The role of cognitive biases in the maintenance and management to fear of cancer recurrence or progression

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A thesis submitted in fulfilment of the requirements for the degree of

DOCTOR OF PHILOSOPHY (PhD)

September 2022

Statement of Originality

I certify that the intellectual content presented in this thesis is the product of my own work and the guidance that I received from my supervisors during my PhD candidature. All the sources that have helped in writing this thesis have been acknowledged.

This thesis has not been submitted for any other degree or other purposes.

Poorva Pradhan

18th September 2022

Acknowledgements

There are a number of people who I want to deeply thank for their guidance and support during my PhD journey.

The first and foremost in this list is my lead supervisor, Professor Louise Sharpe, who I deeply respect as a clinician and researcher. Louise, you have effortlessly mentored and supported me through the challenges throughout my candidature. Our lengthy and conceptual discussions about the project not only helped me immensely to formulate the ideas in this thesis but also shaped my scientific temperament. I am also very grateful for your critical comments on my writing, which greatly improved my writing skills specifically for manuscripts. I have learnt so much from you Louise during this course which will be treasured throughout the rest of my career. You are truly inspirational, Louise.

I was also very fortunate to be supervised by Emeritus Professor Phyllis Butow and Dr Jemma Todd. Phyllis, thank you so much for bringing your extensive expertise into my PhD project as well. You are truly a legend in the field of Psycho-oncology. Thank you so much Jemma for bringing your 'Cognitive biases' expertise to my project and for giving me feedback on endless drafts and for giving me some valuable ideas to improve in our lab group presentations. I feel so honoured and fortunate to have had such an exceptional supervisory team. It could not have been better! Also, a special mention to Dr Lauren Heathcote, whose Cancer Threat Interpretation model formed the basis of this thesis and for being such an amazing collaborator to work with. A special thanks to two of my collaborators – Dr Wendy Lichtenthal and A/Prof Courtney Beard for providing their valuable expertise in designing the last study (Chapter 8).

Next, I would like to extend my sincere gratitude and appreciation to all the wonderful participants who contributed their invaluable time to the series of empirical studies

in this thesis. A cancer diagnosis is one of the most distressful experiences and having to recall their experiences is no small feat. This thesis would not have been possible without the support of the participants. Also, a special thanks to Ovarian Cancer Australia (especially Hayley Russell) and Breast Cancer Network Australia to help me recruit participants from their respective registries throughout this project. I really hope this work goes some way in helping these patients through this difficult journey.

Lastly and most importantly to my parents (Prof. Prakash Sharma and Mrs. Shashi Sharma), my brother (Siddharth Pradhan) and all my friends. Dad, I don't have words to describe how invaluable your contribution is towards my academic career. You are my source of motivation everyday especially when I was writing this thesis and I kept doubting myself. To my mum, thanks for being so patient during these four years. Thank you so much for your endless love and support and for providing me this excellent opportunity to come to Australia to pursue my dreams. This thesis is dedicated to you. To my friend - Janette, for providing a balance in my life! A special thanks to Andres Bagadion - you kept me sane and constantly encouraged me during the last stages of my PhD.

Publications Included in the Thesis

1. Pradhan, P., Sharpe, L. & Butow, P. (2021). The role of attentional biases in the context of cancer. *Psycho-Oncology, 30* (5), 649-658. doi: 10.1002/pon.5617.

2. Pradhan, P., Sharpe, L., Butow, P. & Russell, H. (2021). The role of interpretation biases and symptom burden in fear of cancer recurrence/progression among ovarian cancer survivors. *Psycho-Oncology, 30* (11), 1948-1956. doi: 10.1002/pon.5748.

3. Pradhan, P., Sharpe, L., Butow, P., Coutts-Bain, D. & Heathcote, L.C. (2022). Does interpretation bias moderate the relationship between pain and fear of cancer recurrence? *Health Psychology.* https://doi.org/10.1037/hea0001217

4. Pradhan, P., Sharpe, L., Butow, P., Smith, A., Russell, H. (2021). Is a brief online booklet sufficient to reduce fear of cancer recurrence or progression in women with ovarian cancer? *Frontiers in Psychology*, 12, 634136.

5. Pradhan, P., Sharpe, L., & Menzies, R. E. (2021). Towards a stepped care model for managing fear of cancer recurrence or progression in cancer survivors. *Cancer Management and Research*, *13*, 8953.

Other related publications

1. Coutts-Bain, D., Sharpe, L., Pradhan, P., Russell, H., Heathcote, L. C., & Costa, D. (2022). Are fear of cancer recurrence and fear of progression equivalent constructs?. *Psycho-oncology*, *31*(8), 1381–1389. https://doi.org/10.1002/pon.5944

2. Sharpe, L., Jones, E.B., Pradhan, P., Todd, J., & Colagiuri, B (2022). A double-blind Phase II randomized controlled trial of an online Cognitive Bias Modification for Interpretation program with and without psychoeducation for people with chronic Pain. *Pain*. (in-press)

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Abstract

Introduction: With an increase in cancer survival rate, a growing number of survivors are faced with a wide range of survivorship issues. Fear of cancer recurrence/progression (FCR/P) is amongst the most reported long-term consequences, which makes the survivorship phase challenging. Life after cancer can be characterized by an altered sense of bodily perception; in particular about interpreting the meaning of physical sensations, such as pain, which promotes fear about cancer recurrence. According to information processing frameworks, cognitive biases such as, attentional and interpretation biases explain how an individual processes information related to threat. Whereas extensive research has established a link between cognitive biases and anxiety, much less is known about the interplay of these processing biases in terms of FCR/P. The broad aim of the research is to gain understanding on the role of cognitive processing biases in the maintenance and development of FCR/P.

Aims: More specifically, this project aims to: (1) to summarize and synthesize the literature on the presence and impact of cognitive biases in cancer survivors, (2) to examine whether people with cancer are more likely to interpret ambiguous stimuli as illness-related as compared to people without cancer, (3) to test the central tenet of the Cancer Threat Interpretation model of FCR/P, that that interpretation bias moderates the relationship between the severity of symptoms (e.g., pain) and FCR/P in two samples of women with ovarian, and breast cancers, (4) to propose a stepped care model of FCR/P and, (5) to test the efficacy of two minimal interventions to reduce FCR/P, namely a psycho-educational booklet on FCR/P and a cognitive bias modification for interpretation (CBM-I).

Methods: The thesis is comprised of five parts. In Study 1, a meta-analysis on attentional bias amongst cancer patients was conducted and also a scoping review to highlight the

potential gaps in this area. Both Study 2 and 3 tested the central tenet of Cancer Threat Interpretation model in an ovarian, and breast cancer sample. In particular, Study 2 examined the present of interpretation biases in ovarian cancer patients (N = 62) as compared to healthy controls. Study 3 was an extension on the Study 2 in terms of including a larger sample size and examining other predictors of FCR/P in a sample of breast cancer patients (N = 147). Both study 2 and 3 used Ambiguous cues task to measure interpretation biases. Study 4, which was conducted in part to Study 2 tested the efficacy of an online booklet to manage clinical FCR/P after a week of reading this booklet (N = 50). Finally, based on the recommendations from the review on FCR/P interventions, study 5 tested the CBM-I versions (pain and cancer-specific) compared to placebo in sample of people with ovarian or breast cancer (N = 174).

Conclusions: the results from the meta-analysis suggests that people with cancer display a significant attentional bias compared to people without cancer. This bias was stronger in cancer survivors who were more distressed versus to those who were not. The scoping review also highlighted a paucity of evidence in terms of interpretation and memory biases. Following the recommendations arising from the review, a series of two empirical studies suggested the presence of interpretation bias in both breast and ovarian cancer patients compared to people without cancer. Furthermore, these studies also concluded that this bias was stronger in patients who had high levels of FCR/P as compared to people with low FCR/P. In the breast (but not ovarian) cancer sample, interpretation bias moderated the relationship between pain-specific symptoms and FCR/P. Study 4 found that a booklet that addressed key aspects of FCR did not reduce FCR/P in women with ovarian cancer. Indeed, the review paper presented in Chapter 7 confirmed no evidence for any minimal intervention for FCR/P. To fill that gap, the results from Study 5 provided promising support for CBM-I interventions to manage clinical FCR/P. That is, both pain and cancer-specific

CBM-I were effective in reducing both co-primary outcomes (FCR and FoP) in people with breast or ovarian cancers. The present research has a number of theoretical and clinical implications which will be beneficial in advancing this emerging field of research. Hence, this understanding of impact of implicit cognitive processing biases for clinical levels FCR/P informed a novel intervention to manage FCR/P to improve patient care.

Chapter 1: Overview of the thesis

This chapter outlines the background of the thesis leading to research aims and the methods used to achieve these aims. Hence, the chapter aims to provide the basic structure of the entire thesis.

1.1.

Background

Cancer is a term used for describing over a collection of hundreds of diseases resulting from the abnormal division of cells, which rapidly multiply and spread throughout one or more than one organ in the body. Given, the nature of this group of diseases, the diagnosis of cancer is often regarded as a 'death sentence'. In a cross-sectional survey of over 7500 adults, the majority of participants (more than 61%) perceived cancer as a 'death sentence' (Moser et al., 2014). While historically being perceived as a fatal disease, substantial progress has been made for over a decade in oncology field specifically in terms of early detection of the disease and its treatment. These treatments have been shown to be effective in eliminating or slowing down its progression. As a result, there are now an increasing number of people who are achieving remission and live beyond their cancer diagnosis (Allemani et al., 2018). In addition, even when cancer cannot be treated with curative intent, many survivors now live for decades with active disease.

As per the Australian Institute of Health and Welfare (AIHW, 2021), there are now over one million people who are either living with or have survived cancer. As per the estimates, this number will continue to rise in the future (AIHW, 2021). Despite such advancements, people who have had cancer or are faced with an array of physical, psychosocial and financial hardships. One such psychosocial challenge is the fear of cancer coming back or progressing. In the literature, fear of cancer recurrence or progression (FCR/P), is defined as the "fear, worry or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016, p. 3265).

Such fears are expected and is often considered as a normal or adaptive response as a part of adjusting the life after cancer. It is adaptive in the sense that it enables an individual to be vigilant in order to look out for potential signs of recurrence and promoting health behaviours (Lee-Jones et al., 1997). However, for some of the cancer survivors, this fear can become severe and has debilitating impact on one's quality of life (Tran et al., 2021) and often requires a specialized psycho-social intervention (Butow et al., 2018). According to a recent meta-analysis, approximately 59% of cancer survivors report moderate FCR/P, while 19% report high or severe levels of FCR/P (Luigjes-Huizer et al., 2022). Heightened levels of FCR/P are often associated with increased depressive, anxiety and post-traumatic symptomatology (Koch, Jansen, Brenner & Arndt, 2012). In fact, help with FCR/P is cited as one of the topmost unmet needs across studies (Ellegaard, Zachariae & Jensen, 2017; Lisy, Langdon, Piper & Jefford, 2019; Lou et al., 2021).

Given, the fact that FCR/P is such an important survivorship issue, it has gained a lot of research interest in the last five years. Numerous theoretical frameworks have been developed to explain the aetiology and conceptual nature of clinical FCR/P. The original theoretical models, such as the Lee-Jones' (1997) focus very much on the content of one's cognitions such as unhelpful beliefs and worries. However, the newer models focus not only

on the content of such cognitions but also the way an individual tends to process information (e.g., Fardell et al., 2016; Heathcote & Eccleston, 2017; Simonelli et al., 2017). In other words, these models clearly highlight the crucial role of implicit cognitive processes (or cognitive biases) in the formulation and maintenance of clinical levels of FCR/P. For example, the Cancer Threat interpretation framework by Heathcote & Ecclestone (2017) highlights that the occurrence of bodily symptom such as, pain which demands interpretation and can be negatively interpreted as a sign of cancer recurrence. This negative interpretation leads to bodily vigilance and increased FCR/P. These models are described in detail in Chapter 2. Despite numerous theoretical conceptualizations for FCR/P, there seems to be a gap in the literature in terms of testing these models.

Therefore, the current thesis aims to bridge this gap in the existing literature by examining the role of such implicit processing biases and their relation to clinical levels of FCR/P. This thesis focuses predominantly on attention and interpretation biases. The existence and relevance of these cognitive biases are well established in psychiatric conditions (e.g., anxiety) (Bar-Haim et al., 2007). However, their relevance in the context of FCR/P is less clear. Although there has been research on attentional biases in cancer the context, the evidence is not robust and has not been synthesised. For interpretation biases, only two studies have been conducted (Lam et al., 2018; Lichtenthal et al., 2017). Given that in the anxiety literature these processes have been harnessed to reduce anxiety, their role in FCR/P should be further examined.

1.2.

Research aims and thesis structure

The over-arching aim of this thesis is to understand the role of cognitive biases in the maintenance and development of Fear of Cancer Recurrence/Progression. For this purpose, the thesis is further divided into chapters addressing the individual aims. These individual aims are outlined in Table 1.1, along with the methods used to address these aims. The following section will briefly provide an overview of each of these chapters:

Chapter 2: this is a comprehensive review of literature, describing in detail: (1) Cancer prevalence rates, (2) Cancer treatments and their side effects (including physical and psychological), (3) Psychosocial challenges associated with cancer survivorship, specifically FCR/P, (4) Cognitive processing biases and their association with clinical FCR/P, and (5) Existing interventions to manage FCR/P that target such cognitive processes.

Chapter 3: this is a meta-analytic synthesis of studies that have assessed attentional biases in the cancer survivors. This also presents a scoping review on the cognitive biases (specifically interpretation and memory), where there has been a lack of research by providing future recommendations in this emerging field. This chapter was published in: Pradhan, P., Sharpe, L. & Butow, P. (2021). The role of attentional biases in the context of cancer. *Psycho-Oncology, 30* (5), 649-658. doi: 10.1002/pon.5617.

Chapter 4: based on the future research recommendations from the previous chapter, this empirical study investigated the role of interpretation bias in a sample of ovarian cancer patients (n = 62). The study tested one major tenet of the Cancer Threat Interpretation model (Heathcote & Eccleston, 2017) to determine whether interpretation bias moderated the relationship between pain and FCR/P. The results provided partial support for the model as

interpretation bias did not moderate the relationship between FCR/P and overall symptom burden. Nonetheless, the study found a significant association between FCR/P and interpretation biases and found the evidence of this bias in people with cancer as compared to people without cancer. This study was published in: Pradhan, P., Sharpe, L., Butow, P. & Russell, H. (2021). The role of interpretation biases and symptom burden in fear of cancer recurrence/progression among ovarian cancer survivors. *Psycho-Oncology, 30* (11), 1948-1956. doi: 10.1002/pon.5748.

Chapter 5: this study was an extension of the study described in chapter 4 in that; (i) sample size was larger (n= 147), (ii) women with breast cancer were recruited (as Cancer Threat Interpretation model was initially developed for people with cancers that were treated with curative intent), (iii) the study included both a measure of FCR and FoP, and (iv) the study also assessed other known theoretical predictors of FCR/P to examine if interpretation bias still predicts FCR/P over and above these variables. The results confirmed that interpretation bias moderated the relationship between pain and FCR, but not FoP. Furthermore, interpretation bias predicted FCR/P over and above the known predictors. This has been published in: Pradhan, P., Sharpe, L., Butow, P., Coutts-Bain, D. & Heathcote, L.C. (2022). Does interpretation bias moderate the relationship between pain and fear of cancer recurrence? *Health Psychology.* https://doi.org/10.1037/hea0001217

Chapter 6: this study was conducted using the same sample who were recruited for Chapter 4. After people with ovarian cancer completed the baseline measures reported in Chapter 4 participants were followed up a week later to assess the level of FCR/P after reading the booklet. The booklet had information on FCR/P that was deemed to be helpful for people with ovarian cancer. This study aimed to determine if a minimal intervention in the form of a static pdf 'booklet' was sufficient to reduce FCR/P in people with ovarian cancer. 50 out of 62 participants completed the questionnaires after reading a booklet. The results of

this study suggested that although participants rated the booklet highly in terms of giving relevant information and were very satisfied, the booklet was insufficient to reduce FCR/P. The study has been published in: Pradhan, P., Sharpe, L., Butow, P., Smith, A., Russell, H. (2021). Is a brief online booklet sufficient to reduce fear of cancer recurrence or progression in women with ovarian cancer? *Frontiers in Psychology*, 12, 634136.

Chapter 7: this is a narrative review on the existing FCR/P interventions with specific reference to the level of support needed, ranging from minimal to more intensive interventions. The review found that the existing evidence-based interventions are intensive requiring specialised skills and clinician time.

Like our FCR/P booklet, a number of recent minimal interventions had failed to reduce FCR/P. The review revealed that not a single RCT of a minimal intervention that had successfully reduced FCR/P. The review further highlights that there is an urgent need to develop minimal interventions (requiring less time and skills) that could manage sub clinical levels of FCR/P, which could ultimately be implemented in routine clinical practice in order to meet the needs of increasing number of cancer survivors. The review further proposed a stepped-care model and also recommended the ways to improve the existing interventions. The paper has been published in: Pradhan, P., Sharpe, L., & Menzies, R. E. (2021). Towards a stepped care model for managing fear of cancer recurrence or progression in cancer survivors. *Cancer Management and Research*, *13*, 8953.

Chapter 8: this chapter presents a randomised controlled trial of Cognitive bias modification for interpretation (CBM-I) in order to manage the clinical FCR/P in people with breast or ovarian cancer. The study examined the efficacy of two types of CBM-I (cancer-specific and pain-specific) in managing FCR/P compared to placebo. The manuscript for this study has been completed.

Chapter 9: this chapter summarises the major findings, evaluates the strengths and weaknesses of the present series of studies, along with theoretical and clinical implications. In addition, this chapter proposes future research directions in this emerging field.

Table 1.1. Overview of individual aims and methods used to achieve these aims along with chapters

AIM	METHODS USED TO ADDRESS EACH AIM	CHAPTER
(1) Synthesize the available research literature on cognitive biases in the context of cancer through a scoping review with meta-analysis.	**Study 1**: A meta-analysis of published peer reviewed articles (N = 25) investigating attentional biases in cancer survivors. A scoping review was also conducted in order to highlight gaps in this area particularly for interpretation and memory biases.	Chapter 3
(2) Examine whether people with cancer are more likely to interpret ambiguous stimuli as health-related than people without cancer	**Study 2**: This was an empirical study. People with (n = 62) and without cancer (n = 96) were recruited from Ovarian Cancer Australia registry. Participants completed interpretation bias assessment followed by FoP-Q-SF and physical symptoms inventory. ANCOVA across participant groups (with and without cancer) was conducted to assess if people with cancer had higher levels of illness-related interpretation bias than people without cancer.	Chapter 4
(3) Examine whether people with breast or ovarian cancer who have clinically significant levels of FCR/P are more likely to interpret ambiguous stimuli as health-related than those whose FCR/P levels are below the clinical range	**Studies 2 and 3:** These were cross-sectional studies which recruited people with ovarian (n = 62) and breast cancers (n = 147). Student t-test was conducted to examine this between group difference in terms of interpretation bias	Chapter 4 and 5
(4) Test one of the major tenets of the Heathcote and Eccleston (2017) Cancer Threat Interpretation model. That is, to determine whether interpretation biases moderate the relationship between pain and FCR/P	**Studies 2 and 3:** As above these were cross sectional studies. A moderation analysis was conducted to determine if interpretation bias moderated the relationship between pain FCR/P.	Chapter 4 and 5
(5) Propose a potential stepped care model of cancer care that can increase accessibility to effective treatments for FCR/P	A literature and a narrative review was conducted in order to highlight gaps in the FCR/P interventions literature (in terms of minimal interventions) and subsequently a stepped care model of cancer was proposed, with each stage emphasising different levels of care based on FCR/P levels.	Chapter 7

(6) Develop and test the efficacy of two potential minimal interventions to reduce FCR/P of increasing levels of complexity, namely a simple static pamphlet containing psychoeducation about FCR/P and a cognitive bias modification for interpretation (CBM-I).	**Study 4:** this study was a pre-post evaluation of a static pdf booklet in 50 people with ovarian cancer. These patients were a sub-sample of those who took part in Study 2. They completed baseline assessments (Study 2) and were then given access to the booklet. After one week they were re-contacted to re-administer a measure of FoP. A paired samples t-test was conducted to assess the level of FCR/P after reading the online resource. **Study 5:** this study evaluated the efficacy of CBM-I in reducing FCR/P in a sample of breast (n = 115) or ovarian cancer survivors (n = 59). This was a double blind RCT where participants were randomly allocated to one of the three groups (cancer or pain specific CBM-I or placebo). Linear mixed model regression (LMMR) analyses were performed to assess the degree to which CBM-I impacted the FCR and FoP levels, which were measured at baseline, after 14 days (post-intervention) and 28 days (follow-up) of baseline assessments.	Chapter 6 and 8

Chapter 2: Introduction and Literature Review

This chapter outlines the theoretical and conceptual background of the thesis by providing a comprehensive literature review on cancer, common psychological sequalae and fear of cancer recurrence and progression.

2.1. Cancer: definition, prevalence and classification

According to the World Health Organization (WHO), cancer is a group of diseases that is characterized by abnormal and uncontrollable cell growth in any organ or part of the body. The abnormal cells can be located in a single organ or system, but in some cases this abnormal cell division invades other adjoining organs or systems, a process known as metastasis. According to the WHO (2020), cancer accounted for an estimated 10 million deaths in 2020 and was the second most common cause of death. Cancer remains one of the major contributors of health-care related burden including financial burden due to treatment related costs. In a recent estimate, in Australia, cancer constitutes to 18% of the total global burden of disease (in terms of mortality and disability) as compared to cardiovascular, musculoskeletal disease, mental and substance abuse disorders (each constituting to 13%) (Australian Institute of Health and Welfare; AIHW, 2021). The most common cancers are breast and prostate, but lung and colorectal are the cancers that claim the deaths of the most Australians each year (AIHW, 2021).

With the recent advancements in medical technologies in terms of early detection and improved treatments, there has been an increase in the proportion of cancer survivors living years beyond their diagnosis (Allemani et al., 2018). According to the Australian Institute of Health and Welfare (AIHW), there are over a million people alive in Australia who are either currently living with or have survived cancer. The five-year relative survival rate for all cancers combined has increased to 70% in Australia in 2018 (AIHW, 2021). However, survival rates vary enormously depending on the type of cancer and the stage at which the cancer is diagnosed. For example, the survival rate for breast cancer is as high as 92%. This is, in part, because the majority of people are diagnosed with early-stage breast cancer, and treatments are very effective (surgery with a number of adjuvant treatment options; see section 2.3.). In contrast, for ovarian cancer, only 48% of those diagnosed are expected to survive more than five years after first diagnosis (AIHW, 2021). The prognosis for people with ovarian cancer has changed little in the past decade, largely because the symptoms of ovarian cancer are non-specific and only occur in later stages of disease. Hence, most people diagnosed with ovarian cancer are diagnosed at later stages when the cancer is already likely to have metastasized.

2.1.1. Cancer Staging

As cancer can form in any organ, it is usually named according to the organ in which the primary cancer occurred (e.g., liver cancer) or the cell type (e.g., adenocarcinoma). Cancers are also classified according to the staging system which refers to the extent to which the cancer has spread (National Cancer Institute, NCI). However, there are some cancers that are not staged using the five-stage model, such as leukaemia and some brain cancers (NCI, 2015). For example, gliomas are graded according to whether the cells are low-grade (good

prognosis) or high-grade (poorer prognosis). However, for most solid tumour cancers, including ovarian cancer and breast cancer, the following staging is typically used.

The most widely used staging system is TNM which refers to (NCI, 2015):

- T refers to the primary tumour and is based on its size and the extent to which it is spread.
- N represents the number of adjoining lymph nodes where the cancer is detected.
- M indicates whether the primary cancer tumour has spread to other parts of the body (NCI, 2015).

Based on the TNM staging system (see Table 2.1), a simplified version called '5 level staging system' (ranging from Stage '0' to Stage 'IV') is commonly used in clinical settings to describe the stage of cancer for prognostication. Table 2.1 outlines the 5-level staging system. Both breast cancer and ovarian cancer are usually staged according to this system.

Table 2.1: TNM Staging System

Category	Description
T category: original (primary tumour)	
TX	Primary tumour cannot be evaluated
T0	No evidence as primary tumour
TIS	Carcinoma in situ (early cancer that has not spread to neighbouring tissue)
T1-T4	Size and/or extent of the primary tumour
N category: Lymph nodes	
NX	Regional lymph nodes cannot be evaluated
N0	No regional lymph node involvement (no cancer found in the lymph nodes)
N1 -N3	Involvement of regional lymph nodes (number and/or extent of spread)
M category: Metastasis	
M0	No distant metastasis (cancer has not spread to other parts of the body)
M1	Distant metastasis (cancer has spread to distant parts of the body)

For many solid tumours, the first line of treatment is surgery and, additional information will be gathered during surgery to the pathological staging. The pathological staging gives more precise information and therefore will be relied upon to determine adjuvant and neo-adjuvant therapies. For others, surgery will not be possible and in some instances other treatments (e.g., chemotherapy or radiation therapy) will be used to shrink the tumour before surgery. Post-therapy staging is used in these circumstances. Finally, staging can be done again should recurrence or progression occur. This is typically referred to as recurrence or re-treatment staging.

Typically, when cancer is diagnosed, clinical staging will be completed. This is done usually before the commencement of any treatment and provides an estimate of the staging of cancer based on physical exams, blood tests and other imaging scans such as, X-rays, CT scans, MRI etc. Clinical Staging will use results from any biopsy completed (i.e., laboratory examination of a tissue or a lymph node where a cancer may be present). Clinical staging enables medical oncologists to determine the initial treatment plan.

2.2. Breast and ovarian cancer

2.2.1 Prevalence rates

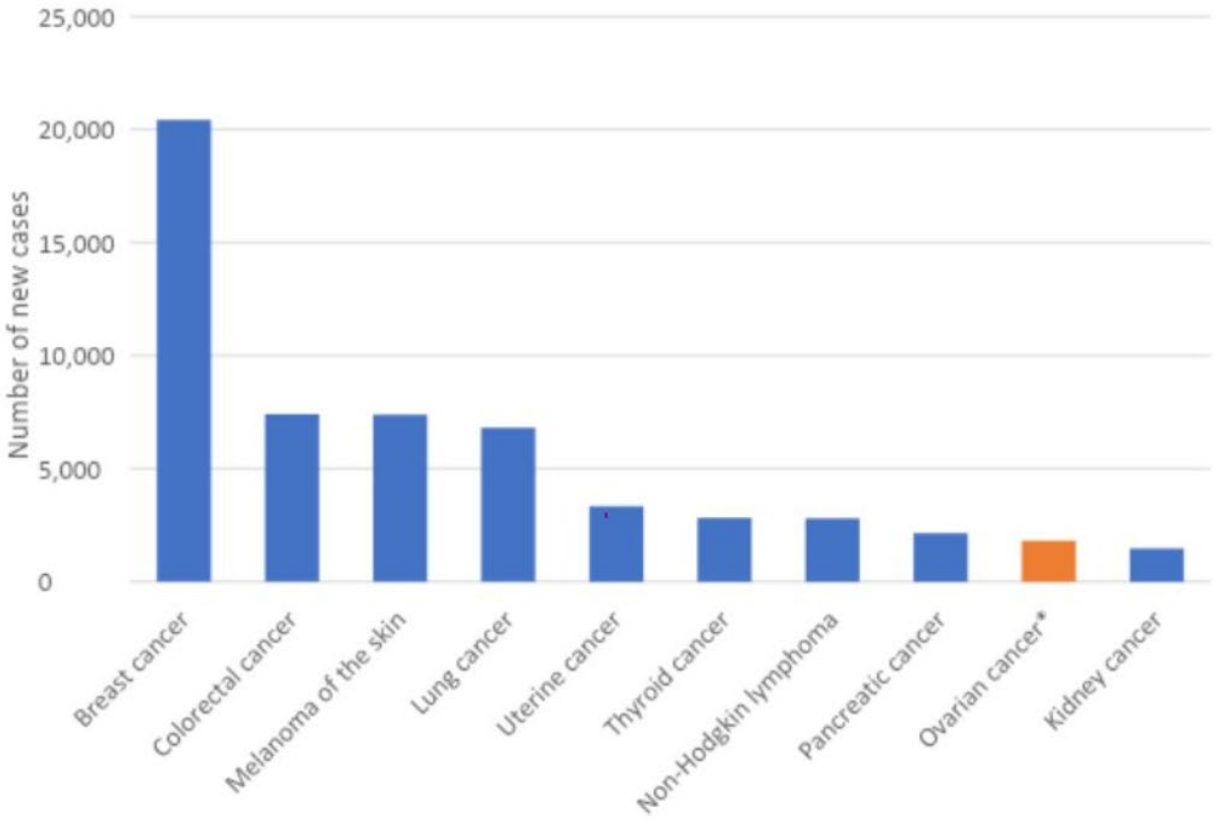
Breast cancer was the most common form of cancer in Australia in 2021, with numbers increasing from 11,941 people in 2001 to 20,030 people being diagnosed in 2021) (See Figure 2.1; AIHW, 2021). Moreover, it is estimated that 20,741 new cases of breast cancer will be diagnosed in Australia in 2022, which is roughly 57 people per day being newly diagnosed (AIHW, 2021). One in seven women across their lifetime will be diagnosed with breast cancer. Although breast cancer has high incidence rates, five-year survival rates have increased from 76% in 1988-1992, to 91.5% in 2013-2017 in Australia. However,

prognosis does differ in different parts of the world, with the global five-year survival rate remaining around 75% (Maajani et al., 2019).

Ovarian cancer:

Compared to breast cancer, the incidence rate of ovarian cancer is low (see Figure 2.1). Each day only five people in Australia are diagnosed with ovarian cancer as compared to 57 with breast cancer (Ovarian Cancer Australia, OCA). However, ovarian cancer is a relatively poor prognosis cancer. According to AIHW, the five-year survival rate of ovarian cancer is only 48%. Furthermore, despite being a relatively uncommon cancer, ovarian cancer is the sixth most common cause of cancer deaths among women in Australia and has a poorer prognosis than any other gynaecological cancers (AIHW; Cancer Australia, 2022).

One of the reasons for the poorer prognosis of ovarian cancer, as compared to breast cancer is that ovarian cancer is typically diagnosed later in the course of the disease because early-stage ovarian cancer is usually asymptomatic. In contrast to breast cancer, where there are surveillance programs that can identify breast cancer during the early stages, there are no such screening tests for ovarian cancer. The absence of a national surveillance program or any observable or obvious symptoms during early stages of ovarian cancer lead to cancers being identified when the disease is more advanced and, in turn, lead to the poorer prognosis (Werness & Eltabbakh, 2001). As ovarian cancer progresses, symptoms emerge but tend to be non-specific, including gastrointestinal symptoms such as, abdominal bloating, indigestion or constipation (Stewart, Ralyea & Lockwood, 2019).



Note: Figure sourced from: https://www.canceraustralia.gov.au/cancer-types/ovarian-cancer/statistics

Figure 2.1

Estimated cancer incidence in Australia in 2022.

2.2.2 Rationale for including breast and ovarian cancer sample

The research in this thesis will focus on two types of cancer, predominantly affecting women: breast and ovarian cancer. Breast cancer, as previously described, is the most commonly diagnosed cancer in women and, if identified at an early stage, has a good prognosis. Much of the psychosocial literature has, for these reasons, focused on breast cancer. Hence, including breast cancer samples will allow us to generalise to previous work conducted on this group. In contrast, gynaecological cancers, and in particular, ovarian cancer

are less well researched, in part because ovarian cancer is not a common form of cancer and in part because prognosis is considerably poorer (Collins et al., 2014). As indicated previously, the five-year survival rate is less than 50% and ovarian cancer is associated with increased symptom burden, which contributes to greater reduction in quality of life among women who are diagnosed with this cancer (OCRFA, 2016; DellaRipa et al., 2015). Studying ovarian and breast cancer allows us to examine two conditions that represent conditions that typically represent early-stage disease and more advanced disease, both of which predominantly affect women.

2.3. Cancer Treatments

Cancer can be treated using different approaches, which are chosen depending on the nature and extent of the cancer. The treatment can either involve a single therapy (e.g., surgery) or a combination or sequence of these therapies to make it more effective (e.g., surgery followed by chemotherapy) (NCI, 2015). Overall, cancers are either treated with curative or palliative intent. Where the treatment given is expected to remove all cancer cells, such as surgery to excise the tumour in early-stage disease, it is usually given with an intent to fully eliminate the disease in the hope that it has not already spread. This refers to treatments given with curative intent. When the cancer is already known or suspected to have spread, treatments will often be focused on palliative or non-curative treatment. Treatments with palliative intent are given to reduce the size of tumours (e.g., chemotherapy or radiation therapy) so that the person with cancer will have fewer symptoms, and better quality of life/or live longer. However, treatments with palliative intent are only adopted when a cure is unlikely to be achieved, such as in case of more advanced cancer (Craft et al., 2005).

Treatments can also be further classified based on the area or region that they target in the body, as either local or systemic treatments (Merriel & Hamilton, 2020). Localised treatments are specifically used to treat a tumour or area of the body where a tumour was found, such as surgery or radiation therapy. In contrast, treatments like immunotherapy or chemotherapy are classified as systemic therapies as they affect a wide range of cells in the body. The section below outlines specific treatments broadly and their physiological and psychological impacts.

2.3.1 Surgery

This is the most common and direct first-line treatment strategy for different types of solid tumour cancers, including breast and ovarian cancer. Surgery involves the removal of the cancerous tumour (either partial or complete) or the entire organ where the tumour originates, such as the breast tissue or ovary (NCI, 2015). For cancers that are diagnosed in the early stages, such as breast cancer, surgery may be the only treatment needed and additional treatments may confer little additional benefit depending upon the pathological staging. However, for some cancers, such as ovarian cancer, surgery is typically performed in combination with other treatments in order to reduce the risk of recurrence.

Where possible, surgical excision of the tumour will precede any additional treatments, such as chemotherapy or radiation therapy. For some cancers, the tumour might be too large to remove and other treatments, such as chemotherapy, may be used initially to shrink the tumour in order to allow surgery to have the best chance of success. However, once cancer has metastasized, surgery is not typically recommended unless it is for the sake of relieving symptoms to improve quality of life (palliative surgery) (Cancer Council, 2019).

