uterine, Lung and Thyroid	Cancer patients with moderate to severe fatigue for at least 1 week who had completed their primary treatment (within the past 24 months)

HRQL – Health-related quality of life.

Intervention Characteristics

All the studies reported a guiding conceptual framework and/or combination of evidence-based intervention techniques, such as the self-regulation theory (n=1), the contextual model of the HRQL (n=2), the stress coping theory (n=2), the transtheoric model and (n=1) and the cognitive-behavioral framework (n=4). The interventions were delivered and/or developed by healthcare professionals such as nurses, physicians and psychologists, or paraprofessional and clinically trained research assistants.

A variety of resources were utilized to conduct the psycho-educational interventions, including the internet, telephone, videotapes and booklets. Of these interventions, 3/8 were telephonically delivered [34–36] and 3/8 utilized an educational website or e-mail as the only resource [32,33,38]. Out of the eight available interventions, only one [37] used multiple delivery resources combining the usual face-to-face care with psycho-educational videos and telephone counseling sessions.

The content of the assessed interventions focused largely on cancer information and management of the symptoms and specific concerns (e.g. family, social, sexual and employment) integrating intervention techniques such as training in coping skills (n=5), problem solving (n=2) and emotional regulation strategies (n=2). In one study [32], an intervention protocol had a predominantly educational focus providing participants with general information on the disease and related distress and, more specifically, issues related to nutrition and energy conservation considering patients with post-treatment fatigue. Components of another study included supportive techniques [38], sitting cancer patients and their family care-givers side by side to promote dyadic interactions in management of the disease and addressing communication problems. This protocol was originally developed for use with women suffering recurrent breast cancer and their families [38] and here it was adapted to a web-based format.

Two studies using the same intervention protocol in African American [34] and Latin American [36] breast cancer survivors added to telephone sessions a survival booklet including also basic information on breast cancer and its psychosocial impact, surveillance and the psychosocial services available. While these programs were not delivered by professional facilitators, each trained interventionist was supervised.

Table 2. Description of the psychoeducational interventions using distance approaches.

Author, year	**Design**	**Resource**	**Theory**	**Comparator**	**Type of focus**	**Delivery**	**Duration**	**Assessment time points**	**Outcome variables**	**QoL and/or distress as primary outcome** Y/N
Allard [35]	Randomized	Telephone	Self-regulation theory	Usual care group	Predominantly psychological	Nurse	Two sessions (one phone call per week)	Pretest and post-test (9-10 and 17-18 days after surgery)	Functional status (daily activities), emotional distress	Y
Ashing and Miller [34]	Randomized	Survivorship booklet + Telephone	Contextual model of HRQL and cognitive-behavioral framework	Survivorship booklet only	Educational and psychological	Clinically trained research assistants (in social sciences)	Eight sessions (40-50 min) biweekly	Baseline and 4-6 months after randomization	HRQOL	Y
Ashing and Rosales [36]	Randomized	Survivorship booklet + Telephone	Contextual model of HRQL and cognitive-behavioral framework	Survivorship booklet only	Educational and psychological	Paraprofessional trained	Eight sessions (40-50 min) biweekly	Baseline and 3-4 months after intervention	Depression	Y
David et al. [33]	Randomized	E-mail	Evidence-based	Waiting list group	Predominantly psychological	Psychologists	Two-month	Pretest and post-test	Distress, HRQOL, satisfaction	Y

HRQOL – Health-related quality of life; QoL – Quality of life. Y – Yes; N – No

Table 2. (continued)

Author, year	**Design**	**Resource**	**Theory**	**Comparator**	**Type of focus**	**Delivery**	**Duration**	**Assessment time points**	**Outcome variables**	**QoL and/or distress as primary outcome** Y/N
Lee et al. [31]	Non-randomized control group	Tablet PC (movie clip using Powerpoint slideshow)	Evidence-based	A movie clip containing scenic images with relaxing	Educational and psychological	Material originally developed by a psychiatrist	20 min-long movie clip	Baseline, 2-4 weeks after intervention and six months after (to assess the use of the psychosocial services)	Depression, anxiety, HRQOL physical symptoms, intensity of insomnia, posttraumatic stress symptoms, satisfaction	Y
Northouse et al. [38]	Pretest-posttest without control group	Web-based program patient and caregiver side-by-side at the computer (using email)	Stress-coping theory	Not applicable	Educational and psychological	Nurse	Three sessions over six weeks with two weeks between each session	Baseline and two weeks after intervention	Distress, QoL, appraisal, communication, social support, self-efficacy, satisfaction	Y

HRQOL – Health-related quality of life; QoL – Quality of life. Y – Yes; N – No

Table 2. (continued)

Author, year	**Design**	**Resource**	**Theory**	**Comparator**	**Type of focus**	**Delivery**	**Duration**	**Assessment time points**	**Outcome variables**	**QoL and/or distress as primary outcome** Y/N
Sherman et al. [37]	Randomized	Videotapes or telephone	Stress-coping theory, Crisis Intervention Model (and evidence-based)	Usual care group; Usual care + 4 psychoeducation videos; Usual care + 4 telephone counseling sessions; Usual care + 4 psychoeducation videos + 4 telephone counseling sessions	Educational and psychological	Nurse (telephone-counseling sessions)	Not reported	Baseline, one week following biopsy, 72 hours following surgery, during discussions of adjuvant therapy (within 72 hours) and within 14 days of the completion of adjuvant therapy or 6 months after surgery	Emotional, physical and social adjustment	Y
Yun et al. [32]	Randomized	Web-based program (using a website)	Transtheoretic model and cognitive-behavioral framework	Waiting-list group	Predominantly educational	Nurse (coordinator)	12-week intervention	Pretest and post-test	Fatigue, HRQOL, energy conservation, nutritional status, anxiety, depression, pain, quality and quantity of sleep	N

HRQOL – Health-related quality of life; QoL – Quality of life. Y – Yes; N – No

In general, all distance approaches had common aims, but focused their contents on each disease phase. However, internet-based programs utilized electronic media such as text and/or video and guided self-navigation as educational elements. The duration of these protocols varied from 6 weeks [38] to 12 weeks [32]. In turn, psycho-educational telephone sessions ranged from two calls [35] to eight calls [34,36]. Additionally, one study offered brief psycho-education to cancer patients arriving at chemotherapy [31] through a movie clip utilizing a tablet PC. Educational and psychological elements were included in line with the other studies, but using a substantially shorter approach of a single 20-minute session.

Of the identified studies, six were two-arm controlled comparing an active psycho-educational treatment to either the usual care group (n=1), waiting list group (n=2) or attention control (n=3). Attention control was used when the participants received a booklet or a scenic movie that did not have any psycho-educational contents (Table 2).

Methodological Quality

The 8 studies included were reviewed for their quality. All studies provided an evidence-based rationale justifying the interventions developed and their components. Six studies used a randomized design. Regarding their methodological rigor, these studies used a randomization procedure to allocate participants, a similar treatment for groups beyond the intervention of interest and the same assessment. However, subject and assessor blinding were unattainable and only three of the studies provided complete information on the loss of participants. Two of the studies utilized a quasi-randomized and pretest-posttest design without control group (see Table 2). Adapting other intervention protocols, these studies described the detailed methodology for their replication. The retention rate of the pretest to posttest was 97.2% and 86%, respectively for quasi-randomized and pretest-posttest designs. In terms of the key outcome variables, all eight studies measured psychosocial variables through self-reported questionnaires but two studies did not report the reliability of the measures for any of their variables. Furthermore, appropriate design and statistical analysis were conducted, but two studies, identified as pilot studies [31,34], did not provide a meaningful effect size estimate due to the imprecision inherent to small sample sizes [39]; and one study presented only preliminary results of the program [33] (Table 3).

Table 3. Critical appraisal of the studies with randomized design included in the review based on Joanna Briggs Institute guidelines [22].

Critical Appraisal Checklist	Frequency n(%)
Random allocation	6(100)
Similar groups at the baseline	5(83.3)
Groups treated identically	6(100)
Follow-up complete	3(50.0)
Intention-to-treat analysis	1(16.7)
Outcomes measured in the same way for groups	6(100)
Reliable measures	5(83.3)
Appropriate statistics analysis	5(83.3)
Design appropriate for the topic	6(100)

Outcomes of interventions

There was a lack of consistency in the measures used to assess emotional distress and QoL. Seven of the eight studies examined the specific or non-specific distress symptoms through measures such as Profile of Mood States (POMS) (n=2), Centre for Epidemiological Studies Depression Scale (CES-D) (n=1), Brief Symptoms Inventory (BSI) (n=1), Breast Cancer Treatment Response Inventory (BCTRI) (n=1) and Hospital Anxiety and Depression Scale (HADS) (n=2). QoL was included as an outcome in 5/8 of the studies with tools for its assessment including the Functional Assessment of Cancer Therapy-General [FACT-G] (n=2); the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 [EORTC QLQ-C30, version 3] (n=2); and Short-form 8 Health Survey (SF-8) (n=1). The measures presented good internal consistency between $\alpha=0.64$ and $\alpha=0.94$ for distress symptoms and between $\alpha=0.82$ and $\alpha=0.90$ for QoL.

Seven studies explored treatment-promoted changes in emotional distress and QoL as a primary outcome. In two studies, there was a statistically significant difference between the intervention group and the comparator group at post-treatment regarding overall distress symptoms [31,35]. More specifically, in the telephone intervention used by

Allard [35], the group undergoing treatment showed lower perceived distress after the first phone call, 9-10 days after a day surgery of the breast cancer patients, with a medium effect size (*d*=0.41). Although it was not possible to estimate the effect size, participants undergoing chemotherapy that received a single session of brief psycho-education [31] reported more improvements over 3 weeks than did the attention control group regarding non-specific distress symptoms and depression symptoms. Notwithstanding, two longer distance approaches presented a longer effect of treatment on depression levels in patients with cancer [33] and survivors [36]. Participants within the intervention conditions presented a significant improvement from baseline to follow-up (effect sizes ranging from 0.15 to 0.79). Even with limited statistical power, the preliminary results from David et al. [33] supported the psycho-educational interventions via e-mail as promoting the decrease of these specific symptoms, but also overall distress level (η^2=0.12). One more recent study [38] joining patient and care-giver reinforces the significant decrease of distress (*d*=0.18) over time and improvement of mood states such as anger-hostility (*d*=0.14) and fatigue-inertia (*d*=0.41), also using e-mail.

A significant increase in QoL over time was observed in 3 out of 5 studies [33,34,38]. The studies demonstrated a small to medium effect of psycho-educational intervention on global QoL scores with the estimated effect ranging from 0.10 to 0.53 for protocols using e-mail and telephone, respectively. Two of these studies indicated an improvement of dimensional QoL scores, such as social (η^2=0.08), emotional (η^2=0.16) [33] and physical functioning (*d*=0.43) [38], but the effect size value for social functioning suggested a null effect of the intervention on this outcome. Additionally, the pilot study conducted by Ashing and Miller [34] showed that survivors reporting moderate QoL concerns presented greater overall QoL than the control group at follow-up (*d*=0.13). Also, cognitive functioning, as a QoL dimension, differed between groups using a predominantly educational web-based program, but with small effect size (*d*=0.25) [32].

Highlighting the intervention used by Sherman et al. [37] with 249 breast cancer patients, data suggested that the addition of psycho-education videos or telephone counseling or both to the usual care of patients in an early stage of the disease did not change distress levels from post-surgery to ongoing recovery and improved overall QoL over time, although between-group differences were not found.

The effect of interventions protocols on other variables was also reported in 6 out of 8 studies. The study by Allard [35] found a trend towards between-group differences in home management after the first and second intervention phone call assuming a small effect size (*d*=0.32 and *d*=0.12, respectively). Fatigue was a primary outcome variable of the 12 week intervention proposed by Yun et al. [32]. The results indicated that the intervention group had a greater decrease in global fatigue, severity and interference of this symptom in daily life, with estimated *d* ranging from 0.21 to 0.29, also indicating small effect sizes. Northouse et al. [38] assessed self-efficacy over time in their protocol, but no effect of the intervention on patients was found (*d*=0.05). However, the program had a large within-group effect size regarding benefits of illness perceived by patients (*d*=0.77). No significant intervention effects were identified for variables such as sleep quality, pain, energy conservation, nutritional status, social support and communication, which were also assessed in the studies. Finally, participants reported satisfaction with the contents and structure of the two programs that used e-mail [33,38] and with the brief psycho-education protocol [31] delivered through a movie clip. In this brief intervention, besides between-group differences in primary outcomes, major improvements over 3 weeks were found for the group that received psycho-education regarding insomnia severity and avoidance after chemotherapy.