2.3.2 Chemotherapy

Chemotherapy is a common treatment approach for a range of cancers that uses chemicals or drugs to destroy cancer cells and may be used on its own or in combination to other treatments (NCI, 2015). Because chemotherapy is a systemic treatment, the chemotherapy agents also affect healthy cells and, as such, chemotherapy is often associated with considerable toxicity. That is, as these cytotoxic drugs circulate throughout the body, they destroy other non-cancerous cells such as hair cells and mucous membranes of mouth or gut (NCI). Damage to such healthy cells causes a patient to experience side effects, most commonly hair loss, nausea, bone pain (Thiagarajan et al., 2016; Liu et al., 2021) and change in taste (Joseph et al., 2021). Sometimes chemotherapy may be the only treatment option for cancers, such as in the case of leukaemia or lymphoma. However, for most people with ovarian and breast cancer, chemotherapy – where appropriate – is used after surgery to remove the tumour. Chemotherapy remains one major treatment option when cancer metastasizes.

2.3.3 Radiation Therapy (Radiotherapy)

Radiation treatment is a focused treatment and targets a precise area which is thought to potentially hold residual cancer cells, rather than affecting the whole system as chemotherapy does. Radiation can be delivered internally to reach affected organs where necessary by placing radioactive materials in the body or externally where a machine radiates a beam externally (Cancer Council, 2021). External beam radiotherapy is the most common form of radiation treatment. According to Cancer Research UK, nearly 50% of cancer patients have had radiotherapy at some point in their cancer treatment. The greatest advantage of radiotherapy is that it reduces the risk of side-effects by targeting only cancer-affected

area. However, it can produce long-term side effects, such as lung damage in the context of breast cancer.

2.3.4 Hormone Therapy (Endocrine therapy)

Some forms of cancer, such as some breast and ovarian cancers, can be hormone receptive and for hormone receptive cancers, patients might receive endocrine therapy for years after their primary treatment is complete. Approximately 70-80% of breast cancers are particularly sensitive to oestrogen (ER) or progesterone (PR) (Cancer Council, 2022). The aim of endocrine therapy is to inhibit or slow the growth of certain cancers (such as breast, ovarian, thyroid or prostrate) that are hormone dependent. That is, endocrine therapy prevents these hormones from making cancer cells grow and replicate. The type of hormone therapy essentially depends on the type of cancer and which hormones the therapy needs to target. For example, there are different forms of hormone therapies for breast as well as ovarian cancer that target hormones such as, progesterone and/or oestrogen. Tamoxifen is the most common endocrine treatment which acts by blocking oestrogen receptors. Tamoxifen can be administered to both menopausal and post-menopausal women and has shown to be effective in terms of reducing breast cancer recurrences and risk of death (Davies et al., 2013). Side effects of tamoxifen include hot flushes and irregular menses, with blood clots (Visovsky, 2014). Fulvestrant is another endocrine therapy typically given to women who have metastatic breast cancer that is hormone receptive. Fulvestrant also targets oestrogen receptors by reducing the number of these receptors in cancer cells. The mechanism of action is to block the action of oestrogen on cancer cells.

A more recent medication that also works by blocking oestrogen are Aromatase Inhibitors. This newer form of therapy blocks the production of aromatase, which is an enzyme responsible for converting androgen to oestrogen in post-menopausal women. Common side-effects of this treatment are osteoporosis and other musculoskeletal symptoms (Visovsky, 2014). Finally, Luteinising hormone releasing hormone (LHRH) agonists or LH blockers are used in ovarian cancer because they prevent the production of luteinising hormone (LH) by the ovaries. LHRH is not recommended for women who are in post-menopausal stage (Fabi & Catania, 2019).

2.3.5 Other treatments for cancer

In addition to the commonly used therapies described above, it should be noted that there are other forms of treatment, including haematopoietic stem cell transplantation, immunotherapy and the use of precision medicine to give more specifically targeted interventions is increasing. However, these treatments are infrequently used in either breast or ovarian cancer and so a full review is beyond the scope of the thesis. Nevertheless, although the side effect profiles of different treatments are different, each available treatment is associated with side effects, including persistent pain, nausea, cognitive impairment and fatigue that impact on quality of life during survivorship. This is discussed in the next section.

2.4. Physical consequences of cancer treatment

The treatment approaches noted above are commonly used in routine clinical practice for cancer management, and in particular in the management of breast and ovarian cancer. However, it should be noted that while there is evidence that these treatments are life-saving,

these treatments also have widely documented physical side-effects (Mohan et al., 2019; Cukier, Santini, Scaranti & Hoff, 2017). Although different treatments have different side effect profiles, each available treatment is associated with side effects, including persistent pain, nausea, cognitive impairment and fatigue that have been associated with a reduction in social functioning and excessive stress (Jakovljevic, et al., 2021) and a decrease in overall quality of life (Shapiro, 2016). Some studies have even shown that side effects can lead to therapy discontinuation, even where the treatment might confer survival benefits (Kidwell et al., 2014; Neugut et al., 2016). Importantly, while some of these effects (e.g. chemotherapy induced nausea) are typically experienced during treatment, other side effects can persist throughout the survivorship period (Hsiao et al., 2019; Tao, Visvanathan & Wolff, 2015). The following section provides an overview of the most common physical symptoms experienced by cancer survivors.

2.4.1 Nausea

Chemotherapy induced nausea and vomiting (CINV) remains the most common side-effect after each cycle and is experienced by an approximately 40% of the cancer patients, despite of novel anti-emetic agents (Dranitsaris et al., 2017). Dranitsaris and colleagues (2017) identified several risk factors for CINV including, younger age, female gender, history of nausea and vomiting, less sleep before a chemotherapy dose amongst others. Severe symptoms can potentially have inverse impacts on quality of life of survivors and can also deter future treatments and is thus still poses a problem in cancer care (Gupta, Walton & Kataria, 2021; Lorusso et al., 2017). There is also a substantial financial burden associated with the treatment-related costs to treat CINV (Basch et al., 2011). In addition to chemotherapy, nausea is also one of the common symptoms associated with opioid intake used for treating pain and radiation therapy (Sande, Laird & Fallon, 2019; Paiar et al., 2020). Besides, recognizing and subsequent treatment of nausea becomes difficult as it subjectively

measured by the patient (Grunberg et al., 2004). That is, both patients and oncology clinical staff may have different perceptions about nausea and therefore, emphasizing the importance of doctor-patient communication for its treatment.

2.4.2. Fatigue

Fatigue is the most common physical symptom associated with cancer treatment (Liu et al., 2021; Joseph et al., 2021) and occurs in almost 90% of the patients undergoing chemotherapy (Bower, 2008). Fatigue is also commonly noted after other treatments such as radiation therapy (Avelar et al., 2019). Chemotherapy-related fatigue includes a sensation of tiredness and lethargy and is different to normal tiredness as it does not tend to go away despite adequate rest (Cella et al., 2001). In the cancer context, treatments such as chemotherapy used to eradicate tumours activates cytokine dysregulation, which is thought to be the leading cause of cancer-related fatigue (Barsevick et al., 2010). For most patients, fatigue usually improves over time, however approximately 20% patients, continue to experience fatigue years after a successful treatment (Joly et al., 2019). Cancer-related fatigue is also associated with a decrease in interest, motivation and concentration thereby impairing mood and functional abilities (Cella et al., 2001). In fact, cancer-related fatigue has been shown to be strongly correlated with depression (Jacobsen, Donovan, & Weitzner, 2003). One of the problems is that not only is persistent fatigue a common experience thought to arise as a long-term effect of chemotherapy, but fatigue can also be an indicator of recurrence. Hence, fatigue can be a source of worry for survivors, specifically for ovarian cancer, where fatigue is one major indicator of recurrence.

2.4.3 Pain

Similarly, to fatigue, pain is commonly associated with cancer, both as a cancer symptom and a treatment side-effect, and is the most feared symptom by survivors, in part because of its significance as a potential sign of recurrence (Swarm et al., 2019). According to International Association for the study of pain (IASP, 2020; Raja et al., 2020), pain is "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (pp. 1976). Pain is associated with psychological distress in cancer survivors (Broemer, Hinz, Koch, & Mehnert-Theuerkauf, 2021) and untreated pain is still the most common cause of hospital admissions (Mayer et al., 2011). As revealed by a meta-analysis, the presence of pain as a treatment side effect is prevalent in nearly 60% of the patients (van den Beuken-van Everdingen, 2007). Although the under treatment of pain has improved since 2007, still one third of patients with pain are undertreated (Greco et al., 2014). Indeed, persistent pain is experienced even amongst 39% of survivors who were treated with curative intent and as many as 66% of those with advanced disease. Moderate to severe persistent pain is reported by nearly 40% of all cancer survivors (Van Den Beuken-Van et al., 2016). In fact, pain management still remains as one of the top-most priorities for patients with advanced cancer receiving palliative care (Zimmermann et al., 2014). Despite improvements in the field of cancer survivorship, undertreatment of pain still remains a significant issue for cancer survivors (Gallaway et al., 2020). In fact, pain is one of the most common signs of a recurrence for breast cancer.

2.4.4 Cognitive impairment

Cancer-related cognitive impairment is another frequently reported side effect of cancer treatment, mainly occurring after chemotherapy. The subjective cognitive impairment

reported by patients is widely referred to as ‘chemobrain’ or ‘chemofog’ in the literature. Impairments in cognitive functioning includes deficits in short-term memory and executive functions (Hodgson et al., 2013). Research suggests that cancer-related cognitive impairment occurs in nearly three-quarters of patients during their cancer treatments and continues to persist in up to 35% of survivors at least after 6 months of treatment completion (Janelsins et al., 2018).

2.4.5 Gastrointestinal symptoms

Research has shown that almost half of the cancer patients frequently report adverse effects of cancer treatment and majority of these complaints are gastrointestinal (GI) in nature (Tong, Isenring & Yates, 2009). This is especially true for patients with advanced cancers (Engelhardt et al., 2018; Henson et al., 2020). Cancer treatments frequently disturb physiological functioning in more than one part of the GI tract (Muls et al.,2013). There are as many as twenty GI symptoms identified which are associated with cancer treatment and specifically occurring after a pelvic radiotherapy (Benton et al., 2011). Often these symptoms are presented simultaneously, with a median of 11 symptoms in women (Muls et al.,2013). According to Ovarian Cancer Australia, the most common GI symptoms in ovarian cancer treatment are loss of appetite and bowel changes (includes constipation, diarrhoea and bowel obstructions). In addition to being as a side-effect of cancer treatment, GI symptoms are also one of the primary indicators of ovarian cancer and its recurrence and still remains misdiagnosed in the context of cancer (Chase et al., 2021; Smith et al., 2005).

2.5. Psychosocial concerns and unmet needs associated with cancer survivorship

In addition to the many physical sequalae that cancer survivors experience, there are also a range of psychosocial challenges associated with cancer and its treatment. These psychological issues are common amongst the survivors – for example, distress is almost ubiquitous (Carlson et al., 2019). However, psychological distress is a broader construct which not only comprises of depression and anxiety but stress in other practical domains of life (Carlson et al., 2019). Although, anxiety and depression are more common than in the normal population, anxiety and depressive disorders respectively only account for about 10% and 14% of people with cancer (Mitchell et al., 2011). Post-traumatic stress (PTSD) symptoms also very common and in fact, in the fourth edition of DSM, life threatening illnesses such as cancer were also included as a contributor to PTSD. However, this has been changed very recently in the DSM-5 (APA, 2013) version, where PTSD can be diagnosed in case of a sudden and catastrophic event such as waking up in the middle of surgery, but not for a diagnosis for a cancer (Kangas, 2013). As a result of these changes in the existing version of DSM-5, this version specifically exclude cancer as a trauma that is sufficient for Criterion A. In other words, future-oriented concerns do not qualify for PTSD. Nevertheless, intrusive thoughts that are qualitatively indistinguishable from PTSD are very common amongst cancer patients. In the literature the most common form of anxiety in cancer survivors is the fear of cancer returning or progressing. Therefore, the following section aims to outline this common psychosocial sequalae in-depth.

2.5.1

Fear of cancer recurrence or progression (FCR/P)

The number of cancer survivors is steadily increasing over the past two decades owing to early diagnosis and advanced treatments. While this is a positive outcome, this also means that there are more cancer survivors than ever and many of them live with long-term side effects that spans the entire illness trajectory (Ng et al., 2020). Therefore, this has resulted in an increase focus in survivorship issues over the recent years. One of the survivorship issues that has recently attracted an enormous increase in research is fear of cancer recurrence or progression. FCR/P is consistently identified as the most prominent and persistent concern revealed by cancer survivors (Armes et al., 2009; Simard et al., 2013; Butow et al., 2019). According to widely adopted consensus definition, FCR/P is defined as "*the fear, worry or concern relating to the possibility that cancer will come back or progress"* (Lebel et al., 2016, p. 3265). While some degree of fear of the cancer returning or progressing is considered normal and even thought to serve an adaptive function, for a minority of patients, these fears become preoccupying and debilitating in that FCR/P interferes with their quality of life (Simard et al., 2013). According to Lebel et al (2016), FCR/P is thought to exist in a continuum, with low levels being normal – or even adaptive - but becoming unhelpful when severe. A large meta-analysis comprising of 9311 patients recently found that almost 59% of cancer survivors reported moderate levels of FCR/P, and 19% reported severe FCR/P. The authors argued that severe levels of FCR/P were clinically significant in that they warranted treatment (Luigjes-Huizer et al., 2022).

Studies have consistently reported that high FCR/P inversely affects overall quality of life including relationships, work, mood and goal setting (Hodges & Humphris, 2009; Hart et al., 2008) and are also associated with increases in health-care costs (Williams et al., 2021;

Lebel et al., 2013). Prior research has also shed some light on how FCR/P leads to some maladaptive health-related behaviours. For example, a large study by Fisher et al (2016) involving colorectal cancer patients found that patients who had high levels of FCR/P tend to partake in unhealthy behaviours such as, lack of physical activity and smoking. Additionally, FCR/P has also been associated with other unhelpful behaviours such as excessive need to check for signs of cancer, and/or reassurance seeking, such as seeking unnecessary professional advice (Mellon, Northouse, Weiss, 2006; Brach et al., 2010). While there have been hundreds of studies investigating predictors of severe FCR/P, there have been only a few factors that are consistently associated with severe FCR/P. Surprisingly, research has failed to find that medical variables such as cancer stage, size of tumour, time since diagnosis or type of cancer treatment are associated with FCR/P (Crist & Grunfeld, 2013). Instead, consistent predictors are being female, younger age and having increased physical symptom burden (Simard et al., 2013). Since FCR/P is a crucial issue amongst survivors, it is important that the key underlying mechanisms of FCR/P are well researched and understood. This level of understanding becomes important as this would ultimately lead to the development of evidence-based approaches to manage clinical FCR/P (Butow et al., 2019).

In order to understand the aetiology of FCR/P, numerous theoretical models have been proposed (Fardell et al., 2016; Simonelli et al., 2017; Heathcote & Eccleston, 2017). The original model of FCR/P (Lee-Jones et al, 1997) drew largely from Leventhal's self-regulation theory in highlighting the role of illness perceptions and appraisals. More recent models have largely incorporated some of these early constructs but placed more emphasis on cognitive (or metacognitive) processes. These models have been explained in the subsequent paragraphs.

The earliest theoretical conceptualizations of FCR/P was proposed by Lee-Jones and colleagues (1997). This model was developed from Leventhal's self-regulation model of

illness (Leventhal, Diefenbach & Leventhal, 1992), which emphasized the role of illness attitudes and perceptions. Leventhal's model proposes that each individual has a unique illness representation which is triggered by one's experiences when situations or sensations are interpreted as a health threat. This illness representation leads people to develop a risk perception of the likelihood of their cancer returning (or progressing), irrespective of the actual prognosis. Individuals then engage in behaviours that aim to provide reassurance (such as body checking and seeking reassurance) and prevent individuals from being able to plan for the future. See figure 2.2.

According to Lee-Jones' (1997) model, mild FCR/P can be adaptive in terms of regularly checking one's signs and symptoms and becoming more aware of changes in your body, since recurrence is always a possibility after cancer, even after successful treatment. However, when such fears become excessive, they have behavioural consequences (described above), as well as leading to increased worry, somatic symptoms and potentially misinterpretation of symptoms. This formulation further proposes that external cues such as, attending an oncology appointment or reading cancer-related articles in magazines or newspapers, can also activate cancer-related worry in addition to somatic cues.

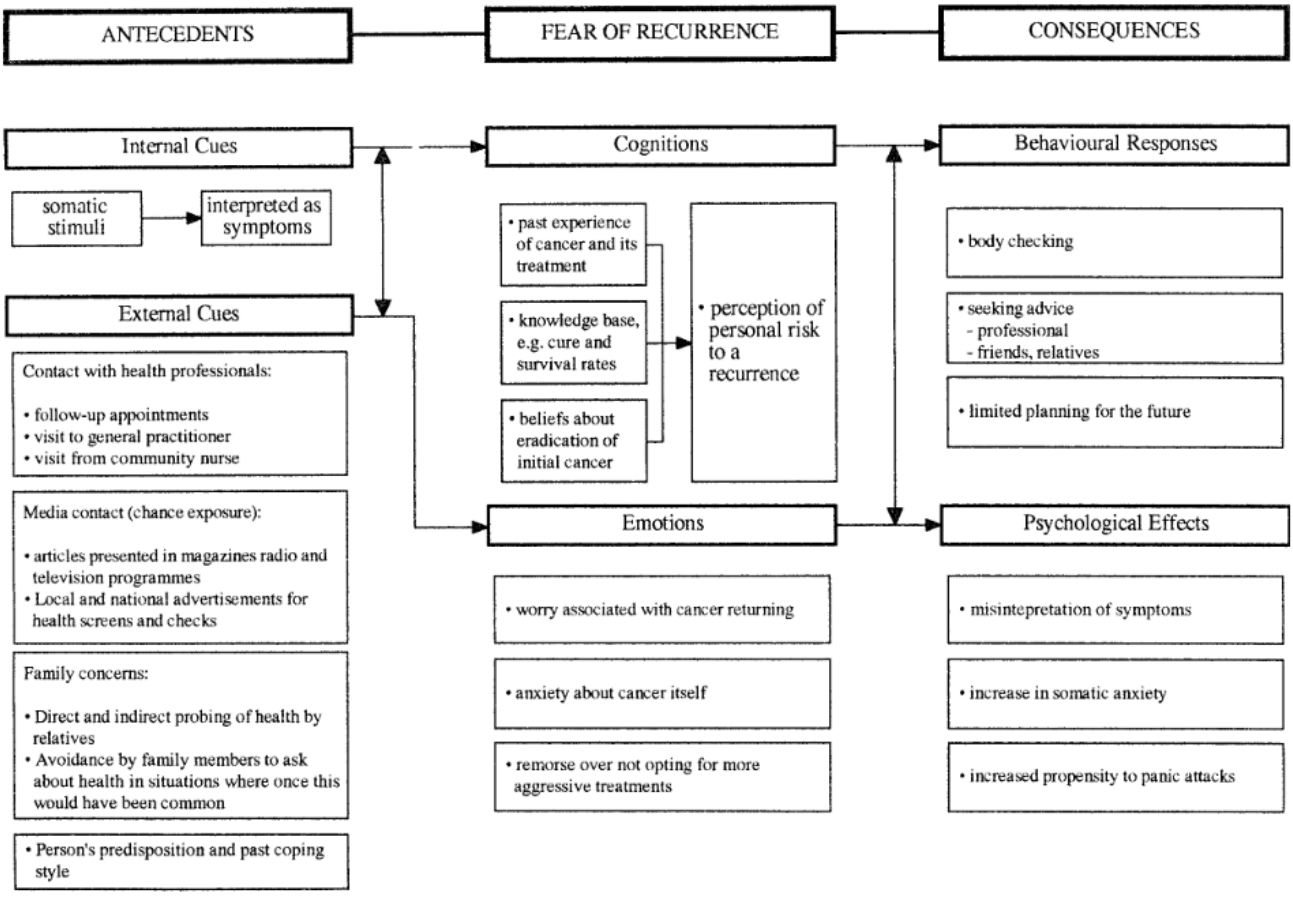


Figure 2.2

Lee-Jones' early model of FCR/P.

Figure reproduced from: Lee-Jones et al., 1997. Psycho-Oncology

Fardell et al (2016) conducted a systematic review of available frameworks for FCR/P and the review identified six models applied to FCR/P. By synthesizing all these frameworks, they developed a novel 'Cognitive Processing Model' (Figure 2.3). This novel theoretical framework combined the elements of S-REF (Self-Regulatory Executive Function; Wells & Matthews, 1996), RFT (Relational Frame theory; Fletcher & Hayes, 2005) and the CSM (Common Sense Model; Leventhal, Diefenbach & Leventhal, 1992). Fardell et al.'s (2016)

model posits that it is normal to experience intrusive and frightening thoughts about cancer in response to a diagnosis of cancer. For the majority of people with cancer, whilst these thoughts are understandably anxiety provoking in the context of a potentially life-limiting disease, these intrusive thoughts typically reduce over time. However, for a small but significant number of survivors, these intrusive thoughts continue and become the source of worry. The model proposes that when individuals believe that worry is either helpful, harmful or uncontrollable, they attribute significance to these intrusive thoughts. In other words, it is beliefs about worry (or metacognitions) that are believed to lead to a series of cognitive processes that exacerbate FCR/P. Vulnerability factors for developing FCR/P include previous traumatic events, losses, insufficient information about the risk of recurrence and other psychological stressors. Specifically, metacognitions are thought to give rise to the "cognitive attentional syndrome (CAS)", a cycle characterized by worry, rumination and focus on threat (i.e. attentional bias), which in turn perpetuates FCR (Wells & Matthews, 1996).

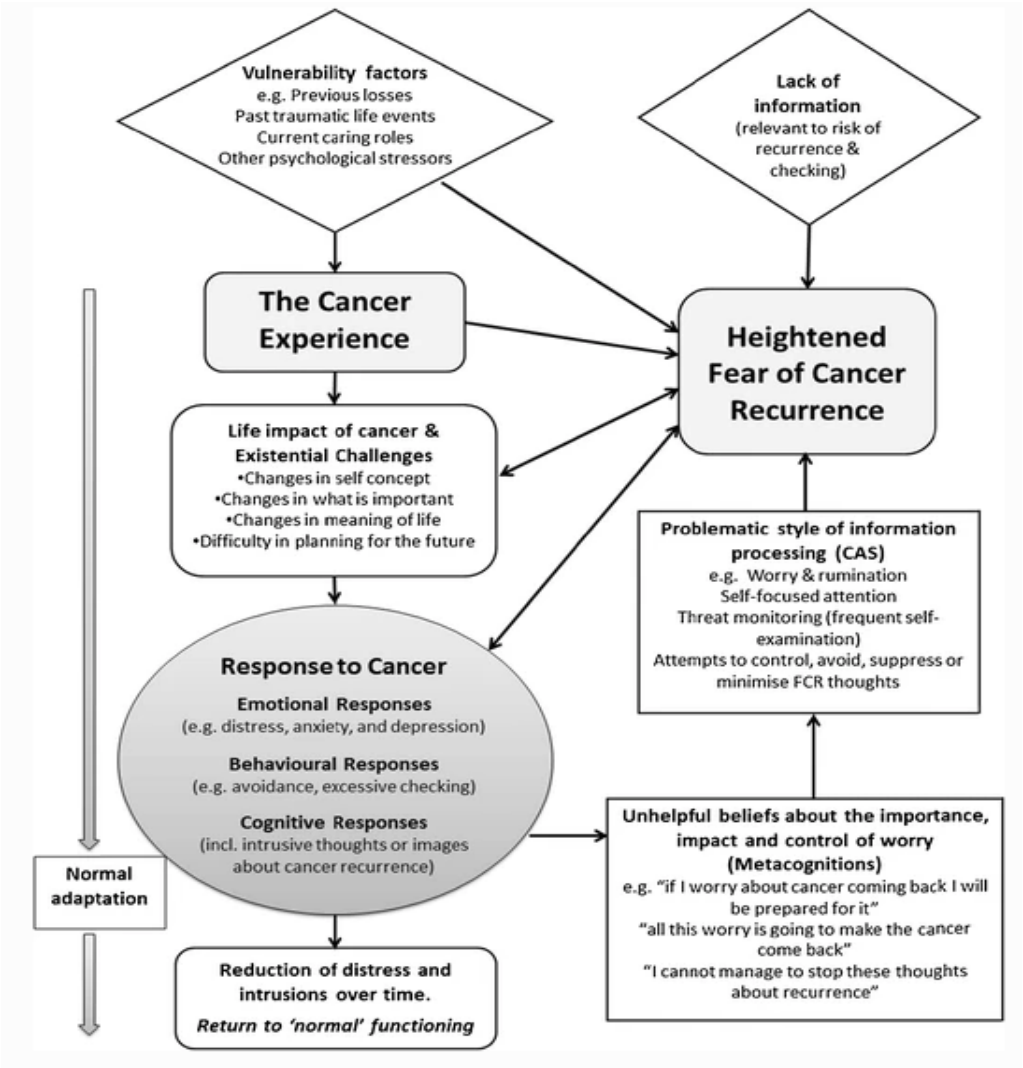


Figure 2.3

The Fardell et al (2016) Cognitive Processing Model

Figure reproduced from Fardell et al (2016): Journal of Cancer Survivorship.

The focus on cognitive processes as a key maintaining or causal factor has become consistent in recent models, which all focus on cognitive processes as key maintenance factors in FCR.

The previously described Fardell model focuses on the 'cognitive attentional syndrome' (CAS), which is triggered by unhelpful metacognitions. The CAS is characterized

by worry, rumination and attentional focus on symptoms and signs of cancer. The Simonelli model also proposes that cognitive attentional processing is central to the development of FCR/P but views the triggers as mortality salience.

Simonelli's model focuses on the role of death anxiety in developing FCR and \ incorporates components of Terror Management Theory (Simonelli et al., 2017, Figure 2.4). Simonelli et al. (2017) emphasize that cues such as physical symptoms trigger mortality salience, leading to the triggering of terror management defences. According to Terror Management Theory, one of the most commonly used proximal defences for death anxiety is avoidance. Avoidance is thought in turn, to result in cognitive emotional processing whereby these cues are interpreted as threatening. When danger appraisals are made, a series of cognitive processes, such as hypervigilance, symptom checking, and suppression emerge, which create a vicious cycle leading to clinical levels of FCR. This vicious cycle leads to increases in worry, rumination and distress, which is further amplified by social context and other contextual factors such as age, physical symptoms, concurrent family stressors. In other words, the cues related to potential death are buffered through Terror Management Theory defence mechanisms and appraisals that contribute to the severity of FCR/P.

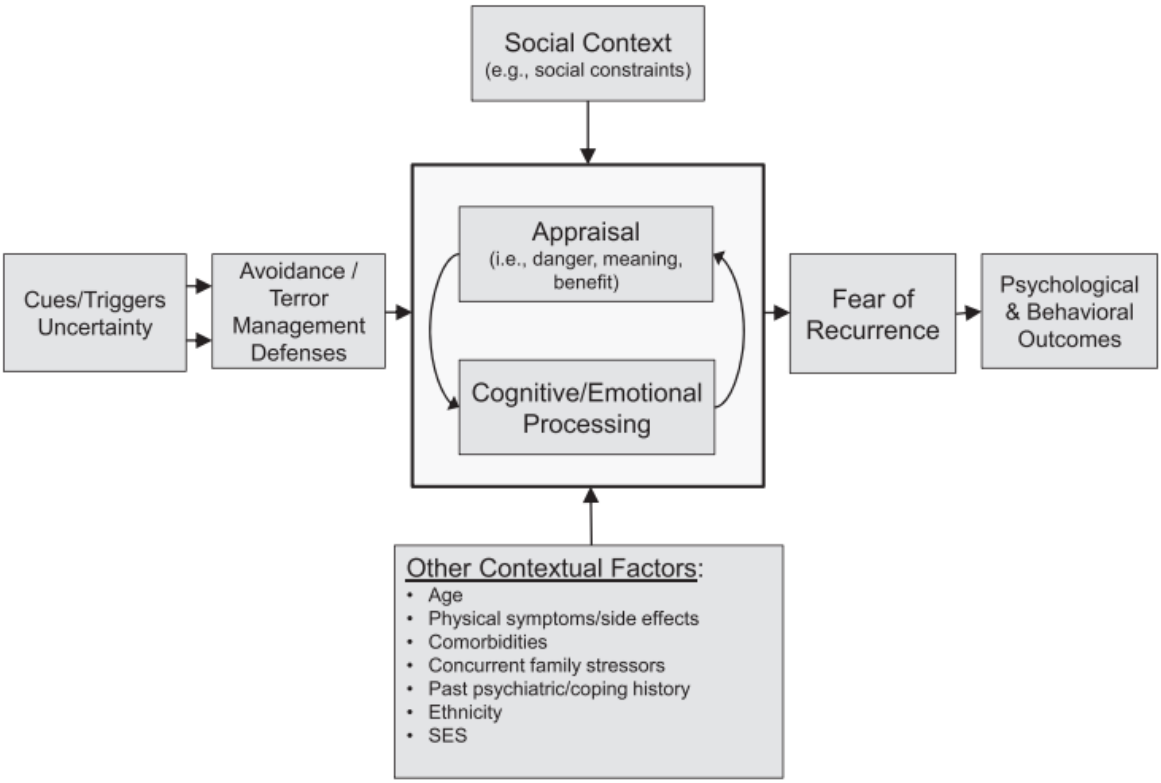


Figure 2.4

The Simonelli et al (2017) Conceptual Model of FCR

Figure reproduced from Simonelli et al (2017) Psycho-Oncology

In Simonelli's (2017) model fears of death are seen to drive threat appraisals of situations that cascade to impact other cognitive processes that contribute to FCR/P. Hence, the interpretation of situations as threatening are central to the model but arise from death-related fears. Similarly, the Cancer Threat Interpretation Model also centres threat interpretation, although specifies the importance of interpretation of pain and other somatic symptoms as a central to development of clinically significant FCR/P. Heathcote and Eccleston (2017) explain that when people are living with or beyond cancer, the experience physical sensations, such as pain, become threatening (i.e., does this pain mean my cancer is

returning or progressing?). According to this model, pain (and other symptoms) are a potential sign of cancer recurrence and hence are inherently threatening in the context of a previous diagnosis of cancer. However, the occurrence of physical symptoms, such as pain or other symptoms, is ambiguous. On the one hand, pain and symptoms such as fatigue are common in daily life in the population and are also more common in people after cancer treatment. For example, persistent pain can result from surgery or the long-term consequences of radiation therapy. However, in the context of cancer, these same symptoms could signal a recurrence. The model suggests patients who understandably interpret pain as a possible recurrence become more anxious about recurrence. The more anxious people become, they more they monitor for symptoms and become vigilant to future bodily sensations, further increasing anxiety. In order to reduce fears, people engage in bodily checking, excessive reassurance seeking and avoidance, all of which further reinforce the fear of cancer recurrence through the immediate reduction of anxiety. Refer to figure 2.5.

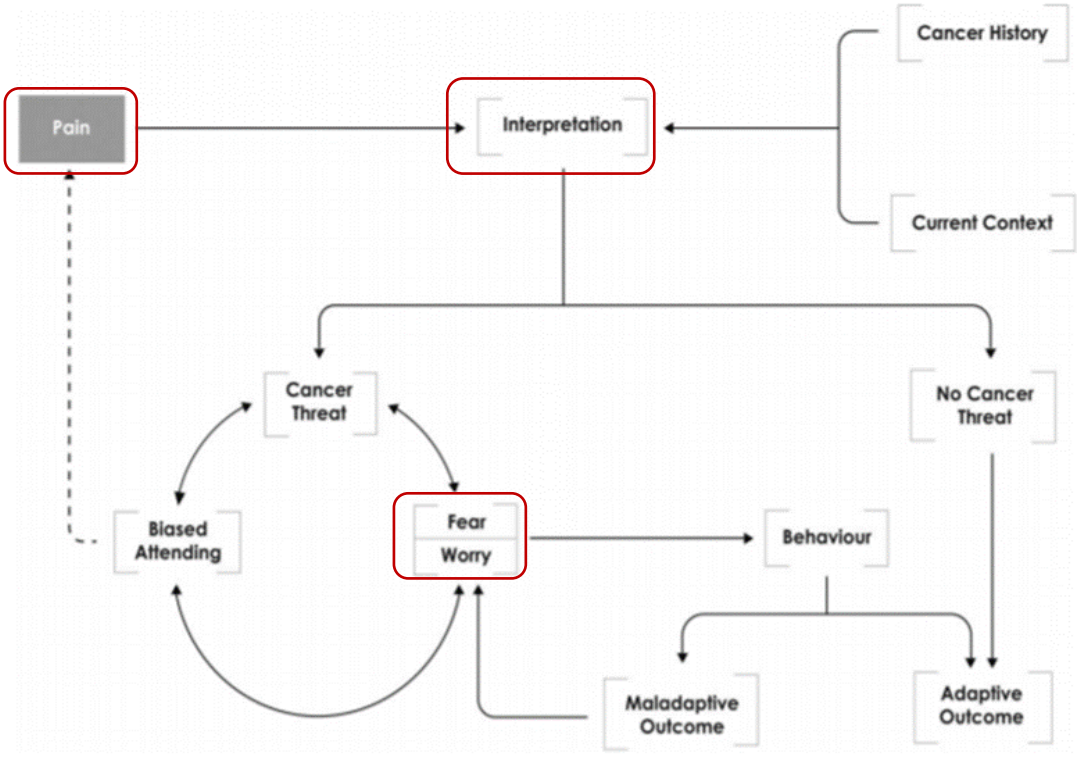


Figure 2.5

The Cancer Threat Interpretation model (2017)

Figure reproduced from Heathcote &Eccleston's (2017) paper. Pain

As the previous sections indicated, over the past 5-10 years, numerous theories have extended the theory of FCR/P by Lee-Jones et al. (1997) which had predominated for 20 years. Most of those theories have accepted some of the tenets of Lee-Jones' model, but all of the models have emphasized the fact that it is not just the content of beliefs that contribute to severe levels of FCR, but rather the way in which people process information. That is, most recent models emphasize hypervigilance (i.e., biases in attention) and threat appraisal (i.e., biases in interpretation) as important maintaining factors in severe levels of FCR/P. This is particularly the case for threat interpretation model by Heathcote and Eccleston (2017).

On the basis of these models numerous psychosocial interventions have been developed particularly in the last five years to manage high levels of FCR/P. For example, Van der Wal et al. (2017) developed a blended cognitive behaviour therapy (bCBT) known as SWORD ("Survivors' Worries of Recurrent Disease"). The intervention was based on Lee-Jones' theoretical model on FCR/P. SWORD intervention resulted in moderate to large effects over time as compared to care-as-usual group. Similarly, Butow et al (2017) developed the ConquerFear program based on the Fardell's cognitive processing model. ConquerFear was more effective treatment with a medium to large effect size. These theoretically driven interventions have been part of a large increase in RCTs for the management of FCR/P.