Discussion

Concerning the effectiveness of psycho-educational interventions using telecommunication technologies in the cancer setting, this systematic review provided an overview of the current literature. The findings suggested that intervention approaches at a distance including educational and psychological components had a significant effect on reducing non-specific distress and depressive symptoms and improved overall QoL, using a variety of delivery resources. However, small effect sizes pointed to the need to conduct well-designed studies using mainly RCT designs which are viewed as the “gold standard” of clinical research to test the efficacy of interventions [40].

Summary of evidence

This systematic review examined the findings of eight studies on psycho-educational interventions which were largely focused on breast cancer patients generally over 45 years of age. The available programs were based on a diversity of theoretical frameworks, but the cognitive-behavioral model guided 50% of the protocols. Techniques such as health education, enhancement of problem-solving skills and stress management, supported by this conceptual framework, were used in telephonically delivered psycho-educational interventions and web-based protocols.

In terms of the efficacy of psycho-educational interventions, this review indicated that telepsychology approaches demonstrated improved global distress outcomes, compared to the usual care or attention control groups, and promoted the reduction of depression symptoms over time. However, these effects were typically not robust, having a small effect size. Only one study based on telephonic delivery of psycho-education in the survival period showed a medium effect on depression [36]. Also noteworthy is the significant increase of overall QoL from baseline to follow-up as a result of the interventions conducted by telephone or e-mail. Telephonically delivered psycho-education [34] in the survival phase seems to have a medium effect size also in this domain, although this finding is limited by the small sample size in this study [39]. Additionally, web-based interventions reported a small effect on the QoL dimensional scores regarding emotional, physical and cognitive functioning.

The RCT conducted by Sherman et al. [37] appears to be the only trial to explore the effects of interventions through information and communication technologies combined with the usual care of cancer patients. The findings showed that the association between usual care and any psycho-educational support and counseling (videos or telephone) promoted psychosocial outcomes in the continuum from post-surgery to ongoing recovery.

Furthermore, others factors such as fatigue, home management and benefits of the illness perceived by cancer patients were positively affected by the interventions. More specifically, the web-based intervention with patients and caregivers side by side [38] demonstrated the highest within-group effect size in the patient’s appraisal.

In the studies included in this systematic review, there was lack of focus on interventions directed to patients at an early or advanced stage of cancer and at the disease-free survival stage, but the trend towards significantly reduced emotional distress remained, even for patients undergoing the first surgery [35] or first day of the chemotherapy [31]. Also, the variable duration of the interventions did not seem to affect their effect on these non-specific symptoms and QoL scores. Indeed, brief psycho-education after chemotherapy led to significant changes in patient adjustment over time.

As proposed in the recent review by Zhao et al. [41], advances in communication technologies can simulate therapist-patient interactions minimizing the lack of face-to-face contact. The findings of that review regarding depressive patients were replicated within the field of oncological disease. Also here, psycho-educational interventions employed more basic resources such as websites, e-mail and videos to conduct the program. Multiple and more interactive features could potentially increase the modest effects found in this overview. RCT protocols designed specifically to test more interactive interventions are available, mainly for breast cancer patients [25,26], but their effects have not yet been tested.

While the effects of telephonically delivered interventions have been underlined in psychosocial oncology research [42], only three protocols included this single intervention and failed to provide details for its replication. Another problematic issue was a lack of information on retention rates in follow-up in the studies included. Of those reporting the barriers to retention, patients dying, being too ill or too busy, and poor use of technological resources were mentioned. Three of the studies did not include significant levels of distress as eligibility criteria, and this can be a determinant factor on the small effects obtained.

Summarizing, based on the present findings, evidence for the effectiveness of psycho-educational interventions using telecommunication technologies on reducing emotional distress and increasing QoL and its dimensions is not definitive. Although the trend towards significant effects lends further support to the existing literature, the estimated effect sizes limits generalization. Considering the advantage of studies with RCT designs in forming comparable groups of patients regarding prognostic factors [40], detailed protocols should be tested considering diverse cancer types, stages and types of care.

Limitations and future directions

Several key limitations of this comprehensive systematic review should be acknowledged. First, the characteristics of the studies included vary greatly, for example, in study design, the main focus of the intervention, number of sessions, delivery resources and a lack of consistency in the measures and sample size. For this reason, meta-analysis and statistical comparisons were not possible. Second, by restricting the literature search to include only quantitative studies, articles in English and published in the last decade, relevant research published in other languages or less recent research may be missing. Finally, even though the methodological rigor of studies was assessed, it is important to note that this only gives an indication of the overall quality of each study, including program details, but not specifically how well cancer information and coping strategies were dealt with in the intervention.

The results of the current review point towards the need for further studies and clinical practices. First of all, there is a need to continue to invest in the assessment of the psycho-educational needs of cancer patients at various stages of the disease, in order to reduce disparities between the contents of different programs. Secondly, previous studies addressed interventions for older patients with an average age of about 50. Clearly, examining the role of psycho-educational support in young adult cancer patients should be a high priority in future research. These patients have specific requirements, for example, associated with the reproductive role and fertility. Hence, distance approaches should include interactive modules that satisfy their informational needs in this domain and support the decision-making process. Finally, future research should test the effect of psycho-educational interventions on psychosocial outcomes with more representative samples and controlled designs. In addition, cost analysis will identify the advantage of telecommunication technologies applied in the cancer setting compared to traditional in-person care.

Conclusion

There is little evidence in the last decade for the effectiveness of psycho-educational interventions using distance approaches in cancer patients. Only 8 studies measuring emotional distress symptoms and QoL as outcomes of these interventions were identified.

Even with a limited effect size, there was a trend towards significant reduction of distress and improved QoL during the active disease and survival phases after interventions with educational and psychological components. These effects seem to remain stable irrespective of the delivery resources or the longer or shorter duration of the intervention. So far, e-mail, websites, booklets and telephone were the main resources employed to deliver the interventions, but concentrating on exploring a variety of modalities using interactive features that can simulate therapist-patient interactions is a current need.

To summarize, this comprehensive systematic review pointed towards communication technologies as a new way to provide more cost-effective psycho-educational support for cancer patients. However, the existing body of literature does not yet support these distance approaches as a well-defined intervention modality within this setting with a direct effect on psychosocial outcomes.

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***Note:** Reference list formatted according to the National Library of Medicine (NLM) style based on Disability and Rehabilitation guidelines*

STUDY 6

Reproduction-related cognitive processing and distress among young adult women: The role of personal breast cancer history

Publication

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Abstract

Breast cancer diagnosis can threaten fertility and biological motherhood in women of reproductive age due to the gonadotoxic effects of treatments. Much evidence documents these women fertility-related concerns and distress, but no study has attempted to understand how implicit cognitive processes can contribute to this maladjustment. In this research, we explored whether reproduction-related stimuli interfere with cognition among cancer survivors with infertility risk using an emotional Stroop Task. Furthermore, we investigated the relationship between reproduction-related cognitive processing and psychological morbidity. Young cancer survivors aged 18 to 40 years who received anticancer treatments and an age-matched non-cancer control group without known fertility problems were compared. Color-naming times and error rates were assessed. Participants in both groups were slower naming the color of reproduction-related words in comparison to unrelated negative valence words. Although in the same direction, this difference did not reach statistical significance for positive and neutral unrelated word lists. Further analysis suggested that greater allocation of attention toward reproduction-related information was associated with higher depression levels in young women with personal breast cancer history, but not in healthy women. These findings suggest that biased processing of reproduction-related cues might be a vulnerability factor after a breast cancer diagnosis. Additionally, this study puts in evidence the potential usefulness of using experimental tasks to investigate attentional bias in a context where fertility is at risk.

Keywords: attentional bias, reproduction-related stimuli, oncology, depression.

Introduction

A substantial body of evidence suggests that breast cancer has a negative impact on fertility and the ability to carry a pregnancy. Potentially gonadotoxic anticancer treatments [e.g. alkylating chemotherapy (Overbeek et al. 2017)] can result in damage to the ovary. It should be noted that some women experience irreversible chemotherapy-related amenorrhea and even those who still continue menstruating may have premature ovarian failure, depending on the specific agents used, dose and duration of treatments (Partridge et al. 2001). However, family planning is not always completed at the time of breast cancer diagnosis.

Current estimates have shown that this cancer type is the most common malignancy in women of reproductive age, registering an incidence rate of 49.5 per 100.000 in Europe (Ferlay et al., 2018). Therefore, some women diagnosed with breast cancer see their future as biological mothers at risk. Furthermore, there is concern and debate about the safety of pregnancy after a diagnosis of breast cancer (Lopresti et al. 2018), especially in women with hormone receptor-positive cancers. More recent research has indicated that a subsequent pregnancy in women with a history of an endocrine-sensitive breast cancer is not detrimental (Azim et al. 2013). Despite this, cancer survivors report concerns related to fertility, but also to the risks of pregnancy for themselves (e.g. negative impact on the evolution of cancer) or their offspring (e.g. congenital abnormalities) (Logan et al. 2018; Bártolo et al. in press).

Increased knowledge regarding the psychosocial impact of the threats to developmental tasks that characterize a woman's reproductive years, such as having a (another) child, provides new routes for interventions. Not fulfilling a desire for children is known as a factor associated with psychological morbidity (Armuand et al. 2014). Accordingly, there is growing concern about establishing guidelines for fertility counseling among breast cancer patients (Lambertini et al. 2013). Moreover, new psychosocial interventions aimed at young women have been developed to facilitate the patients' decision-making process about fertility care and improve stress management (Bradford and Woodard 2017). It has been suggested, however, that gaps still exist and that even cancer survivors who receive counseling remain concerned and distressed (Young et al., 2019).

As a result of these findings, understanding of other mechanisms that can contribute to maintaining the maladjustment is sought.

Studies focused on implicit cognitive processes may be a promising avenue. One well-investigated cognitive process in relation to psychopathology is attentional bias, defined as a phenomenon of hyperattention to certain stimuli (Muris and Merckelback, 1998). Researchers have consistently shown that selective processing of threatening cues is a vulnerability factor playing a key role in emotional regulation difficulties (Hankin et al. 2010; MacLeod and Hagan, 1992). In clinical populations, stimuli with content relevant to their condition can also originate biased cognitive processing. For example, individuals with cancer (Butow et al. 2015), chronic pain (Fashler and Katz 2016) and asthma (Jessop et al. 2004; Lowther et al. 2016) presented cognitive bias towards cancer-related information, pictures of injuries and asthma cues, respectively. This bias is reflected in faster/slower response times (depending from the experimental paradigm used) in the identification or recognition of these stimuli.

Therefore, we decided to develop an emotional Stroop task to examine whether known infertility risks can result in attentional bias toward reproduction-related stimuli among breast cancer survivors, which could contribute to an increased level of distress. The emotional Stroop task is classically one of the most frequent methods used to assess attentional bias, exposing participants to relevant words and asking them to name the colors in which they are presented (Williams et al. 1996). Several variations of this paradigm have been applied in the cancer context. Findings obtained from two studies (Carpenter et al. 2014; Erblich et al. 2003), showing an increased attentional allocation towards cancer-related stimuli in women with family history of breast cancer or BRCA genetic mutation, are consistent with the common theories of attention, which suggest that attention allocation to a stimulus is dependent on its meaning and momentary pertinence (Norman 1968).

We are aware of no published studies in which reproduction-related attentional processing has been investigated even in healthy women from the general population. We defined a study design involving a cancer group and control group composed of women without cancer history. We anticipated that there would be increased attention to reproduction-related cues in all young women, even when fertility and biological motherhood are not at risk. This is because these stimuli may activate appetitive mechanisms due to their relationship with promoting the survival and continuity of the species (Bradley e al. 2010). Thus, longer reaction times to target reproduction-related words and more errors in this condition, relative to other conditions, are expected as indicators of cognitive bias (DiBonaventura et al. 2010; Erblich et al. 2003). However, we expected this cognitive processing bias to vary as a function of personal breast cancer history and consequent threat to reproductive potential. On the one hand, for young women diagnosed with cancer, stimuli related to reproduction are appetitive and simultaneously represent a potentially threatened life goal. Thus, there is a co-occurrence of an aversive state (Bradley e al. 2010) and the attention bias can be significantly larger in this group. On the other hand, based on the principles of Higgins' regulatory-focus theory (Higgins, 1997), to avoid anticipated pain, some younger women may also try actions of withdrawal reducing increased awareness or natural focus on reproduction-related stimuli.