Although, Tauber et al (2019) in their meta-analysis of 23 trials found that on average, these trials reported small effect sizes at post-intervention (Hedge's g = 0.33) and these effects were also observed at follow-ups (Hedge's g = 0.28). Although this meta-analysis

confirms a number of potentially efficacious treatments, the majority were face-to-face (requiring a median of 6 sessions) and were associated with extensive specialist psycho-oncology care. With over one million cancer survivors in Australia alone there is no way that these interventions can meet the needs of all survivors – particularly since nearly 1 in 5 survivors have severe FCR (Luigjes-Huizer et al., 2022).

However, Tauber et al's meta-analysis also included two trials of a minimal intervention: (Cognitive Bias Modification for interpretation bias) (CBM-I; Lichtenthal et al., 2017) and gratitude intervention (Otto et al., 2016). While neither study resulted in a reduction in FCR/P scores overall, both reduced at least one subscale. The CBM-I intervention targeted biases in interpretation and attention, the mechanisms highlighted in Heathcote & Eccleston's model. In anxiety, interventions based on modifying cognitive biases have been found to be efficacious, particularly interpretation bias (Jones & Sharpe, 2017; Fodor et al., 2020). While CBM-I interventions typically have small to medium effects on anxiety, their attraction is that (at least in theory) they can be administered remotely, hence can increase accessibility. Arguably, Lichtenthal et al's RCT was pre-mature in that whether FCR/P was associated with biases in attention or interpretation has yet to be clearly established. The reason that the study of implicit cognitive biases is of interest, is that support to manage FCR remains the most commonly unmet need amongst cancer survivors.

2.6.

Cognitive biases

The theoretical frameworks described above places a heavy emphasis on the role of implicit processing biases in aetiology of FCR/P. Cognitive biases refer to the selective ways that individuals process information in order to make sense of their environment (Haselton, Nettle & Murray, 2015). In other words, cognitive biases are the way in which we prioritise information from the environment and make sense out of it. Prior learning and experience lead us to focus more on salient information and to interpret cues in the environment consistent with prior experiences. So, in the context of cancer, it makes sense that somatic symptoms or other cancer-related triggers may be particularly salient and interpreted as a potential threat. Contemporary literature examining cognitive biases usually highlight three types of such biases: (1) Attentional biases (e.g., hypervigilance, difficulty disengaging and cognitive avoidance), (2) Interpretation biases (e.g., threat appraisal), and (3) Memory biases (being more likely to recall prior negative events).

2.6.1

Attentional bias

Attentional biases refer to preferentially attending to threat relevant and emotionally salient stimuli in the environment over and above other competing stimuli (Cisler & Koster, 2010). Attention is characterized by the orientation of attention, shifting away from threat stimuli once engaged, and updating attentional focus based on new information (Barry, Vervliet & Hermans, 2015). Typically biases in attention are categorised into three potential

sources of bias: (a) Vigilance: the initial focus of attention; (b) difficulty disengaging: which refers to the difficulty of being able to shift attention away from the salient stimulus; and (c) avoidance: which refers to the immediate and strategic disengagement from the threatening stimulus (Cisler & Koster, 2010). A variety of computer-based tasks have been used in the literature to measure attentional bias phenomenon. The most common tasks being the modified version of Stroop and dot-probe, visual or spatial cueing and more recently eye-tracking, with a variety of paradigms.

Biases in attention have been clearly established across anxiety disorders. There is a large meta-analysis showing that in general anxious individuals have biases towards threatening information in attention as compared to non-anxious people (Bar-Haim et al., 2007). In fact, a review of the causal role of attentional biases in anxiety concluded that there is a good evidence that biases in attention are causally associated with anxiety disorders (van Bockestale et al., 2014). However, whether cognitive biases are associated with anxiety in the context of physical illness is unclear.

Research on information processing bias has now been extended to other physical health conditions, such as chronic pain and fatigue (Hughes, Hirsch, Chalder & Moss-Morris, 2016). In terms of attentional bias, there is some support to indicate the presence of this bias amongst people with pain compared to those without. An early review exploring the attention bias in pain found weak evidence of attentional bias in people with pain as compared to people without pain, although there was only a single dot-probe study (Pincus & Morley, 2001). This early review proposed that biases may be specific to those depression, but anxiety and fear of pain were not addressed. Another, meta-analysis which specifically focused on dot-probe studies, found evidence of attentional bias in chronic pain patients as compared to healthy individuals, with a medium to small effect size (Schoth, Nunes & Liossi, 2012). However, this review did not address fear of pain. Similarly, Todd et al's (2018) meta-

analysis also included studies using the dot-probe paradigm and they also concluded that both patients with chronic and acute pain displayed a small but significant bias towards 'sensory pain words'. Moreover, this was maintained across different task parameters (e.g., stimulus orientation and presentation timing). But this effect was not observed for those anticipating pain or healthy individuals. Similarly, Crombez et al's (2013) meta-analysis also found a small but significant effect for sensory pain words only in people with chronic pain as compared to people without pain. In neither the Crombez et al (2013) and Todd et al (2018) meta-analyses, fear of pain was not associated with biases. The findings from these meta-analyses indicate that although there is a small bias towards sensory pain words that differentiates chronic pain versus control groups, but this is not associated with fear of pain and other pain outcomes.

In other chronic conditions such as cancer, there are several studies that focuses on assessing attentional bias in cancer patients typically using Stroop or dot-probe tasks. Earlier studies for example, by DiBonaventura et al (2010) and Erblich et al (2003), aimed to determine whether or not participants who were at a genetic risk of developing cancer displayed biases in attention as compared to participants who were not at risk. Both studies found the evidence for increased interference scores on a Stroop task for genetically vulnerable group, which indicate that cancer-related stimuli interrupt cognitive processing. A similar pattern of results was obtained in a study of women who were the carriers of either breast or ovarian cancer genetic mutations (BRCA 1/2) (Carpenter et al., 2014). The study found the evidence of biased cancer-related cognitive processing or higher response latencies in Stroop task, and this was also present among women with a personal history of breast and ovarian cancers. However, Cobeanu et al (2013), failed to find attentional bias towards 'chemotherapy-related symptoms', using a dot-probe task in a sample of breast cancer patients. While another study by Glinder et al (2007), found attentional bias towards cancer-

related words on supraliminal presentation (stimulus existing above the threshold of sensory awareness) and away from cancer-related words on subliminal presentations (stimulus existing below conscious awareness) on a dot-probe task. Of note, both of these studies did not include any active control group. In contrast, Sullivan-Singh and colleagues (2015) recruited an active control group comprising of women without cancer. However, they did not find attentional bias towards emotional faces (presented for 1000 ms) in breast cancer patients on a dot probe task as compared to healthy women. To date, there has been no attempt to synthesize the mixed results of this literature.

There are only a handful of studies that directly examine attentional biases and their relationship with FCR/P. Custers et al. (2015), for example investigated whether the level of interference on the Stoop task for cancer stimuli in a sample of breast cancer patients was dependent on their level of FCR/P. Their study concluded that cancer survivors with high recurrence fears displayed a greater interference score than those with low levels of such fears. Butow and colleagues (2015) on the other hand, utilized the dot-probe task as a measure of attentional bias. The study categorized words into 2 types (cancer and non-cancer related emotional words) and three valences for these words (positive, negative and neutral). However, the study did not find any evidence that attentional bias was associated with FCR/P in a cross-sectional study. Waroquier et al (2022) used the dot probe to investigate attentional biases in people with breast cancer with high vs low FCR/P. Words were presented at subliminal levels (17 ms), and supraliminal (500 ms) and found no differences in attentional bias indices for people with high compared to low FCR/P at any of the time points. All patients showed a bias to cancer-related emotional words (both for positive and negative words) as compared to non-cancer words, although the effect was more pronounced for negative cancer words (Waroquier et al., 2022).

A similar pattern of findings was observed in a longitudinal study by Ng et al (2020). The study tested if attentional bias mediated the relationships between metacognitive beliefs and FCR/P trajectories over time in people with breast and colorectal cancers. Attentional bias was assessed using a dot probe paradigm involving cancer-related and negatively valenced words at baseline. Participants were then followed up over a period of 12 months, where FCR was assessed. No association was found between attentional bias and FCR/P levels. Ng et al. (2020) assessed attentional bias at both subliminal and supraliminal word presentations, but found neither of these word presentations were associated with FCR/P. Hence, in line with chronic pain studies, the evidence for attentional bias does not suggest the same strong and robust relationship between attention bias and FCR/P, as found in anxiety disorder. However, it is noted that there are only three studies, with relatively small samples to compare survivors with clinically significant FCR, compared to those without. Nevertheless, the results do question whether attention bias is likely to be a putative mechanism in FCR/P. This is particularly the case since it is evident that attentional bias is largely related to the task used. That is, biases were observed on the one study using the Stroop task and the two studies using the dot probe failed to find evidence of attentional bias.

This pattern of results casts doubts on the importance of attentional biases in FCR/P. The Stroop task is not an unambiguous measure of attentional bias. That is, participants will read words more slowly if their attention is drawn to cancer-related stimuli. However, it is also known that the Stroop is vulnerable to response bias because only a single stimulus is visible at any time. That is, if the emotionally salient word evokes anxiety, which results in a generally slowed response, an interference effect will also be observed. In other words, this delayed responding to negative or threat words could be related to either general slowing in response or to attentional mechanisms. However, the Stroop paradigm does not allow these

different mechanisms to be differentiated (Phaf & Kan, 2007; Chajut, Mama, Levy & Algom, 2010). In order to overcome the shortcomings of the Stroop paradigm, the dot probe task was developed. The dot-probe task presents two different stimuli (one emotionally salient and one neutral) at the same time, followed by a probe. The probe replaces either the emotionally salient stimulus or the neutral stimulus. Because every trial has BOTH an emotionally salient AND a neutral stimulus, general slowing cannot account for any observed difference in responding to probes that replace the emotionally salient versus neutral word. Hence, the difference in response times between congruent trials (trials where the probe replaces the emotionally salient word) and incongruent trials (trials where the probe replaces the neutral word) is taken to be the index of attentional bias. (MacLeod, Mathews & Tata, 1986). Nevertheless, the dot probe task is not without problems such as poor reliability and being an indirect measure of attention. The role of attentional bias in the context of cancer has not been systematically synthesized and this remains a gap in the literature.

2.6.2

Interpretation bias

Interpretation bias refers to the process of encoding a particular ambiguous stimulus with its possible multiple meanings (Trotta et al, 2021). In other words, it is the process whereby ambiguous information is assigned a threatening meaning or a tendency to interpret ambiguous information, situations or events as threatening (Lee, Matthews, Shergill & Yiend, 2016). Tasks used to measure interpretation bias involve ambiguous stimuli that must be resolved. Each ambiguous stimuli can be resolved in either a benign or a threatening manner. An interpretation bias is observed when more threatening than benign resolutions are

endorsed. Most of these tasks are word and language based (Schoth & Liossi, 2017). The most common tasks are: (i) *homophone tasks*, where participants listen to a word that has two alternative meanings and spellings such as *die/dye*. Participants are then asked to spell the word. For example, if they spell the word as 'die', this indicates an evidence of interpretation bias. That, is a greater proportion of threat spellings of ambiguous words, indicates a threat-based interpretation bias (Matthews, Richards & Eysenck, 1989); (ii) *word stem completion task* (Edwards & Pearce, 1994). Here individuals are presented with word fragments, with either a threatening or neutral resolution, where a threat resolution indicates a bias and; (iii) homograph task. In homograph task, participants are presented with a list of ambiguous words (e.g., 'terminal') and participants are instructed to read the list and write down the first word that comes to their mind. Other tasks include word sentence association paradigm (WSAP) and ambiguous scenarios tasks. See Schoth and Liossi (2017) for a complete review of these tasks.

Interpretation bias has been extensively explored in the anxiety literature, where it has been shown to be strongly associated with anxiety (Wilson, MacLeod, Mathews & Rutherford, 2006). It has been the most common form of bias across anxiety disorders such as social anxiety (Amir, Beard & Bower, 2005) or generalized anxiety (Hirsch, Meeten, Krahé & Reeder, 2016). For example, a recent meta-analysis (Chen, Short & Kemps, 2020) comprising of 44 studies found a strong evidence of interpretation bias in socially anxious individuals, with a large effect size (Hedge's $g = 0.83$).

Similar to anxiety, interpretation bias has also studied in other physical health conditions such as chronic pain. That is, a range of experimental paradigms show that when compared to a control group, chronic pain patients tend to have biased interpretation towards ambiguous stimuli (Pincus et al., 1994; Pincus, Pearce, & Perrott, 1996; Khatibi, Sharpe, Jafari, Gholami, & Dehghani, 2015; Schoth and Liossi, 2016). A recent study further found a

significant moderate correlation between pain intensity and interpretation bias in a sample of chronic pain patients (Jones et al., 2021). In addition, there also exists a number of theoretical conceptualizations, which incorporates the role of interpretation bias as integral to the maintenance of chronic pain (e.g., Vlaeyen et al., 2016; Crombez et al., 2012). Likewise, the Threat Interpretation model in the context of pain by Todd and colleagues (2015) proposes that an individual when encounters stimuli (e.g., sensation, situation, picture or a word), they initially categorize information as pain or non-pain related. If the stimulus is categorized as pain-related, then the degree to which one interprets stimulus as threatening (interpretation bias) determines whether the attentional bias will be displayed. In this way, the models suggests that in the pain, there is an interpretation bias of whether a stimulus is pain or health-related and then a potential bias as to whether the pain threatening. In the area of chronic pain, meta-analysis confirms that there are moderate to large interpretation biases observed in people with pain as compared to those without pain. However, the largest meta-analysis has only seven studies, but all studies – regardless of paradigm – found evidence of interpretation bias (Schoth & Liossi, 2016). As such, this phenomenon is robust that attentional biases in pain. However, no studies have investigated the role of interpretation bias in fear of pain.

The evidence of interpretation bias in both anxiety and chronic pain is more consistent and robust as opposed to attentional biases. The manifestation of interpretation bias is largely constant across a variety of psychopathology, however, is dependent on the content of the stimulus (Trotta et al, 2021). In other words, the bias would be stronger when the information being processed has a more direct relationship with symptoms of a particular disorder. This has been referred to as the notion of *content specificity* (Yiend, Barnicot, Williams, & Fox, 2018). From the above reviewed literature, it has become clear that the evidence of interpretation bias is more consistent and robust in both anxiety and chronic pain, as opposed to attentional biases. However, the role of interpretation bias in the context of cancer or more

specifically FCR/P is less clear. Given the fact that FCR/P is a cancer-specific anxiety, it is hardly unsurprising that these biases do exist in FCR/P as well.

Most of the theoretical models described in previous sections do highlight the important role of misinterpretation of ambiguous information specifically somatic symptoms as a causal factor in aetiology of clinical FCR/P. However, only two studies have assessed interpretation biases amongst cancer patients in the context of FCR/P (Lichtenthal et al., 2017; Lam et al., 2018). Lam et al (2018) utilized the ambiguous cues task to measure interpretation bias in a sample of breast cancer patients in a longitudinal study. They further subdivided participants on the basis of persistent high and low distress (anxiety and depression). The study concluded that breast cancer patients who were persistently highly distressed were more likely to interpret ambiguous words as cancer-related than those with low levels of distress.

Lichtenthal et al (2017) recruited women with a history of breast cancer who scored in the clinical range for fear of cancer recurrence and used Word Sentence Association paradigm as a measure of interpretation bias. Participants completed attention and interpretation bias measures before they were randomized to either receive cognitive bias modification (CBM) or placebo. CBM is a procedure that trains people to interpret information in a non-threatening way and/or to attend to neutral rather than threatening stimuli. When assessed at baseline, Lichtenthal et al (2017) found participants with breast cancer made more threat-related interpretations than benign interpretations when interpreting ambiguous sentences, although there was no control group of either people without cancer or people with cancer but no clinically significant level of FCR. Following a combined attentional and interpretation CBM, interpretation biases had been successfully modified such that women were less likely to interpret ambiguous sentences as threatening, but attention biases were not reliably changed compared to placebo. There were also changes on the health

worries subscale of the concerns about recurrence scale (although not on the full scale) in the CBM group compared to placebo. These results were interpreted to suggest that changes in interpretation bias were likely to have driven the observed symptom changes, although the authors did not present mediation analyses. While there are only two studies, it is notable that both studies find evidence to support the role of interpretation biases in distress and/or FCR. Therefore, it is clear that the investigation of interpretation biases in the context of cancer generally, and FCR specifically, is a worthy area of future research.

2.6.3

Memory bias

Memory bias is the tendency to selectively recall illness-related or negative information from memory (Lau et al., 2018). A meta-analysis of 171 papers found that individuals with high anxiety show a memory bias for threatening stimuli compared to people with low anxiety (Herrera, Montorio, Cabrera & Botella, 2017). Memory bias has also been examined in the context of chronic pain. An early systematic review (Pincus & Morley, 2001) concluded there was sufficient evidence for memory biases in individuals with chronic pain from studies using recall tasks, although the more recent literature has found mixed results (Schoth, Parry & Liossi, 2018; Serbic & Pincus, 2014). However, in cancer context, there are only two studies which directly examined the relationship of memory biases. Neither of them found evidence of a memory bias in people with cancer compared to those without cancer (Sullivan-Singh, Stanton & Low, 2015; Besharat & Firoozi, 2013). Hence, it is unclear whether further research into memory bias is warranted.

Overall, there is strong evidence that cognitive biases in attention, interpretation and memory exist in anxiety disorders, and that these biases are likely to have a causal role (see

van Bockestale et al., 2014). However, there is considerably less evidence about the role of cognitive biases in the cancer context, generally or in FCR/P more specifically. There is a need to (a) synthesize the literature, and (b) to further research biases in relation to the most common psychosocial issue facing people living beyond cancer – fear of cancer recurrence or progression.

2.7.

The Present Study:

FCR/P remains one of the most commonly reported survivorship issues in oncology services (Crist & Grunfeld, 2013) and is associated with a range of negative psychosocial outcomes (Koch, Jansen, Brenner & Arndt, 2012). The theoretical frameworks proposed to explain why some people develop clinically significant levels of FCR/P all highlight the crucial role of implicit cognitive processes in the development and maintenance of clinical levels of FCR/P. The Cancer Threat Interpretation (Heathcote & Ecclestone, 2017) argues that the occurrence of bodily symptoms such as pain demands interpretation and is often interpreted as a sign of cancer recurrence. This interpretation of ambiguous bodily sensations as both painful and a sign of recurrence is viewed as the putative mechanism in the development of severe FCR. However, there is only a single study that has investigated interpretation biases in the context of FCR (Lichtenthal et al, 2017). There is a clear need for more research on cognitive biases and any potential role in FCR.

Specifically, this thesis aims to:

(1) Synthesize the available research literature on cognitive biases in the context of cancer through a scoping review with meta-analysis. (Chapter 3)
(2) Examine whether people with cancer are more likely to interpret ambiguous stimuli as health-related than people without cancer (Chapters 4 and 5)
(3) Examine whether people with breast or ovarian cancer who have clinically significant levels of FCR/P are more likely to interpret ambiguous stimuli as health-related than those whose FCR/P levels are below the clinical range (Chapters 4 and 5).
(4) Test one of the major tenets of the Heathcote and Eccleston (2017) Cancer Threat Interpretation model. That is, to determine whether interpretation biases moderate the relationship between pain and FCR/P. (Chapters 4 and 5)
(5) Propose a potential stepped care model of cancer care that can increase accessibility to effective treatments for FCR/P (Chapter 7).
(6) develop and test the efficacy of two potential minimal interventions to reduce FCR/P of increasing levels of complexity, namely a simple static pamphlet containing psychoeducation about FCR/P and a Cognitive Bias Modification for Interpretation (CBM-I). (Chapters 6 and 8)

Chapter 3: The role of attentional biases in the context of cancer: A systematic review and meta-analysis

The following chapter is the reproduction of the material contained in the published manuscript:

Pradhan, P., Sharpe, L. & Butow, P. (2021). The role of attentional biases in the context of cancer. *Psycho-Oncology, 30* (5), 649-658. doi: 10.1002/pon.5617.

The contributions of each of the authors are as follows:

Poorva Pradhan developed the research aims, study design and protocol, conducted the literature search title and abstract review, full text review, analysis of included papers and extracting information from included papers and wrote the first draft of the manuscript.

Signature: **Date:18/09/2022**

Professor Louise Sharpe provided the supervision and critical review regarding the study concept and research questions. Also reviewed 10% of the titles and abstracts and 100% of the included studies and performed and data analysis. Professor Sharpe also provided critical revision of the manuscript.

Signature: **Date: 18/09/2022**

3.1. Introduction

Although most people cope well following cancer treatment, a small but important minority develop clinically significant levels of anxiety, depression or fear of cancer recurrence (Jean & Syrjala., 2017; Boyes, Girgis, D'Este & Zucca., 2011; Linden, Vodermaier, MacKenzie & Greig, 2012; Mehnert & Koch, 2007). These psychosocial sequalae are known to impair the quality of life of cancer survivors (Cheng, Wong & Koh., 2016; Jarrett et al., 2013). One factor thought to contribute to a vulnerability to anxiety and depression is attentional bias towards threatening or negative stimuli (Kircanski, Joormann & Gotlib., 2012; Williams, Watts, MacLeod & Mathews., 1988; Bar-Haim, et al., 2007). Attentional biases refer to the tendency of individuals to have their attention drawn to threatening (personally salient) stimuli and have difficulty disengaging from those stimuli.

A systematic review (Curran, Sharpe & Butow., 2017) of theoretical models on the development of cancer-related anxiety found that recent models specified a role for attentional biases in the development of anxiety in the cancer context. Historically, models focused on the content of beliefs, such as appraisals of threat (e.g., Fardell et al., 2016; Edmondson, 2014), illness representations (e.g., Lee-Jones, 1997; Lebel et al., 2014) or beliefs about death and dying (e.g., Edmondson, 2014). However, more recent models also emphasized cognitive processing, such as attentional bias (e.g., Lepore, 2001; Fardell et al., 2016). However, contemporary models suggest that it is not just the content of beliefs, but also the way people attend to potentially threatening information, such as focusing on intrusive thoughts, physical symptoms or other cancer-related cues (attentional biases), which contribute to the development and maintenance of anxiety (Fardell et al., 2016; Heathcote & Eccleston, 2017; Simonelli et al., 2017).

However, investigation of attentional biases in relation to cancer-related cues is sparse. Furthermore, findings of the studies conducted to date are mixed, with some studies finding attentional biases amongst people with cancer compared to controls (Balandin, 2014; Custers et al., 2015), others finding biases only amongst people with cancer who are distressed (Lam et al., 2018) and some finding no biases in cancer survivors (Butow et al., 2015). Different results likely reflect differences in methodology, such as different paradigms, valence of stimuli, type of stimuli and different stimulus presentation timings.

While little is yet known about attentional biases in relation to cancer, it is important to synthesize the literature at this early stage to guide future research. Therefore, the aims of this review were to summarise the literature on: a) the presence of attentional biases in cancer survivors, and b) the relationship between attentional biases and cancer-related distress; and (c) to make recommendations for future research. We proposed three specific research questions:

1. Do cancer survivors show attentional biases in processing cancer-related and/or negative (i.e. salient) stimuli as compared to people without cancer?

2. Do cancer survivors show attentional biases in processing salient stimuli as compared to neutral stimuli?

3. Are attentional biases in cancer survivors associated with distress, such as fear of cancer recurrence (FCR), depression, or anxiety?

3.2. Method

The protocol of the review was pre-registered with PROSPERO (ID CRD42019117140)

3.2.1 Search strategy

Comprehensive searches were conducted up until May 2020 in six online databases: PsycINFO, Medline, Web of Science, Scopus, Embase, and CINAHL. Key search terms were related to cognitive bias; "attention* bias*, interpret* bias*, memory bias*". These were combined with cancer population related keywords "cancer or neoplasm" (see Appendix C for complete search string). The reference lists of selected articles were manually screened to identify additional papers.

3.2.2 Selection of studies

Titles and abstracts were screened according to inclusion and exclusion criteria (PP) and 10% were reviewed by another author (LS) with almost perfect (Landis & Koch, 1977) inter-rater agreement of k = 0.83. All full text article screening and data extraction were conducted by two authors (PP and LS). Disagreements were resolved by consensus.

The following inclusion criteria were applied:

(1) Studies using standard experimental paradigms to measure attentional biases with and without control group were included. Experimental paradigms typically use reaction time to determine whether individuals respond more quickly to salient stimuli than neutral stimuli (or probes that replace salient stimuli), such as the Dot-Probe or Stroop task (Cisler, Bacon & Williams, 2009).

(2) Participants who have had or currently have cancer of any type or stage

(3) Studies that were published as a peer-reviewed journal article or dissertation thesis.

3.2.3 Data extraction:

The following data points were extracted from included studies: publication year, nature of sample(s) (cancer survivor; control), mean age, sample size, type of cancer, type of task used to assess attentional biases, means and standard deviations for attentional biases for cancer survivors and controls, and the relationship between attentional biases and distress. The attentional bias index scores on the dot probe task were calculated by subtracting mean reaction times to probes appearing in the same location as neutral stimuli from mean reaction times to probes appearing in the same location as salient stimuli. The Stroop interference effect was calculated by subtracting mean reaction time on neutral stimuli from mean reaction time on salient stimuli. A positive bias index indicates attention towards salient stimuli. Hence, a positive effect size indicates evidence of attentional bias towards salient stimuli (Cisler, Bacon & Williams, 2009).

Where data were not available, we contacted the authors. If unavailable, we used other statistical information to calculate an effect size, wherever possible. Where multiple stimuli were used, we used the stimuli that we considered most salient to cancer survivors. Hence, we prioritised stimuli in following order: cancer-related stimuli (if differently valenced, we opted for negative cancer-related stimuli), over health-related stimuli, over negative stimuli (often facial expressions of fear or sadness) and finally threat stimuli. Where multiple presentation times were used in a single study, we prioritised 500 milliseconds over 1000milliseconds over subliminal presentation. Only one study used a subliminal presentation time and therefore subliminal attention was not assessed in this meta-analysis. To investigate distress, studies included different measures, including measures of FCR,

anxiety or general distress. Where multiple assessments of distress were included, we included the relationship according to the order above.

3.2.4 Quality assessment:

For assessing the methodological quality of included studies, a modified version of Downs and Black (1998) quality index checklist was used. The modified checklist has 18 items relating to 5 criteria: reporting, external validity, internal validity (bias), selection bias, and power of the study, where a higher score indicates higher quality. Two reviewers (PP; LS) performed quality ratings for each article. Inter-rater reliability was $k = 0.86$, indicating almost perfect reliability (Landis & Koch, 1977). Discrepancies were resolved through discussion.

3.2.5 Statistical analysis:

The analyses were performed with the Comprehensive Meta-analysis software (CMA; version 3). We report Hedge's g as the effect size. We pooled these effect sizes for individual studies to calculate whether the attentional bias was larger for people who had cancer compared to people with no personal or family history of cancer (*between-subjects analysis*). We then examined all studies that investigated attentional bias in people with cancer, to determine whether people with cancer exhibited more attention to salient than neutral stimuli (*within-subjects analysis*). Finally, we examined studies where distress (e.g., FCR, anxiety, depression) was measured to determine whether distressed people with cancer had greater attentional biases than those who were not distressed. Study characteristics, including, type of paradigm (Dot-probe or Stroop), type of stimuli (words or faces) and exposure duration (500 ms or $\geq$ 1000 ms) were used as moderator variables. As suggested by Cohen (1988), the following conventions were used to interpret effect sizes: 0.2 represents a small, 0.5 represents a medium and 0.8 represents a large effect size.

All analyses used random-effects models, which allow more weight to be given to studies with larger samples (Borenstein et al., 2009). To determine heterogeneity, we assessed Cochran's Q and I^2 statistic which is an estimate of heterogeneity across studies. Increasing values indicate increasing heterogeneity. A p-value of less than 0.05 was considered statistically significant for all analyses.

To assess for publication bias, we tested the asymmetry of the funnel plot and used Egger's test to determine overall symmetry. We conducted Duval–Tweedie trim and fill analysis, which provides an estimate of missing studies and recalculates the adjusted effect size. Finally, Rosenthal fail-safe N was also computed to determine how many additional studies would need to be unpublished for the p-value to become non-significant (Rothstein, Sutton & Borenstein., 2005)

3.2.6 Differences from the published protocol:

We intended to review studies for all cognitive biases (including interpretation and memory biases) and investigate cognitive biases in caregivers. However, there were insufficient data to meta-analyse these outcomes.

3.3. Results

The search strategy yielded 6233 articles, 4105 after removal of duplicates (See figure 1). Titles and abstracts of the 4105 results were screened and 75 full text articles were retrieved. Details of the reason for exclusion are listed in Figure 3.1. Eighteen studies met our inclusion criteria.

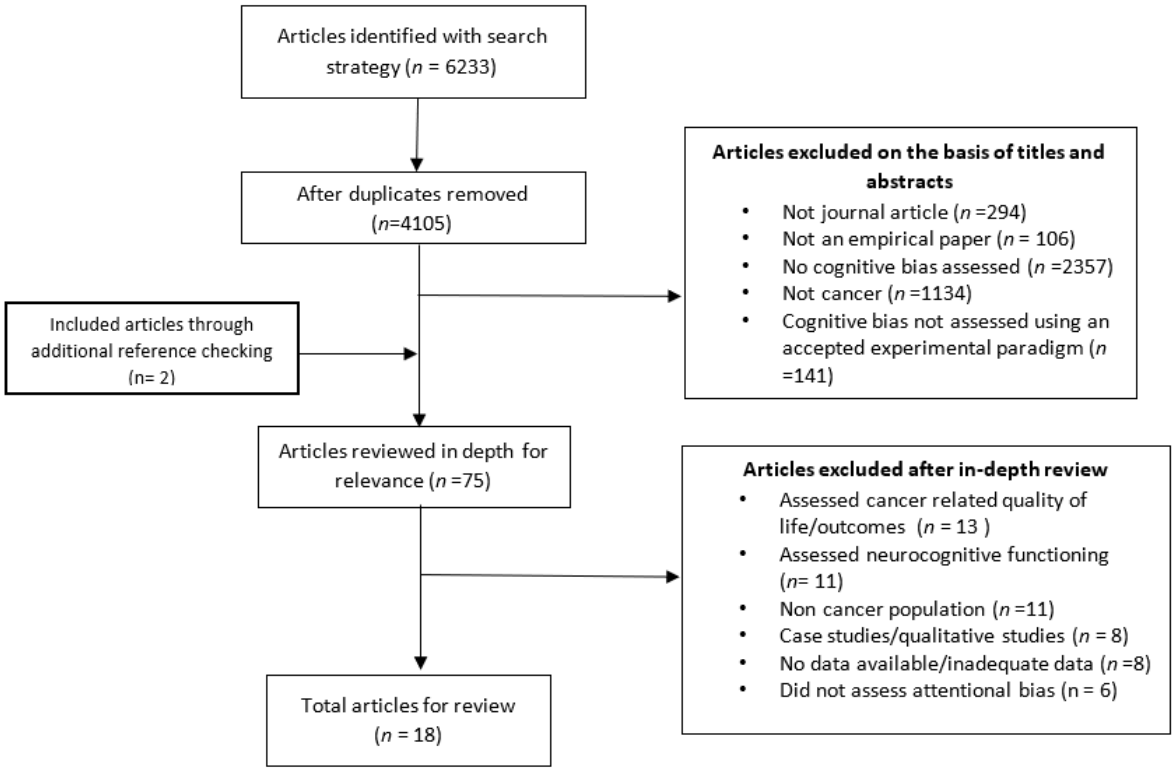


Figure. 3.1 Prisma flow diagram depicting the selection process of final included articles

3.3.1 Study characteristics

Study characteristics are presented in Table 3.1. All 18 included studies recruited adult participants (n = 1273). Eleven studies utilized the Dot-probe paradigm (MacLeod, Mathews & Tata., 1986) and seven used the Stroop paradigm (MacLeod, 1991). Thirteen studies used linguistic stimuli and five studies used pictorial or face stimuli. Stimuli presentation time for the Dot-probe ranged from 500 milliseconds (ms) to 1250 ms. The average sample size for cancer survivors was 71 (SD = 33.9) and their mean age was 56.07.

3.3.2 Meta-analytic Results:

Research Question 1: Do cancer survivors show attentional biases to cancer-related stimuli as compared to people without cancer?

Only six studies included a comparison of cancer survivors and a control group. There was a significant bias towards salient stimuli for people with cancer compared to those without, with a large effect size ($k = 6$, Hedge's $g = 0.82$, 95% CI [0.081, 1.568], $p < 0.001$; See Figure 3.2). There was significant heterogeneity ($Q = 98.24$, $p < 0.001$). There was asymmetry evident in the Funnel plot upon visual inspection, with one study falling far to the right of the distribution and two studies falling to the left. However, Egger's regression was not significant ($t = 0.0178$, $p = 0.99$), nor was Begg and Mazumdar's rank correlation ($tau = 0.33$, $p = 0.34$). Duval and Tweedie's trim and fill analysis did not indicate that any studies needed to be trimmed, supporting an absence of publication bias effects. The failsafe n was 6, although this may simply indicate the small number of available studies. Removing one outlying study in a sensitivity analysis, confirmed a significant difference on salient stimuli between people with and without cancer, but with a small effect size (Hedge's $g = 0.378$, $p < 0.0005$).

Study name	Time point	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value
Carpenter 2014	Blank	0.201	0.186	0.034	-0.163	0.565	1.083	0.279
Custers 2014	Blank	0.509	0.201	0.041	0.114	0.903	2.525	0.012
Naidich 2000	Blank	0.436	0.254	0.064	-0.062	0.933	1.717	0.086
Shi 2014	500.000	1.184	0.303	0.092	0.590	1.779	3.904	0.000
Sullivan-Singh 2016	1000.000	0.252	0.180	0.032	-0.101	0.604	1.399	0.162
Balandin 2014	Blank	2.372	0.184	0.034	2.011	2.733	12.880	0.000
		0.824	0.379	0.144	0.081	1.568	2.174	0.030

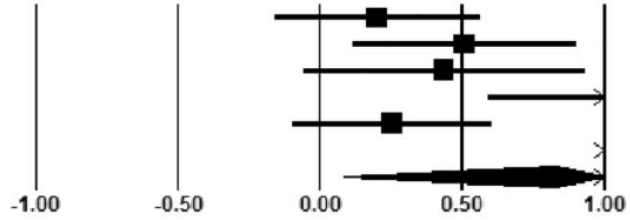


Figure 3.2: Forest plot for attention biases between those who have had cancer and those who have not

Research Question 2: Do cancer survivors show attentional biases to cancer-related or negative stimuli as compared to neutral stimuli?

Data was available for attentional biases towards salient stimuli in 12 studies. Within-group analysis indicated a small attentional bias towards salient compared to neutral stimuli in cancer patients (k = 12, Hedge's g = 0.50, 95% CI [0.223, 0.779], p < 0.001). There was significant heterogeneity (Q= 155.142, p< 0.001). The funnel plot appeared to be symmetrical and Egger's regression was not significant (t= 1.35, p= 0.196) nor was Begg and Mazumdar's rank correlation (tau = 0.26, p = 0.15). Duval and Tweedie's trim and fill indicated that no studies needed to be trimmed and the fail-safe n was 408.

Both cancer-related (k = 10, Hedge's g = 0.54, 95%CI [0.157, 0.929], p = 0.006) and negative stimuli (k = 7, Hedge's g = 0.435, 95%CI [0.029, 0.841], p= 0.036) resulted in a significant effect and did not differ from each other (t= 0.144, p= 0.71).Overall there was a significant attentional bias on the Dot-probe paradigm (k = 10, Hedge's g = 0.33, 95% CI [0.081, 0.572], p = 0.009) and Stroop paradigm (k = 7, Hedge's g = 0.71, 95% CI [0.126, 1.301], p = 0.017) and no difference between the tasks (t= 1.418, p= 0.234). There was no difference between studies where trials were presented for 500ms compared to those with > 1000ms presentation (k = 10, t = 0.00, p = 0.988)

Research Question 3: Are attentional biases in survivors associated with distress?

There were 10 studies that reported effect sizes relevant to this question. There was a significant bias towards salient stimuli in people who were distressed that was significantly larger than for people who were not distressed with a small effect size (k = 10, Hedge's g = 0.31, 95%CI [0.031, 0.576], p = 0.001). There was no asymmetry evident in the Funnel plot upon visual inspection and Egger's regression was not significant (t = 0.66, p = 0.53), nor was Begg and Mazumdar's rank correlation (tau = 0.08, p = 0.75). Duval and Tweedie's trim

and fill indicated that no studies needed to be trimmed. The failsafe n was 24, which likely indicates the early stage of research in this area. As in previous analyses, there was significant heterogeneity ($Q = 24.19$, $p = 0.002$), therefore we conducted moderator analyses using stimuli (cancer vs negative) as the moderator. The moderator analysis for stimuli did not show a difference between cancer-specific and other negative stimuli ($t = 0.109$, $p = 0.742$).

3.3.3 Study Quality:

Quality scores on attentional bias studies ranged from 2 to 15 (out of 19). The quality of reporting was good in most studies (14/17). There was insufficient data to rate one study for quality, so ratings were available for 17/18 studies. External validity was of poorer quality with 11 studies being either unclear or low quality. Similarly, for internal validity only three studies were scored as high quality. Only six studies clearly reported power analysis.

TABLE 3.1: Study characteristics and effect sizes of included studies for meta-analysis

Study	Nature of Sample	Sample Size	Type of Cancer	Type of task	Duration of trials/stimuli	Type of stimuli	Effect size (Hedge's g)	95% CI	Quality index scores (max score = 19)
Aramaki et al, 2019	Cancer patients	17	Multiple cancers	Stroop task		words	0.401	(-0.262, 1.065)	3
Bakhshaie et al, 2019	Cancer patients	123	Multiple cancers	Stroop task		words	0.005	(-0.244, 0.254)	11
Balandin, 2014	Cancer survivors controls Caregivers	Cancer survivors - 100 controls - 100 Caregivers - 100	Breast Cancer	Stroop task		words	2.372*	(2.011, 2.733)	12

Boyle et al, 2017	Cancer survivors	91	Breast Cancer	Dot probe task	1000 ms	faces	1.056*	(0.587, 1.525)	9
Butow et al, 2015	Cancer survivors	63	Breast and Prostate cancer	Dot probe task	500 ms	words	0.099	(-0.394, 0.592)	12
Carpenter et al, 2014	Cancer survivors Controls	Cancer survivors - 61 Controls - 54	Breast and Ovarian cancer	Stroop task		words	0.201	(-0.163, 0.565)	15
Chan et al, 2013	Cancer patients	56	Breast Cancer	Dot probe task	1000 ms	faces	0.619*	(0.041, 1.198)	7
Cobeanu, 2013	Cancer patients	30	Breast Cancer	Dot probe task	500 ms	words	0.275	(-0.466, 1.016)	6

Custers et al, 2014	Cancer survivors and Controls	Cancer survivors - 67 Controls - 40	Breast cancer	Stroop task		words	High vs Low FCR: 0.136 Cancer patients vs Controls: 0.509*	High vs Low FCR: (-0.338, 0.611) Cancer patients vs Controls: (0.114, 0.903)	11
Glinder, 2007	Cancer patients	127	Breast cancer	Dot probe task	20ms 1000ms	words	0.491*	(0.131, 0.852)	6
Koizumi, 2018	Cancer patients	27	hematopoietic tumor patients	Dot probe task	500 ms	faces	N/A		4
Lam et al., 2018	Cancer patients	140	Breast Cancer	**Attentional bias**: dot probe task **Interpretation bias**: Ambiguous cues task	500 ms and 1250 ms	words	500 ms: 0.222	500 ms: (-0.176, 0.620)	12
Lautenbacher et al., 2011	Cancer patients	58	Mutliple cancers	Dot probe task	500 ms	words	0.245	(-0.281, 0.770)	7

Lichtenthal et al., 2017	Cancer survivors	110	Breast cancer	**Attentional bias**: dot probe task **Interpretation bias**: word-sentence association paradigm (WSAP)	Dot probe: 500 ms WSAP: 500 ms	Dot probe: words WSAP: word-sentence pairings	0.319	(-0.051, 0.688)	11
Naidich & Motta, 2000	Cancer patients and controls	Cancer patients - 31 Controls - 31	Breast cancer	Stroop task		words	0.436	(-0.062, 0.933)	5
Shi et al., 2014	Cancer Patients and controls	Cancer patients-54 Controls-52	Multiple cancers	Dot probe task	500ms 1250ms	faces	500 ms: 1.184*	500 ms: (0.590, 1.779)	N/A
Sullivan-Singh et al., 2014	Cancer patients and controls	Cancer patients - 85 Controls - 49	Breast cancer	**Attentional Bias**: Dot probe task **Memory Bias**: Recognition task	1000 ms	faces	0.252	(-0.101, 0.604)	11
Taylor et al., 2003	Cancer patients	33	Mutliple cancers	Stroop task		words	0.295	(-0.378, 0.967)	2

*p < .05

3.4. Discussion

The results of the meta-analysis demonstrate that cancer patients exhibit a greater attentional bias towards salient stimuli than people without cancer and a greater bias towards salient stimuli compared to neutral stimuli. The difference between people with and without cancer was smaller following sensitivity analyses, confirming that the large effect could be an overestimate. Nevertheless, we can be confident that those living with and beyond cancer have attentional biases towards salient stimuli. Importantly, our results also confirm an association between distress and attentional bias to salient compared to neutral stimuli.

People who are more anxious are known to be more likely to attend towards threatening stimuli (Bar-Haim et al., 2007), and that bias towards stimuli is greater when the stimuli is specific to their concerns) (Pergamin-Hight et al., 2015). Indeed, there is evidence from both prospective studies and studies in which attentional biases are manipulated, that attentional bias has a likely causal role in the development of anxiety (Dear et al., 2011). For these reasons, theoretical models that attempt to explain why some people develop clinically significant anxiety in the context of cancer, have also focused on the way that people process or attend to information (Fardell et al., 2016; Heathcote & Eccleston, 2017). It is proposed that survivors who are anxious are vigilant to cues of cancer in the environment and are unable to disengage from these cues. It is these attentional biases that the experimental paradigms aim to identify, and therefore we would expect that cancer survivors who are distressed would have greater attentional biases to salient stimuli than those who are not distressed.

In anxiety disorders, there is evidence that this bias is particular to disorder-specific stimuli (Pergamin-Hight et al., 2015). However, in none of our analyses was the difference

between cancer-specific stimuli and other negative stimuli (typically faces) significant. One possible explanation is the nature of cancer-specific versus negative stimuli. Most negative stimuli were facial expressions, while most cancer-specific stimuli were words. It may be that cancer-specific stimuli that were pictorial might produce larger effects. Alternatively, since studies varied in how they categorised distressed participants, biases to negative stimuli may be due to general anxiety and/or depression, and it may be cancer-specific anxiety, such as FCR, that is linked to cancer-specific stimuli. These explanations are speculative and the results may simply reflect insufficient power.

3.4.1 Limitations

The main limitation of this meta-analysis is the paucity of current research on attentional biases in the context of cancer. There was considerable heterogeneity between studies in relation to stimuli, presentation time and measures of distress used to characterize the samples. Further, there were no studies that used more direct measures of attentional bias, such as eye tracking methodology. There was only one study that assessed attentional biases subliminally (i.e., at presentation times too short for participants to be aware of the stimuli) and so we can draw no conclusions about subliminal presentations. Studies used different measures of "distress" and we collapsed these. Further, we had intended to include other cognitive biases, such as interpretation and memory biases but there were too few studies to do so.

The conclusion of this review is that cancer survivors have attentional biases towards salient stimuli, and this bias is greater amongst those who are more distressed. Nevertheless, the review raises more questions than it answers due to the limitations in the literature. We make eight recommendations that stem from these findings (see Table 3.2).

(1) Given the lack of clarity surrounding what stimuli are associated with an attention bias in the cancer context, we recommend that authors include at least negative and cancer-related stimuli. Further, researchers should develop stimuli specific to the cancer type, since one might expect that mastectomy may elicit more of a response in breast cancer survivors than other tumour groups (See Hughes et al., 2016 for a discussion).

(2) All studies of attentional bias used reaction time measures, which are known to be unreliable (Dear et al., 2011). Future research would benefit from measuring gaze behaviour more directly.

(3) The inclusion of well-matched control groups is important because many measures of attentional bias are influenced by factors, such as age or education.

(4) There were only two studies of interpretation bias (Lam et al., 2018; Lichtenthal et al., 2017) and memory bias (Besharat, 2011; Sullivan-Singh, Stanton & Low., 2015). More research of these constructs in the context of cancer is needed.

(5) Ideally research would investigate multiple cognitive biases within the same sample, as it has been argued that cognitive biases interact, known as the 'combined cognitive bias hypothesis' (Hirsch, Clark & Mathews, 2006)

(6) Only two studies specifically examined FCR, which is the leading psychosocial unmet need of cancer survivors (Armes et al., 2009). Recent FCR theories have all emphasized cognitive processes as important to the development or maintenance of FCR (e.g., Fardell et al., 2016; Heathcote & Eccleston., 2017; Simonelli et al., 2017).

(7) From the broader emotion research, we would expect attention and interpretation bias to be the primary biases involved in constructs like FCR, whereas memory biases have been more implicated in depressive mood (Mitte., 2008). Therefore, it would be

important for research to investigate the impact of depressed mood on memory biases in the cancer context.

(8) Much of the research was pragmatic, rather than theoretically driven. Future research should be designed to try and test relevant theories of the role of attentional biases in the cancer experience.

Table 3.2: Identified gaps in the literature and recommendations for future research.

IDENTIFIED GAPS	RECOMMENDATIONS FOR FUTURE RESEARCH
STUDIES HAVE NOT DEVELOPED STIMULI SPECIFIC TO THE RELEVANT SAMPLE	**AT LEAST, CANCER-RELATED *AND* NEGATIVE STIMULI should BE INCLUDED IN STUDIES**
NO STUDIES OF EYE GAZE BEHAVIOUR	**MORE DIRECT METHODS OF ASSESSMENT, SUCH AS EYE TRACKING METHODS ARE NEEDED**
FEW STUDIES COMPARING PEOPLE WITH AND WITHOUT CANCER, CAREGIVERS VS CONTROLS	**NEED TO INCLUDE APPROPRIATE CONTROL GROUPS**
ONLY TWO STUDIES OF INTERPRETATION BIASES, AND MEMORY BIASES	**NEED MORE RESEARCH INTO INTERPRETATION AND MEMORY BIASES**
ONLY TWO STUDIES ASSESSING ATTENTION AND INTERPRETATION BIAS IN ONE STUDY	**IMPORTANT TO MEASURE MORE THAN ONE COGNITIVE BIAS TO DETERMINE INTERACTIONS**
RELATIVELY FEW STUDIES SPECIFIC TO FCR, DESPITE THEORIES EMPHASIZING COGNITIVE BIASES	**NEED TO ASSESS SPECIFICALLY IN RELATION TO FEAR OF CANCER RECURRENCE**
NO STUDIES OF IMPLICIT MEMORY, NO STUDIES LINKING MEMORY BIAS TO DEPRESSION	**NEED TO EXAMINE MEMORY IN RELATION TO DEPRESSIVE SYMPTOMS**
STUDIES WERE RARELY THEORETICALLY DRIVEN	**NEED TO DEVELOP STUDIES TO TEST THE ROLE OF COGNITIVE BIASES, NOT JUST THEIR PRESENCE**

3.4.2 Clinical implications

Further research into attentional biases is important because procedures have been developed to modify cognitive biases and use these for interventions (Cognitive bias modification; CBM). In a systematic review of meta-analyses of CBM, Jones and Sharpe

(2017) concluded that CBM for interpretation biases (CBM-I) reduced ***anxiety symptoms***, while CBM for attentional biases (CBM-A) reduced ***stress vulnerability*** (i.e. how anxious people felt in a stressful situation). The only study of CBM applied to cancer found that combined CBM (for attention and interpretation) modified negative interpretations (but did not change attentional bias) and reduced one subscale of Concerns about Recurrence Scale (Lichtenthal et al., 2017). These results are consistent with the anxiety literature, where we would expect CBM-I to be efficacious for worry-type symptoms. In the cancer context there are many stressful situations, in which CBM-A may be particularly suited to reducing the increase in anxiety associated with particular situations, such as prior to regular scans (Derry et al., 2019; Feiler, 2011). However, in order for such interventions to be developed and tested, we first need to characterise the nature of cognitive biases in the context of cancer and their relation to distress and other constructs.

3.5. Conclusion

In conclusion, our meta-analysis provides evidence for attentional biases towards cancer-specific and/or negative stimuli amongst cancer survivors. Importantly, the results also suggest survivors who are distressed have larger attentional biases than those who are not distressed. Overall, there is a need to expand research in this area by including appropriate stimuli, more direct measures of cognitive processes, appropriate control groups, and more research on other cognitive biases, particularly in the same sample. Currently, little of the research is theoretically driven. Examining cognitive biases using a theoretical framework will undoubtedly help us better understand the role of cognitive biases in the context of cancer, and their clinical potential.

Chapter 4: The role of interpretation biases and symptom burden in fear of cancer recurrence/progression among ovarian cancer survivors

The following chapter is the reproduction of the material contained in the published manuscript:

Pradhan, P., Sharpe, L., Butow, P. & Russell, H. (2021). The role of interpretation biases and symptom burden in fear of cancer recurrence/progression among ovarian cancer survivors. *Psycho-Oncology, 30* (11), 1948-1956. doi: 10.1002/pon.5748.

Poorva Pradhan developed the research aims and study design in consultation with her lead PhD supervisor Professor Louise Sharpe. The candidate completed the ethics application, recruited participants, analysed the data and wrote the first version of the manuscript.

Signature: **Date: 18/09/2022**

Professor Louise Sharpe provided supervision and critical review regarding the study concept and design, performed post-hoc data analysis and interpretation and reviewed the manuscript.

Signature: **Date: 18/09/2022**

Both Emeritus Professor Phyllis Butow and Hayley Russell provided critical feedback to improve the manuscript. In addition, Hayley Russell helped with participant recruitment.

4.1. Introduction

Ovarian cancer is the 10th most commonly diagnosed cancer among Australian women, with a poorer prognosis than more common cancers. Only 46% of women diagnosed with ovarian cancer are expected to survive to five years. Consequently, women with ovarian cancer live with a significant risk of cancer recurrence or progression and have high symptom burden, making fear of cancer recurrence or progression (FCR/P) an important survivorship issue (Ozga et al., 2015). FCR/P is defined as the "fear, worry, or concern about the cancer returning or progressing" (Lebel et al., 2016, pp. 3267). FCR/P was recently found to be the highest unmet need for women with ovarian cancer in a large Australian survey (Tan, Sharpe & Russell, 2020).

While some degree of FCR/P is natural and even adaptive, severe levels of FCR/P compromise quality of life for an important minority of cancer survivors (Baker, Denniston, Smith & West, 2005), and are associated with depressive, anxiety and post-traumatic stress symptoms (Crist & Grunfeld., 2013; Simard et al., 2013). FCR/P has also been associated with impairment in future planning (Simard et al., 2013; Koch et al., 2013; Hart et al., 2008) and for some survivors, increased visits to doctors and Oncology services, thus increasing health care costs (Thewes et al., 2012; Lebel et al., 2013). FCR/P tends not to resolve over time and hence, individuals experiencing clinically significant levels of FCR/P often require specialized psychological support and intervention (Butow et al., 2018).

Most recent models of FCR/P have focused on cognitive or metacognitive processes, an increased focus on physical sensations and increased misinterpretation of these symptoms. For example, Fardell et al.'s (2016) cognitive processing model proposes that individuals who believe that worry is either helpful, harmful or uncontrollable, attribute significance to intrusive thoughts and worries. This increases anxiety which leads to the "cognitive

attentional syndrome", that is, characterized by worry, rumination and focus on threat (including physical symptoms), which in turn perpetuates FCR/P (Wells & Matthews, 1996). Similarly, Simonelli et al. (2017) emphasize that cues such as physical symptoms trigger FCR/P-related cognitive schemas that lead to an avoidant response towards these cues as a method for protecting the self from threat. This results in cognitive emotional processing whereby these cues are interpreted as threatening. When danger appraisals are made, less adaptive coping outcomes, such as hypervigilance, symptom checking, and suppression emerge, which creates a vicious cycle leading to increased FCR/P. Similarly, the Cancer Threat Interpretation Model (Heathcote & Eccleston., 2017), focuses on the ambiguous nature of physical symptoms such as pain or other symptoms, which on the one hand, are common in daily life but in the context of cancer, could signal recurrence. The model suggests that those patients highly anxious about recurrence, interpret these symptoms (specifically pain) as a sign of recurrence, and become hypervigilant, monitor excessively, and seek reassurance, all of which further reinforces FCR/P through the immediate reduction of anxiety, but increase FCR/P in the longer term.

In the anxiety literature, cognitive processes have been the subject of a large body of literature which suggests that the tendency to interpret ambiguous situations as threatening (interpretation bias) and biases in attention allocation to threatening situations (attentional bias) play a key role in the development and maintenance of maladaptive anxiety (Bar-Haim et al., 2007; Hirsch et al., 2016).

In the cancer context, a recent meta-analysis has confirmed the presence of *attentional* biases to cancer-related or negative stimuli in cancer patients as compared to controls and that these biases were larger in patients who were highly distressed (Pradhan, Sharpe & Butow, 2021; See Chapter 3). However, only two studies have measured interpretation biases in cancer patients, both in breast cancer populations (Lam et al., 2018; Lichtenthal et al., 2017),

and neither included a control group who had not had cancer. Lichtenthal et al (2017) recruited women with a history of breast cancer who scored in the clinical range for FCR/P. Participants completed attention and interpretation bias measures before they were randomized to either receive cognitive bias modification (CBM) or placebo. The CBM procedure trained people to interpret information in a non-threatening way and to attend to neutral rather than threatening stimuli. Participants made more threat-related interpretations than benign interpretations when interpreting ambiguous sentences before the intervention but there was no control group. Following CBM, participants were less likely to interpret ambiguous sentences as threatening, but attention biases were not reliably changed compared to placebo. There were also changes on the health worries subscale of the concerns about recurrence scale (although not on the full scale) in the CBM group compared to placebo. These results were interpreted to suggest that changes in interpretation bias were likely to have driven the observed symptom changes, although the authors did not present mediation analyses. Likewise, Lam et al (2018) did find that breast cancer survivors with high levels of anxiety showed more interpretation bias than those with low levels of anxiety, but did not specifically assess FCR/P. These results suggest that interpretation biases could be relevant to increased worry in the cancer context and may contribute to clinical levels of FCR/P, but more research is needed.

The current study aims to fill this gap and test the central tenet of Heathcote and Eccleston's (2017) threat interpretation model of FCR/P, that interpretation bias moderates the relationship between the severity of symptoms (e.g. pain, fatigue) and FCR/P in a sample of women with ovarian cancer. It is hypothesised that

1. Women with ovarian cancer will be more likely to interpret ambiguous words with an illness-related meaning than women without cancer.
2. Greater interpretation bias will be associated with more severe levels of FCR/P.

3. Interpretation biases will moderate the relationship between symptoms and FCR/P.

4.2. Methods

4.2.1. Participants

One-hundred and fifty-eight participants volunteered for the study. Sixty-two women diagnosed with ovarian cancer were compared with 96 women who constituted the control group. Eligibility criteria for the cancer group were aged over 18 years of age, and English speaking; women could be on active treatment or have completed treatment. Women with ovarian cancer were recruited online through Ovarian Cancer Australia when they sought access to a newly developed resource about FCR/P (See Chapter 6 for more details). Those without cancer were recruited online through social media announcements requesting volunteers. In order to participate in the study, the healthy individuals were required to be: female, over 18 years of age, without a personal or family history of cancer and fluent in English.

Informed consent was obtained from all participants, and they were free to withdraw from the study at any time. Ethics approval was provided by the University of Sydney's Human Research Ethics Committee (HREC) (Project no.: 2018/993).

4.2.2. Procedure:

A cross-sectional study was conducted and participants were invited to follow the link to an online survey, which displayed the participant information and consent forms. After giving consent, women were asked to complete some demographic and medical information followed by a measure of interpretation bias (ambiguous cues task). Clinical data such as cancer stage, cancer status (active disease and in remission), history of recurrence, treatment and

surgery for cancer were self-reported and were collected via self-report, through a web-based platform, Qualtrics. The ambiguous word task was administered prior to questionnaires on symptoms or FCR/P to ensure these did not prime participants' responses. Women with ovarian cancer were asked to respond to questionnaires assessing FCR/P and the presence of various symptoms and were asked whether they experienced any pain in the past month.

4.2.3. Materials:

4.2.3.1 Interpretation Bias Assessment:

Illness-relevant interpretation bias was assessed through participants' response to a set of 14 ambiguous words which have both an illness-related or non-illness related meaning (Pincus et al., 1994). In this task, participants are instructed to write down the first word that comes into their mind when they read each (e.g. "needle" or "terminal"). The responses were then categorised into health-related (e.g. needle-injection or terminal-death) or neutral (e.g. needle-sewing or terminal-bus). Participants' responses were independently coded by two researchers (LS and PP) as illness-related '1'or not '0'. Inter-rater reliability between the two raters was substantial (kappa = 0.80) and discrepancies were resolved through consensus.

4.2.3.2 Fear of Cancer Recurrence/Progression:

The Fear of Progression Questionnaire- Short Form (FoP-Q-SF) (Herschbach et al., 2005) was administered to assess FCR/P. It consists of 12 items, with response options of never (1), rarely (2), sometimes (3), often (4), and very often (5). Thewes et al (2012) reviewed measures of FCR/P and concluded that the Fear of Cancer Recurrence Inventory (FCRI) and FoP-Q-SF were the most psychometrically sound measures and we chose the FoP-Q-SF because many women with ovarian cancer have active disease and therefore 'recurrence' is arguably less relevant. Total FoP scores range from 12-60. A score of 34 is

recommended as the clinical cut-off for clinically significant levels of FCR/P) (Herschbach et al., 2010). The reliability index of Lambda-2 in the current sample was 0.86 (Sijtsma, 2009).

4.2.3.3 Symptom Checklist:

The physical symptoms inventory (Spector & Jex, 1998) is an 18-item questionnaire where participants indicate whether or not they experience each symptom (during the past 30 days) and if they did, whether they had sought medical attention. Symptoms are scored as absent (0), present (1) and needed to seek medical attention (2). Items are summed. The Guttman's Lambda-2 for this scale was found to be 0.67 in the current ovarian cancer sample.

4.2.4 Data Analysis:

All statistical analyses were conducted in SPSS version 26. Preliminary analyses investigated differences between participants with and without cancer on demographic variables, using Mann Whitney U tests for categorical variables and t-tests for continuous variables. Spearman's correlation was conducted to examine the association between interpretation bias and ordinal variables such as education and employment status. Demographic variables (age, education and employment status) differing between cancer and control groups that were also associated with the dependent variable (i.e. interpretation bias), were included as covariates. An ANCOVA analysis was conducted to compare women with and without cancer in illness-related interpretation bias. Although no study has previously compared interpretation biases of people with and without cancer, a meta-analysis of studies in another health group (chronic pain) found an effect size of Cohen's d = 0.67 between people with and without chronic pain on interpretation bias (Schoth & Liossi., 2016). Assuming a similar effect size, we needed at least 118 participants to have 95% power to detect this difference between groups with an alpha set at 0.05.

In the cancer group, we tested Heathcote and Eccleston's (2017) Cancer Threat Interpretation Model. We first conducted Pearson product-moment correlation analyses between continuous variables such as interpretation biases, symptom burden and FCR/P. We tested whether interpretation bias moderated the relationship between symptom burden and fear of cancer progression, using the Hayes (2013) PROCESS macro in SPSS. The PROCESS program determines whether symptom burden and FCR/P independently contribute to variance in FCR/P and then tests whether the interaction term also predicts variance in FCR/P.

4.3. Results

4.3.1 Preliminary Analyses:

Participant demographic characteristics are displayed in Table 1. Ten women (16%) reported being diagnosed with Stage I cancer, 11 (18%) Stage II, 30 (47%) Stage III and 9 (15%) Stage IV. The majority of women reported they were currently in remission (n = 42; 67%), with 18 (29%) currently receiving active treatment. Just over one third of the women (n = 22; 35%) had experienced a cancer recurrence.

Table 4.1: Demographic and clinical characteristics of the sample

	Cancer Patients (n=62)		Controls (n=96)	
Variable	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Age (years)	56.9	11.64	43.2	13.87
Time since diagnosis (years)	3.45	3.29		
	Frequency (percentage)		**Frequency (percentage)**	
Marital status				
Married	41(65.45%)		50(52.08)	
Widowed	2(3.64)		1(1.04)	
Divorced	9(14.55)		10(10.42)	
Separated	3(5.45)		3(3.13)	
Never married	7(10.71)		32(33.33)	
Children				
None	13(20.97)		49(51.04)	
One	9(14.52)		13(13.54)	
Two	32(51.61)		19(19.79)	
More than two	8(12.9)		15(15.62)	
Education level				
Did not complete high school	0(0)		0(0)	
Completed high school	24(38.18)		10(10.42)	
Undergraduate degree at university	22(36.36)		20(20.83)	
Postgraduate degree at university	16(25.45)		66(68.75)	
Employment status				
Currently employed	28(45.16)		75(78.13)	
Currently unemployed	34(54.83)		21(21.88)	
Stage at diagnosis				

Stage 1	10(16.36)
Stage 2	11(18.18)
Stage 3	30(47.27)
Stage 4	9(14.53)
Not known	2(3.64)
Current cancer status	
Currently on treatment	18(29.09)
Active disease	2(3.64)
In remission	42(67.27)
Cancer recurrence	
Yes	22(36.36)
No	40(63.64)
Surgery	
Yes	1(1.12)
No	61(98.88)
Treatment type	
Radiotherapy	0(0)
Chemotherapy	46(74.19)
Hormonal therapy	12(19.35)
No treatment	4(6.45)
CA-125 testing	
Yes	60(96.23)
No	2(3.77)
Not known	0(0)

On average, women with cancer fell within the clinical range on the Fear of Progression Questionnaire (FoP-Q) (M= 35.58, SD= 8.52). Based on the clinical cut-off score of 34, 35 (56%) women reported clinically significant levels of FoP. A high level of symptom burden on the Physical Symptoms Inventory was reported (M= 26.77, SD=4.03), which was, on average, one standard deviation above the mean in the normative sample (Spector & Jex, 1998).

On average, women with cancer were older (M = 56.9; SD = 11.64) than women in the control group (M = 43.2; SD = 13.87) [$t_{(1,156)} = 6.45$, $p < 0.0005$, Mean difference (MD) = 13.71, 95% CI of MD (9.51, 17.9)]. Control participants were more highly educated (U= 1497, $p < .001$) and more likely to be employed [$\chi^2_{(1,158)} = 18.04$, $p < .001$]. A greater interpretation bias score was associated with participants who were older ($r = 0.21$, $p = 0.008$), employed ($r = 0.20$, 0.01) and had received less education ($r = -0.31$, $p < 0.0005$). We controlled for all three variables in our main analyses.

4.3.2 Between group comparisons (women with and without cancer):

We conducted an ANCOVA across participant groups (with and without cancer), controlling for age, educational status and employment status, with interpretation bias scores as the dependent variable. Between group comparisons indicated no significant effect of age [$F_{(1,153)} = 1.61$, $p = .21$], educational level [$F_{(1,153)} = 1.14$, $p = .29$], or employment status [$F_{(1,153)} = 1.05$, $p = .31$], on interpretation bias scores. However, there was a significant effect of cancer status on interpretation bias score [$F_{(1,153)} = 37.62$, $p < .001$; Cohen's d= 1.28; 95% CI = 0.92 – 1.62], indicating that women with ovarian cancer had higher levels of illness-related interpretation bias compared to women without cancer.

Correlational analyses revealed a moderate association between interpretation bias score and FCR/P in women with ovarian cancer ($r = 0.41$, $p = 0.001$), and a small relationship between total symptom burden and FCR/P ($r = .25$, $p = .04$), as predicted. However, no significant association was found between interpretation bias score and symptom burden ($r = .22$, $p = .09$). To test Heathcote and Eccleston's (2017) model, we conducted moderation analyses to determine whether interpretation biases moderated the relationship between total symptom burden and FCR/P. The overall model was significant ($F_{(2, 59)} = 7.15$, $p = 0.002$).

While symptom burden did not predict FCR/P [β = .36, t = 1.44, p = 0.16, 95% CI (-.143, .871)], interpretation bias independently did predict FCR/P [β = .97, t = 3.09, p = 0.003, 95% CI (.342, 1.593)]. The interaction term was not significant ($F_{(1, 58)}$ = 0.0365; p = 0.84), indicating that interpretation bias did not moderate the relationship between symptom burden and FCR/P.

4.3.3 Post-Hoc Analyses

We extrapolated from Heathcote and Eccleston's (2017) model to indicate that those with higher levels of symptom burden would have higher levels of FCR/P, which would be moderated by interpretation biases because in ovarian cancer the most common symptoms of recurrence are not pain, but gastrointestinal symptoms or fatigue (Hay et al., 2016; Donovan et al., 2017). However, the model nominates that it is pain rather than overall symptom burden which contributes to fear of progression. Therefore, we conducted additional exploratory analyses to test this assertion. Firstly, we computed the total of all items on the symptom burden checklist that related to pain. There was no correlation between pain and FCR/P (r= .09, p= .50) or between pain and interpretation bias score (r= .13, p= .30). Therefore, the inclusion of other symptoms could not explain the results.

Since interpretation biases have been rarely studied in this area, we conducted additional exploratory analyses to determine whether there were particular symptoms that were associated with both interpretation bias and FCR/P as the model predicts. We examined each symptom (whether present or not) and its association with FCR/P using independent t-tests and Spearman Rho correlations. While there were 18 symptoms, and therefore, we had multiple comparisons, we decided against adjusting for these, since this was an exploratory analysis and the need to be cautious did not arise. There were no effects of nausea, back pain,

insomnia, rash, breathlessness, fever, infection, eye strain, diarrhoea, heartburn, cramps, dizziness or headache on FCR/P. There was a significant difference in FCR/P for those experiencing chest pain ($t = 3.258$, $p = 0.002$), constipation ($t = 2.224$, $p = 0.03$), a pounding heart ($t = 2.693$, $p = 0.009$), loss of appetite ($t = -2.111$, $p = 0.039$) and fatigue ($t = -2.875$, $p = 0.006$). We therefore conducted a hierarchical regression (see Table 2) analysis where we added demographic variables to predict FCR/P in step 1 of the model, interpretation bias in step 2, and the five symptoms for which there was a significant difference in step 3. The results showed that demographic variables added 13% to the explanation of variance in FCR/P ($F = 2.854$, $p = 0.045$), interpretation bias another 10% ($F = 7.495$, $p = 0.008$) and the five symptoms added an additional 18% of the variance in FCR/P ($F = 3.299$, $p = 0.012$).The individual symptoms that added to the variance were constipation ($p = 0.045$) and fatigue ($p = 0.028$).

Table 4.2: Hierarchical regression table showing individual variables predicting FCR/P

Step 1	***Adjusted R^2***	***df***	***F change***	***Significance***		
	.084	3, 58	2.854	.045		
Individual predictors	***Unstandardized b***	***Std. Error***	***t statistic***	***Significance***	***95% CI for b***	
					Upper	***Lower***
Age	-.26	.09	-2.77	.008	-.454	-.073
Educational Status	-1.471	1.4	-1.050	.298	-4.27	1.33
Employment Status	3.044	2.18	1.4	.17	-1.32	7.41

Step 2	***Adjusted R^2***	***df***	***F change***	***Significance***		
	.176	1, 57	7.495	.008		
Individual predictors	***Unstandardized b***	***Std. Error***	***t statistic***	***Significance***	***95% CI for b***	
					Upper	***Lower***
Age	-.198	.093	-2.15	.039	-.385	-.011
Educational Status	-1.057	1.337	-.791	.432	-3.734	1.619
Employment Status	1.783	2.117	.842	.403	-2.458	6.023
I.B.	.873	.319	2.738	.008	.234	1.511

Step 3	***Adjusted R^2***	***df***	***F change***	***Significance***		
	.314	5, 52	3.299	.012		
Individual predictors	***Unstandardized b***	***Std. Error***	***t statistic***	***Significance***	***95% CI for b***	
					Upper	***Lower***
Age	-.129	.094	-1.370	.177	-.336	.055

Educational Status	-.063	1.273	-.049	.961	-3.353	1.759
Employment Status	.870	1.996	.436	.665	-3.324	4.963
I.B.	.847	.343	2.470	.017	.006	1.399
Chest pain	4.433	2.592	1.710	.093	.236	8.472
Constipation	4.315	2.100	2.055	.045	-1.218	5.729
Pounding heart	-1.461	2.344	-.623	.536	-4.465	3.615
Loss of appetite	1.139	2.132	.534	.596	-1.762	5.078
Fatigue	6.356	2.814	2.258	.028	-1.090	5.945

Consistent with the t-test results above, we found that a number of symptoms were significantly associated with FCR/P. These symptoms were: chest pain (r= .40, p= .001), heart pounding (r= .27, p= .03), loss of appetite (r= .27, p= .03), and fatigue (r= .35, p= .006). In the literature fatigue is indicated as one of the most common symptoms of recurrence in ovarian cancer patients (Hay et al., 2016; Donovan et al., 2017). Interestingly, fatigue and heart pounding were associated with both FCR/P and interpretation bias. Furthermore, stomach cramps (r= .27, p= .03) and dizziness (r= .43, p< .001) were also associated with interpretation bias.