We also hypothesized that breast cancer survivors who exhibit a greater bias to reproduction-related cues will have more fertility concerns and increased distress. This positive relationship should not occur in young women with no infertility risks. This last hypothesis is in line with the literature that demonstrate that the adoption of hypervigilant mode to stimuli associated with a stress source may have unintended negative consequences (see Mathews and McLeod, 2005).

Materials and Methods

Participants

Thirty-seven female breast cancer survivors and 37 non-cancer women, aged 18 to 40 years were included in the current study. To be eligible, breast cancer survivors had to have a history of early-stage breast cancer (≤ IIIA) without recurrence and be disease-free at the time of participation. Young women were eligible for the control condition if they had no cancer history or known fertility problems. Furthermore, for both groups we chose to exclude women who were not Portuguese-speaking, who were pregnant at the time of enrollment and had undergone hysterectomy, prophylactic oophorectomy or tubal ligation procedures. Both groups were matched on age, education level and reproductive characteristics whenever possible.

Word selection for the Emotional Stroop Task

We developed an emotional Stroop Task and used it to compare reproduction-related attentional processing between a sample of breast cancer survivors and a sample of healthy women without personal cancer history. To the best of our knowledge, this study is the first to use such a task to explore an eventual reproduction-related attentional bias in this population. The task included four 20-word lists: one list of reproduction-related words (e.g. fertility, pregnancy), and three lists of non-reproduction related negative words (e.g. loneliness, lie), positive words (e.g. happy, victory) and neutral words (e.g. beverage, dustpan), for the purpose of comparison.

The selection of items for the reproduction-related word list involved two preliminary studies. In the first preliminary study, in order to generate a pool of potential stimuli, we asked 14 healthy women (26-40 years old) from the general population to freely write words that they thought were related to reproductive health, in blank sheets of paper. Based on this procedure, participants generated altogether 76 distinct reproduction-related words.

A second preliminary study was then carried out involving the 50 most frequently reported words in the previous study. A sample of 33 women (15 young women previously diagnosed with cancer and 18 women without cancer history), aged 25 to 40 years (M=32.58; SD=4.88), who did not participate in the main task, were recruited. Participants evaluated the words in the affective dimensions of valence and arousal using the Self-Assessment Manikin (SAM) through a web survey. Moreover, words were also rated for their relation to reproduction, between 0 (not at all related) and 100 (very related). The 20 words rated as more related to reproduction were selected for the final reproduction-related Stroop list.

In turn, negative, positive and neutral words were selected from the Affective Norms for English Words (ANEW) database, which was adapted for European Portuguese (Soares et al. 2012). The selection of stimulus words to include in each list was based on their affective ratings of valence. Additionally, we tried to match the four lists in terms of mean word length, number of syllables and frequency of usage in the Portuguese language. More specifically, values of word frequency were computed with P-PAL Web application (Soares et al. 2010).

Table 1. Word lists: Affective ratings and other characteristics.

List	Valence	Arousal	Letters per word		Number of syllables		Word frequency (per million)	
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**F,p**	**Mean (SD)**	**F,p**	**Mean (SD)**	**F,p**
Reproduction-related	6.52 (1.18)	5.99 (.87)	8.10 (3.01)	.22, .88	3.45 (1.28)	.07, .98	20.73 (49.95)	2.68, .053
Negative	2.31 (.45)	5.94 (.87)	8.15 (2.11)		3.45 (1.10)		15.08 (26.99)	
Positive	7.61 (.27)	6.01 (.95)	8.05 (2.50)		3.50 (1.05)		52.22 (55.14)	
Neutral	5.36 (.36)	5.10 (.65)	7.60 (1.96)		3.35 (.88)		30.62 (41.42)	

One-way analyses of variance (ANOVAs) were performed with list as a grouping factor, indicating non-significant differences between the fours lists on these parameters (p>.05) [see Table 1]. It should be noted that the relatively higher mean frequency score for the positive word list may be due to the very high frequency of certain words such as “victory” and “achievement”.

Questionnaires

Demographic and clinical history. A questionnaire was created to collect information about age, partnership status, education, nulliparity and desire for biological motherhood. Breast cancer survivors were asked to provide information about age at diagnosis, disease duration, previous anticancer treatments and fertility care.

Fertility concerns. The Reproductive Concerns After Cancer Scale [RCACS (Gorman et al. 2014, 2019)] was used to assess fertility-related concerns among young women. Based on this, three subscales of the Portuguese version (Bártolo et al. 2020) were administered: fertility potential (4 items), partner disclosure about fertility status (3 items) and acceptance of the possibility of not having children (3 items). Participants are asked to give their answers on a 5-point Likert scale, with higher scores reflecting greater concerns and lower acceptance. Internal consistency (Cronbach’s alpha values) for the dimensions ranged from .78 to .87 for the cancer survivors and .70 to .91 for the control group.

Psychological distress. The 14-item Hospital Anxiety and Depression Scale [HADS (Pais-Ribeiro et al. 2007)] was administered to evaluate the severity of anxiety and depression symptoms. This measure consists of two subscales, both with seven items. Participants are asked to give their answers on a 4-point scale. Total scores range from 0 to 21 for each dimension, with higher scores reflecting greater severity of the symptoms. In the present sample, the Cronbach's alpha values for the anxiety subscale were .85 and .70 for the cancer survivor and the control groups, respectively. In turn, the depression subscale also presented acceptable internal consistency with alpha values of .74 and .67 for the cancer survivor and the control groups, respectively.

Procedure

This study was approved by the Ethics Committee of the Centro Hospitalar Universitário de São João. Eligible cancer survivors were identified by medical staff and contacted via phone. After explaining the study, a session was scheduled on the day of the medical appointment with those who verbally consented to participate. The control group was recruited from the general population. The call for the study was circulated online and, after expressing their interest by filling a short questionnaire, eligible participants were contacted via e-mail and/or phone to schedule participation. Written informed consent was obtained from all participants before data collection. Participants were seated comfortably in front of a computer screen in a quiet room. In order to perform the emotional Stroop task, subjects were instructed to indicate the color of each word (red, green or blue) displayed on the screen by pressing designated keys on the keyboard as quickly and as accurately as possible. Response bottoms ("f", "j" and "k") were color-coded with a sticker. The color code was counterbalanced across participants. To respond, participants were instructed to place their left index finger on the "f" key and their right index and middle fingers on the "j" and "k" keys, respectively. Words were presented in random order in one of the three colors. Each word on the four lists was displayed three times (once in each color) for a total of 240 experimental trials. Trials began with a fixation cross shown for 500 ms. After that, a stimulus was presented at the center of a white screen and remained there until a response was given. The computerized Stroop task included ten practice trials (using additional neutral words). These practice trials were only used to familiarize the subjects with the task and response keys, being excluded from data analysis. Depending on participants response speed, the duration of the task varied between 11 and 17 minutes, without breaks. For each trial, response time and accuracy were recorded. Participants did not receive feedback about their performance. The emotional Stroop task was run on a 15.4 inch monitor using E-Prime 2.0 Professional (Psychology Software Tools, Inc.). Self-reported measures were administered to young adult women after completing the task. Participants were debriefed on the underlying purposes of the study at the end of the session and all questions were answered.

Data analysis and Results

Descriptive statistics: Sociodemographic, clinical and psychosocial factors

Mean age of the breast cancer survivors was 36.3 years (SD=3.1; range= 26-40). Regarding education level, 45.9% had a university degree, 32.4% had completed high school and 21.6% had no more than middle school education. The majority of cancer survivors were married or lived in cohabitation (75.1%), had a biological child (70.3%) and wished to have one or another biological child (64.9%). Mean age at breast cancer diagnosis was 33.8 (SD=3.2; range=25-39) years. The mean length of survival was 30 months (SD=21.1; range= 9-96). All women underwent surgery. Most of these patients received chemotherapy (89.2%) and radiotherapy (81.1%) and 81.1% were currently undergoing endocrine therapy. Among this group, 75.7% had amenorrhea. Fertility care was received by 40.5% of cancer survivors before anticancer treatments (e.g. oocyte cryopreservation). Within the control group involving young women with no cancer history, the mean age was 34.9 years (SD=3.7; range=25-40). These women presented similar sociodemographic characteristics to the cancer group. Twenty-five (67.6%) of the 37 women had a university degree. Eighty-one percent of the controls were currently married or lived in cohabitation and 64.9% had a biological child. Independent t-tests and chi-square tests (χ^2) of independence were performed to compare the groups and confirm whether the match was successful. No group differences were found in terms of age [$t(72) = 1.77$, $p = .82$], education level ($\chi 2 = 3.66$, $p = .19$), partnership status ($\chi 2 = 0.32$, $p = .57$) and nulliparity ($\chi 2 = 0.25$, $p = .62$). Nor did groups differ in the desire for biological motherhood ($\chi 2$ = 1.46, p = .23). Additionally, between-groups comparisons were made with regard to fertility concerns and psychological distress. Table 2 shows means and standard deviations for these variables. The findings indicate that breast cancer survivors had higher scores in anxiety [t(61,19) = 3.50, p = .001] compared to healthy women. Concerning depressive symptoms and fertility-related concerns, there were no statistically significant differences. However, there was a trend for higher concerns related to fertility potential among breast cancer survivors [t(72) = 1.90, p = .062].

Table 2. Descriptive statistics (means and standard deviations) regarding fertility-related concerns and psychological distress.

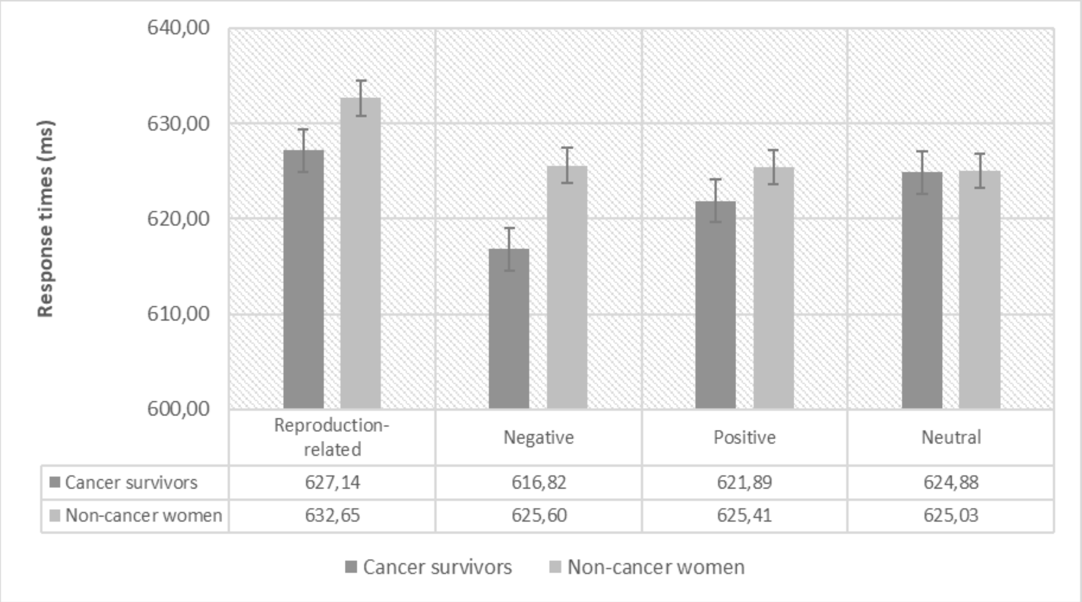
	Cancer Survivors (n=37)		**Non-cancer women (n=37)**	
Variable	**M**	**SD**	**M**	**SD**
Fertility-related concerns				
Fertility potential	2.82	.97	2.36	1.11
Partner disclosure about fertility status	2.27	1.09	2.15	1.11
Acceptance of the possibility of not having children	2.23	.86	2.23	.92
Psychological distress				
Anxiety	8.92	4.16	6.00	2.81
Depression	3.83	3.35	2.70	.44

Stroop Task – Response times and Error rates

Response times were analyzed through ANOVAS. This study used a 2-way mixed factorial design with group as a between-subjects factor (breast cancer survivors and non-cancer women) and list type as a within-subjects factor (reproduction-related, negative, positive and neutral). Following the procedure of other studies, we only considered trials with response latencies >300 ms or <2000 ms in the analysis (e.g. Carpenter et al. 2014). The ANOVA yielded a significant main effect of list type [F(3, 72)=3.08, p = .028, η^2_p=.041], although there was no significant Group X List interaction [F(3, 72)=.753, p = .521].

Overall, post-hoc comparisons indicated significant differences (p=.018) between the reproduction-related list (M=629.90 ms; SD=79.50) and the negative content list (M=621.21 ms; SD=82.82). No differences were found between the remaining word lists. However, descriptive data indicated that the color-naming times for the reproduction-related list were longer than all comparison lists, in the two groups. The main effect of group was also not significant [*F*(1, 72)=.061, *p* = .806]. Means and standard errors for response times are presented in Figure 1.