4.4. Discussion

The aim of the present study was to examine whether interpretation bias was associated with FCR/P and symptom burden. Consistent with predictions, the results showed that controlling for demographic factors (age, education and working status), women with ovarian cancer were more likely to interpret ambiguous words as health-related compared to women without cancer. Furthermore, the higher the levels of FCR/P women with ovarian cancer reported, the more likely they were to interpret ambiguous words as illness-related. Women with higher symptom burden were also more likely to make more illness-related interpretations. We also predicted that interpretation biases would moderate the relationship between symptom burden and FCR/P, however, that hypothesis was not supported. Hence, the threat interpretation model was not supported.

Nevertheless, these results clearly show that individuals with cancer exhibited a greater interpretation bias than those without cancer and this difference was robust, resulting in large effect size (Cohen's d = 1.28). It is worthwhile noting that the groups with and without cancer were not ideally matched. That is, women in the control group were younger,

more highly educated and more likely to be employed. This could potentially have contributed to the size of the difference, given that this is considerably larger than the effect sizes that have been seen in people with other health problems. For example, Schoth and Liossi (2016) found that people with chronic pain exhibited an interpretation bias towards illness related information more than those without pain, but with a moderate effect size (Cohen's d = 0.67). However, in a recent meta-analysis, the attentional bias exhibited by those with cancer was greater than those without cancer and the estimated effect size was also large (Cohen's d = 0.82) (Pradhan et al., 2021), and again compared to attentional biases reported between those with and without chronic pain (Cohen's d = 0.2) (Todd et al., 2018), the effect size amongst cancer survivors was much larger. Hence, taken together, these results do suggest that a history of ovarian cancer is associated with interpretation biases and the effect is larger than that observed in other conditions where these have been more thoroughly researched.

Clearly the propensity to interpret otherwise ambiguous stimuli as illness-related is affected by cancer, which is hardly surprising given the ramifications of a diagnosis of cancer, its treatment and ongoing risk. Indeed, one could argue that not only is it normal for people with cancer to interpret ambiguous stimuli as illness-related, but potentially adaptive. That is, survivors need to remain somewhat vigilant to bodily cues, and to notice changes that could indicate recurrence (Heathcote et al., 2018). The finding that those cancer survivors with higher levels of FCR/P are more likely to interpret ambiguous information as illness-related is important, indicating that these biases are associated with cancer-specific anxiety. Interpretation biases have been found to be associated with a range of emotional disorders, such as social anxiety (Miers et al., 2008; Amir, Beard & bower, 2005), generalized anxiety disorder (Hirsch & Mathews, 2012) and depression (Everaert, Podina & Koster, 2017). Indeed, the moderate to large effect size of the correlation observed here is at least comparable to the

effect size observed in meta-analysis of interpretation biases in depression (Cohen's d = 0.72). Our results are also consistent with Lam and colleagues' (2018) finding that higher levels of anxiety amongst breast cancer survivors were associated with greater interpretation biases.

The moderate correlation between interpretation biases and FCR/P is consistent with the recent emphasis placed on cognitive processes in recent theories of FCR/P (Fardell et al., 2016, Simonelli et al., 2017; Heathcote & Eccleston., 2017) and cancer-related anxiety (Curran, Sharpe & Butow, 2017). In this study, we aimed to test one of the central predictions of the threat interpretation model (Heathcote & Eccleston., 2017). Although the predicted relationships between symptom burden and FCR/P and interpretation bias and FCR/P were found, interpretation bias did not moderate the relationship between symptom burden and FCR/P. However, a number of reasons may explain this finding. Firstly, our measure of symptom burden used a range of symptoms, whereas the model specifically indicated pain. However, we conducted post-hoc analyses to determine whether this could account for the failure to find moderation effects and it did not. Secondly, it would make sense if the specific symptoms that might be open to interpretation differ amongst those with different cancer types, depending on what survivors had been told could be indicative of a recurrence. We tested this hypothesis using post-hoc analyses and did find some evidence that the primary symptoms associated with FCR/P in this sample were fatigue, constipation and loss of appetite, which are also the cardinal symptoms of a recurrence in women with ovarian cancer (Hay et al., 2016; Gosain & Miller, 2013; Ebell, Culp & Radke, 2016; Donovan, Hartenbach & Method, 2015). Our results indicated that two of these three cardinal symptoms of recurrence were associated with FCR/P, and one with interpretation bias. This finding, should however, be treated cautiously since it was post-hoc and we conducted a large number of correlations without controlling for multiple comparisons. Future research could test the

threat interpretation model with specific symptoms nominated a priori that are both common but associated with recurrence in a particular cancer type.

Interestingly, the other symptoms associated with FCR/P were heart pounding and chest pain. These did not contribute independently to FCR/P in the regression analysis, but it is worthwhile noting that these are two common symptoms of anxiety. Indeed, all the symptoms that were either associated with FCR/P or interpretation bias were either key symptoms associated with recurrence in ovarian cancer or symptoms attributable to anxiety. Future research is needed to determine how these symptoms and interpretation biases contribute to persistent FCR/P and anxiety in cancer survivors.

4.4.1 Study Limitations

A number of methodological limitations should be noted while interpreting results from the study. First, our control group was not well matched to the cancer group, and this could have contributed to the very large effect observed when comparing people with and without cancer. Nevertheless, we did control for confounders, and the effect appears robust and unlikely attributable to these differences. It is also true that women with ovarian cancer were recruited when accessing a resource for FCR/P and therefore may not be representative of all women with ovarian cancer. Of note, however, it is the findings related to FCR/P that are arguably of most interest and these are not affected by the control group, nor the representativeness of the ovarian cancer sample. Second, the sample size for the cancer group could have limited the detection of small effects or the association between interpretation bias and overall symptom burden. Power issues are particularly relevant to the moderation analysis, which should be considered to be less conclusive than other analyses. Finally, this is a cross-sectional study and therefore causal relationships cannot be established and measures

could have been related to a number of external variables, such as the timing of medical appointments.

4.4.2 Clinical Implications

These limitations notwithstanding, the findings of the present study confirm a potential role of interpretation biases in the development and/or maintenance of FCR/P, which means that interpretation biases could be a useful target for intervention. Lichtenthal et al. (2017) conducted a pilot study to investigate the potential therapeutic use of modifying cognitive biases, such as interpretation biases, to reduce FCR/P. They randomized participants to receive placebo or cognitive bias modification that trained participants to interpret ambiguous information in a benign (rather than threatening) manner and to attend less to threatening information. The manipulation check confirmed that participants had learned to interpret ambiguous information as more benign compared to the placebo group, although participants had not learned to attend less to threatening information. The intervention also reduced the health worries subscale of the Concerns about Recurrence scale (Vickberg, 2003), although not the total score. This is consistent with a large body of literature showing that cognitive bias modification is an effective intervention for anxiety symptoms (see Jones & Sharpe, 2017 for a review of meta-analyses). Future studies should confirm whether interventions such as cognitive bias modification can help to manage FCR/P.

4.5. Conclusions

Overall, there were three main findings that should be highlighted. First, the results clearly show that women with ovarian cancer are more likely to interpret ambiguous words as illness-related compared to women without cancer. Second, the results show a moderate relationship between the tendency to interpret ambiguous information as illness-related and FCR/P. Third, although we did not find that interpretation biases moderated the relationship between symptom burden and FCR/P. In our exploratory analysis, gastrointestinal symptoms seemed associated with fear of recurrence in ovarian cancer, or well-known symptoms of anxiety. The field would benefit from future research to confirm these exploratory results.

Chapter 5: Does interpretation bias moderate the relationship between pain and fear of cancer recurrence?

The following chapter is the reproduction of the material contained in the published manuscript:

Pradhan, P., Sharpe, L., Butow, P., Coutts-Bain, D., & Heathcote, L. C. (2022). Does interpretation bias moderate the relationship between pain and fear of cancer recurrence? *Health Psychology.* https://doi.org/10.1037/hea0001217

Poorva Pradhan developed the research aims and study design in consultation with her lead PhD supervisor Professor Louise Sharpe. The candidate completed the ethics application, recruited participants, analysed the data and wrote the first version of the manuscript.

Signature: **Date: 18/09/2022**

Professor Louise Sharpe provided supervision and critical review regarding the study concept and design, and critically reviewed the manuscript.

Signature: **Date: 18/09/2022**

All remaining co-authors (Emeritus Prof. Phyllis Butow, Daelin Coutts-Bain and Dr Lauren Charlotte Heathcote) provided critical feedback to the manuscript.

5.1. Introduction

Despite the fact that breast cancer survival rates have continued to improve in recent decades, help with fear of cancer recurrence or progression (FCR/P) continues to be the most common unmet need amongst breast cancer survivors (Ellegaard et al., 2017). FCR/P is important because research indicates that clinically significant levels of FCR/P are associated with poorer quality of life, depression, anxiety or distress (Humphris et al., 2003; Koch et al., 2014; Liu et al., 2018) and increased health care utilisation (Williams et al., 2021). In a Delphi study about research priorities for FCR/P research, testing theoretical models of FCR/P was amongst the top five priorities (Butow et al., 2019), particularly to improve our conceptual understanding of why some people develop clinically significant levels of FCR/P and others do not.

Numerous theoretical models have been developed to explain the aetiology and maintenance of FCR/P in the past five years (Fardell et al., 2016; Simonelli et al., 2017; Heathcote & Eccelston, 2017). One such model, the Cancer Threat Interpretation Model (Heathcote and Eccelston, 2017), proposes that pain occurring in the context of cancer can be interpreted as a sign of recurrence. When pain is interpreted in a threatening manner (i.e. a potential recurrence), FCR/P increases. As such, one major tenet of the Cancer Threat Interpretation model is that those individuals who are prone to interpreting ambiguous symptoms, such as pain, in a threatening way (or interpret this as a sign of health problems) will have higher levels of FCR/P, specifically in the face of high symptom burden.

The Cancer Threat Interpretation Model emphasizes cognitive processes, such as interpretation and vigilance towards ambiguous physical sensations (Heathcote and Eccleston, 2017). However, cognitive processing biases are also core processes that escalate FCR/P in other theories, including a cognitive attentional syndrome (Fardell et al., 2016) and

cognitive/emotional processing (Simonelli et al., 2017). This has increased interest in the identification of cognitive processing biases in people with cancer, and in particular, the relationship of these biases to FCR/P. However, this literature is in its infancy.

A recent meta-analysis confirmed that people with cancer demonstrate an attentional bias towards salient stimuli (i.e. vigilance) compared to people without cancer and these biases were larger in people with cancer who were more distressed (Pradhan et al., 2021a). However, there were only two studies identified that investigated interpretation biases in cancer. These studies pointed to the possible importance of interpretation biases. For example, Lam et al. (2018) demonstrated that people with cancer who showed a trajectory of persistently high anxiety also exhibited higher levels of interpretation bias. Further, Lichtenthal et al. (2017) found 120 women with breast cancer who were trained, using a cognitive bias modification training program, to attend less to cancer-relevant stimuli and to interpret ambiguous stimuli in a non-threatening way, were less likely to interpret ambiguous situations as threatening and were less worried about their cancer following intervention than those in the placebo group.

Since this review, one further paper has been published which confirmed that people with ovarian cancer had larger interpretation biases than those without cancer and that interpretation biases were associated with both symptom burden and FCR/P. However, interpretation biases did not moderate the relationship between symptoms and FCR/P, as the Cancer Threat Interpretation Model predicted (Pradhan et al, 2021b). Pradhan et al. (2021b) suggested that there were several reasons for this. Firstly, ovarian cancer has high rates of recurrence and many women in their sample had active disease. Arguably, monitoring one's body for signs and symptoms of cancer and interpreting these as possible threats would be more indicated given the relatively poor prognosis of ovarian cancer compared to other cancers, such as breast cancer. Secondly, the sample size of that study (n = 62) was relatively

small, and therefore the failure to find evidence for a significant moderation could be due to insufficient power.

One of the most consistent findings in the FCR literature is that more physical symptoms are associated with higher FCR (Hall et al., 2019). These results suggest that this relationship occurs only if the person also has a propensity at the time to interpret ambiguous information as pain-related (Heathcote & Eccleston., 2017). This is important because the results suggest that simply treating the symptoms may be insufficient. Particularly since nearly 30% of cancer patients have persistent pain following treatment (Wang et al., 2018). These results suggests that clinicians need to help survivors to better understand the cause of pain (e.g., post-surgical persistent pain, radiation-related neuropathy) so that people do not immediately assume that the pain reflects the cancer returning. Furthermore, interventions that directly target an individual's tendency to interpret ambiguous information as threatening (e.g.; Cognitive Bias Modification for Interpretation or CBM-I) may have clinical utility to reduce FCR (Lichtenthal et al., 2017). It is for these reasons that it is important to test the hypothesis that threat-related interpretation of ambiguous information moderates the relationship between pain and FCR.

Most of the recent models on FCR emphasizes the role of cognitive processes rather than cognitive content (Heathcote & Eccleston, 2017; Fardell et al., 2016; Simonelli et al., 2017; Curran et al., 2020; Lebel et al., 2014). For example, all these models share a number of underlying features of FCR such as, intrusive thoughts about physical or external reminders of cancer and threat appraisals of these reminders. In a recent study by Curran et al (2020), all of these features were tested, and the study concluded that factors such as metacognitions, intrusive thoughts and threat appraisals contributed to the variance in FCR. However, less is known about the cognitive processing bias such as interpretation bias.

Therefore, we aimed to examine if interpretation bias alone can contribute to variance in FCR over and above these known predictors.

The aim of this study is to extend the research presented in Chapter 4: (1) replicating the methods in a group of women with breast cancer rather than ovarian cancer; (2) including a larger sample; (3) including measures of both FCR and FOP; and (4) including other known predictors, such as metacognitions, intrusive thoughts and threat expectancy to determine whether interpretation biases contribute to FCR/P over and above other known predictors.

We hypothesised that:

1. Women with clinically significant levels of FCR/P will demonstrate greater interpretation bias and higher pain-specific symptoms compared to women with levels of FCR/P in the normal range.
2. Interpretation bias will moderate the relationship between pain-specific symptoms and FCR/P.
3. Interpretation bias will continue to predict independent variance in FCR/P, even after controlling for other known predictors of FCR/P (e.g. metacognitions, intrusive thoughts and threat expectancy).

5.2. Method

5.2.1 Transparency and Openness:

The present study is not a replication but an extension of a previous study by Pradhan et al (2020b) investigating the role of interpretation biases in women with ovarian cancer. We determined our sample size, included measures our analytic plan in advance, although we did not register the study or analyses. However, we clearly differentiated in the data analysis

section as to which analysis were planned and post-hoc. We used the PROCESS macro (Hayes, 2012) for our primary analysis. Research materials, such as questionnaires, have been appropriately cited. The APA Journal Article Reporting Standards (JARS) for Quantitative studies have been adhered to throughout (JARS- Quant, Table 1; https://apastyle.apa.org/jars/quant-table-1.pdf). Lastly, the data that support the findings of this study are available from the corresponding author upon request.

5.2.2 Participants

Participants for the study were recruited from a Cancer Consumer Registry, Breast Cancer Network Australia (BCNA). BCNA is an independent national not-for-profit organisation. It has a large database of women who are diagnosed with breast cancer. The website provides resources and support to those women who are diagnosed with breast cancer and people are able to indicate their willingness to be contacted about research (https://www.bcna.org.au/). Eligible participants were female, aged over 18 years and diagnosed with breast cancer of any stage, with or without any evidence of current disease. Participants not fluent in English were excluded from the study. The study was conducted under the University of Sydney Human Research Ethics Committee approval (Project no.: 2019/1042), and all participants provided informed consent online.

5.2.3 Procedure

Members of an online research registry for people with breast cancer (the BCNA Research and Survey group) were invited to participate by email, which included a detailed study description and the link to the online questionnaire. Participants were recruited between August and September, 2020. Those who gave informed consent first completed

demographic and disease-specific questions and then an assessment of interpretation bias. The interpretation bias paradigm was administered prior to the remaining questions to ensure these questions did not prime participants' responses to the task. Participants were then asked to respond to questionnaires pertaining to other theoretical constructs related to FCR/P. The order of these questionnaires was counterbalanced across participants.

5.2.4. Measures

5.2.4.1 Fear of Progression (FoP):

The Fear of Progression Questionnaire- Short Form (FoP-Q-SF; Herschbach et. al, 2005) was administered to assess the level of fear of progression. FoP-Q-SF consists of 12 items, where responses are categorized into: never (1), rarely (2), sometimes (3), often (4), and very often (5). Scores on FoP-Q-SF range from 12 to 60 and a score of 34 and above have previously been used to indicate a clinically significant level of FoP (Herschbach et al., 2010; Dinkel & Herschbach, 2018; Sarkar et al., 2014). The Cronbach's alpha on the FoP-Q-SF for the current sample was 0.89.

5.2.4.2 Fear of cancer recurrence (FCR) (Simard & Savard, 2009):

The Fear of Cancer Recurrence Inventory (FCRI) severity subscale, which consists of 9 items, was used to measure concerns about cancer recurrence. Participants were required to rate their responses under one of 5 options: not at all (0), a little (1), somewhat (2), a lot (3) and a great deal (4). Although there is some controversy about which cut-off score best represents people likely to have clinically significant FCR, the cut-off score of 13 or higher was the original cut-off score suggested to indicate clinically significant levels of FCR (Simard & Savard, 2015). The authors in this study reported a cut-off of ≥13 on the FCRI-SF and it demonstrated optimal sensitivity (88%) and specificity (75%) to screen for FCR. Although this cut-off score remains the most frequently used in research (e.g., Mahendran et

al., 2021; Otto et al., 2018) and treatment (e.g., Butow et al., 2017), some authors have suggested that 22 would be a more suitable cut-off score (e.g., Fardell et al., 2018). Therefore, we have also provided analyses with this cut-off score in the Appendix F. The Cronbach's alpha was 0.80 for the sample.

5.2.4.3 Interpretation Bias (IB):

Interpretation bias was assessed through the ambiguous words task (Pincus et al., 1994). There are 14 ambiguous words which can either have a neutral or illness-related meaning. In this task, participants were instructed to write down the first word that comes into their mind when they read the cue word on the screen. For example, the word "needle" was presented on the computer screen and the participants were instructed to write whatever word comes to their mind. The responses were then categorised into threat/health-related (1) (e.g. injection) or neutral (0) (e.g. sewing). This task has previously been used in relation to cancer and FCR/P (Pradhan et al., 2021b).

5.2.4.4 Symptom Burden:

The physical symptoms inventory (Spector & Jex, 1998) is an 18-item questionnaire where participants indicate whether they experience each symptom during the past 30 days and, if they did, whether they sought medical attention for it. Three sets of scores are computed for each item: no symptoms (0), symptoms for which doctor was not seen (1), and symptoms for which doctor was seen (2). The total score, therefore, gives an indication of total symptom burden. In order to test Heathcote and Eccleston's (2017) model, we summed the items that specifically asked about pain to give us an indication of pain-specific burden. The Cronbach's alpha for the pain items was 0.77, suggesting that it was reasonable to sum these items.

5.2.4.5 Metacognitions:

The Metacognitions Questionnaire (MCQ, Wells & Cartwright-Hatton, 2004) has 30 items measuring five factors. We administered the three subscales found to predict FCR/P: positive beliefs about worry, negative beliefs associated with uncontrollability and danger of worry, and beliefs about harmful consequence of not controlling thoughts. Participants indicate their beliefs about worry on a 4 point scale: do not agree (1), agree slightly (2), agree moderately (3), and agree very much (4). Higher scores indicating higher levels of unhelpful metacognitions. The Cronbach's alpha for this sample was 0.86.

5.2.4.6 Impact of Events scale- Revised:

The Impact of Event Scale - Revised (Weiss, 2007) was included to assess the frequency of intrusive thoughts after the traumatic experience of cancer. The intrusions subscale has 8 items. For every statement, the respondent answers on a 4-point scale—0 (not at all), 1 (little bit), 2 (moderately), 3 (quite a bit) and 4 (extremely)—during the past 7 days, with higher scores reflecting more frequent and intrusive thoughts about cancer. The Cronbach's alpha for this scale was 0.93.

5.2.4.7 Threat appraisal:

The Appraisal of Life Events threat subscale was used to assess how people evaluate the threat of cancer (Ferguson, Matthews & Cox, 1999). It lists six adjectives (e.g., fearful) and participants answer how well each word describes their perceptions about having cancer, using a 6 point scale; not at all (0) to, very much so (5). Therefore, possible scores range from 0-30 with higher scores indicating cancer experience to be more threatening. The Cronbach's alpha for the scale was 0.70.

5.2.5. Data Analysis

A power calculation was completed based on the correlation of r = 0.22 ($f^2 \geq .11$), which was found in our prior study between FCR and interpretation bias (Pradhan et al., 2021b). According to G*Power software, for a linear multiple regression with five independent predictors, we needed 123 participants to achieve 80% power to detect an effect ($p < .05$).

We first categorized participants into groups that were in the likely clinical range on the two measures of FCR/P, using a cut-off of ≥ 13 (FCRI) or ≥ 34 (FoP-Q). A series of independent t-tests for continuous variables, Kruskal Wallis H tests for categorical variables and Chi-square tests for dichotomous variables were conducted to determine differences between women with clinically significant levels of FCR/P versus those who scored in the normal range. We calculated Pearson's product moment correlation coefficients to examine the degree of association between FCR/P and other measures.

To test the moderation effect of interpretation bias, we first computed correlation coefficients between interpretation bias, pain-specific symptoms and FCR/P. As these variables were correlated, we conducted a moderation analysis to examine if interpretation bias moderates the relationship between FCR/P and pain-specific symptoms using the Hayes (2012) PROCESS macro in SPSS, where the individual contribution of pain-specific symptoms and interpretation bias were determined on the first step of a multiple regression equation. Then, the interaction term was added on a second step to test the moderation effect. Finally, we constructed a series of hierarchical regression equations to determine whether interpretation biases predict FCR over and above known predictors of FCR/P derived from theoretical models. Demographic variables that differed between those with and without clinically significant levels of FCR/P were entered on the first step of the model. On the

second step, we included theoretically relevant variables, such as metacognitions, intrusive thoughts and threat expectancy. On the final step, we included interpretation bias. All analyses were carried out using IBM SPSS version 26.

5.3. Results

5.3.1. Participant characteristics

One hundred and forty-seven participants consented to take part in the study. Participants had a mean age of 60.02 years. Approximately, two-third of women were married (n= 98; 66.7%), nearly half of the women had post-graduate qualifications (n= 52; 45.4%), and more than half were unemployed (55.1%). In terms of illness-related characteristics, the majority of the women (n= 101; 68.7%) had early-stage cancer (Stage I and II). Furthermore, most women reported they were currently in remission (n= 105; 71.4%) with no history of cancer recurrence (n=119; 81%). Refer to Table 5.11 for further demographic details.

Table 5.1: Demographic and clinical characteristics of the sample (N= 147)

Variable	Mean (SD)
Age	60.02 (10.31)
	Frequency (percentage)
Marital status	
Married	98 (66.7%)
Widowed	7 (4.8%)
Divorced	15 (10.2%)
Separated	5 (3.4%)
Never married	21 (14.3%)
Children	
None	31 (21.1%)
One	25 (17%)
Two	61 (41.5%)
More than two	30 (20.4%)
Education level	
Did not complete high school	7 (4.8)
Completed high school	46 (31.3%)
Undergraduate degree at university	42 (28.6%)
Postgraduate degree at university	52 (35.4%)
Employment status	
Currently employed	66 (44.9%)
Currently unemployed	81 (55.1%)
Stage at diagnosis	
Stage 1	50 (34%)
Stage 2	51 (34.7%)
Stage 3	27 (18.4%)
Stage 4	6 (4.1%)
Not known	13 (8.8%)
Current cancer status	
Currently on treatment	42 (28.6%)
In remission	105 (71.4%)
Cancer recurrence	
Yes	28 (19.0%)
No	119 (81.0%)
Treatment type	
Radiotherapy	4 (2.7%)
Chemotherapy	12 (8.2%)
Hormonal therapy	48 (32.65%)
No treatment	83 (56.46%)

Self-report outcomes on FCRI indicate that the majority of the women reported clinically significant symptoms (> 13; M= 17.73, SD= 6.41) of FCR (n= 118; 80.3%). When using the more restrictive cut-off of 22, the proportion of those reporting clinically significant symptoms was 25.9%. Sixty-four women (43.5%) women reported FoP symptoms in the likely clinical range. The mean score on FoP-Q-SF was 32.6 (SD= 9.98). The average score of the participants on the symptom checklist was 24.51 (SD= 3.95).

5.3.2. Impact of clinically significant FCR and FoP:

Preliminary analyses indicated that there was a significant difference in terms of FCR status (clinically vs non-clinically significant symptoms) on cancer status (in treatment and remission) [$\chi^2_{(1,147)} = 3.87$, $p = .04$]. That is, participants in remission reported higher FCR levels than those who were on treatment. Participants who had levels of FoP in the normal range were more likely to be in remission [$\chi^2_{(1,147)} = 25.5$, $p < .001$]. Similarly, women with no history of cancer recurrence were more likely to fall in the non-clinically significant range for FoP compared to women whose disease had recurred [$\chi^2_{(1,147)} = 6.06$, $p = .01$]. Furthermore, women with clinically significant FoP were younger than women who scored in the normal range [$t_{(145)} = -3.86$, $p < .001$].

In terms of outcome measures, there were significant differences between participants who were scored in the likely clinical compared to non-clinical range for FCR, such that those with clinically significant symptoms had higher interpretation bias (IB) scores [$t_{(145)} = 2.65$, $p = .009$; Cohen's $d = 0.55$; (95% CI = 0.13, 0.96)], more pain symptoms [$t_{(145)} = 4.06$, $p < .001$; Cohen's $d = 0.85$; (95% CI = 0.42, 1.26)], more unhelpful metacognitions [$t_{(145)} = 2.96$, $p = .004$; Cohen's $d = 0.61$; (95% CI = 0.2, 1.02)], higher threat appraisal [$t_{(145)} = 3.90$, $p < .001$; Cohen's $d = 0.8$; (95% CI = 0.38, 1.22)] and more intrusive thoughts [$t_{(145)} = 4.42$,

p < .001; Cohen's d = 0.92; (95% CI = 0.49, 1.33)] (refer to Table 5.2). A similar pattern of results was obtained for clinically significant FCR (>22) and FoP (refer to Appendix F).

Table 5.2: t-test values: Difference between clinical and non-clinical FCR (>13) in terms of interpretation bias, physical symptoms, metacognitions, body threat monitoring, threat expectancy and intrusive thoughts.

Psychological measure	Clinical FCR		Non-clinical FCR		$t_{(145)}$	*p*
	M	*SD*	*M*	*SD*		
Interpretation Bias	6.17	3.44	4.38	2.43	2.65	.009
Pain Symptoms	5.83	1.16	4.86	1.09	4.06	.000
Metacognitions	34.02	8.11	29.10	7.64	2.96	.004
Threat Expectancy	18.92	4.82	14.66	6.93	3.90	.000
Intrusive Thoughts	7.92	6.63	2.28	3.61	4.42	.000

FCR: Fear of Cancer Recurrence

We also performed Pearson product-moment correlation analysis. The analysis revealed that there was a significant moderate association between IB and FCR (r= .45, p < .001), pain-specific symptoms and FCR (r= .40, p < .001) and IB and pain-specific symptoms (r= .31, p < .001). Similar correlations were found between IB and FoP (r= .51, p < .001) and

pain-specific symptoms and FoP (r= .44, p < .001). Table 5.3 outlines correlations between FCR/P and other theoretical constructs.

Table 5.3: Descriptive and correlational data of variables under investigation.

Psychological measure	Mean (SD)	FoP-Q-SF	FCRI
1. FoP-Q-SF	**32.59 (9.98)**		
2. FCRI	**17.73 (6.41)**	**.75****	
3. IB	**5.82 (3.33)**	**.51****	**.45****
4. Pain Symptoms	**24.5 (3.95)**	**.44****	**.40****
5. MCQ	**33.05 (8.22)**	**.40****	**.37****
6. Threat Expectancy	**18.08 (5.54)**	**.33****	**.35****
7. Intrusions	**6.8 (6.54)**	**.76****	**.70****

FoP-Q-SF: Fear of Progression Questionnaire – Short Form

FCRI: Fear of Cancer Recurrence Inventory

IB: Interpretation Bias

MCQ: Metacognition Questionnaire

BTMS: Body Threat Monitoring Scale

*p < .05

**p < .01

5.3.3. Testing the moderation effect of interpretation bias:

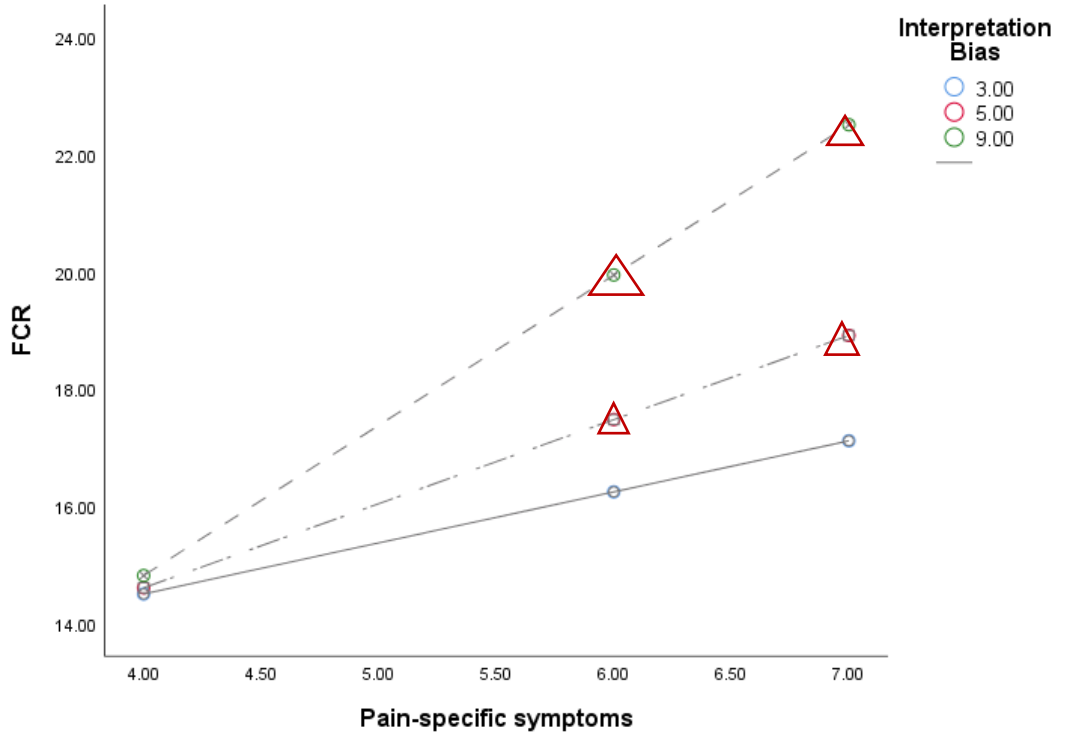
To test the moderation hypothesis, we conducted moderation analyses to determine whether interpretation bias moderated the relationship between pain-specific symptoms and FCR. The overall model was significant ($F_{(2, 144)} = 27.45$, $p < 0.001$) (refer to Table 4). Pain-specific symptoms did predict FCR [$\beta = 1.52$, $t = 3.86$, $p < .001$, 95% CI of β (.74, 2.31)], as did interpretation bias [$\beta = .69$, $t = 4.80$, $p < 0.001$, 95% CI of β (.41, .97)]. Importantly, the interaction term was found to be significant ($F_{(1, 143)} = 5.76$; $p = 0.01$), confirming that interpretation bias moderates the relationship between pain and FCR. Examination of the conditional effects within 1 standard deviation (1SD) of the mean, and 1 SD above and below the mean (See Figure 5.1) revealed that as interpretation bias increases, the relationship between pain-specific symptoms and FCR also increases. When pain-specific symptoms are low, FCR remains low regardless of the degree to which women interpret ambiguous information as threatening. However, when pain-symptoms are moderate to high, FCR levels increase as the degree of interpretation bias increases ($t = 4.4$, $p < .001$).

Table 5.4: Regression (with interpretation bias and pain symptoms as predictors of FCR) and moderation analysis (with interpretation bias as a moderating variable).

Predictors	**Unstandardized β**	**SE**	**t**	**p**	**95.0% CI for β**	
					Lower	Upper
IB	.69	.14	4.8	.000	.41	.97
Pain symptoms	1.52	.40	3.86	.000	.742	2.31
Interaction effect	**R^2 change**	**F**	**df**	**p**		
IB X pain symptoms	.05	10.34	1, 143	.001		

Overall model summary	R^2 change	F	df	p	Adjusted R^2	SE
	.28	27.45	2, 144	.000	.27	5.49

IB: Interpretation Bias



Note.

△ : indicates significant relationships

Figure 5.1:

Values represent the increase in pain-specific symptoms and FCR as a result of greater interpretation bias.

We conducted the same analyses to explain variance in FoP. Similar to FCR, both pain-specific symptoms [β = 2.58, t = 4.42, p < .001, 95% CI of β (1.42, 3.73)] and interpretation bias [β = 1.24, t = 5.84, p < .001, 95% CI of β (.82, 1.66)] also accounted for significant variance in FoP. However, the interaction term failed to reach significance ($F_{(1, 143)} = 0.21$; p = .65), indicating that both interpretation and pain-specific symptoms were important in accounting for variance in FoP, but that the relationship between pain-specific symptoms and FoP did not depend on the level of interpretation bias.

5.3.4. Post-Hoc analysis:

We also conducted a moderation analysis to determine if interpretation bias moderates the relationship between FCR/P and overall physical symptoms. In line with above results, the overall model was significant ($F_{(2, 144)} = 26.08$, p < .001). Both overall symptom burden [β = .44, t = 3.56, p = 0.01, 95% CI of β (.19, .68)] and IB [β = .70, t = 4.78, p < .001, 95% CI of β (.41, .98)] accounted for individual variance in FCR. The interaction term, also significantly accounted for variance in FCR ($F_{(1, 143)} = 10.34$; p = 0.001), indicating that IB did moderate the relationship between total symptom burden and FCR in the same way as for pain-specific symptoms. Similarly, both symptom burden [β = .89, t = 5.06, p < .001, 95% CI of β (.54, 1.24)] and IB [β = 1.19, t = 5.68, p < .001, 95% CI of β (.77, 1.6)] contributed to the variance in FoP. However, as with FoP, the interaction term failed to reach significance ($F_{(1, 143)} = 0.84$; p = .36).

Furthermore, we also conducted hierarchical regression (see Appendix F) to examine if interpretation bias continued to account for variance in FCR over and above other theoretical predictors. The results showed that cancer status added 20% to the variance (F = 36.02, p < .001) in step 1 of the model and other theoretically relevant variables added 34% in step 2 (F = 34.21, p < .001). Finally, interpretation bias continued to contribute

significantly to the variance in FCR (F change = 7.70, p = .006), although added only 2.4% to the variance in FCR. Refer to Appendix F. Similarly, age, cancer status and history of recurrence accounted for 32% to the variance in FOP on Step 1 of the regression equation (F = 22.11, p < .001). For Step 2, an additional 31% of the variance in FOP was added by theoretically important variables (F = 38.99, p < .001). Finally, interpretation bias was added to the regression equation and accounted for an additional 3.8% of the variance in FoP (F = 15.66, p < .001).

5.4. Discussion

The aim of the current study was to test if interpretation bias moderates the relationship between pain and FCR (Heathcote & Eccleston, 2017). Our results corroborate previous findings that interpretation and pain were both associated with FCR/P. We found that theoretically important variables, such as unhelpful meta-cognitions, intrusive thoughts and threat expectancy were all associated with FCR/P, as expected. However, interpretation bias accounted for independent variance in FCR/P, even when these constructs were controlled for. Arguably the most important finding was that interpretation bias moderated the relationship between pain-specific symptoms and FCR, as predicted. Interestingly, although both interpretation bias and pain contributed independently to the variance in FoP, interpretation bias did not moderate the relationship between pain or symptoms and FoP.

It is generally accepted that some level of FCR is normal and potentially even adaptive (at least at lower levels), given that cancer is a potentially life-threatening illness. According to this argument, monitoring one's body for symptoms and/or interpreting information as threatening may be helpful in identifying recurrence earlier and therefore improving survival (Fardell et al., 2016). Our findings suggest that the tendency to interpret

ambiguous words as health-related does increase the propensity to develop clinically significant levels of FCR. This research is partially consistent with the previous findings. Lam et al. (2018) found that women with breast cancer who were persistently anxious were more likely to interpret ambiguous information as health-related. However, they did not measure FCR. In ovarian cancer, Pradhan et al. (2021b) found a significant association between FOP and interpretation bias which was roughly similar to the relationships observed in this breast cancer sample ($r = .41$ vs $r = 0.51$). Hence, our results add to a small but consistent literature that confirms that interpretation biases are associated with anxiety and/or FCR/P in the context of cancer.

Importantly, we tested the assumption from the Cancer Threat Interpretation model (Heathcote & Eccleston, 2017) that interpretation bias would moderate the relationship between FCR and pain-specific symptoms. We found strong evidence to support this contention. That is, both interpretation bias and pain symptoms were independently associated with FCR, but the relationship between pain symptoms and FCR was larger amongst those with moderate to high levels of interpretation bias. Amongst those with the lowest levels of interpretation bias, pain and FCR were not significantly related. These results were predicted, but not consistent with our earlier study with ovarian cancer survivors where we failed to find the predicted moderation effect (Pradhan et al., 2021b). There are a number of possible reasons why the model might have been better supported in a breast cancer sample than an ovarian cancer sample. Firstly, as in most FCR research (see Thewes et al., 2013), the current sample included women with breast cancer where the majority of participants were in remission and had been treated with curative intent. It may be that the Cancer Threat Interpretation Model (Heathcote & Eccleston, 2017) which was largely developed to explain FCR in survivors successfully treated with curative intent is more relevant in the breast cancer context than for women with ovarian cancer. Secondly, in our

ovarian cancer study, we measured FoP rather than FCR. Prevailing definitions of FCR conflate these two constructs (Lebel et al., 2016), however, the current results suggest that interpretation biases only moderate the relationship between pain and FCR, not pain and FOP.

Finally, in breast cancer, one of the primary symptoms of recurrence is pain (e.g. when the cancer has spread to the bone), whereas in ovarian cancer recurrence is more commonly associated with fatigue and gastrointestinal symptoms (Hay et al., 2016; Donovan et al., 2017). Therefore, it may be that using total symptom burden or pain in our previous study failed to identify the symptoms that are ambiguous in the context of ovarian cancer. Indeed, in post-hoc analyses, it was fatigue and gastrointestinal symptoms that were the symptoms most strongly associated with FOP in the ovarian cancer sample (Pradhan et al., 2021b). Interestingly, in the current study, we found evidence of moderation when using pain-specific symptoms (as the model predicts) as the independent variable, but we also found evidence when total symptom burden was used as the independent variable. This is a potentially interesting finding because the Cancer Threat Interpretation Model specifically describes interpretation of pain as threatening as the putative mechanism in the development of clinical levels of FCR (Heathcote & Eccleston, 2017). While our results did support the relevance of pain, they also supported the relevance of more general somatic symptoms. It seems intuitively likely that the importance of symptoms and their interpretation depends very much on which symptoms are likely to signal a recurrence in the context of a survivor's particular cancer. The specificity of symptoms and their relationship to FCR and FOP would be important to test in future research.

However, it is unclear why interpretation bias failed to moderate the relationship between pain and FoP. It is possible that those worried about the cancer returning view the pain as a sign that the cancer will recur. Whereas, pain itself may not be indicative of

progression, which may be marked by other signs and symptoms, such as fatigue. In our previous study in ovarian cancer, we found that the symptoms associated with recurrence were uniquely associated with FoP and interpretation biases (See Pradhan et al., 2021b). However, this explanation is speculative and future research should investigate the different predictors of FCR and FoP.

5.4.1 Study Limitations

Several important limitations must be noted while interpreting results from the study. First, our study was cross-sectional. It has long been known that symptoms are a strong predictor of FCR (Thewes et al., 2013), however, the fact that an implicit cognitive bias to interpret ambiguous stimuli as health-related moderates this relationship is a novel finding. However, whether this is a causal relationship, as proposed, cannot be answered in the present, cross-sectional study. However, other research has found that there is a positive association between somatic symptoms and stress, with FCR as a mediating factor (Hall et al., 2017), which is consistent with general findings that fear and anxiety worsen pain outcomes (Martinez-Calderon et al., 2019; Marshall et al., 2017). In all likelihood, these are bidirectional relationships that create a vicious cycle amplifying somatic symptoms, which are interpreted as indicative of a recurrence and further exacerbate FCR.

As with much of the FCR literature, more than two-thirds of the women in the study had an early stage breast cancer and therefore, findings may specifically apply to early stage survivors. Consequently, these results may not be generalizable to people with advanced disease. Interestingly, an extremely high proportion of the sample had FCR levels that placed them in the clinical range. There is still debate in the literature regarding the clinical cut-off score on FCRI and some authors favour a more stringent cut-off point (> 21). However, it is possible that the sample took part due to the relevance of FCR to them which would mean

these results may not generalise to those with very low levels of FCR. Another possible limitation is that the recruited participants were a part of the research pool of BCNA. The women enrolled in this registry may not be representative of all women with breast cancer. Indeed, this particular sample was highly educated and mostly had early stage disease. Finally, the study was not pre-registered.

5.4.2 Clinical Implications

Despite these limitations, the study findings confirm an important role for interpretation biases in FCR/P. Interpretation biases have been shown to have a putative role in other anxiety disorders (e.g. Everaert et al., 2018; Chen et al., 2020). On the basis of these experimental findings, methods of modifying these biases (known as Cognitive Bias Modification [CBM]) have been developed. Jones and Sharpe (2017) conducted a systematic review of 14 meta-analyses on CBM, which confirmed that CBM for interpretation biases [CBM-I] was efficacious in reducing anxiety symptoms, with a moderate sized effect [Cohen's d = 0.13–0.74]. This finding was also confirmed by a recent network meta-analysis (Fodor et al., 2020). Indeed, CBM-I has already been applied to FCR.

Lichtenthal et al. (2017) developed an intervention to implicitly modify both attentional and interpretation biases. They randomized participants with breast cancer to receive either CBM-I training or placebo training. The study showed that interpretation biases (but not attentional biases were successfully modified for those in the CBM-I group compared to placebo. Furthermore, those who received CBM-I had larger reductions in the health-worries subscale of the Concerns about Recurrence Scale (CARS), although not the entire scale. Our results would suggest that CBM-I is worthy of further study, but would also suggest that CBM-I might be particularly relevant for those with high levels of symptom

burden. The potential benefits of CBM-I should further research prove it to be efficacious in the context of FCR would be large, given that CBM-I can be delivered remotely and therefore is highly scalable. The majority of interventions included in a recent meta-analysis (Tauber et al., 2019) of psychological trials for FCR/P were intensive, face-to-face treatments, which on average achieved a moderate effect (Hedge's $g = 0.38$). However, given the large number of survivors and the high prevalence of FCR, we need scalable interventions to help manage those with milder symptoms. CBM-I could potentially be such an intervention that could form part of a stepped care model for managing FCR, if proven efficacious (see Pradhan et al., 2021 for further discussion).

5.5. Conclusions

In conclusion, the results clearly show that survivors of breast cancer who tend to interpret ambiguous information as health-related are more likely to have clinically significant levels of FCR. More importantly, interpretation biases moderated the relationship between pain-specific symptoms and FCR. This finding supports the notion of cognitive processing theories of FCR/P, such as the Cancer Threat Interpretation model (Heathcote & Eccleston, 2017), which argue that it is not simply the content of worries that differentiate those with clinically significant FCR from those without, but also the way in which they process information. Women with clinical levels of FCR/P also reported higher levels of unhelpful metacognitions, intrusive thoughts and threat expectancy as compared to women who scored in the normal range for FCR/P, as predicted by a range of theoretical models (see Fardell et al., 2016, Curran et al., 2017, Simonelli et al., 2017, Heathcote and Eccleston, 2017). However, interpretation biases continued to predict FCR/P over and above these

factors, which suggests that interpretation biases could be a target for intervention which might augment successful available treatments for FCR/P.

Chapter 6: Is a brief online booklet sufficient to reduce fear of cancer recurrence or progression in women with ovarian cancer?

The following chapter is the reproduction of the material contained in the published manuscript:

Pradhan, P., Sharpe, L., Butow, P., Smith, A., Russell, H. (2021). Is a brief online booklet sufficient to reduce fear of cancer recurrence or progression in women with ovarian cancer? *Frontiers in Psychology*, 12, 634136.

Poorva Pradhan developed the research aims and study design in consultation with her lead PhD supervisor Professor Louise Sharpe. The candidate completed the ethics application, recruited participants, analysed the data and wrote the first version of the manuscript.

Signature: **Date: 18/09/2022**

Professor Louise Sharpe provided supervision and critical review regarding the study concept and design, and critically reviewed the manuscript.

Signature: **Date: 18/09/2022**

All remaining co-authors (Emeritus Prof. Phyllis Butow, Dr Allan 'Ben' Smith and Hayley Russell) provided critical feedback to the manuscript.

The past three chapters have focused on whether cognitive biases are associated with FCR/P. Evidence from all three studies confirmed a small to moderate association between attentional biases and FCR/P and interpretation bias and FCR/P. One possible implication of these chapters is that an intervention that is focused on promoting less threatening interpretations of physical symptoms and minimising bodily checking may reduce FCR/P. one way to encourage helpful interpretation is the provision of information (See Butow et al., 2018). Therefore, the following chapter will evaluate a simple intervention in the form of a booklet for people with ovarian cancer.

6.1. Introduction

Ovarian cancer is the leading cause of death among gynaecological cancers with a 46% five-year survival rate, as the disease is often diagnosed at an advance stage (AIHW, 2020). Approximately 70% of women with ovarian cancer are expected to experience recurrence of their cancer, particularly when diagnosed at later stages (Ovarian Cancer Research Alliance, 2020). Not surprisingly given this high recurrence rate, fear of cancer recurrence or progression (FCR/P) is one of the most common psychosocial concerns reported by this population (Matulonis et al., 2008; Kyriacou et al., 2017). FCR/P, defined as "fear, worry, or concern about the cancer returning or progressing" (Lebel et al., 2016, p.3267), continues to be the most cited unmet need for ovarian cancer survivors (Tan et al., 2020).

Studies have identified that higher levels of FCR/P are associated with reduced quality of life (Hart, Latini, Cowan, & Carroll, 2008), increased anxiety and depressive

symptoms (Humphris et al, 2003; Koch et al, 2014) as well as post-traumatic stress symptoms (Mehnert, Berg, Henrich & Herschbach, 2009). In addition to psychological symptoms, FCR/P is also characterized by increased healthcare costs (Thewes et al., 2012) and frequent reassurance seeking, such as through additional oncology appointments and increased medication use (Lebel et al., 2013). Therefore, individuals experiencing high levels of FCR often require specialized psychological support and intervention (Butow et al., 2018).

Despite clear evidence that high FCR/P is associated with poorer psychological outcomes and additional medical costs, specific interventions to manage FCR/P are still relatively scarce. In a meta-analysis of RCTs, Tauber et al. (2019) found over 23 controlled trials that had examined the efficacy of a psychological intervention and measured FCR, however, only 8 of these had specifically targeted FCR/P. The majority of those evaluated face-to-face interventions (e.g. ConquerFear, Butow et al., 2018) or blended interventions (e.g. SWORD, van de Wal et al., 2017) which required highly trained therapists and considerable time commitment (minimum of four sessions). In that meta-analysis, there was only one trial of a self-administered approach (i.e. minimal intervention). The study by Otto and colleagues (2016) found that such self-guided interventions (in this case, gratitude training) can promote well-being leading to a decrease in reducing death-related FCR. One other randomized controlled trial, by Dieng et al. (2016), with melanoma survivors combined psychoeducational materials, as well as three telephone consultations with a psychologist, and found improvements in FCR/P, which were maintained at 12 month follow-up (Dieng et al., 2019). However, the telephone support still required specialist psycho-oncology skills. Given the number of survivors, and the fact that help with FCR/P remains a leading unmet psychosocial need, most services do not have the capacity to support all survivors with elevated levels of FCR/P.

Consequently, researchers are investigating other ways to increase access to information that might reduce or prevent persistent FCR/P. For example, brief interventions led by health professionals who manage the medical needs of survivors (most commonly nurses) have been developed. A recent systematic review of these approaches found that evidence to support their use is still lacking (Liu et al., 2019). Similarly, there has been interest in developing internet-delivered interventions specifically targeting FCR. Most of these are either in early stages of development (Smith et al., 2020) or currently being tested (e.g. Lyhne et al., 2020) and the only online intervention which specifically targeted FCR/P produced largely null results (Van Helmondt et al., 2020).

Self-help materials have been used for other survivorship issues, including to reduce anxiety and depression and/or to improve quality of life. Cuthbert et al (2019) identified 41 studies of self-help interventions that had been evaluated in randomized controlled trials. The results were largely mixed, with some showing short-term benefits and others showing little improvement in outcomes. None of these studies targeted FCR/P.

However, even in the absence of evidence, several non-profit organizations such as, Cancer Council Australia, National Breast Cancer Foundation, Breast Cancer Network Australia and Lymphoma Australia have developed online booklets or leaflets for addressing concerns related to cancer coming back or progressing. Whether these self-help materials attenuate FCR/P has not been the subject of research. Lynch et al. (2020) have recently completed a preliminary evaluation of a stepped care approach for survivors of melanoma who were treated with novel immunotherapies. The first step in their "FearLESS" program was a self-help intervention. Of those who scored in the sub-clinical range and were offered self-help, 90% did not feel the need for referral to individual therapy at the end of the study (Lynch et al., 2020). However, the authors did not evaluate whether changes in FCR/P were significant for those who received the booklet.

The evidence examining informational needs of cancer survivors suggests that most patients want to receive as much information as possible about their disease and its consequences (Fletcher, Flight, Chapman, Fennell & Wilson, 2017; Shea–Budgell, Kostaras, Myhill & Hagen, 2014). A systematic review of 10 studies that assessed a range of patient outcomes in RCTs of educational resources specific to cancer, found that the provision of psychoeducation was associated with better outcomes for satisfaction, symptom management and anxiety and depressive symptoms (McPherson, Higginson & Hearn, 2001). However, we could not identify a purely psychoeducational resource that had been developed specifically for FCR/P which had been evaluated in terms of its acceptability and effect on FCR/P.

Therefore, we (PB & ABS) developed a simple online booklet that (a) outlined the nature of FCR/P, (b) provided information about how FCR/P becomes persistent, (c) suggested strategies (based on evidence-based treatments) that might help survivors to better manage FCR/P; and (d) provided links to where survivors can find additional help. The aims of this study were to determine whether (i) the booklet was acceptable to survivors (ii) survivors were satisfied with the booklet and would recommend it to others; and (iii) the booklet reduced levels of FCR/P.

It was hypothesised that

1. Women with ovarian cancer will be satisfied with the booklet and would recommend it to other survivors.
2. Women with ovarian cancer will have lower levels of FCR/P a week after reading the booklet compared to baseline.
3. The booklet will lead to a greater reduction in FCR/P for women with low to mild FCR/P.

6.2. Method

6.2.1 Design

Women with ovarian cancer completed measures of FCR before and 1 week after reading an online psychoeducational booklet about FCR/P. In addition, a measure of satisfaction was given 1 week after women accessed the booklet.

6.2.2 Participants:

Women who had been diagnosed with ovarian cancer, were over 18 years of age, and fluent in English were eligible to take part in the study. Participants were recruited online through Ovarian Cancer Australia (OCA) (see below). Ethical approval was provided by the University of Sydney's Human Research Ethics Committee (Project no.: 2018/993). Informed consent was obtained from all participants online, and they were free to withdraw from the study at any time.

6.2.3 Procedure:

The new online FCR booklet developed by the authors was released through OCA and advertised to its members. When women indicated they would like to access the booklet, a pop-up window asked whether they would like the option of taking part in some research to evaluate the impact of the booklet on FCR/P. Women who chose not to do so, were directed immediately to the booklet, while those who indicated their interest in taking part in the research were invited to follow a link which described the study in more detail. After providing consent, participants were directed to an online questionnaire including some

demographic and medical information and a measure of FCR/P[1]. On completion, women were given access to the booklet. One week later participating women were sent an email and asked to complete measures of FCR/P and satisfaction with the FCR/P booklet.

6.2.4 Fear of cancer recurrence factsheet:

The factsheet was developed in conjunction with OCA and input from oncology health writer in terms of translating information from ConquerFear study suitable for women with ovarian cancer. It aims to provide information on FCR/P, which is identified as a significant survivorship issue for women with ovarian cancer (Kyriacou et al., 2017), and also suggest strategies to manage these fears. The techniques to manage FCR in this factsheet were adapted from the ConquerFear program by Butow and colleagues (2017). See Table 6.1 for the list of contents in the booklet (online link to the booklet: https://www.ovariancancer.net.au/page/94/support-resources). See Appendix G for complete booklet.

Table 6.1: List of contents in Fear of Recurrence factsheet

1. What does 'cancer recurrence' mean?
2. Why are women fearful?
3. Types of fears
4. Common worry times
5. Day-to-day approaches to managing your fears
6. Carers' feelings
7. Some techniques for managing the fear of recurrence

[1] Measures of interpretation bias and physical symptoms were included, the results of which are presented elsewhere.

8. Finding information online
9. Further information and support

6.2.5 Materials:

6.2.5.1 Satisfaction questionnaire:

The satisfaction questionnaire has three items that assess: satisfaction with the information provided in the booklet; helpfulness for managing the concerns about cancer coming back or progressing; and whether women would recommend it to another woman diagnosed with ovarian cancer. The participants rated each item on a 10-point scale, from 1 (not at all) to 10 (completely). A higher score indicates that women are more satisfied with the booklet. Women completed this questionnaire one week after reading the booklet.

6.2.5.2 Fear of Cancer Recurrence/Progression:

The 12-item Fear of Progression Questionnaire- Short Form (FoP-Q-SF; Herschbach et. al, 2005) was administered to assess the level of FCR/P. Responses options ask how often a particular symptom of FCR/P is experienced on a five-point scale from 1 (never) to 5 (very often) (5). Thewes et al. (2012) conducted a systematic review of assessment measures for FCR/P and recommended the use of the Fear of Cancer Recurrence Inventory (Simard & Savard, 2009) and the FoP-Q-SF for assessing FCR/P. We opted to use the FoP-Q-SF because for women with ovarian cancer, many of whom have already experienced a recurrence, fear of recurrence is less relevant than fear of progression. Scores on FoP-Q-SF

range from 12-60 and a score of 34 and above is taken to indicate a clinical level of FoP (Herschbach et. al, 2010). The Cronbach's alpha for the current sample was 0.85.

6.2.5 Data Analysis:

All statistical analyses were conducted in SPSS version 26. Preliminary analyses compared those women that completed the study versus those who accessed the booklet but did not complete questionnaires after reading the booklet. For continuous variables, we used independent t-tests and for other variables we used Mann Whitney U tests (categorical variables) or Chi-square (dichotomous).

Mean scores and frequencies were examined for satisfaction ratings. For FCR/P, a paired samples t-test was used to compare the level of FCR/P before and after reading the booklet. Using the cut-off of 34 on the FoP-Q, we identified women with clinically significant levels of FCR/P versus those who scored in the normal range to determine whether clinical FCR/P affected the impact of the booklet. To investigate the impact of clinical status, we conducted a mixed-model 2 (FCR/P: Clinical range vs within normal range) x 2 (time: before vs after reading the pamphlet) ANOVA. Finally, we conducted correlations between FCR/P and satisfaction ratings to determine whether level of FCR/P affected the satisfaction that women reported after reading the booklet.

6.3. Results

6.3.1 Participant Characteristics:

Sixty-two women diagnosed with ovarian cancer were recruited for the study. Participants had a mean age of 56.9 years. In terms of stage of disease, relatively few women had Stage I (n= 10; 16%), or Stage II (n= 11; 18%) disease, with 47% (n= 30) reporting Stage III and 9 (15%) reporting stage IV cancer. See Table 6.2 for demographic and medical details. Of the 62 participants who commenced the study, 50 (19% attrition rate) completed the questionnaires again a week after reading the pamphlet.

Table 6.2: Demographic and clinical characteristics of the sample

	Cancer Patients (n=62)
Variable	**Mean**
Age	56.9 (11.64)
Time since diagnosis	3.45 (3.29)
	Frequency (percentage)
Marital status	
Married	41(65.45%)
Widowed	2(3.64)
Divorced	9(14.55)
Separated	3(5.45)
Never married	7(10.71)
Children	
None	13(20.97)
One	9(14.52)
Two	32(51.61)
More than two	8(12.9)
Education level	
Did not complete high school	0(0)
Completed high school	24(38.18)
Undergraduate degree at university	22(36.36)
Postgraduate degree at university	16(25.45)
Employment status	
Currently employed	28(45.16)
Currently unemployed	34(54.83)
Stage at diagnosis	
Stage 1	10(16.36)
Stage 2	11(18.18)
Stage 3	30(47.27)
Stage 4	9(14.53)
Not known	2(3.64)
Current cancer status	
Currently on treatment	18(29.09)
Active disease	2(3.64)
In remission	42(67.27)
Cancer recurrence	
Yes	22(36.36)
No	40(63.64)
Surgery	
Yes	1(1.12)
No	61(98.88)
Treatment type	
Radiotherapy	0(0)
Chemotherapy	46(74.19)
Hormonal therapy	12(19.35)
No treatment	4(6.45)
CA-125 testing	
Yes	60(96.23)

No	2(3.77)
Not known	0(0)

Between group comparisons revealed that there was no significant difference between participants who completed the study and those who did not for age ($t_{(60)}$= 1.13, p= .26), education (U= 216, p= .11), cancer stage (U=276, p= .65), number of children (U= 289.5, p= .84), marital status (U= 284, p= .73), cancer status ($\chi^2_{(1, 62)}$= 1.06, p= .33) or employment status ($\chi^2_{(1, 62)}$= .14, p= .76). Likewise, there were no significant differences between participants in terms of FCR/P scores ($t_{(60)}$ = -.26, p= .79).

6.3.2. Satisfaction with the booklet:

Almost 75% (37/49) of the respondents rated the booklet to be relevant to people with ovarian cancer and indicated it provided the needed information about FCR/P (as indicated by ratings > 80/100). Only 1 woman indicated that the booklet was not at all relevant. More than two thirds of women (32/49) rated the booklet as at least moderately helpful (ratings > 50/100) in managing their worries about cancer coming back or progressing. Of those, 14/49 reported that it was completely helpful, and only 3/49 thought it was not helpful at all. Importantly, 93% (41/44 women) of the participants would recommend the booklet to other women.

6.3.3 FCR/P Results:

Self-reported outcomes on the FoP-Q indicated that, on average, women with ovarian cancer fell within the clinical range (M= 35.58, SD= 8.52). Based on the cut-off score on the FoP-Q of 34, 56% (n = 35/62) of the participants reported clinically significant levels

of FCR/P and the remainder (44%; n = 27/62) reported FCR/P scores within the normal range.

Overall, significant differences were not observed in the FoP-Q scores before (M= 35.4, SD= 8.59) compared to one week after reading the booklet (M= 33.94, SD= 9.00) ($t_{(49)} = 1.71$, p= .09; Cohen's *d* = 0.17; 95% CI -0.22 – 0.55), indicating that the booklet did not change levels of FCR/P. In considering whether the booklet had a differential impact based on level of FCR/P, we conducted a 2 x 2 mixed-model ANOVA. Consistent with the t-test reported above, there was no significant main effect of time [$F_{(1,48)} = 2.69$, p= .11] on FCR/P scores. There was a significant main effect of FCR/P level indicating that women scoring in the clinical range had higher levels of FCR/P throughout the study [$F_{(1,48)} = 81.96$, p > .001]. The interaction between time and FCR/P level indicated that clinical status did not impact the effect of time on FCR/P scores [$F_{(1,48)} = .13$, p= .72].

Finally, we performed Pearson product-moment correlations to investigate the relationships between FCR/P and ratings of satisfaction. There was no significant correlation between ratings of satisfaction of the booklet in terms of providing sufficient information and level of FCR/P (r= -.24, p= .10). However, correlations indicated that women with higher levels of FCR rated the booklet as less helpful in managing their worries about FCR/P (r= -0.316, p= .03).

6.4. Discussion

The aim of this study was to determine whether an online booklet about FCR/P led to reductions in FCR/P and whether women were satisfied with the resource. The results demonstrated that there were high levels of satisfaction, and that most women would recommend the booklet to others. However, the booklet did not significantly improve levels

of FCR/P, nor did it worsen them. The impact of the booklet on FCR did not differ for women in the clinical range for FCR/P compared to those with lower levels of FCR/P, although women with higher FCR/P rated the booklet as less helpful. Taken together, these results suggest that women believed that the booklet provided relevant information and was helpful, but the booklet was insufficient to reduce FCR/P.

These results are not entirely inconsistent with the previous literature and there are a number of potential reasons that might account for the failure to find an effect of this online resource. Firstly, Cuthbert et al. (2019) found mixed effects of self-help interventions, with some studies finding an effect and others not. They noted that very few self-help resources included specific behaviour change techniques (e.g. Michie et al., 2011) and this could account for the failure of some interventions to affect change. This is true of the online resource in this study, which did not specifically include behaviour change techniques.

Secondly, Cuthbert et al. (2019) described that in many self-help resources, there was an absence of a theoretical basis for the information provided. The information in the current booklet was adapted from the ConquerFear program (Butow et al., 2017), which was based on Fardell et al.'s (2016) model of the development of persistent FCR/P. This was the same model that was used as the first stage of the stepped care package developed by Lynch et al. (2020) for melanoma survivors who had responded to immunotherapy. However, in that study, the authors also included exercises as well as information, and there were three brief telephone conversations. Nevertheless, results on the FoP-SF-Q were similar to our results. Lynch et al. (2020) did not report the significance of their results for the 21 people that completed the self-help component, but the Cohen's *d* was similarly small (*d*= 0.02, 95% CI -0.59 – 0.62). Thus, even though both interventions were based on a theoretical model, neither appeared able to change FCR/P significantly.

Thirdly, it has been suggested that some level of FCR/P is adaptive for people following cancer (Butow et al., 2018). This is because for all people who have been diagnosed with cancer, a recurrence is possible. For those in our study, with ovarian cancer, this is particularly the case since up to 70% of women with ovarian cancer will have a recurrence. According to this argument, FCR/P can provide the motivation to adhere to surveillance and therefore identify when a recurrence occurs. While this explanation cannot be excluded, it should be noted that for more than half of the women in this study, their levels of FCR/P were in the clinical range (Herschbach et al., 2010). Therefore, it is unlikely that this can explain the results. Some of the strategies in the booklet also aimed to reduce FCR/P related distress around particular events, e.g. follow-up appointments, so it may be that the resource did not reduce overall FCR levels, but was helpful in managing FCR around those specific time points.

Finally, it is likely that the simple static FCR/P booklet, available in a PDF, was not sufficient to bring about change for the women who accessed it through this study who had high levels of FCR/P. FCR/P levels that were demonstrated by women in this study can be persistent and very distressing. It is perhaps unsurprising that a brief resource would not be sufficient to reduce FCR/P when one considers that even amongst the 8 available RCTs of psychological interventions with FCR as primary target, the effects were relatively small (Cohen's $d = 0.44$) (Tauber et al., 2019). However, it does pose a problem. With the increasing number of survivors, the small psycho-oncology workforce and the high levels of FCR/P, how can we meet the needs of survivors for help managing FCR?

We urgently need to focus on research that can develop cost-effective interventions that can be implemented in practice. Both the ConquerFear and SWORD studies (Butow et al., 2017; van de Wal et al., 2017) were shown to be cost effective, in that they had reasonable willingness to pay thresholds. However, we also need to consider stepped care

models, such as FearLESS, which have less time intensive interventions (such as self-management components that can be delivered via internet or telehealth) and/or utilise other members of the oncology workforce. Liu, Butow & Beith (2019) in their review, concluded that there was insufficient evidence to support the delivery of interventions by non-specialists. However, there have been successful applications of nurse-led approaches, or clinician-driven interventions (Davidson, Malloch & Humphris, 2018; Humphris, & Ozakinci, 2008, Reb et al., 2020). This needs to be a priority for research, particularly as patients themselves are more likely to take up the offer of therapy with nurses than with psychologists or psychiatrists (Brebach et al., 2016).

6.4.1 Study limitations:

A number of methodological limitations are to be noted in the current study. Firstly, we did not recruit participants from clinical services and so relied on self-report regarding medical details. We did not take into account specific anxiety provoking situations such as oncology or scanning appointments. Studies have consistently shown that the time period when scan results are due can trigger significant anxiety in some patients (Feiler, 2011). This was not assessed and may have impacted the levels of FCR/P for some participants. Secondly, we are uncertain as to how much the booklet was read prior to the follow-up survey and the time was one week, and it might take longer for women to process apply the information, or it may have had immediate effects that tapered over time. The levels of motivation and engagement of the participants with the material could vary and could possibly provide a partial explanation for the results. Lastly, our sample included all English-speaking participants, therefore, the generalisability of this online resource across people from diverse backgrounds is unknown.

6.4.2 Implications:

Findings of the present study suggest that we need to develop brief interventions, like internet-based self-help treatment or cognitive bias modification (CBM). Both internet-based psychotherapy (Andrews et al., 2018) and CBM have been found to be effective in anxiety (Jones & Sharpe, 2017). Further, CBM has shown some promise in managing some aspects of FCR/P (Lichtenthal et al., 2017), although internet-delivered treatments for FCR/P evaluated to date produced disappointing results (van Helmondt et al., 2020). Nevertheless, to be able to meet the growing needs of survivors to help them manage FCR/P, there is an urgent need to develop minimal interventions that are efficacious. If effective minimal interventions can be developed, they could be a useful addition to a stepped care approach in reducing FCR/P.

6.5 Conclusion:

In conclusion, the online resource developed for women with ovarian cancer was rated as helpful. Women reported high levels of satisfaction and almost all women reported that they would recommend the resource to a friend. Despite these positive findings, the online resource did not lead to reductions in FCR/P and importantly it was those women with the highest levels of FCR/P who found the resource least helpful. Future research needs to investigate ways in which interventions can be delivered to the large number of cancer survivors who need help to deal with FCR/P.

Chapter 7: Towards a Stepped Care Model for Managing Fear of Cancer Recurrence or Progression in Cancer Survivors

The following chapter is the reproduction of the material contained in the published manuscript:

Pradhan, P., Sharpe, L., & Menzies, R. E. (2021). Towards a stepped care model for managing fear of cancer recurrence or progression in cancer survivors. *Cancer Management and Research*, *13*, 8953.

Professor Sharpe initially conceptualised the literature review. Both first and second authors (PP and LS) jointly decided on the scope and format of the paper and reviewed the extensive literature. Poorva Pradhan wrote the first draft of the paper. Professor Sharpe provided her critical feedback and revisions to manuscript. Dr Rachel Menzies also provided the critical feedback to the manuscript.

Signature: **Date: 18/09/2022**

(Poorva Pradhan)

Signature: **Date: 18/09/2022**

As indicated in Chapter 6, there have been a number of meta-analyses and systematic reviews focusing on intervention of FCR/P. however, reviews have not examined all potential levels of care and, in particular, there is no existing systematic review specifically for minimal interventions – for which the need is clear. Before embarking a trial of another intervention, Chapter 7 aims to synthesize the literature on treatments for FCR/P across all levels of intervention to identify gaps in the literature as optimal models of care.

7.1. Introduction

Improved methods for early cancer detection and more effective treatment have significantly decreased cancer mortality rates (Allemani et al., 2018). As a result, there is a growing number of cancer survivors who are faced with a wide range of survivorship issues. The most prominent and persistent concern revealed by cancer survivors is the fear of cancer recurrence or progression (Simard & Savard, 2009; Kim et al., 2012; van den Beuken-van Everdingen et al., 2008, Simard et al., 2013). According to the recent consensus definition, FCR is the "fear, worry or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016, pp. 3267). FCR has been identified as one of the most common concerns of survivors and help with FCR is amongst the most cited unmet needs of cancer survivors (Simard et al., 2013).