The number of errors was also calculated for each participant in each condition. Because errors were not normally distributed, Friedman tests were conducted as a non-parametric alternative. For the full sample, there were no statistically significant differences in error rates depending on list type [χ2(3)=4.65; *p*=.199]. Also, there was no significant effect of list within each group [χ2(3)=6.70, *p*=.082 and χ2(3)=2.01, *p*=.571, for the cancer survivors and for the control group, respectively]. Additionally, no group differences were observed in the number of errors within each list using the Kruskal-Wallis test [Hs<2.996; *p*s>.83]. Despite the non-significant results, descriptive statistics indicated that cancer survivors made more errors in the word lists involving negative and reproduction-related content compared to the other word lists (see Figure 2).



	Reproduction-related	Negative	Positive	Neutral
■ Cancer survivors	627,14	616,82	621,89	624,88
■ Non-cancer women	632,65	625,60	625,41	625,03

Figure 1. Descriptive statistics: Mean Stroop color-naming times (response times) for breast cancer survivors and young women without cancer history, considering each word list. *Note:* Error bars represent ± 1 SE (standard errors).

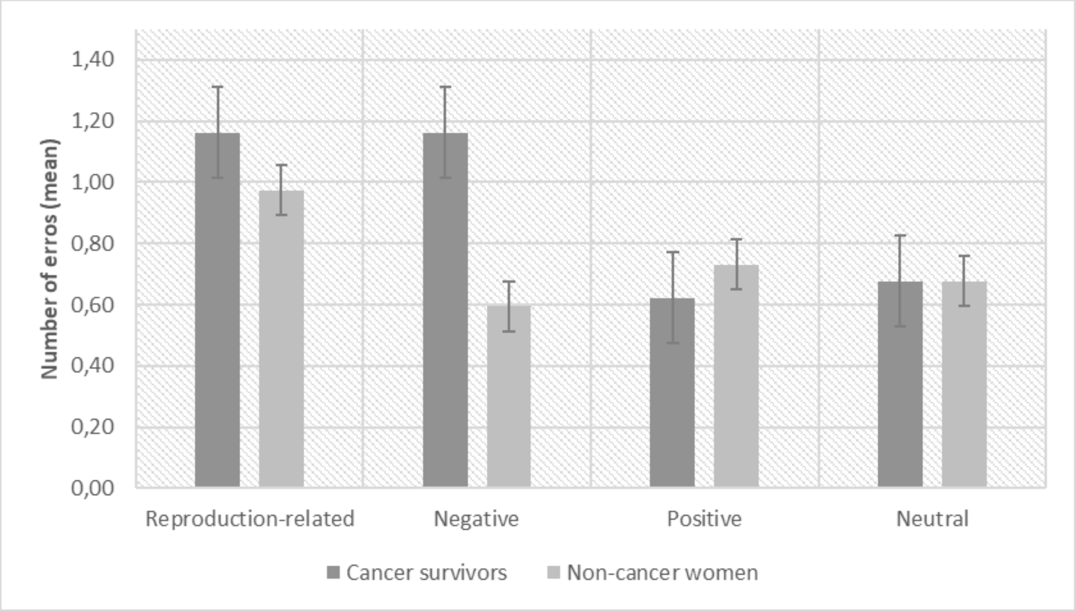


Figure 2. Descriptive statistics: Mean Stroop color-naming errors for breast cancer survivors and young women without cancer history, considering each word list.

Note: Error bars represent ± 1 SE (standard errors).

Association between reproduction-related Stroop list performance and psychological variables: exploratory analyses

In order to explore the association between reproduction-related Stroop list performance and fertility concerns and psychological distress, we performed bivariate correlations. Firstly, to examine the role of potential confounders, we tested the relationship between some demographic variables (continuous or dichotomous) and response times and error rates. Results indicated that age, being a mother, being married or living in cohabitation and wishing to have a (or another) child were not significantly associated with performance in any of the groups (*r*s<.214, *p*s>.225 and *r*s<.176, *p*s>.299, for the cancer group and the control group, respectively). When testing the association between response times and fertility concerns, the relationship was non-significant within each group. However, these analyses indicated that there was a positive correlation between Stroop color-naming times and depressive symptoms among breast cancer survivors, but not among healthy women. Therefore, a linear regression model with this single explanatory variable was conducted, showing that response latency to the reproduction-related list accounted for 13% (R^2adjusted =.127) of the variance in depressive symptoms in the cancer group [$F(1,34)=6.08$, $p=.019$; $\beta=.389$, $t=2.47$, p=.019]. Regarding error rates, the results did not reach statistical significance (see Table 3).

Table 3. Association between reproduction-related Stroop task performance and fertility concerns and distress outcomes.

	Cancer Survivors		**Non-cancer women**	
	Error Rate^a	***Response time***	***Error Rate***^{a}	***Response time***
Fertility potential	-.306	.073	.273	-.194
Partner disclosure	-.233	-.057	.076	-.114
Acceptance	-.291	.020	.074	.019
Anxiety	-.043	.284	-.009	.271
Depression	.131	.389*	-.068	.000

Note. ^{a}Spearman's rank correlation coefficients are presented because error rates were not normally distributed. *p<.05, ***p<.001

Discussion

To our knowledge, this is the first study to examine reproduction-related cognitive processing during women's reproductive years using the emotional Stroop task. Overall, results provided preliminary support for the hypothesis that enhanced attention toward reproduction-related stimuli may contribute to psychological morbidity among young breast cancer survivors.

One of the primary purposes of the current study was to compare the attentional bias to reproduction-related information in two groups: women who had a personal history of breast cancer and a matched group of women without cancer history or known fertility problems. On the basis of the common theories of attention (McLeod and Hagan 1992; Norman, 1968), we hypothesized that biases towards reproduction-related stimuli would be evident in both groups, although significant group differences should be revealed based on the presence of a known high infertility risk in the cancer survivor group. Indeed, descriptive data pointed to longer Stroop color-naming times in reproduction-related words compared to all comparison lists within both groups, although this effect only reached statistical significance for the negative content list. Additionally, there were no differences between cancer survivors and the control group with respect to response times or error rates for any list type.

The significant main effect observed for list content, with generally longer RTs for the reproduction-related list, is consistent with the broader research, which shows that reproduction-related stimuli and threat cues activate different motivational systems that mobilize attention. More specifically, contexts that promote survival activate the appetitive system and contexts involving threat activate the defense system (Bradley et al. 2001). Perhaps for this reason, response times were significantly shorter in the condition with negative emotional valence stimuli. It is possible that young women exhibited a bias away from negative-stimuli as a protective strategy (Browning et al. 2010). Correspondingly, we found an increased number of errors among breast cancer survivors in the two lists mentioned, but without statistical significance. These results are in line with previous studies using variants of verbal emotional Stroop tasks, which have also failed to find significant effects with this indicator (Custers et al. 2015; DiBonaventura et al. 2010; Suárez-Pellicioni et al. 2015).

Examination of whether reproduction-related cognitive processing was associated with fertility concerns and psychological distress symptoms (anxiety and depression) only partially confirmed our second hypothesis. First, we did not find any significant correlations between fertility-related concerns and reproduction-related Stroop list performance. Concerning this matter, there might be different reasons for this result. Unlike previous studies (Ruddy et al. 2011), we verified that there were no statistically significant group differences in terms of concerns related to fertility potential (although there was a trend in the expected direction for this variable), partner disclosure and acceptance of the possibility of not having children. In this sample, breast cancer survivors presented levels comparable to the non-cancer controls. However, attentional bias to reproduction-related cues may be associated with other concerns specifically reported by cancer survivors, which were not evaluated in the present study. Especially in a sample in which not all young women express a subjective desire to have a (another) child in the future, concerns suggested in the studies conducted by Gorman et al. (2012, 2015), such as pregnancy risks for personal health and survivorship, and a child's genetic risk, may be more related to implicit cognitive processes. This should be explored in future studies.

Interestingly, longer reaction times in the reproduction-related Stroop list were a significant predictor of depressive symptoms among breast cancer survivors, but not in young women from the general population, as expected. This finding provides support for the notion that cognitive bias to reproduction-related information may predict psychopathological symptomatology in breast cancer. Previous research with other types of emotional stimuli has already highlighted the attentional bias to threat as a key mechanism underlying affective disorders and, more importantly, as a relevant factor in the persistence and/or recurrence of depressive symptoms (Cowden Hindash and Amir 2012; Elgersma et al. 2018). The content of reproduction-related stimuli does not represent, in itself, a threat, and an approach behavior toward them is expected due to their connection with survival (Bradley et al., 2001), as mentioned above. However, elevated awareness or focus in the group with threatened fertility may interfere in daily activities and hinder the pursuit other life goals, increasing morbidity.

This study illustrates the utility of combining experimental and self-report methods to understand the full range of responses to potential fertility loss among young women diagnosed with breast cancer and their relation with psychological maladjustment. Still, it is important to point out that the present results are exploratory and are not exempt from methodological limitations. As suggested by Moritz et al. (2008), an explanation for the absence of significant differences in task performance between the two groups may be the fact that verbal stimuli have less potential to elicit attentional bias than pictorial stimuli (that are commonly used in other tasks, such as the visual dot-probe task). Moreover, participants can also use specific strategies while completing the Stroop task (Egner and Raz 2007), such as looking away from the target words and visual blurring, which suppress the potential effects of the content. Therefore, despite the scientific and clinical promise of using the emotional Stroop task (McLeod and Hagan 1992) for the purposes stated in the present work, future studies should also explore other attentional paradigms. Additionally, another potential limitation is that the breast cancer patients included in this research varied in the level of risk associated with fertility and future parenthood. For example, 10.8% of young women did not undergo chemotherapy and 18.9% did not undergo endocrine therapy, a treatment with teratogenic risks (Sutter and Pagani 2018). These and other clinical and socio-demographic characteristics of the patients sample may contribute to minimizing the expressiveness of the results. Put another way, it would be interesting to see whether young cancer survivors with a higher infertility risk, according to the specificities of the anticancer treatments used, were more likely to show a bias toward or away from reproduction-related stimuli. Limitations of this study also include the small sample size. This factor contributes to potentially limiting the power to detect as significant small to moderate differences that are evident in the descriptive data. Finally, further studies aiming to investigate the relationship between biased reproduction-related cognitive processing and distress should also include a self-report measure to assess infertility stress (e.g. see Moura-Ramos et al. 2012).

In sum, given that there was no clear evidence that breast cancer survivors exhibit differential attention to reproduction-related stimuli above young women without cancer in the current sample, care should be taken in interpreting our findings. However, overall, these results offer partial support for the idea that vigilance to reproduction-related information may be maladaptive in breast cancer survivors and strategies should be provided to deal with the threat to fertility in this context. In this respect, and particularly with women who need to postpone family building projects due, for example, to prolonged endocrine therapy (Rosenberg and Partridge 2015), interventions that aim to enrich and improve attentional processing and monitoring, thereby helping to regulate negative cognitions, can be a way forward. Techniques aiming to improve attentional flexibility may prevent the attentional bias towards reproduction-related cues from getting out of control and turning into hyperawareness and catastrophizing in relation to the infertility risk.

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STUDY 7

Attentional bias toward reproduction-related stimuli and fertility concerns among breast cancer survivors

Publication

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Abstract

The current study examined whether an attentional bias exists for reproduction-related visual cues among breast cancer survivors and its relationship with fertility concerns and emotional distress. Breast cancer survivors (n=38) aged 18 to 40 were compared to 37 healthy women recruited from the general population. Attentional bias was investigated using a visual dot-probe task and response times (RT) were measured. Participants also completed several questionnaires, including the Reproductive Concerns After Cancer Scale [RCACS] and the Hospital Anxiety and Depression Scale [HADS]. Biased cognitive processing toward reproduction-related stimuli was observed for all young women. However, attentional bias was a significant predictor of concerns about partner disclosure of fertility status, with higher bias scores associated with higher levels of concern only for breast cancer survivors. There was also a significant association between desiring to have a (or another) biological child and higher concerns related with fertility potential and lower acceptance of the possibility of not having children for all young women. Higher vigilance regarding reproduction-related cues seems to lead to higher concerns among women with breast cancer history whose fertility is threatened. This result may have important research and clinical implications. Interventions focused on goal-oriented attention self-regulation and problem-solving can help to manage fertility concerns and distress in the course of the disease.

Keywords: concerns, dot-probe, infertility, motherhood, oncology.