Following a cancer diagnosis and its treatment, it is normal and potentially adaptive for survivors to be concerned about the possibility that their cancer may recur. Such concerns can motivate the adoption of a healthy lifestyle, vigilance towards potential signs and symptoms of recurrence and promote adherence to medical follow-up (Fardell et al., 2016; Wang & Chung, 2012). For this reason, it is unsurprising that FCR is common and research

shows that almost 73% of cancer survivors across different cancers report some degree of FCR. Importantly, nearly half of all survivors (49%) report a moderate to high degree of concern about FCR with approximately 7% reporting a severe level of FCR (Simard et al., 2013). Amongst those with moderate to severe concerns, FCR can become chronic and cause a range of negative consequences, even when the risk of recurrence of disease is low (Simard et al., 2013; Mehnert et al., 2013; Koch et al., 2013). Clinically significant levels of FCR are characterized by persistent worry, preoccupation with bodily checking for signs of cancer, and the frequent need for reassurance from hospital services (Mutsaers et al., 2020; Lebel et al., 2013). As a result of reassurance seeking, clinically significant levels of FCR are typically associated with increased health-care costs (Thewes et al., 2012; Williams et al., 2021).

In addition to the costs, higher levels of FCR have consistently been associated with increased depressive, anxiety and post-traumatic stress symptoms (Humphris et al., 2013; Koch et al., 2013; Mehnert et al., 2009), as well as the experience of psychiatric disorders (Kim et al., 2012). Since clinical levels of FCR do not appear to dissipate over time, individuals often require specialized psychological support and intervention to manage symptoms of FCR (Butow et al., 2018). A survey conducted in 2014, however, showed that there was little agreement about the best approach to managing FCR. Thewes et al (2014) conducted a survey amongst 141 oncology health-care workers (77 health professionals and 64 psycho-oncologists) about their current approaches to managing FCR. The respondents reported that more than half of the survivors whom they saw in their practice had an issue with FCR. Amongst the health professionals, only 21% reported referring survivors with FCR to psycho-oncologists. Further, while psycho- oncologists used a range of interventions to manage FCR, all bar one of the respondents wanted additional training to help manage FCR. Thewes et al (2014) highlighted the need for the development of effective, theoretically

driven treatments for FCR and, since the publication of that survey, there have been randomized controlled trials (RCTs) of different approaches for the management of FCR.

7.2. Evidence-Based Approaches to FCR

While FCR has been an outcome in RCTs of psychosocial interventions that generally aim to reduce distress (Fisher, Byrne & Salmon, 2017; Heinrichs et al., 2012; Lengacher et al., 2009), there have been fewer interventions that have explicitly targeted FCR, as a primary outcome. The earliest approaches used a cognitive behavioural approach, likely due to the fact that the prevailing model of FCR was based on the self-regulation theory (Lee-Jones, 1997). This model argued that FCR is a multidimensional construct comprised cognitive and emotional components. According to this model, an emotion (eg, fear) results when one misinterprets neutral bodily sensations. That is, it is those individuals who believe that cancer is likely to recur, who become anxious and then behave in ways to reduce the anxiety, such as checking or avoiding hospital appointments, which leads to increased fear responses over time. However, these approaches had modest success. For example, Herschbach et al (2010) found that CBT was more effective than a (non-randomized) no treatment control group, but not a non-directive supportive control group. Similarly, the AFTER intervention25 showed some evidence of improvement in FCR following treatment in oral cancer patients, but the median number of sessions attended was two, indicating less than ideal attendance. However, with a proliferation of new theoretical models (e.g., cognitive processing model; Fardell et al., 2016), so too followed a number of interventions based on those theories (e.g., ConquerFear; Butow et al., 2017).

In the most comprehensive meta-analysis to date, Tauber et al (2019) evaluated 23 controlled trials (21 of them were randomised controlled trials) of a psychological

intervention where FCR was measured as an outcome. Their results confirmed that psychological treatments are effective for FCR; however, the effect is small (Hedge's g = 0.33). The quality of the evidence overall led the authors to be moderately confident of the estimate of their effect size using the GRADE criteria.

Tauber et al (2019) also examined a range of moderators, including type of therapy (contemporary or traditional CBT), cancer type, FCR as primary or secondary target, intervention format (group or individual) and delivery (face to face or other). The type of therapy did give rise to different treatment effects. Specifically, Tauber et al (2019) categorised interventions into traditional CBT which focused on challenging beliefs and changing behaviours (10 interventions) and contemporary CBT which focused on cognitive processes and encourages people to accept negative beliefs and emotions based on more recent theoretical views of FCR (9 interventions). The results showed a difference between traditional and contemporary CBTs that favoured contemporary CBT (Hedge's g = 0.42) as compared to traditional CBTs (Hedge's g = 0.24). However, these benefits were only observed at post- treatment. Interestingly, only 8 of the interventions included in the meta-analysis included FCR as a primary outcome. It is also worthwhile noting that majority of the FCR-specific interventions were face to face (for example, ConquerFear; Butow et al., 2017 CBT; Herschbach et al., 2010) or adopted a blended approach that is combined online with face to face (e.g., van de Wal et al, 2017). The 19 face-to-face interventions in the Tauber et al (2019) meta-analysis involved between 1 and 15 sessions, with a median of 6 sessions. Further, interventions that were not face-to-face, did not result in significant change in total FCR when considered alone. Hence, the results of this meta-analysis suggest that even reasonably intensive interventions that are administered by highly trained psycho-oncology professionals give rise to modest effects. Further, a number of gaps were evident in the literature, more than half of the included trials were in early-stage breast cancer treated with

curative intent, and the majority of trials were with survivors who were currently disease free. Given the recent efficacy of novel interventions including immunotherapies and personalised medicine that are leading survivors to live long lives with disease in many cases (see Thewes et al., 2017), we need more trials in other cancer types, particularly those with advanced disease.

While Tauber et al's (2019) meta-analysis confirmed the efficacy of available interventions, it also highlighted a number of important limitations to the literature. Given the estimated and growing unmet need for management of FCR, it will be impossible to implement the intensive face- to-face approaches with established efficacy to all participants with moderate to severe FCR. Instead, there is a need to develop a model of care where we stratify care to the level of severity with increasingly intensive interventions reserved for those with the most serious or severe difficulties. However, to have an optimal stepped care model, we need to (a) prevent the development of clinically significant levels of FCR, where possible; (b) develop effective minimal interventions for FCR; (c) up- skill non psychology health-care professionals in managing FCR; and (d) develop more efficacious treatments for a greater range of survivors. See Table 1 for a detailed account of these studies.

7.2.1 Can Clinically Significant Levels of FCR Be Prevented?

Most models of FCR identify that a survivor's knowledge of the realistic likelihood of recurrence and likely signs of recurrence contribute to clinically significant levels of FCR (Fardell et al., 2016; Lee-Jones et al., 1997). That is, a lack of information about prognosis and signs of recurrence increases the likelihood that people will experience a clinically significant level of FCR. As such, it is possible that good doctor-patient communication about these topics at the end of treatment may help reduce the chance of developing clinically

significant levels of FCR. Butow et al (2018) recommended that all members of the oncology team should consider FCR to be a topic of relevance to their care of the patient.

The literature on potential preventative programs is in its infancy. A systematic review by Liu et al (2019) identified only five trials of non-psychologist delivered (four of them were nurse led) communication. Only three of the trials had a control arm (the remainder were Phase I pilot interventions), hence these trials were at a high risk of bias. One intervention (the AFTER intervention: Adjustment to the Fears, Threat and Expectation of Recurrence, Humphris & Rogers, 2012) consisted of 6 weekly sessions with a nurse. This intervention comprised CBT, relaxation and patient-centred approach and reduced FCR levels at post-intervention, but not follow-up. The second trial was a single-session nurse-led coaching intervention, where nurses coached survivors to communicate more with their oncology team about recurrence (Shields et al., 2010). Although participants were satisfied with the intervention, there were no impacts on FCR. However, the study had only 44 participants and so was likely under-powered. According to Liu et al (2019) some approaches have shown feasibility and a lack of harm in early trials. The most common strategies were allowing participants to discuss their fears, and providing reassurance and normalisation. More recently, Liu et al (2021) also conducted a single-arm study of an oncology delivered intervention that normalised FCR, provided personal prognostic information, educated survivors about symptoms of recurrence and gave advice about managing FCR worries and information about referral, where necessary. This intervention was only 8 minutes long, on average, which was considered to be feasible. FCR did improve over the trial, although whether this is as a result of the intervention is unclear. As such, there remains insufficient data to recommend widespread adoption of these approaches.

7.2.2 Up-skilling health professionals to deliver psychosocial interventions

Whilst the systematic review of Liu and colleagues (2019) confirmed that it was premature to confirm the efficacy of clinician-based interventions designed to prevent FCR, there were some indications that nurse-delivered interventions could be efficacious. As described previously, Humphris & Rogers (2012) trained nurses to administer a CBT-based intervention to reduce FCR amongst head and neck cancer patients. There was evidence for efficacy of this intervention compared to a control in the short-term, showing strong proof of concept that nurses can be trained to use CBT to help survivors manage FCR. In a similar vein, researchers have attempted to adapt the ConquerFear program as a nurse-led intervention (Reb et al., 2020a). The ConquerFear program was based on Fardell et al.'s (2016) model of FCR and combined components of acceptance commitment therapy, meta-cognitive therapy and behavioural strategies based on self-regulation theory. The ConquerFear program was used with patients with early-stage breast or colorectal cancer or melanoma, who had been treated with curative intent and were in the clinical range on FCR Inventory (Butow et al., 2017). In a phase I trial, in 33 survivors with advanced lung or gynaecological cancer, Reb et al., (2020b) found significant improvements in fear of progression for 21 participants who completed the ConquerFear program in a mixed (zoom/face to face) approach. As an uncontrolled trial, this study was at a high risk of bias, however, the effect sizes that were achieved when ConquerFear was adapted to more advanced disease and administered by nurses were roughly similar to those achieved in the ConquerFear arm in the original study, which is extremely encouraging (Reb et al., 2020b). There is considerable evidence that patients show a preference for receiving supportive care from nurses, in comparison to psychologists or psychiatrists (Brebach et al., 2016), however, it is only recently that psychological interventions for FCR have been nurse-led. Given the larger nursing workforce in comparison to the psycho-oncology workforce, the ability of

nurses to achieve similar outcomes could begin to bridge the gap between effective treatments being available and accessible. Although given the number of survivors, making help with FCR available to all survivors for whom this is an issue will likely require effective minimal interventions

7.2.3 Minimal Interventions:

Minimal intervention is an umbrella term for interventions that do not require large amounts of therapist time and are typically delivered remotely (e.g. telephone, online, a booklet), which allows these interventions to be scalable for a very common problem, where the available workforce cannot meet the needs of the population. These interventions require less time commitment, expertise and resources to achieve an improvement in a particular outcome (Glasgow et al., 2014). FCR amongst cancer survivors can be seen as an area in which minimal interventions may be necessary to ensure that help with FCR does not remain the leading unmet survivorship needs.

The most minimal of interventions are self-help materials, such as pamphlets, information sheets and online resources. While many cancer organisations internationally have developed their own FCR resources to provide some information and support around FCR/P, these have rarely been evaluated. The efficacy of self-help resources in general was extensively evaluated in a systematic review by Cuthbert and colleagues (2019) which included 41 randomised trials with psychoeducational self-help component for cancer survivors. The results of this review were mixed across studies, indicating that while some self-help approaches can produce positive outcomes, many fail to and some even produce unintended negative impacts. However, none of the 41 included trials targeted FCR. Only recently has there been research evaluating the efficacy of brief online FCR resources. In the

previous study presented in Chapter 6, an online self-help pamphlet was developed by Ovarian Cancer Australia and its effect on FCR was evaluated. The pamphlet provided information about FCR and suggested strategies to better manage FCR (Pradhan et al., 2021). These results were consistent with another RCT conducted of information provided either via social media or in group face to face. Omidi and colleagues (2020) found that there was a significant impact of group education (but not social media information) on quality of life, compared to a control group. However, the provision of information did not have an impact on FCR. As such, it seems unlikely that the provision of simple information will be sufficient to meet the needs of survivors with elevated FCR levels.

In the Tauber et al. (2019) meta-analysis, there were only three minimal interventions that were included. For example, an intervention by Dieng et al. (2016) consisted of a psychoeducational pamphlet and three 15-minute telephone based psychotherapy sessions by a psychodynamic therapist. It was concluded that this blended intervention was effective in improving the levels FCR in early-stage melanoma survivors. These results were maintained at a 12-month follow-up (Dieng et al., 2019). The telephone sessions in this intervention however, require specialist skills. It is however unclear whether the self-help resources would be efficacious without that input. The intervention by Otto et al. (2017) involved an online self-directed gratitude training on overall FCR and death-related FCR. The intervention produced an improvement in reducing death-related FCR and promoting well-being in the gratitude intervention group, but there was no impact on FCR total severity. Similarly, Lichtenthal and colleagues (2017) used a novel Cognitive Bias Modification (CBM) to reduce FCR amongst 120 women with early stage breast cancer compared to a placebo. CBM is a novel approach which directly aimed to modify implicit cognitive processing biases such as attention or interpretation (Beard, 2011). The intervention consisted of 8 personalised treatment sessions that were computerized over the span of 4 weeks. Their intervention was

successful in modifying interpretation bias and produced an improvement in the health worries subscale of concerns about recurrence scale as compared to a placebo group. However, the total score for worries about cancer was not significantly improved compared to the placebo group. Therefore, while these approaches showed some promise, more research is definitely needed.

Despite the proliferation of internet-delivered interventions in other areas of psychology (Barak et al., 2008; Gainsbury & Blaszczynski, 2011; Andersson et al., 2009; Karyotaki et al., 2018), the FCR literature has been somewhat slow to develop and evaluate online versions of the face to face interventions. For instance, Van de Wal et al.'s (2017) SWORD study ("Survivors' Worries of Recurrent Disease") also known as blended cognitive behavioural therapy (bCBT) or partly online. Participants in the intervention condition received 5 individual face to face sessions in combination with three e-consultations. The intervention successfully reduced the severity of FCR on Cancer Worry Scale as compared to control group. SWORD does of course have evidence for efficacy – suggesting that at least part of the intervention could be offered online. However, stand-alone internet delivered interventions thus far have failed to show clear evidence of efficacy. The only one to be evaluated in an RCT so far is CAREST (van Helmondt et al., 2020). CAREST was a carefully developed intervention based on psychoeducation and CBT principles for FCR. The trial was relatively large (n = 262), but failed to show any difference between women who received CAREST or treatment as usual. This was despite reasonable completion rates: 83% at post-treatment and 70% at follow-up. This trial therefore questions whether an unsupported, stand-alone intervention will be efficacious when delivered online.

There are, however, a number of other internet-delivered interventions that have been developed. For example, iConquerFear has been co-designed by adapting ConquerFear to an online platform (Smith et al., 2020). It is currently being evaluated (Lynhe et al., 2020).

Akechi et al. (2018) have developed a smartphone intervention, in the SMILE trial, which is currently underway and will deliver a combination of problem-solving therapy and behavioural activation in an attempt to lessen FCR/P. Finally, the FORTitude study (Wagner et al., 2017) developed an eHealth intervention based on treatments for anxiety disorders but applied to FCR/P. The three active strategies included in the program were relaxation, cognitive restructuring and scheduled worry time. The trial was designed to be able to comment on the relative efficacy of each of these strategies, however, to date the results have not been published. Interesting, a recent study has compared a generic online treatment (Wellbeing after cancer) with and without support and included FCR as an outcome. Dirkse et al. (2020) found that there was a moderate sized effect for reducing FCR of this program, even without support, which shows that internet-delivered interventions have the capacity to be efficacious for FCR.

7.2.4 Stepped-care approaches:

There are over 2 million cancer survivors currently living in Australia alone [AIHW, 2020]. Nearly half of all survivors will have moderate levels of FCR (Simard et al., 2013) and in some groups (such as young women with breast cancer), up to 79% have clinically significant levels of FCR (Thewes et al., 2012). Without specific effective minimal interventions, there will be no realistic way in which to meet the needs of cancer survivors to manage FCR. Most oncology services have limited resources to support all survivors with elevated FCR, and thus there seems to be an urgent need to develop evidence-based approaches with different levels of intervention. Although stepped care is often described as any model of service provision with different levels of care, there are three main models for how to determine the flow of patients through services (Linton et al., 2018). True ‘stepped

care' approaches propose that a simple, inexpensive intervention be tried first for all survivors. If the survivor continues to have clinically significant levels of FCR, then a more complex intervention is tried, and so the process continues as the steps become more complex. The second model is stratified care. These approaches tailor FCR interventions, based on the severity of FCR or other known risk factors for poor prognosis. Those survivors deemed to have mild, but still bothersome, levels of FCR are referred to minimal interventions, such that more intensive interventions (requiring high professional skills) are reserved for people with clinical FCR who are unlikely to benefit from minimal interventions. The final type of stepped care approach is matched care. Matched care, like stratified care, assesses survivors at baseline, and determines not only the intensity of intervention, but also the nature of intervention based upon different presenting risk factors.

To date, there has been a single stepped care approach described in the literature, the 'FearLESS' program (Lynch and colleagues, 2020). FearLESS was developed for advanced melanoma survivors who had responded to immunotherapies, and as a result had a large degree of uncertainty in relation to the potential for recurrence or progression. The FearLESS program was a stratified version of stepped care where those survivors who scored in the normal range received treatment as usual. Those scoring in the sub-clinical range for FCR were directed to a self-help intervention, supported with phone calls and screened again five weeks later. In contrast, those who scored in the clinical range for FCR were provided with individualised therapy sessions based on ConquerFear (Butow et al., 2017). The FearLESS model holds some promise, as the results showed that participants engaged with the intervention offered and the majority of those assigned to self-help indicated that they did not want further intervention (90%). Although 13 of the 21 completers in the self-help condition reported numerical decreases in their FCR scores, the effect size was very small (Cohen's d = 0.11) (Lynch et al., 2020). The individual therapy resulted in larger changes (Cohen's d =

0.7), which were similar to the within-group effects in the ConquerFear trial, suggesting that the approach is likely suited to more advanced patients. Nevertheless, this was a study with a high risk of bias given the absence of a control group, and the absence of evidence-based minimal interventions makes the provision of effective stepped care approaches challenging.

In order to develop an effective stepped care approach, or to determine the nature of a stepped care approach that might be most suited to FCR, we need more research. If a brief oncologist delivered intervention at the end of treatment, such as that developed by Liu et al. (2021) was to prove efficacious in RCTs, this would potentially be an easily delivered universal step. That is, an oncologist based intervention could be incorporated into routine care of all survivors with the hope of preventing clinically significant levels of FCR. Currently, we desperately need to evaluate the available internet-delivered minimal interventions specific to FCR which could then be used as a second step in the stepped care program. We have effective individual face-to-face interventions that produce modest changes in FCR/P. There are few moderation studies of who benefits most, but we know that the relative benefit of ConquerFear was greater for those with higher baseline levels of FCR (Sharpe et al., 2019). This would suggest that a matched approach to stepped care might be most useful. However, it would be important to demonstrate that those with higher FCR/P did not also benefit most from minimal interventions.

One could envisage a model of stepped care, where on a first, universal step, oncologists were encouraged to normalise FCR/P, provide reassurance and accurate prognostic information, as well as specifying the likely symptoms associated with FCR/P to all their patients (e.g. Liu et al, 2019; See Figure 7.1). Survivors might then be screened at routine follow-up appointments. Those who developed a “sub” clinical level of symptoms, might be encouraged to engage with an efficacious minimal intervention, while those with moderate symptoms might be referred for brief nurse-led interventions. This would reserve

specialist psycho-oncologists to work with those survivors with the most severe levels of FCR/P. However, we should also be investigating ways to improve the outcome of existing treatments, which continue to leave a large proportion of survivors in the sub-clinical and clinical range for FCR/P.

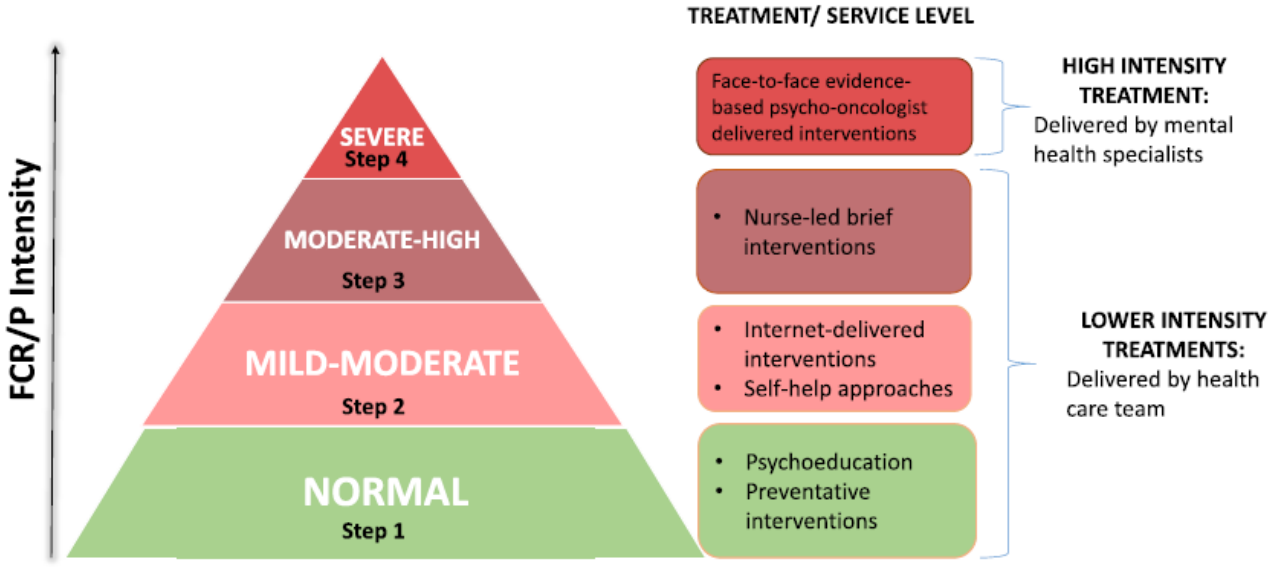


Figure 7.1 Stepped care model to fear of cancer recurrence/progression in oncology services.

Table 7.1: Study characteristics and results of included papers.

	Sample size	Type of cancer	No. of arms	Delivery mode	Intervention	Outcomes	Effect size Cohen's *d* (Time of assessment)
I. PSYCHOEDUCATION AND PREVENTATIVE INTERVENTIONS							
Pradhan et al (2021)	62	Ovarian Cancer	Single-arm	Online: Psychoeducational booklet	Psychoeducation: Online PDF booklet.	No effect on fear of progression	0.17 1 week
Liu et al. (2021)	61	Breast Cancer	Single-arm	Face-to-face	Oncologist delivered preventative intervention	FCR reduced	0.39 (1 month) 0.68 (3 months)
Dieng et al (2016)	164	Melanoma	Two	Psychoeducational booklet 3 Telephone sessions	Psychoeducation plus psychodynamic-based psychotherapy	FCR reduced	0.5 (1 month) 0.3 (6 months)
Sterba et al (2015)	92	Breast Cancer	Two	Mixed	In-person video sessions and educational booklets	No effect on cancer-related worries	-0.22
II. SELF-HELP AND INTERNET-DELIVERED INTERVENTIONS							

Otto et al (2017)	67	Breast Cancer	Two	Online	Positive psychology: Gratitude intervention	No effect on FCR	0.21 (1 month) 0.1 (3 months)
Lichtenthal et al (2017)	110	Breast Cancer	Two	Online	Cognitive Bias Modification (Interpretation and Attention)	No effect of Cancer Worry Scale	0.35 post-treatment 0.54 (3 months)
van Helmondt et al., (2020)	262	Breast Cancer	Two	Online	Cognitive behaviour therapy	No effect on FCR	Not reported
Omidi et al (2020)	105	Breast Cancer	Three	Face to face Online	Group and social network-based self-management education on lymphedema	No effect on FCR	Group education: 0.21 Social Network-based education: 0.06 (3 months)
Dirkse et al (2019)	86	Multiple	Two	Face to face Online	Cognitive behaviour therapy	Reduction in FCR	0.93-0.85 (1 month)
Lengacher et al (2018)	15	Breast Cancer	Single-arm	Online	Mobile-based Mindfulness Stress Reduction for Breast Cancer	Improvements in fear of recurrence at 6 weeks follow-up	0.74
Germino et al (2012)	313	Breast Cancer	Two	Self-directed	Traditional CBT	No significant improvement in FCR was reported.	Not reported

III. HEALTH-CARE PROFESSIONALS LED INTERVENTIONS							
Humphris & Rogers (2012)	90	Head and Neck	Two	Face to face, nurse-led	Cognitive behavioural therapy	FCR reduced during treatment, improvement not maintained	0.56 (3 months)
Shields et al (2010)	44	Breast Cancer	Two	Single session, tele-coaching	Encourage patients to raise top 3 concerns with oncologist	No effect on FCR	-0.13
Reb et al (2020b)	31	Gynaecology Lung Cancer	Single-arm	In person and online	Contemporary CBT, hybrid online and face-to-face	Reduction in FoP at 8 and 12 weeks after intervention.	1.3 (8 weeks)
IV. INTENSIVE SPECIALIST CARE							
Herschbach et al (2010)	265	Multiple	Three	Face to face	CBT and SET (based on personal experiences)	Reduction in FoP scores after 12 months for both intervention groups.	CBT: 0.61 SET: 0.56 (12 months)
Butow et al (2017)	222	Multiple	Two	Face to face	Contemporary CBT and relaxation training	Improvements in both total FCR-I and severity subscale	0.33 (3 months) 0.39 (6 months)

Van de Wal et al (2017)	88	Multiple	Two	Mixed: Face-to-face and online sessions	Blended cognitive behaviour therapy	Improvements in FCR at 3 months post intervention.	0.76
Bannaasan et al (2015)	59	Breast Cancer	Two	Face-to-face	Buddhist doctrine-based practice	Reduction in FCR scores after 1 month.	1.38 (1 month)
Tomei et al (2018)	25	Multiple	Two	Face to face	Traditional CBT	Reduction in FCR at post-intervention	0.28
Cameron et al (2007)	154	Breast Cancer	Two	Face to face	Contemporary CBT for emotional regulation and adjustment	Decrease in cancer recurrence worries after 4 months, not maintained after 6 and 12 months.	0.59
Lengacher et al (2009)	84	Breast Cancer	Two	Face to face	Mindfulness-based stress reduction	Improvement in FCR after 6 weeks.	0.6
Crane-Okada et al (2012)	49	Breast Cancer	Two	Face to face	Mindful movement program intervention	Decrease in FCR at 6 weeks	0.57
Heinrichs et al (2012)	72	Breast and Gynaecological cancer	Two	Face to face	Couple based coping intervention	Decrease in FoP for intervention participants	0.57
Bower et al (2015)	71	Breast Cancer	Two	Face to face	Mindfulness-based intervention	Improvements in FCR at 3 month follow-up in intervention group	1.39
Dodds et al (2015)	33	Breast Cancer	Two	Face to face	Meditation-based program called CBCT	Reduction in FCR in intervention group	-1.38
Lengacher et al (2016)	322	Breast Cancer	Two	Face to face	Mindfulness-Based Stress Reduction for Breast Cancer	Improvements in FCR at 6 and 12 week follow-up	0.3 (6 weeks) 0.28

							(12 weeks)
Merckaert et al (2016)	159	Breast Cancer	Two	Face to face	CBT and hypnosis	Reduction in FCR severity post intervention	0.33
Manne et al (2017)	352	Gynaecological Cancer	Three	Face to face and 1 telephone session	Communication-enhancing intervention (CCI) and supportive counselling (SC)	No effect on FCR	0.11
Victorson et al (2016)	43	Prostate	Two	Face to face	Mindfulness Based Stress Reduction	Reduction in recurrence fears	0.15
Gonzalez-Hernandez et al (2018)	56	Breast Cancer	Two	Face to face	Compassion-based intervention	Reduction in FCR related stress at post-intervention and 6 mth follow-up	0.68 (post-intervention) 0.46 (6 months)
Chambers et al (2012)	19	Prostate	Single-arm	Face to face	Mindfulness-based cognitive therapy group intervention	Reduction in FCR	0.28
Lebel et al (2014)	56	Breast and ovarian cancer	Single-arm	Face to face	Cognitive-existential (CE) group intervention	Reduction in FCR	0.73
Seitz et al (2014)	20	Multiple cancers	Single-arm	Online	Traditional CBT	Decrease in FoP	0.48
Smith et al (2015)	8	Multiple cancers	Single-arm	Face to face	Contemporary CBT	Reduction in overall FCR scores and severity subscale at 2-month follow-up	FCR Severity: 1.9 FCRI-Total: 1.8

Arch & Mitchell (2015)	42	Multiple cancers	Single-arm	Face to face	ACT	FCR decreased at post intervention, but 1 mth follow-up	0.66 (post-treatment) 0.11 (1 month)
Momino et al (2017)	40	Breast	Single-arm	Face to face Telephone sessions	Collaborative care and need-based intervention	No effect on FCR	0.15
Savard et al (2018)	33	Multiple cancers	Single-arm	Face to face	Group-based CBT	Significant decrease in FCR at post-treatment	Not reported
Davidson et al (2018)	16	Breast Cancer	Single-arm	Telephonic sessions	Intervention based on CBT	Decrease in FCR after 1 week follow-up	0.8
Johns et al (2019)	91	Breast Cancer	Three	Face to face	Group-based ACT and Survivorship education	Significant decrease in FCR severity in ACT group	0.61 (6 months)
STEPPED CARE							
Lynch et al (2020)	61	Melanoma	Single-arm	Mixed	Three step intervention: (1) Treatment as usual; (2) Self-management intervention (3) Individual therapy: contemporary CBT.	Contemporary CBT reduced FCR and FoP.	Self-management- 0.11 for FCR 0.02 for FoP Individual therapy 0.64 FCR 0.4 FOP

ACT: Acceptance and Commitment Therapy

AFTER: Adjustment to the fear expectation or threat of recurrence

bCBT: Blended cognitive behavioural therapy

CAREST: Cancer recurrence self-help training

CAU: Care as usual

CBT: Cognitive-behavioral group therapy

CBCT: Cognitively Based Compassion training

FCR: Fear of cancer recurrence

FoP: Fear of progression

MCT: Meta-cognitive Therapy

SET: Supportive-experiential therapy

S-REF: Self-Regulation of Executive Function

7.3. Maximising existing interventions:

Although existing face-to-face interventions are effective, the effect sizes of treatments are small, on average, and the majority of participants still score in at least the sub-clinical range following treatment (e.g. van der Wal, 2017, Butow et al., 2017). Future research should focus on how to further improve outcomes for survivors with severe FCR and for those with advanced disease (refer to table 7.2 for recommendations for future research). There are a number of ways in which to address the problem of finding more efficacious treatments. Firstly, one can examine mediators of treatments that work, which can indicate the likely treatment mechanism and increase the focus on intervention strategies that target those factors. For example, changes in meta-cognitions and intrusions were found to moderate the relative efficacy of ConquerFear versus relaxation training (Sharpe et al., 2019). Hence, focusing more on metacognitive therapy (Fisher et al., 2017), or interventions (such as the worst case scenario, Moran et al., 2017) may increase the efficacy of existing approaches. Secondly, it is possible that if both traditional and contemporary CBT approaches are both effective, that together they might be more efficacious. A recent case series of a combined approach for transdiagnostic anxiety (including FCR/P) showed that 65% of patients with advanced disease no longer scored in the clinical range following treatment (Curran et al., 2021), but again as a case series this study is at risk of bias. Finally, theoretical models can be used to guide the development of improved interventions, such as focusing on modifying interpretation biases, argued to drive FCR in the threat interpretation model (Heathcote & Ecclestone, 2017) or focusing on death anxiety (Sharpe et al., 2018) which is seen as central in Simonelli et al.'s (2017) model of FCR. While improving treatments will require more research, the existence of moderately effective psychological treatments should be seen as a starting point for further improving approaches to manage FCR.

Table 7.2: Recommendations to guide future research

Recommendations for future research
1. Development and evaluation of universal minimal interventions (e.g., clinician-delivered, psychoeducational interventions, informational resources, apps) designed to help prevent FCR.
2. Development and evaluation of minimal interventions (e.g. internet-delivered treatments) that are targeted for those with mild to moderate FCR
3. Up-skilling oncology professionals to deliver interventions targeting FCR in routine clinical practice.
4. Research to improve existing interventions for severe FCR**.**
5. Adapting available evidence-based FCR interventions for those with advanced disease.
6. Testing models of stepped care to develop the most efficacious and highly implementable service model.

There is no doubt that over the past ten years, numerous efficacious psychological treatments for FCR/P have been developed and evaluated. However, these are associated with small to moderate effects with most survivors who complete treatment remaining in either the clinical or sub-clinical range. It may be that combining efficacious treatments, targeting factors that are associated with FCR or increasing the dose of effective treatment components would result in larger improvements. However, research is needed to determine this. Despite a range of efficacious treatments, there is simply not the workforce available to make these treatments available to all survivors with moderate to severe FCR. Furthermore, based on the past literature, we still do not have evidence-based interventions to be able to implement a stepped care approach for FCR. Therefore, we desperately need evidence-based minimal interventions that can be developed for use as part of a stepped care model, as well as good preventative approaches, to meet the needs of the growing number of cancer survivors who fear recurrence or progression.

Chapter 8: A randomised controlled trial of online Cognitive bias modification for interpretation (CBM-I) for fear of cancer recurrence/progression in women with breast or ovarian cancer

Poorva Pradhan developed the research aims and study design in consultation with her lead PhD supervisor Professor Louise Sharpe. The candidate completed the ethics application, risk assessment application, recruited participants, analysed the preliminary data and wrote the first version of the manuscript.

Signature: **Date: 18/09/2022**

Professor Louise Sharpe provided supervision and critical review regarding the study concept and design, performed the Linear mixed model regression analysis and interpretation and critically reviewed the manuscript.

Signature: **Date: 18/09/2022**

Dr Wendy Lichtenthal and A/Prof Courtney Beard provided their expertise on study design and stimuli for CBM-I trial. Hayley Russell helped with participant recruitment.

8.1. Introduction

In 2020, there were 19.3 million new cases of cancer, and the cancer burden is projected to grow 28.4 million cases by 2040 (Sung et al., 2021). With improved treatments for many forms of cancer, more and more people are living with and beyond cancer. According to a recent review, nearly 60% of survivors experience moderate levels of fear about their cancer returning (FCR), and nearly 20% experience severe FCR (Luigjes-Huizer et al., 2022). Fear of cancer recurrence (FCR) is defined as "fear, worry, or concern about the cancer returning or progressing" (Lebel et al., 2016, p.3267). A recent meta-analysis found that high levels of FCR are associated with poorer overall quality of life (Tran et al., 2021), increased anxiety and depressive symptoms (Koch et al, 2013) increased oncology appointments (Lebel et al., 2013) and health care costs (Williams et al., 2021). Help with FCR remains the highest psychosocial unmet need amongst cancer survivors.