Introduction

Worldwide, breast cancer has been the most prevalent malignancy during the female reproductive years (15 to 49 years) in the last 5 years.[1] This diagnosis is linked to unique challenges and concerns related to the more aggressive phenotypes of tumors, genetic predisposition and infertility risks.[2]

Common anticancer treatments such as chemotherapy and radiotherapy may cause pathological and iatrogenic fertility loss. Breast cancer is one of the cancers that may require more aggressive treatment and subsequently higher risks of gonadotoxicity. [3] Also, endocrine therapies such as tamoxifen administered to women with hormone receptor (HR)-positive cancer may induce menopausal symptoms[4] and amenorrhea,[5] which raises uncertainty about reproductive capacity in younger patients. Moreover, these women are discouraged from becoming pregnant during what is often lengthy therapy [5 to 10 years] [4] due to its adverse teratogenic and fetal effects. [6]

Current scientific evidence shows that young women with breast cancer have various reproductive concerns related to important aspects of fertility and parenthood. In addition to concerns about the ability to conceive[7], women of reproductive age are worried about cancer recurrence after conception, the genetic risk of cancer for the child,[8,9] redefinition of the motherhood role[10] and the negative impact of the fertility status on their partners (or potential partners).[9] Understanding and addressing these reproduction-related concerns becomes particularly relevant for breast cancer survivors who do not have a biological child[11] or wish for (more) children in the future[12,13] since they are at risk of reporting higher levels of concern and subsequently higher emotional distress.[14] Despite generally recommended counseling to discuss fertility risks and preservation options following specific clinical guidelines, a recent cross-sectional study (N=747)[15] involving female cancer survivors showed that even when receiving pre-treatment fertility counseling, young women reported moderate to high reproductive concerns.

So far, nothing is known about how cognitive processing of reproduction-related information occurs among young women faced with risks of infertility and its relation with reproductive concerns, more specifically, concerns related to fertility. Thus, the present study aimed to explore the possible association between basic attentional processes and reproductive issues in this population. Emotional reactions are organized by appetitive and defensive motivation systems that engage processes facilitating attention allocation for specific cues.[16,17] More specifically, activation of the appetitive systems occurs in contexts that promote the survival of individuals and species, including reproduction-related stimuli such as procreation cues and scenes of families.[16] Therefore, actions of approach toward these stimuli are expected. However, when fertility is threatened, as in the case of an oncological disease, actions of withdrawal may be a strategic means. The regulatory-focus theory[18] proposes that people are motivated to avoid anticipated pain and an inclination to avoid negative outcomes is a natural strategy for preventive self-regulation, promoting security. Recognizing the influence of approach and avoidance behaviors on cognitive performance, more specifically, visual selective attention,[19] this study explored whether there was a bias in the allocation of attention toward reproduction-related visual stimuli among young women with or without cancer history.

Attentional bias was examined using a dot-probe experimental paradigm to investigate the attentional processes. [20] This has been widely applied among clinical samples involving emotional stimuli (e.g. Lam et al.[21] and Koizumi et al. [22]). We argued that a natural approach to reproduction-related content would produce a faster orientation toward these specific stimuli among young women. Based on the principles of Higgins' regulatory-focus theory, [18] we also hypothesized that women diagnosed with breast cancer compared to a non-cancer control group would have a smaller bias toward the reproduction-related cues since these stimuli could activate protective strategies associated with self-regulation in survivors.

Secondly, it is not known whether the attentional priority of stimuli related with reproduction may be associated with reported concerns and distress when biological motherhood is at risk. Cognitive research has shown that biased attention to threat meanings has a causal contribution to worry. [23] In a review study, Bockstaele et al.[24] showed that it is plausible that attentional bias maintains or exacerbates cognitive vulnerability to fear and anxiety. Therefore, our last hypothesis was that the degree of attentional bias toward reproductive cues would be a predictor of fertility-related concerns and distress among young women with breast cancer, but not among women without personal cancer history whose family building projects are not threatened and therefore, an aversive state does not co-occur.

Methods

Participants and Procedure

Two groups of young women aged 18 to 40 took part in this study: breast cancer survivors who underwent cancer treatment and women without previous history of cancer. The eligibility criteria for cancer survivors were: i) history of early-stage breast cancer (≤ IIIA); ii) no cancer recurrence; and iii) no current evidence of disease. The criteria for the control group included: i) no cancer history; and ii) no diagnosed fertility problems. Additionally, all participants should be Portuguese-speaking, not pregnant at the time of enrollment and did not undergo hysterectomy, prophylactic oophorectomy or tubal ligation procedures. This study, approved by the Ethical Committees of the Centro Hospitalar Universitário de São João, was conducted from December 2018 to June 2019. Eligible participants were contacted via phone by a researcher who explained the main aim of the study. An individual 45-minute assessment session was scheduled with those who agreed to participate and informed consent was obtained before participation. All participants completed a variant of the dot-probe task and self-report questionnaires. In order not to influence performance in the dot-probe task, participants were informed that the specific objectives of the study would be revealed at the end of the assessment. The debriefing was provided at the end of the session and all questions were answered. Nevertheless, we chose to administer the dot-probe task before the questionnaires since the questions included in the self-report measures could increase the salience of reproduction-related stimuli.

Materials

Visual Dot-Probe Task

Pictures used as visual stimuli for the dot-probe task were selected from the Open Affective Standardized Image Set (OASIS).[25] The OASIS database contains 900 color images including several themes with normative affective ratings on two dimensions: valence (negative to positive) and arousal (low to high). Firstly, a team of three researchers selected a set of images potentially related to reproductive health including scenes of families (mother-child and father-child interactions, families and siblings), partner relationships (e.g. marriage and intimacy) and pregnancy. Stimuli involving erotic and sexual content were excluded from this selection because they activate more strongly the primitive appetite system. [16,26] In a preliminary study, sixty pictures were rated in terms of their association to the reproduction theme by 31 women (14 young women previously diagnosed with cancer and 17 women without cancer history) aged 18 to 40 (M=32.16; SD=4.74) who did not participate in the main task. These women viewed each image individually and indicated their rating between 0 (*not at all related to reproduction*) and 100 (*very related to reproduction*). Based on these results, twenty pictures with higher ratings were selected for the dot-probe task. Still from the OASIS database, a set of images with content not specifically related to reproduction (e.g. people dancing and sports) was collected. The images (n=20) displayed people interacting, in order to be as close as possible in content to the reproduction-related images. Additionally, the two sets of pictures were matched regarding emotional valence and arousal, in order to isolate the effects of content. [26] Mean scores (SD) for arousal and valence were 3.71 (0.33) and 4.17 (0.41), respectively, for the reproduction-related images and 3.84 (0.49) and 3.89 (0.54), respectively, for the images with content unrelated to reproduction. No significant differences were found using *t-tests* (p>.05) for any characteristic. An additional set of control images including inanimate objects (non-human stimuli) and low on arousal (M=1.99; SD=0.13) was also selected from the database (n=10), to be included in the baseline trials. The luminance differences between the three sets of imagens were also tested using one-way ANOVA. There were no significant differences (p>.05). Mean scores (SD) for the reproduction-related images, for the images with content unrelated to reproduction and for the control images were 146.59 (32.34), 122.79 (24.68) and 126.33 (41.46), respectively.

Each trial in the dot-probe task consisted of the simultaneous presentation of two pictures, on the left and right side of the screen, with a resolution of 500 x 400 pixels. The picture pair contained a reproduction-related stimulus and a matched picture without reproduction-related content. In baseline trials, the images consisted of two control stimuli. A fixation cross was initially presented in the center of the screen for 500 ms followed by the presentation of the paired images for 300 ms.[20] Afterwards, a small asterisk appeared for 100 ms in the position previously occupied by one of the images (see Figure 1). Participants were instructed to press the Z or M response key as quickly and accurately as possible, corresponding to left or right location, respectively, to indicate the position of the asterisk (probe detection). A trial was considered to be congruent when the dot emerged on the location of the reproduction-related image and incongruent when the dot emerged on the location of the non-reproduction image. Response times (RT) were recorded for all trials. The control pair RTs (baseline trials) allowed comparison with congruent and incongruent RTs. Participants completed 8 practice trials (using additional neutral images) and a total of 180 experimental trials (60 trials for each type) without a break, presented in randomized order. Subjects did not receive visual feedback. The dot-probe task was run on a 15.4 inch monitor using E-Prime 2.0 Professional (Psychology Software Tools, Inc.).

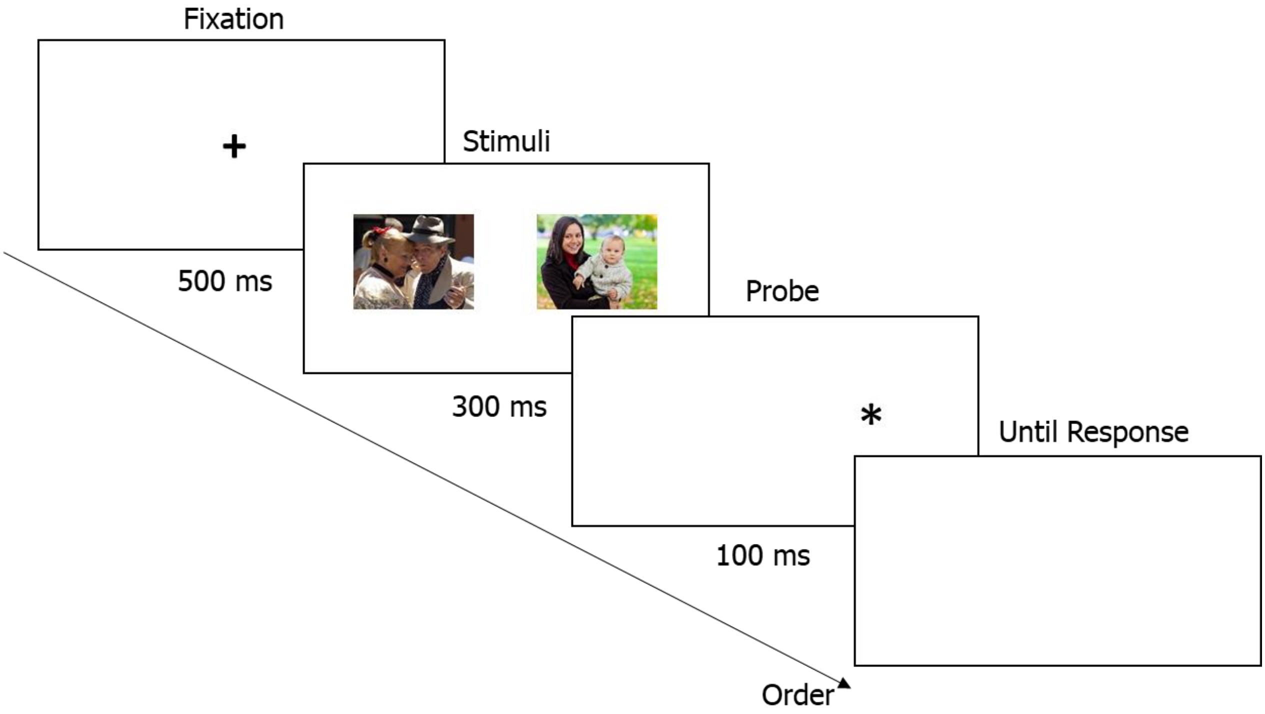

Figure 1. Dot-probe task: experimental trial sequence.

Self-report measures

Reproductive Concerns After Cancer Scale [RCACS] (Gorman et al.[27,28], Portuguese version: Bártolo et al.[29]): This 18-item multidimensional scale is reliable in assessing reproductive concerns among female cancer survivors younger than 45 years old. In this study, we used this measure to assess specific concerns related to fertility among cancer survivors and non-cancer women. For this reason, we only administered three RCACS dimensions: fertility potential, partner disclosure about fertility status and acceptance of the possibility of not having children, following the procedure of Bártolo et al.[30] Items are answered using a 5-point Likert scale. Higher scores indicate higher concerns and lower acceptance of infertility status. In the present sample, Cronbach's α presented acceptable values (ranging from .73 to .87 from fertility potential and partner disclosure, respectively).

Hospital Anxiety and Depression Scale [HADS] (Portuguese version: Pais-Ribeiro et al.[31]): This is a short scale composed of 14 items used in research and clinical practice to assess emotional distress in cancer survivors. This scale includes two subscales of seven items that evaluate anxiety (HADS-A) and depression symptoms (HADS-D). Items of both subscales are answered on a 4-point Likert scale and the total score ranges from 0 to 21, with higher scores indicating higher severity of the symptoms. A cut-off score of 11 or higher indicates moderate to severe anxiety or depression symptoms. In the present sample, Cronbach's α=.81 and α=.70 were found for the anxiety and depression subscales, respectively.

Data Analysis

All the statistical analyses were performed using Statistical Package for Social Sciences, version 24 (SPSS Inc., Chicago). Comparisons of sociodemographic and psychosocial characteristics between groups were performed with independent t-tests and chi-square tests (χ^2) of independence. In the dot-probe task, incorrect trials or trials with RTs longer than 1000 ms were excluded, accounting for 1.51% of the total data. RTs longer than 1000 ms may suggest gaps in processing.[32] As recommended in the review study by Rooijen et al.[20], mean RTs for valid trials were computed separately for congruent, incongruent and baseline trials for better understanding of the underlying mechanisms. RTs were analysed using a mixed-design 2x3 analysis of variance with personal cancer history (breast cancer survivors vs. non-cancer controls) as the between-subjects factor, and trial type (congruent vs. incongruent vs. baseline) as the within-subjects factor. When necessary, significant results were further explored with multiple comparisons with Bonferroni correction. A difference between RTs on the congruent and incongruent trials was also calculated to determine the attentional bias index, with a positive value indicating an attentional tendency toward reproduction-related stimuli. The following formula was used: Attentional bias index = [(trpl – tlpl) + (tlpr –trpr)]/2, where t=reproduction-related stimulus; p=probe location, r=right, l= left.[33] An independent-samples t-test was used to compare the attentional bias scores of the two experimental groups. Additionally, hierarchical linear regression models were used to examine how attentional bias contributed to fertility-related concerns. RCACS dimensions such as fertility potential, partner disclosure and acceptance entered the models as dependent variables. According to previous literature, a priori covariates included having a biological child and the desire to have a (or another) biological child. Lastly, the association between the bias index and the two emotional distress dimensions were determined by Pearson's correlation coefficients. These bivariate analyzes and regression models were conducted within each group. Although there were no differences in bias scores for stimuli related to reproduction between groups, based on our second hypothesis, we believe that awareness or focus on these stimuli can be associated with adjustment, only when an aversive state co-occurs (risks infertility in the case of breast cancer).[16] The size of the sample within each experimental group allowed this preliminary analysis to be carried out, since the assumption of 10-15 cases of data per predictor was met.[34]

Results

Participants' characteristics

In total, 75 Caucasian young women completed the study. Among them, 38 were breast cancer survivors and 37 had no cancer history. Table 1 shows demographic and clinical information for both groups. Between-group comparisons indicated that the match was successful. There were no significant group differences for age ($t_{(73)}$=1.780, p=.079), education ($\chi^2_{(2)}$ = 4.035, p=.136), marital status ($\chi^2_{(1)}$ = 0.585, p=.583), having biological children ($\chi^2_{(1)}$ = 0.107, p=.809), and the desire for biological motherhood ($\chi^2_{(1)}$ = 1.460, p=.324). All participants with a personal history of cancer underwent surgery. Most breast cancer survivors had received chemotherapy (89.5%) and radiotherapy (78.9%), and 81.6% were currently receiving endocrine therapy. All participants were exposed to some toxicity.

Even those who did not receive chemotherapy (10.5%), received radiotherapy with an indirect effect on the ovaries through the internal radiation scatter. The mean length of survival was approximately two and a half years. Twenty-nine cancer survivors (76.3%) had amenorrhea and sixteen (42.1%) reported having undergone fertility preservation before treatment (e.g. oocyte cryopreservation). Comparing the concerns and psychological adjustment of cancer survivors and women without cancer, we found significant group differences in anxiety levels, *t*(63.4)=3.45, *p*=.001. There were no group differences regarding fertility-related concerns and depressive symptoms (p>.05).

Table 1. Sociodemographic, clinical and psychosocial characteristics of participants.

Characteristics	**Breast Cancer Survivors (n=38) n (%)**	**Non-cancer controls (n=37) n (%)**
Age at enrolment (years), M±SD; range	36.3±3.08; 26-40	34.9±3.7; 25-40
Marital status		
Married/cohabiting	28 (73.7)	30 (81.1)
Single/other	10 (26.3)	7 (18.9)
Educational Level		
Middle school	8 (21.1)	4 (10.8)
High school	13 (34.2)	8 (21.6)
University	17 (44.7)	25 (67.6)
Occupation		
Employed/Self-employed	27 (71.1)	32 (86.5)
Unemployed	4 (10.5)	2 (5.4)
Student	0 (0)	3 (8.1)
Retired	7 (18.4)	0(0)
Time since diagnosis (months), M±SD	29.7±20.9	
Cancer treatment		
Chemotherapy	34 (89.5)	
Radiotherapy	30 (78.9)	
Endocrine Therapy	31 (81.6)	

Table 1. (continued)

Characteristics	**Breast Cancer Survivors (n=38) n (%)**	**Non-cancer controls (n=37) n (%)**
Current use of mental health care		
Yes	6 (15.8)	3 (8.1)
No	32 (84.2)	34 (91.9)
History of miscarriages/abortions		
Yes	6 (15.8)	2 (5.4)
No	33 (84.2)	35 (94.6)
Biological child		
No children	12 (31.6)	12 (35.1)
1 child or more	26 (68.4)	24(64.9)
Information about fertility-related implications		
Yes	36 (94.7)	
No	2 (5.3)	
Fertility care before treatment		
Yes	16 (42.1)	
No	22 (57.9)	
Wants a (or another) biological child		
Yes	24 (63.2)	21 (56.8)
No	10 (26.3)	16 (43.2)
Fertility-related concerns, M±SD		
Fertility potential	2.83±.96	2.36±1.08
Partner disclosure	2.28±1.09	2.15±1.11
Acceptance difficulties	2.25±.86	2.23±.92
Emotional distress, M±SD		
Anxiety	8.84±4.13	6.00±2.81
Depression	3.76±2.88	3.35±2.70

Attentional bias toward reprodution-related stimuli

The ANOVA revealed a significant main effect for trial type [*F*(2, 146)= 18.89, p<.001, η^2=.206] indicating that all participants reacted more slowly in both the congruent

(M=289.25, SD=100.16) and incongruent trials (M=294.88, SD=98.67) than control trials (M=281.90, p=99.91), implying a difficulty in disengaging from social-emotional pictures. The analysis also revealed that the congruent trials RTs were significantly lower than the incongruent trials RTs (p=.024). There was no significant main effect of personal cancer history [*F*(1,73) =1.46, p=.704], that is, participants who had previously been diagnosed with breast cancer presented overall similar RTs to those who had no cancer history. Nor was the interaction effect between trial type and personal breast cancer history statistically significant [*F*(2, 146) = 0.590, *p*=.556]. The mean RTs for the breast cancer survivors and non-cancer controls are shown in Figure 2.

Regarding the attentional bias index, no significant group differences were observed, *t*(73)=-0.709, *p*=.481. Positive values indicated biased cognitive processing toward reproduction-related images for all participants. Mean scores (SD) for the cancer group and for the control group were 4.18 (15.51), and 7.11 (20.08), respectively.

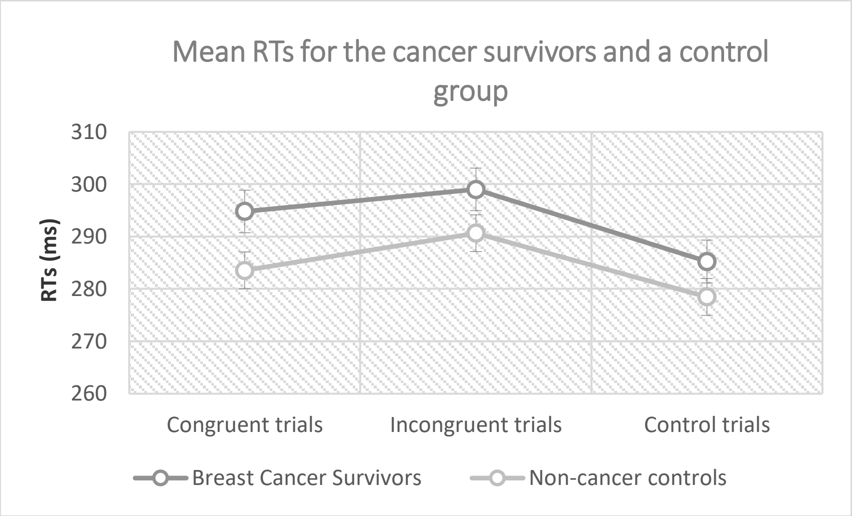

Figure 2. Descriptive statistics: mean response times for congruent, incongruent and control trials in milliseconds in both groups.

Attentional bias for reproduction-related information as a vulnerability factor

Multiple hierarchical regression models were used to examine whether attentional bias toward reproduction-related stimuli was a significant predictor of the three dimensions of reproductive concerns related to fertility. A greater attentional bias index was a significant predictor of higher levels of concern about partner disclosure, only among the breast cancer survivor group (β=.309, p=.040), after controlling the nulliparity and desire to have a child. Attentional bias and not having a biological child yet accounted for 37% of the variance in these specific concerns. A desire to have a (or another) biological child was associated with higher concerns related with fertility potential and lower acceptance of the possibility of not having children in both groups and higher concerns about partner disclosure in the non-cancer control group (see Table 2).

Finally, correlation analyses did not show a significant association between the attentional bias index and anxiety (r=.303, p=.068 and r=-.171, p=.311, for breast cancer survivors and the control group, respectively) and depression symptoms (r=.284, p=.088 and r=-.159, p=.347, for cancer survivors and the non-cancer group, respectively).

Discussion

To the best of our knowledge, this is the first study to examine attentional biases toward reproduction-related information among women of a reproductive age. Overall, the results suggest biased attention toward these specific stimuli using a variant of the dot-probe paradigm. Consistent with our predictions, higher vigilance regarding reproduction-related visual cues was observed. Younger women tended to have shorter RTs in congruent trials, i.e., trials where the probe replaced the reproduction-related image, than in incongruent trials. This is not surprising since biologically significant stimuli modulate attention. Pictures involving survival and procreation scenes elicit activation of the motivational system[16] that prepares the organism for responses to those events, increasing attention allocation. Besides, stimuli involving babies and children, which integrated the set of images with reproduction-related content, may have made the attentional bias more pronounced (e.g. Brosch et al.[35]), as previous evidence revealed an attentional bias toward human infants. [36] Konrad Lorenz[37] even proposed the concept of kindchenschema (baby schema), showing that infantile physical characteristics presented high adaptive value, motivating care.

Furthermore, we found a reduction in the attentional bias index of breast cancer survivors compared to the controls, but group differences failed to reach statistical significance. Thus, withdrawal strategies as a means to cope with reproduction-related stimuli do not seem to be used primarily by patients facing a threat to fertility and consequent family building projects. However, importantly, hypervigilance mechanisms may be maladaptive in this group and contribute to maintaining fertility-related concerns. Regarding this matter, we found that while the attentional bias toward reproductive-stimuli does not seem to differentiate between women with a personal history of cancer and controls, heightened attention to reproduction-related stimuli may become a vulnerability factor for the first group.

Specifically, regarding the expected relationship between attentional bias and fertility-related concerns, results suggested that increased cognitive bias toward reproduction-related clues is associated with higher levels of concerns related to partner disclosure about fertility status, only in cancer-survivors. This result is in line with the literature that presents attentional bias to threat as a causal factor for worry.[23] Although reproduction-related images do not pose a threat in themselves, they illustrate an area of life that is threatened by illness and its treatment, and is commonly associated with psychological suffering.[14] Thus, greater sensitivity to these stimuli and the projects that they represent can prevent the reorganization of other significant life goals and increase the concern and burden. In particular, in the field of romantic relationships, fear of rejection has been reported by younger women who felt pressure to find a partner or give the partner (or potential partner) a child.[8,38]

As in previous studies,[12,13] we also observed that the desire for biological motherhood is an important risk factor for higher fertility concerns and lower acceptance of potential infertility in all young women. Therefore, considering the special biological role of women in motherhood, knowing their family building projects and discussing fertility options during a cancer diagnosis process is essential.

Table 2. Regression models predicting fertility-related concerns.

Dependent variable: Fertility potential													
		Breast cancer survivors F(3,30)=9.345, p<.001						**Non-cancer controls** F(3,33)=4.434, p=.010					
Step	**Variable**	**Adjusted R^2**	***B***	**SE**	***β***	***t***	***p***	**Adjusted R^2**	***B***	**SE**	***β***	***t***	***p***
1	Nulliparity (no biological (children=1)	.412	.250	.308	.112	.811	.424	.238	.478	.349	.209	1.369	.180
	Desire to have a (or another) biological child (no=1)		**-1.375**	**.299**	**-.633**	**-4.605**	**<.001**		**-.945**	**.336**	**-.429**	**-2.811**	**.008**
2	Attentional bias index	.431	.014	.010	.195	1.434	.162	.222	.005	.008	.083	.550	.586

Dependent variable: Partner disclosure													
		Breast cancer survivors F(3,30)=7.345, p=.001						**Non-cancer controls** F(3,33)=4.120, p=.014					
Step	**Variable**	**Adjusted R^2**	***B***	**SE**	***β***	***t***	***p***	**Adjusted R^2**	***B***	**SE**	***β***	***t***	***p***
1	Nulliparity (no biological (children=1)	.292	**1.034**	**.322**	**.485**	**3.215**	**.003**	.214	.328	.354	.143	.926	.361
	Desire to have a (or another) biological child (no=1)		-.453	.311	-.220	-1.455	.156		**-.983**	**.341**	**-.446**	**-2.878**	**.007**
2	Attentional bias index	.366	**.022**	**.010**	**.309**	**2.146**	**.040**	.206	-.007	.008	-.125	-.823	.416

Table 2. (continued)

Dependent variable: Acceptance of the possibility of not having children													
		Breast cancer survivors F(3,30)=3.250, p=.035						**Non-cancer controls** F(3,33)=3.451, p=.028					
Step	**Variable**	**Adjusted R^2**	***B***	**SE**	***β***	***t***	***p***	**Adjusted R^2**	***B***	**SE**	***β***	***t***	***p***
1	Nulliparity (no biological (children=1)	.184	.472	.316	.242	1.494	.145	.193	.431	.298	.227	1.444	.158
	Desire to have a (or another) biological child (no=1)		**-.688**	**.306**	**-.364**	**-2.248**	**.032**		**-.676**	**.287**	**-.369**	**-2.353**	**.025**
2	Attentional bias index	.170	.007	.011	.112	.680	.502	.170	.001	.007	.031	.199	.843

Nevertheless, a number of methodological limitations of the current study need to be addressed. First, due to the small sample size, the power to detect small to moderate differences between groups was limited. Furthermore, a larger sample would have allowed examination of additional predictors and/or moderators of reproductive concerns and distress. Second, this study used a cross-sectional design, and could not establish how attentional bias may contribute to the development and maintenance of fertility-related concerns among breast cancer survivors faced with infertility risks. Longitudinal studies should be conducted to evaluate attentional bias at various points during diagnosis and survival. Third, we were unable to include in our design a comparison group of women with objective fertility problems, but without a cancer history. In the future, this may lead to better conclusions about particular circumstances of the breast cancer survivor. Fourth, no significant results were found regarding distress. However, HADS is a more generalist measure of distress. Future studies should assess infertility stress (e.g. Fertility Problem Inventory; Portuguese version by Moura-Ramos et al.[39]) and its relationship with cognitive bias. Fifth, 42.1% of the cancer survivors reported having undergone fertility preservation. This aspect should be considered in later analysis with a larger sample, although in our preliminary correlation analyzes it has not been shown to be associated with any of the variables studied and, for that reason, it did not enter into regression models. Lastly, future research should use eye-tracking methodology to assess other more objective indicators of attention allocation and bias toward the various types of stimuli.

Conclusions and clinical implications

The findings of the present study contribute to better understanding the cognitive processing of reproduction-related information and its relationship with fertility concerns reported by young women with breast cancer. Overall, the results support the idea that there is hypervigilance to reproduction-related visual cues, which negatively influences concerns related to partner disclosure of fertility status only for cancer survivors. While more research is needed to validate the current results, interventions promoting goal-oriented attention self-regulation and problem-solving strategies may enhance the ability to cope with disruption of family building projects. Strategies focused on identifying and challenging the beliefs associated with biological motherhood may help to improve psychosocial outcomes during the treatment process.

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***Note:** Reference list formatted according to the American Medical Association style based on Behavioral Medicine guidelines*

CHAPTER IV

General discussion

Cancer and its treatments may affect a woman's fertility and with this family building projects (Stensheim et al., 2011). Various studies demonstrate that reproduction-related issues can be an additional challenge in the lives of young women after cancer, with implications for their psychological adjustment (e,g. Howard-Anderson et al., 2012; Logan et al., 2019; Logan & Anazodo, 2019). This work provides innovative, theoretical and empirical contributions about the experience of younger cancer survivors who face fertility risks, with a focus on breast cancer considering the robust data on its impact on reproductive health (Poorvu et al., 2019).

A series of seven studies were conducted, of which five are empirical studies that involved self-report and experimental methods, allowing us to understand the full range of responses to the threat to biological motherhood. In addition, we fill a gap in research at the national level, when we look beyond decision-making in preserving fertility (e.g. Melo et al., 2017) and try to understand the subjective perception of reproductive concerns and uncertainties throughout survival. In this section, to avoid overlapping this general discussion with the discussion of each individual study, an integrated overview of the main results will be presented.

What are the main reproductive concerns reported and how do they affect young women surviving cancer?

In the first study of this work, an overview of the current literature has been provided to guide empirical studies with regard to reproductive concerns among young female cancer survivors. Given the barriers that still exist in fertility care after cancer, from fertility counseling to the referral process (e.g. Logan & Anazodo, 2019; van den Berg et al., 2019; Young et al., 2019), this was a major issue addressed in the present work. We felt the need to provide a conceptual framework to understand the main concerns of cancer survivors and associated factors, which can assist clinical practice (Bártolo et al., in press a; Study 1). This was made possible through a systematic synthesis of mixed-methods.

The data are in line with the literature reviews previously carried out, pointing to concerns related to menstrual changes, fertility, pregnancy and child-referred and partner-referred concerns in female cancer survivors (Anchan & Ginsburg, 2010; Howard-Anderson et al., 2012; Peate et al., 2009; Schmidt et al., 2016; Sobota & Ozakinci, 2014). However, perhaps due to the broad scope of previous research, only with our more focused review was it possible to clearly identify the variability of reported concerns and the impact that the family life cycle phase has on them. For instance, young women with dependent children seem to be more worried about redefining the motherhood role after cancer, while childless women feel the pressure to find a partner and have children (Bártolo et al. in press a).

The United States has undertaken considerable research in this field, unlike Portugal and other European countries. No study had provided a validated scale to assess these issues in Portugal. Accordingly, the multidimensional scale of Gorman et al. (2014) was validated for the Portuguese population, allowing to identify a wide range of concerns related to fertility and parenthood among young women after cancer diagnosis. Possible linguistic and cultural nuances led to finding a factorial structure slightly different from the original version of this scale, distinguishing the concerns of Portuguese women in five dimensions: fertility potential, children's health risk and future life, partner disclosure, barriers to getting pregnant/having children and acceptance (Bártolo et al., 2020a; Study 2). Among Portuguese cancer samples, children's health risk and future life was one of the most cited concerns (Bártolo et al., 2020b; Study 3).

Younger age, reproductive characteristics (e.g. not having a biological child and desire to have children [e.g. Villarreal-Garza et al., 2017]) and previous treatments such as chemotherapy, are well-established (Bártolo et al. in press a) as factors that affect reproductive concerns among young women and this is partially confirmed in our empirical studies using young adults diagnosed with breast cancer (see Bártolo et al., 2020a; Bártolo et al., 2020d; Study 7). There is still a lack of understanding of the mechanisms involved in the maladjustment, which was tackled in this research. The second empirical study of this work (Bártolo et al., 2020b) explored complex relationships. In addition to the direct association of reproductive concerns with quality of life, as recently shown by Benedict et al. (2018), we confirmed a negative relation between the importance of motherhood (that is, more need to have children and a more negative view of a childless life) and physical, social and emotional functioning in breast cancer survivors, when reproductive concerns are present. While a direct effect of these specific concerns on depression (e.g. Gorman et al, 2010; 2015) was not supported in our data, according to this study, reported reproduction-related concerns must be a target for intervention to alleviate the deterioration in quality of life, especially for women who still have unfinished family building projects. It should be noted that the desire to have children can change over time (Armuand et al., 2014) and the need to achieve normality (Schmidt et al., 2016) can encourage women to consider this option later in their lives.

Furthermore, some evidence that cancer survivors present an experience identical to that of young women faced with an infertility diagnosis has emerged (Penrose et al., 2013). In the specific context of breast cancer, Study 4 (Bártolo et al., in press b) follows this line of findings and pointed to similar fertility concerns between cancer survivors who wish to have children and non-cancer infertile women. Our data goes further, showing that even without knowing the fertility status, uncertainty can be linked to fertility-related distress. Infertility risks threaten femininity (Dryden et al., 2014) and the sense of adequacy and connection (Halliday et al., 2014; Loftus & Andriot, 2012), considering that motherhood is expected from a social point of view. In the case of young women with cancer, in addition to experiencing concerns, and consequently, their potential impact on HRQoL (as shown in Bártolo et al., 2020b), there is also the physical wear and tear resulting from the aggressiveness of cancer treatments (Bártolo et al., in press b).

Are psychoeducational interventions using distance approaches an effective alternative intervention to alleviate maladjustment?

Marginalization of the discussion of reproductive concerns is a serious problem considering the impact they can have on psychological morbidity (Gorman et al., 2015) and quality of life (Bártolo et al., 2020b) within a cancer population. Data from our studies showed that about 5.3% (Bártolo et al., 2020d) - 16.7% (Bártolo et al., 2020a) of female cancer survivors aged 40 years and under had not received any information about fertility-related implications, which can cause uncertainty and maladjustment to persist (Logan et al., 2019). Even those women who receive fertility counseling may not have their needs answered (Young et al., 2019; Melo et al., 2018). Therefore, one theoretical challenge of this work was precisely to examine how innovative psycho-educational programs using telecommunication technologies could be a complementary alternative of intervention. Barriers to oncofertility care, such as lack of time, lack of knowledge and the subjective judgment of medical staff (e.g. Melo et al., 2018; Quinn et al., 20007; 2009; van den Berg et al., 2019), can be reduced through these approaches.

Overall, evidence of the effectiveness of interventions was limited by the small effect size. However, most interventions based on a cognitive-behavioral framework, involving health education, training in problem-solving skills and stress management (Bártolo et al., 2019; Study 5), were associated with trends for a reduction in distress symptoms not specific to fertility and better overall quality of life, mainly in a breast cancer setting in women over 45 years of age. Still on this matter, studies conducted in the last 10 years did not cover the wide range of fertility and parenthood issues, although they include specific concerns related to family and sexuality. Therefore, these results cannot be generalized to young women. Despite this, they are the first step to (re)instigating the development of psycho-educational interventions using distance approaches dedicated to cancer survivors in their reproductive years.

Assuming that these interventions may be an effective way to directly mitigate the psychosocial impacts of oncological disease on patients with cancer in an active phase and disease-free survivors, it will be worth investing in new, more cost-effective protocols. The delivery resources used in previous studies are varied, including telephone, internet, video and booklets. Research by Aarts et al. (2012) and Meneses et al. (2010a; 2010b) indicates web-based interventions as a more promising form in the context of infertility, provided they include the simulation of therapist-patient interactions. Importantly, while these programs are mostly delivered by nurses, the presence of a dedicated psychologist can be a facilitator in improving outcomes (Razzano et al., 2014).

Reproduction-related information processing biases: a new path for intervention

It was recognized through this work that younger women with a history of breast cancer may have more fertility concerns than healthy controls, when dealing with the threat to their reproductive potential (Bártolo et al., in press b). In addition, the literature pointed to more survivorship symptoms such as anxiety, depressive symptoms and fatigue among these younger survivors compared to older survivors (Champion et al., 2014). For that reason, in Studies 6 (Bártolo et al., 2020c) and 7 (Bártolo et al., 2020d), a broad understanding of the mechanisms that give rise to emotional responses among breast cancer survivors has been provided. *Quasi*-experimental methodologies were designed to assess hypotheses concerning reproduction-related information processing biases (see McLeod & Bucks, 2011).

Specifically, preliminary evidence indicated that all young women with or without a previous cancer diagnosis presented attentional bias (hypervigilance) to reproduction-related cues compared to identical stimuli in terms of affective ratings, but with unrelated content. This effect was most notorious with the dot-probe paradigm (Bártolo et al., 2020d). In the emotional Stroop task (Bártolo et al., 2020c), participants were slower naming the color of reproduction-related words in comparison to unrelated negative valence words. However, this difference did not reach statistical significance for other unrelated word lists (e.g. positive and neutral). This is not surprising since pictorial cues have been recognized for their greater potential to elicit the allocation of attention (e.g. Moritz et al., 2008).

Because some women diagnosed with cancer avoid thinking about reproductive issues to deal with pain (Canada & Schover, 2012), we expected that the history of cancer and the resulting fertility risks would trigger differences in the performance of survivors and controls in experimental approaches. However, a natural approach to reproduction-related stimuli was suggested, regardless of the co-occurrence of an aversive state, with an impact on morbidity. Longer Stroop color-naming times in reproduction-related words and a greater attentional bias index, after controlling for nulliparity and the desire to have children, in the modified dot-probe task were significant predictors of depressive symptoms and concerns about disclosing fertility status to a partner, respectively. Interestingly, this effect only reached significance among breast cancer survivors at risk of infertility and not in healthy controls from the general population, which is in line with cognitive theories (e.g. Mathews & McLeod, 2005).

Therefore, current data indicate that attentional biases may associate maladaptive cognitive responses to infertility risks in a cancer setting. These findings should be interpreted with caution, as there was no clear evidence that breast cancer survivors exhibited differentiated attention to stimuli related to reproduction. Even so, this knowledge is important to improve the intervention, indicating the need to carry out programs that, in addition to including educational components, are focused on attentional flexibility and self-regulation.

Limitations and implications for future research

First of all, it is important to highlight that one of the strengths of this work lies in taking a comprehensive approach to the impact of reproductive health issues in cancer, drawing attention to how they can be a factor contributing to adjustment difficulties. Most importantly, our studies conducted with female cancer survivors contributed innovatively to the literature and pointed to new intervention proposals in this context. Another strong point is that empirical evidence only included young women diagnosed with cancer in adulthood, whose motherhood was not yet something far out of reach. Some of them stated that they had not yet completed their family at the time the disease appeared. Many previous studies involved diagnoses at different stages of life, including childhood and adolescence (e.g. Benedict et al., 2016b; Carter et al., 2010a; Kim et al., 2016). This could have influenced their results in terms of psychosocial adaptation. Despite this, our results are not exempt from limitations and must be carefully interpreted.

Among the most significant limitations, mentioned in each of the scientific articles, is the fact that the empirical studies have a cross-sectional design. Unfortunately, despite this approach guaranteeing the feasibility of studies within the context of a Ph.D. work, it is not possible to establish the trajectory of reproductive concerns, attentional bias and distress from diagnosis to long-term survival. Future projects should contemplate longitudinal studies, maintaining the same complementarity between self-report measures and experimental approaches. This design would allow not only characterizing the experiences of women after cancer over time, but also capturing better the directionality of the relations between the study variables, and enhance knowledge about potential targets to be considered in prevention. Moreover, to explore hypotheses about specific concerns in Portuguese female cancer survivors qualitatively and, more specifically, to set goals in conducting psychoeducational programs, a mixed methods approach can also be useful.

Numerous arguments supported the use of the RCACS to assess fertility and parenthood concerns in all studies. While the evidence for the validity and reliability of the RCACS for the oncological context was established (Bártolo et al., 2020a), our results were focused mostly on a sample of women with breast cancer. The invariance of this measure should be explored across cancer types, mainly because the factorial structure found was different from the English (Gorman et al., 2014; Gorman et al., 2019) and Chinese (Qiao et al., 2017) versions.

The remaining empirical studies (Bártolo et al., 2020b; 2020c; 2020d; Bártolo et al., in press b) only used women with breast cancer. Although this gives broad knowledge of the experiences in this context, it may not reflect the response of women diagnosed with other malignancies and, consequently, other specificities in the treatment. In Study 6 (Bártolo et al., 2020c), we also speculate that variability in objective infertility risks based on the therapeutics administered to each breast cancer survivor could introduce nuances in the results. Nevertheless, as suggested by the review by Logan et al. (2019) and supported by our results in Study 4 (Bártolo et al., in press b), we must not forget that concerns and distress are also related to the patient's subjective perception of fertility status. We are not able to understand whether previous fertility care at diagnosis could be a protective factor of adjustment in survival. Most women included in this work (57.9%-82.8%) were not subjected to preventive fertility preservation measures (e.g. cryopreservation of unfertilized oocytes). However, future studies should consider the role of this factor. It is known that preserving fertility can be seen as a way of maximizing the chances of being a mother, but also as a factor that generates fear of cancer development/recurrence in some women (Assi et al., 2018).

Considering the studies (Bártolo et al., 2020c; 2020d) that evaluated attentional processes as a factor that may explain adjustment difficulties in reproductive age, it is also possible to go a step further. In addition to overcoming classic limitations, such as increasing the sample size to detect small to moderate effects, or finding visual and verbal stimuli more specifically related to reproduction, we could associate the use of response time paradigms with other more objective measures of attentional allocation. For instance, pronounced heart rate deceleration, greater skin conductance activity and pupil dilation are recognized as physiological indices of attention (Lang & Bradley, 2013). Furthermore, capturing evoked-related potentials (ERPs) using electroencephalography (EEG) with high temporal resolution and, as such, highly sensitive to the temporal dynamics of brain processing (Thomas et al., 2007) will allow more precise identification of the moment when the attention bias occurs. Therefore, this would be valuable to consider in future research.

Finally, data collection included mainly women followed in a public referral hospital from the north region of Portugal and may not be representative of women who live in other areas and are followed by private healthcare services, mainly with regard to reported reproduction-related concerns. Still, at the sociodemographic level, most women eligible for the different studies were married or were cohabiting (about 70%) and it is known that this can influence their experience (e.g. Bártolo et al., in press a; Gorman et al., 2014). Although some of our studies evaluated/controlled this aspect (Bártolo et al., 2020a; Bártolo et al., in press b), we did not consider using dyadic approaches to distinguish between intra-individual and cross-partner influences. However, the literature indicates that members of a couple are non-independent (Kenny et al., 2006), and they can also influence each other in a context where infertility after cancer can limit the plans not only of the woman, but of the couple in terms of family building. Thus, considering the couple as the unit of analysis can be a challenge in the future.

Recommendations for clinical practice emerging from this research

Personalized care in the context of cancer at a young age, more specifically breast cancer, should consider the planning of life after diagnosis including family building projects (Christinat et al., 2012). Figure 1 summarizes the main clinical implications of this work. In fact, the data obtained in this research work suggest that, among younger women, there should not only be screening for psychological distress as a common reaction to cancer, but the assessment of reproductive concerns should also be part of routine clinical practice. This research provided a validated measure to assess these concerns, facilitating the work of clinicians. This will minimize patients' marginalization based on clinical judgment, and in the long-term, can promote their quality of life. A younger age, parenting desires and specific questions related to the therapies used are determinant in the intensity of the concerns experienced and must be considered in a wide initial evaluation by oncologists and/or nurses establishing continuous contact with patients.

As previously mentioned, internationally established guidelines advocate fertility counselling, including referral to fertility preservation care, but do not set out how this should occur (Logan & Anazodo, 2019). Obviously, this has implications from initial assessment to follow-up. As suggested by Benedict et al. (2016a), counselling should include a balanced approach between hope and optimism and the promotion of realistic expectations. In Portugal, it is not yet clear who is responsible for providing information referring to the threat of infertility (Almeida et al., 2016) and the referral process to fertility teams still has gaps (Melo et al., 2017). However, the definition of who should conduct fertility counselling and multidisciplinary collaboration in this process may promote effectiveness in establishing referral paths and a lower burden associated with fertility and motherhood issues in the future.

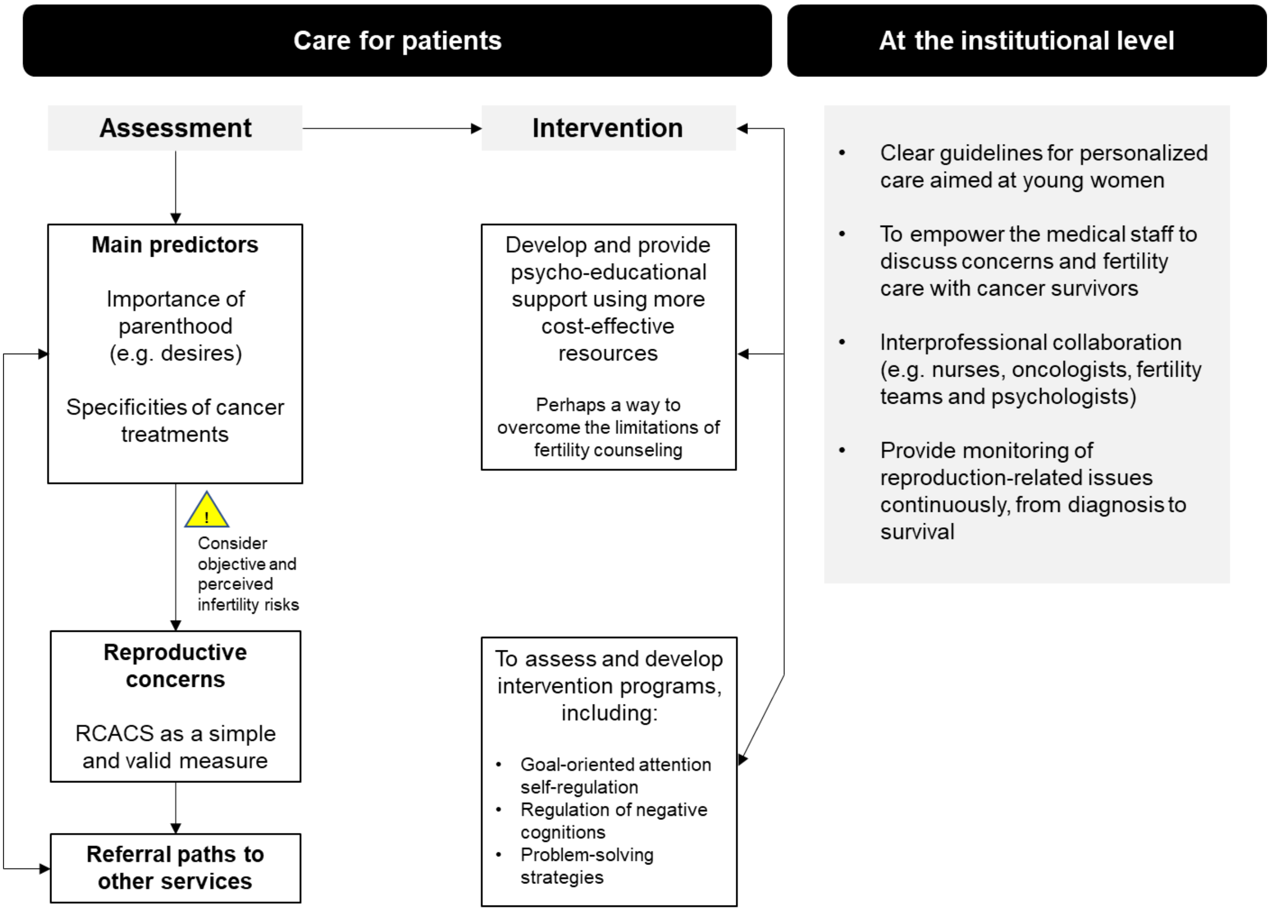

Figure 1. Simplified integration of the main results and their implications.

In this line of thought, our work reinforces the integration of the psychologist, as a member of the team, in this context, both at the remedial and preventive level. This professional may be at the forefront in the provision of support programs, in recognition of the increased risk of psychological morbidity and worse quality of life among patients with breast cancer and uncertainty about fertility. We are aware that not all patients can be part of support programs due to the cost this would represent for health care systems, so again it is important to do an initial screening for fertility-related distress.

The adaptation of psycho-educational programs aimed at women with fertility problems, without cancer history, can be considered in the intervention, given the similarities between their experiences and those of women with cancer, regarding concerns and psychosocial adjustment. However, there must be an additional attempt to provide a more cost-effective response to their needs through, for example, web-based approaches. If, at the time of conducting our studies (prior to the COVID-19 pandemic), the relevance of these approaches in overcoming geographical constraints had been highlighted, maybe today, in the COVID-19 era, these would include useful tools to respond to the needs of social distancing. Furthermore, new directions for intervention emerge with this work. An overall attentional bias toward reproduction-related stimuli and its association with maladjustment in breast cancer patients indicate that early therapeutic interventions aimed at modifying dysfunctional beliefs and interrupting maladaptive information-processing, including intrusion, may benefit such patients.

Lastly, in addition to the aspects that are already part of the training of oncologists and nurses specialized in oncology, the empowerment of these professionals in relation to the reproductive challenges of cancer at a young age becomes important. Their training should include not only information on fertility preservation techniques, but also incorporate information about concerns and emotional symptoms that result from threatened reproductive potential and what it can represent in terms of the family’s life cycle.

CHAPTER V

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