Although there are now efficacious treatments for people with moderate to severe FCR (Tauber et al., 2019), most of these are intensive face-to-face approaches (e.g. Conquer Fear, Butow et al., 2017) or blended approaches still requiring face to face sessions (e.g. SWORD, Van de Wal et al, 2017). It is unlikely with the huge number of survivors currently affected by FCR, let alone the numbers forecast over the next 10-20 years, that the psycho-oncology workforce would be able to meet the needs of these individuals using face-to-face psychological therapy. However, so far, internet-delivered options have failed to provide any benefit (e.g. CAREST, Van Helmondt et al., 2020).

One pilot study that found some benefits for FCR from an online training, used a novel intervention that trained participants with breast cancer explicitly to interpret

ambiguous scenarios (e.g. a pain in my back) as not being related to a recurrence (Lichtenthal et al., 2017). However, this was a pilot study (n = 110) focused primarily on feasibility. The intervention used by Lichtenthal and colleagues was drawn from the anxiety literature and is known as Cognitive Bias Modification (CBM). Lichtenthal et al (2017) used a CBM protocol that modified both attention and interpretation. CBM for interpretation (CBM-I) was effective in changing interpretation bias, whereas CBM did not change attention bias. CBM did result in a reduction in the 'health worries' subscale, but not the total concerns about cancer scale.

Cognitive Bias Modification for interpretation (CBM-I) involves repeatedly training participants to endorse positive and/or benign interpretations of ambiguous stimuli related to their fear (e.g. social situations in social anxiety; cancer-related situations in FCR) (Krebs et al., 2018). The Cancer Threat Interpretation model (Heathcote & Eccleston, 2017) suggests that it is when people interpret a potentially benign sensation (i.e. a twinge in the back, fatigue) as threatening because it is indicative of a recurrence that severe FCR develops. However, whether the general tendency to interpret sensations as pain-related and threatening; or a specific tendency to interpret situations as potentially indicative of a cancer recurrence that underlies FCR is unclear. In Chapters 4 and 5, we found evidence that pain-related interpretation biases were associated with FCR in both ovarian and breast cancer. Further, in people with breast cancer, the tendency to interpret ambiguous words as pain-related moderated the relationship between pain and FCR, as the Cancer Threat Interpretation model predicts.

These results raise the possibility that if one can harness and change interpretation biases, one might be able to reduce FCR. One benefit of CBM-I is that it can be administered entirely online and therefore could be highly scalable. However, first efficacy needs to be established. Further, it is important to determine whether any training needs to be cancer-

specific or whether a more generic training focused on pain—related interpretations is equally efficacious. This is the aim of the present study.

We hypothesize that CBM-I (both pain-related and cancer-specific versions) would result in a reduction of the co-primary outcomes FCR and FoP over time, as compared to placebo. We also expected an improvement with CBM-I in a range of secondary outcomes compared to placebo.

8.2. Methods

8.2.1. Study design:

This was a randomized, double blinded, placebo-controlled trial. Participants were randomly allocated to one of the three groups, using the randomizer algorithm in QUALTRICS: (1) standard CBM-I that trained participants to interpret ambiguous scenarios as NOT being pain-related (Pain-related CBM-I), (2) CBM-I which presented ambiguous scenarios related to either ovarian or breast cancer and trained them NOT to see the scenarios as related to recurrence (cancer-specific CBM-I), or (3) a placebo control arm. The placebo group received identical scenarios as cancer-specific CBM-I, however only 50% of the trials reinforced benign interpretations

8.2.2. Participants:

The participants were recruited from Cancer Consumer registries: Breast Cancer Network Australia (BCNA) and Ovarian Cancer Australia (OCA) or through paid advertisements and cancer-specific groups on social media (Facebook). BCNA and OCA are

not-for-profit independent organizations with a large database of women who are diagnosed breast or ovarian cancer, respectively.

Participants were recruited from October 2021 to February 2022. Participants were eligible based on the following inclusion/exclusion criteria:

i. Have a diagnosis of breast or ovarian cancer

ii. Participants who have at least moderate levels of FCR (cut-off ≥ 13) or FoP (cut-off ≥ 34)

iii. Over 18 years of age

iv. Fluent in English

v. Have access to internet and computer competency and,

vi. Not receiving palliative care.

8.2.3. Procedure:

Members of these registries (BCNA and OCA) were emailed a detailed description about the study along with a link to online consent form and baseline questionnaires. Participants who consented were immediately directed to a series of baseline questions. All questionnaires and training were hosted on a web-based platform, Qualtrics and all participants were randomized through this computer-based algorithm. The group that participants were allocated to was unknown to either the participants or the researchers. After completing baseline and training session 1, participants from all groups were then sent automated emails for subsequent training sessions (2, 3 and 4) along with follow-up two weeks later. The entire study was conducted over 28 days for each participant. The order of

the questionnaires were counterbalanced across all participants. The study was approved by University of Sydney's Human research ethics Committee (Project no.: 2020/835) and the trial is registered with Australian New Zealand Clinical Trials Registry (ACTRN12621000634875; See Appendix I).

At assessment on day 1, participants were asked to complete a series of baseline questions (see measures). Immediately following assessment, participants were randomized to one of the three conditions. Participants were then directed to commence their first training session, which took approx. 15-20 minutes. On days 4, 7 and 14, participants were sent a link via email to the next training session *(training sessions 2, 3 and 4, respectively)*. Immediately following the fourth training session, participants completed the post-intervention measures (post-treatment). Hence, the protocol required participants to complete four training sessions over 14 days.

Two weeks following the post-treatment assessment (day 28), participants were emailed with the follow-up questionnaires.

8.2.3.1 Intervention:

8.2.3.1.1 Cancer-specific Cognitive Bias Modification for Interpretation (CBM-I):

The Word Sentence Association Paradigm (WSAP) was used to modify interpretation bias using word-sentence pairings to train participants to make benign interpretations (Beard & Amir, 2009). In the WSAP task, each trial begins with a fixation cross for 500 ms and participants are presented with a single word (either benign or threatening for 750 ms). Following the presentation of the word, an ambiguous sentence is presented, and the participant is asked whether the two are related or not (in terms of 'Yes' or 'No'). In the CBM-I condition, benign interpretations are CORRECT and threat interpretations are INCORRECT, and patients receive this feedback before proceeding to the next trial.

In this study, there were 80 sentences each with a benign and cancer-related (threatening) option. These scenarios were originally adapted from Lichtenthal et al. (2017) but had been developed to be specific to the type of cancer that the person experienced (in this case either breast or ovarian) with people with lived experience of fear of cancer recurrence. An exemplar item would be an initial word appearing, such as "suspicious mass" [cancer-related] or "thorough" [benign]. Then an ambiguous sentence, such as "The technician takes additional scans" follows. In the cancer-specific CBM-I task, if participants chose the word "thorough", they were told they are 'correct' (for a benign response) whereas if they chose the word "suspicious mass" they were told they were 'incorrect' (i.e. cancer-specific interpretation). Feedback was given after every response in the cancer-specific CBM-I training group.

8.2.3.1.2 Pain-related Cognitive Bias Modification for Interpretation (CBM-I):

The ambiguous scenarios paradigm was used as a way of training participants to make benign interpretations of potentially pain-related situations (Jones & Sharpe, 2014). Participants were presented with 30 ambiguous scenarios, each of which could be resolved to result in a painful or benign resolution, but all of which were unrelated to cancer. Each scenario was followed by a word fragment. They were also instructed to imagine themselves in these scenarios and were asked to solve this word fragment. In order to train participants not to make pain-related interpretations, all word fragments represented benign, rather than pain-related outcomes.

After each scenario, participants were asked a comprehension question about the scenario and were asked to indicate whether the question was related to the previous scenario ('Yes' or 'No'). Participants were then given 'correct' feedback when they endorsed a non-threatening, benign response (not pain-related). However, they were given 'incorrect'

feedback if they endorsed the pain-related response. This training task has been previously used in a sample of people chronic pain and the results indicated that compared to placebo, CBM-I resulted in reduced pain severity and pain interference, as well as reduced fear of pain and reinjury (Sharpe et al., 2022).

Both CBM-I versions (cancer and pain-specific) were matched in terms of time (15 minutes).

8.2.3.1.3 Placebo Condition

Participants in the control condition received the same stimuli as those in the cancer-specific CBM-I group (depending on whether they were living with or beyond breast or ovarian cancer diagnosis). However, in contrast to CBM-I condition, participants were given feedback randomly on each trial as to whether or not they were correct. Overall, 50% of the trials reinforced a benign association, while 50% reinforced a threat interpretation. As such, the training does not influence interpretation bias, because benign and cancer-specific associations are reinforced with equal frequency. Importantly, the placebo condition controls for the impact of the stimuli and all other aspects of the training.

Refer to Tables 8.1 and 8.2 for examples. Also refer to Appendix I.

Table 8.1: Examples of scenarios used in cancer-specific CBMI version

Threat word	Non-threat word	Ambiguous sentence
Cancer	Need new bra	Your breasts look uneven since surgery.
Cancer	Period	Your nipple feels sore.
Cancer recurrence	Gas	Your abdomen seems bloated for a few hours.
Cancer recurrence	Infection	You use your dilator and see a pink tinge.

Table 8.2: Example of stimuli used in pain-specific CBMI version

Scenario
You find that your eyes are sore and swollen. They are so puffy you can barely open them. This is because you have been cr_i_g
Comprehension question:
Did an allergic reaction cause your eyes to swell? Yes No

8.2.3.2 Outcome Measures:

Co-primary outcome measures

8.2.3.2.1 *Fear of Cancer Recurrence Inventory (FCRI, Simard & Savard, 2009):*

The FCRI severity subscale is a 9-item scale used to measure FCR. Each item is rated on a Likert scale ranging from '0' (never) to '4' (all the time). We used the cut-off score of 13 or higher to indicate at least moderate FCR, as this has been consistently used in the literature to identify individual for treatment (e.g. Butow et al., 2017). The Cronbach's alpha for the current sample was 0.79.

8.2.3.2.2 *Fear of Progression Questionnaire- Short form (FoP-Q-SF, Herschbach et al., 2005):*

We included the FOP-Q-SF, which is a 12-item scale to measure fear of progression, in light of data that FCR and FOP might measure related, but different phenomena (Coutts-Bain et al., 2022) Each question is scored between 1-5, with response options of never (1), rarely (2), sometimes (3), often (4), and very often (5). A score of 34 or higher has been previously used as a cut-off for moderately high FoP (Herschbach et al., 2010; Dinkel & Herschbach, 2018; Curran, Sharpe & Butow, 2021). The Cronbach alpha for this measure was 0.87.

Manipulation Check

8.2.3.2.3 *Interpretation bias (IB) assessment:*

Cancer-related interpretive bias was assessed through WSAP (Beard & Amir, 2009), with 12 trials of word-sentence pairings. However, no feedback was presented here as we measured the interpretation bias instead of providing a training. This was done through recording endorsement rates for threat and benign interpretations of ambiguous sentences. These were different to the sentences used in CBM-I cancer-specific and placebo trainings and were specific to cancer type. Each trial began with a fixation cross of 500 ms, followed by a word which was presented on screen for 750 ms and which was then followed by an ambiguous sentence. Finally, participants were then asked to indicate whether the word and sentence were related. For example, “Your doctor suggests genetic testing”, if participant chooses the word “standard practice”, this will be a ‘benign endorsement’ whereas, choosing word “high risk” is considered as ‘threat endorsement’. The rate of threat endorsement (percentage of threat responses) and rate of benign endorsement were calculated to measure interpretation bias. This task was administered at post-treatment but not follow-up, as it was

intended to determine whether the targeted interpretation bias had been induced by the training. Furthermore, the interpretation bias tasks are known to have practice effects over time (Hirsch et al., 2016). This task has been successfully used previously in a sample of breast cancer patients (Lichtenthal et al., 2017).

Secondary outcome measures

8.2.3.2.4 *Symptom checklist:*

The physical symptoms inventory (Spector & Jex, 1998) is an 18-item questionnaire where participants indicate whether or not they experience each symptom (during the past 30 days) and if they did, whether they had sought medical attention for it. Symptoms are scored as absent (0), present (1) and/or needed to seek medical attention (2) and summed. The internal consistency for this checklist was $\alpha = 0.9$.

8.2.3.2.5 *Brief Pain inventory (intensity and severity subscales)*

This measure was used to assess the severity of pain (intensity subscale) and its impact on daily functioning (interference subscale). It comprises of 11 items in total and were scored on 11-point Likert scale (where '0' indicates no pain intensity or interference and '10' indicates worst imaginable pain). Both intensity and interference subscales were found to have excellent internal consistency with $\alpha = 0.86$ and 0.92 respectively.

8.2.3.2.6 *Anxiety and Depression*

Participants' depression and anxiety was measured using the Hospital Anxiety and Depression scale (HADS). The questionnaire comprises of 7 items for anxiety and 7 items for depression. All items are scored on 4-point Likert scale, ranging from 0 to 3 (e.g., 'not at all' to 'nearly all of the time'). The Cronbach alphas for Anxiety and Depression scales were 0.83 and 0.85 respectively.

8.2.3.2.7 *Quality of life (QoL)*

The European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30) was used to measure QoL. It has 30 items comprising distinct scales (*functioning*, *symptom* and *global QoL*), each representing a different aspect of QoL and responses ranged from 1 to 4 ('not at all' to 'very much'). Higher raw scores on this scale indicates a lower QoL. The Cronbach alpha for this scale was 0.84.

8.2.4 Data Analysis

Lichtenthal et al (2017) study obtained an effect size of Hedge's g = 0.25 between change in worries about cancer between the intervention and control condition over time (pre-post treatment). Assuming a similar effect size, we needed at least 165 participants to have 80% power to detect this between groups difference, based on G*Power calculations (Faul et al., 2009).

We initially conducted Student's t-tests in order to assess the baseline differences between completers and drop-outs. Linear mixed model regression (LMMR) analyses were performed in order to assess the degree to which CBM-I training impacted the co-primary outcomes of FCR and FoP as well as the secondary outcomes (pain intensity, pain interference, anxiety, depression and QoL) in relation to time (pre-treatment; post-treatment; follow-up) and treatment groups (cancer-specific CBM-I vs pain-related CBM-I vs placebo) and their interactions. Data were analysed according to intention-to-treat principle and LMMR was used to impute the missing data.

Finally, to assess whether interpretation bias (in terms of proportion of endorsing threat interpretations) played a mediating role between intervention group and symptoms at post-treatment controlling for baseline levels of FCR, we conducted a mediation analysis using model 4 of the Hayes (2013) PROCESS macro in SPSS (version 26). In this model, we

entered group as the independent variable, induced interpretation bias as the mediator and FCR at follow-up as the dependent variable (controlling for baseline FCR). The mediation analysis was based on those who completed assessments.

8.3. Results

8.3.1 Participant characteristics:

Two hundred and forty women with breast or ovarian cancer accessed the link for the study and were assessed for eligibility. Sixty-one participants did not meet the inclusion criteria, leaving 180 participants who were eligible to the study. Five eligible participants declined to participate, and 1 participant consented, but did not commence the assessment. Hence, 174 women completed baseline and were randomized into one of the three groups: cancer-specific CBM-I (N = 60), pain-specific CBM-I (n = 58) or placebo (n = 56). We had high completion rates at post-treatment assessments [Cancer-specific CBM-I (n = 48; 80%) and pain-specific CBM-I (n = 47; 81%)] and 83% (n = 47) in placebo group. Similarly, just less than three quarters (74%) of the sample completed follow-up (cancer-specific CBM-I; n = 46; 77%; pain-related CBM-I, n = 41; 71%; and placebo n = 41; 73%) (see Figure 8.1 for CONSORT diagram).

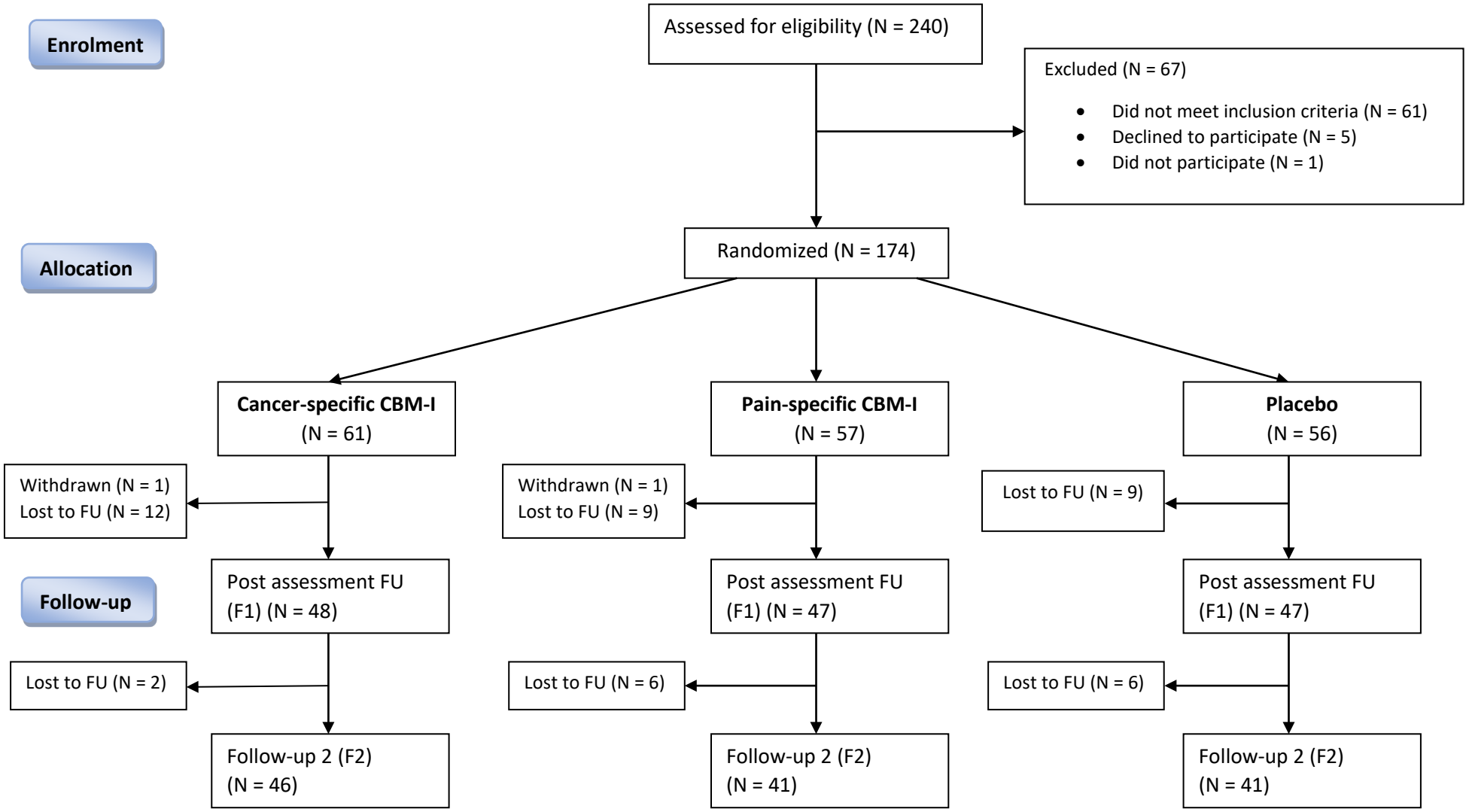


Figure 8.1. CONSORT diagram. FU: Follow-up

We compared completers and non-completers in terms of demographic variables. Analysis indicated that there was a significant difference between both of these groups in terms of age [t (221) = 2.03, p = .04]. That is, women who completed the study were older than women who did not complete. However, no differences were observed for education level, employment, cancer recurrence, cancer stage and cancer status. However, in terms of outcome measures, women who completed the treatment had higher FCR (t= 12.41, p < .001) and FoP (t= 13.5, p < .001) compared to women who did not complete the study. Women who completed also reported more physical symptoms as compared to non-completers (t= -2.94, p = .004). No significant differences existed in other measures i.e., pain intensity, pain interference, anxiety, depression and QoL. See Table 8.3 for participant demographic characteristics.

Table 8.3: Demographic and clinical characteristics of the sample (N= 174)

Variable	Mean (SD)
Age	58.49 (10.33)
	Frequency (percentage)
Cancer Type	
Breast cancer	115 (66.1)
Ovarian cancer	59 (33.9)
Marital status	
Married	102 (58.6)
Widowed	6 (3.4)
Divorced	22 (12.6)
Separated	3 (1.7)
Never married	24 (13.8)
De Facto	17 (9.8)
Children	
None	52 (29.9)
One	18 (10.3)
Two	62 (35.6)
More than two	42 (24.1)
Education level	
Did not complete high school	10 (5.7)
Completed high school	51 (29.3)
Undergraduate degree at university	58 (33.3)
Postgraduate degree at university	55 (31.6)
Employment status	
Currently employed	81 (46.6)
Currently unemployed	93 (53.4)
Stage at diagnosis	
Stage 1	41 (23.6)
Stage 2	46 (26.4)
Stage 3	56 (32.2)
Stage 4	18 (10.3)
Not known	13 (7.5)
Current cancer status	
Currently on treatment	63 (36.2)
In remission	95 (54.6)
Other	16 (9.2)

Cancer recurrence	
Yes	41 (23.6)
No	133 (76.4)
Cancer Surgery	
Yes	168 (96.6)
No	6 (3.4)
Treatment type (also include participants who received more than one treatment type)	
Radiotherapy	49 (28.2)
Chemotherapy	70 (40.2)
Hormonal therapy	48 ((27.6)
Other	43 (24.7)
No treatment	0 (0)

8.3.2. Co-primary outcome measures:

8.3.2.1 FCR:

The linear mixed model regression for the primary outcome of FCR demonstrated that there was a main effect for time, whereby overall participants in the study improved. There was a main effect for group, contrasts demonstrated that the main effect for group was due to the fact that overall, the participants in the cancer-specific CBM-I group had lower FCR scores than those in the placebo ($t = -7.781$, $p < 0.0005$). FCR scores were significantly lower in the pain-related CBM-I group than in the placebo ($t = -5.361$, $p < 0.0005$). These differences were further qualified by a significant interaction effect between time and group, which favored the two CBM-I groups over placebo ($F = 17.19$, $p < 0.0005$). The difference in change over time between pre- and post-treatment was significant for both of the CBM-I groups compared to placebo (cancer-specific: $t = 7.027$, $p < 0.0005$; pain-specific: $t = 4.602$, $p < 0.0005$). Likewise, this difference was maintained at

follow-up 2, where both CBM-I groups (cancer-specific: $t = 7.90$, $p < 0.0005$; pain-specific: $t = 5.20$, $p < 0.0005$) significantly had lower FCR scores than placebo. (See Figure 8.2).

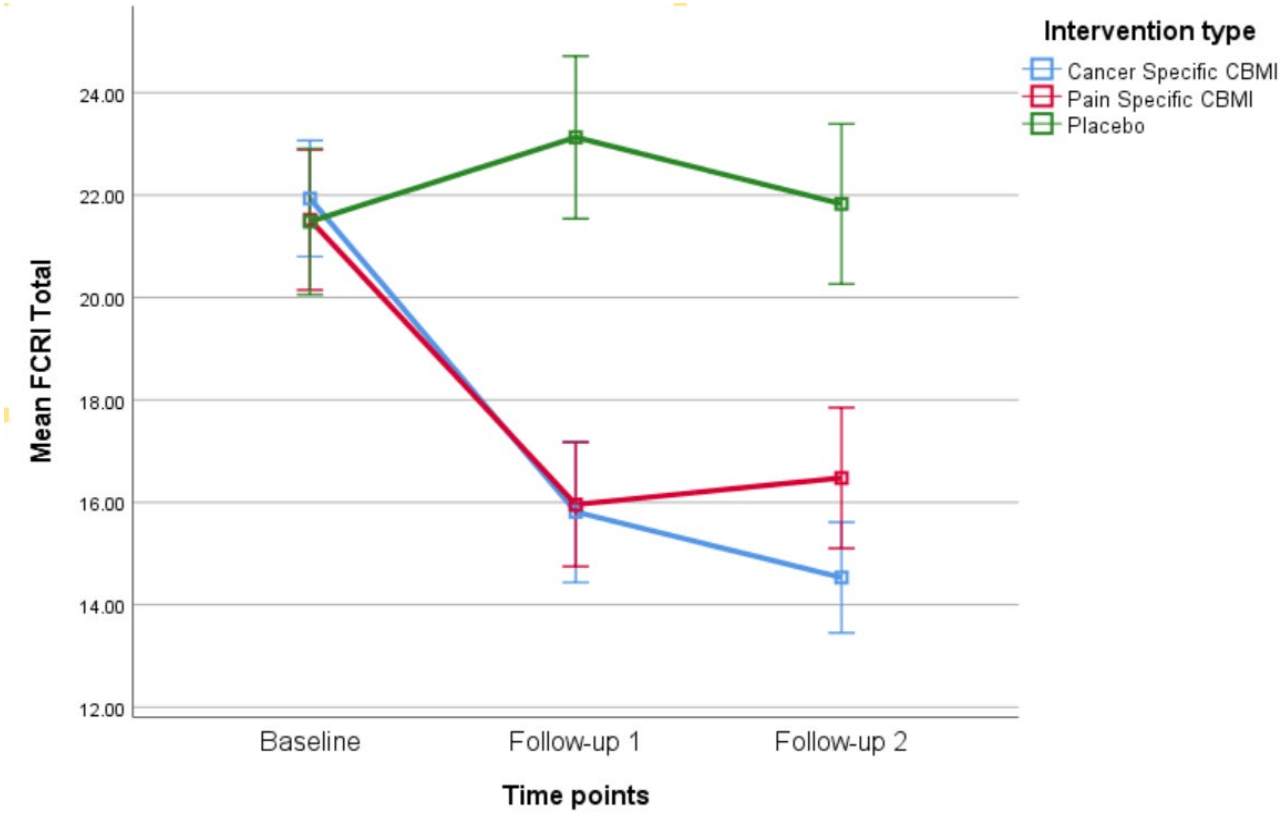


Figure 8.2: Changes in FCR scores over time

1: Baseline

2: Post-intervention (F1) (after 14 days)

3: Follow-up 2 (after 28 days)

FCR: Fear of cancer recurrence

8.3.2.2. FoP:

Likewise, for FoP there was a main effect of time and group. That is, the participants in the cancer-specific CBM-I group had lower FoP scores than those in the placebo ($t = -9.952$, $p < 0.0005$). Likewise, FoP scores were significantly lower in the pain-related CBM-I group than in the placebo ($t = -5.386$, $p < 0.0005$). These differences were further qualified by a significant interaction effect between time and group, which favored the two CBM-I groups compared to placebo ($F = 15.03$, $p < 0.0005$). The difference in change over time between pre- and post-treatment was significant for both of the CBM-I groups compared to placebo (cancer-specific: $t = 7.136$, $p < 0.0005$; pain-related: $t = 3.934$, $p < 0.0005$). Similar changes were also observed at follow-up, favoring both intervention types (cancer-specific: $t = 10.39$, $p < 0.0005$; pain-specific: $t = 4.97$, $p < 0.0005$) than placebo. Refer to Figure 8.3.

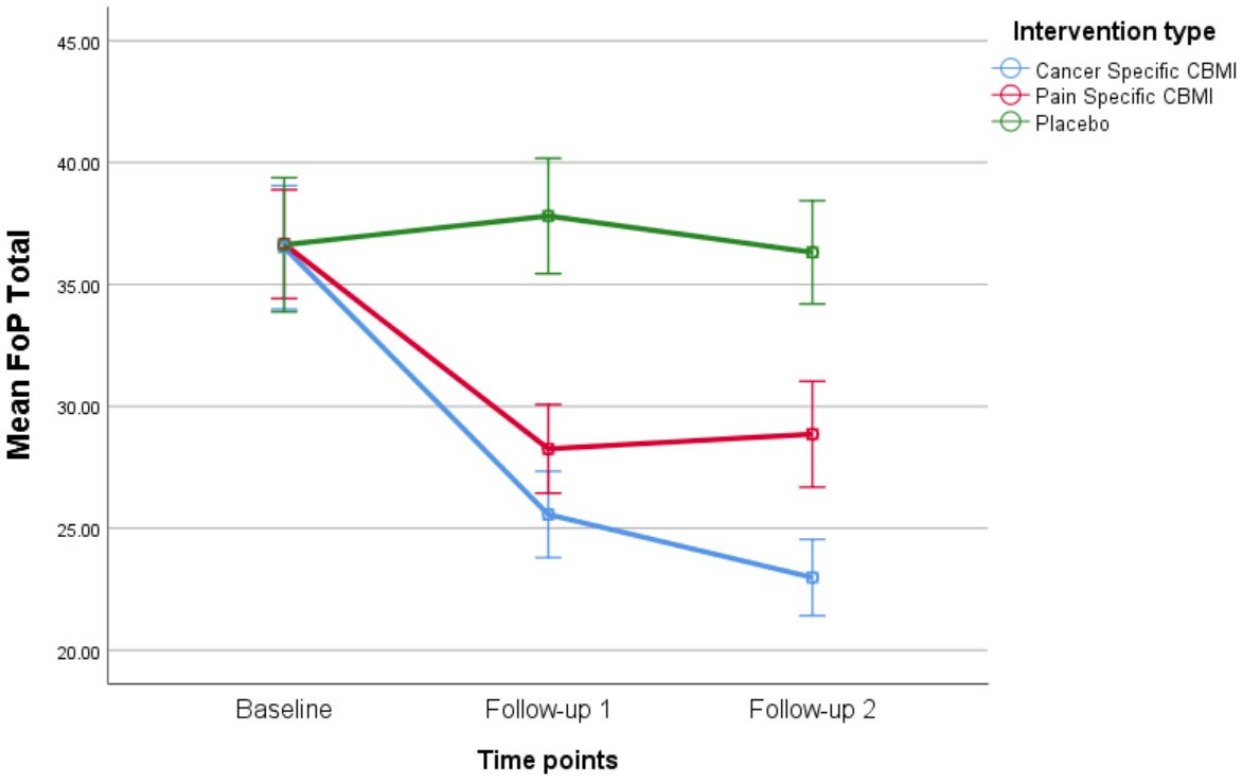


Figure 8.3: Changes in FoP scores over time

1: Baseline

2: Post-intervention (F1) (after 14 days)

3: Follow-up 2 (after 28 days)

FoP: Fear of progression

8.3.3 Manipulation Check

8.3.3.1 Interpretation bias

We conducted a 3 (treatment group) x 2 (valence; threat or benign) between subjects ANOVA to examine the differences in terms of interpretation bias for people who completed the

training. Participants who were allocated to both CBM-I versions [cancer-specific (M = 79.85, SD = 12.01) and pain-specific (M = 69.5, SD = 16.23)] had higher rates of benign responses as compared to those who were allocated to placebo group (M = 46.62, SD = 17.86) at post intervention ($F_{(2, 139)} = 56.68$, $p < 0.0005$). Likewise, both CBM-I groups [cancer-specific (M = 20.14, SD = 12.01) and pain-specific (M = 30.5, SD = 16.23)] made fewer rates of threatening responses than those allocated to placebo (M = 53.37, SD = 17.86) following the intervention phase.

8.3.4 Secondary outcomes:

Analyses demonstrated the main overall effect of group and time such that both CBM-I groups significantly reduced pain intensity as compared to placebo group [cancer-specific CBM-I: $t = 4.485$, $p < 0.0005$; pain-related CBM-I: $t = 5.508$, $p < 0.0005$). As for FCR and FOP, the LMMR analyses revealed a significant effect of time by group, favoring both CBM-I groups for pain intensity ($F = 6.14$, $p < 0.0005$). That is, pain intensity on post-treatment was reduced for both CBM-I groups vs placebo (Cancer-specific: $t = 3.113$, $p = .002$; Pain-related: $t = 3.862$, $p < 0.0005$). This was further maintained at follow-up.

For pain interference, similar results were found. There was also an overall main effect of group and time favoring CBM-I training over placebo (Cancer-specific CBM-I: $t = -5.436$, $p < 0.0005$; Pain-related CBM-I: $t = -4.759$, $p < 0.0005$). There was also a significant interaction of time by group ($F = 5.223$, $p = .001$). Participants in both cancer-specific ($t = 2.652$, $p = .009$) and pain-related ($t = 3.116$, $p = .002$) CBM-I had reductions in interference scores at post-treatment when compared to placebo. Similar effects were observed at follow-up. Refer to Figure 8.4 and 8.5 respectively for change in pain intensity and interference scores over time.

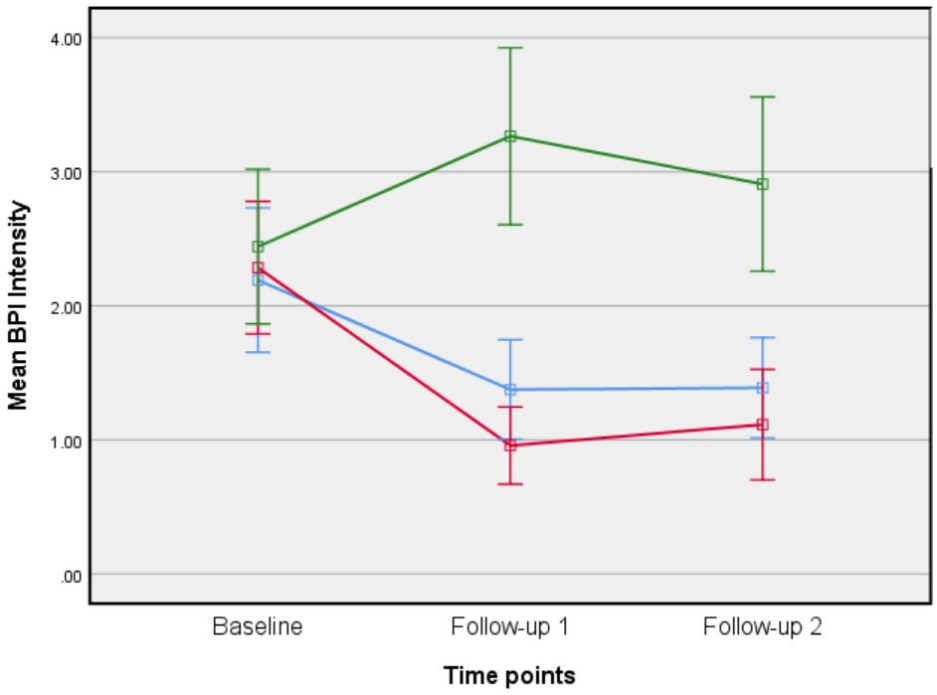


Figure 8.4: Changes in pain intensity scores over time

1: Baseline

2: Post-intervention (F1) (after 14 days)

3: Follow-up 2 (after 28 days)

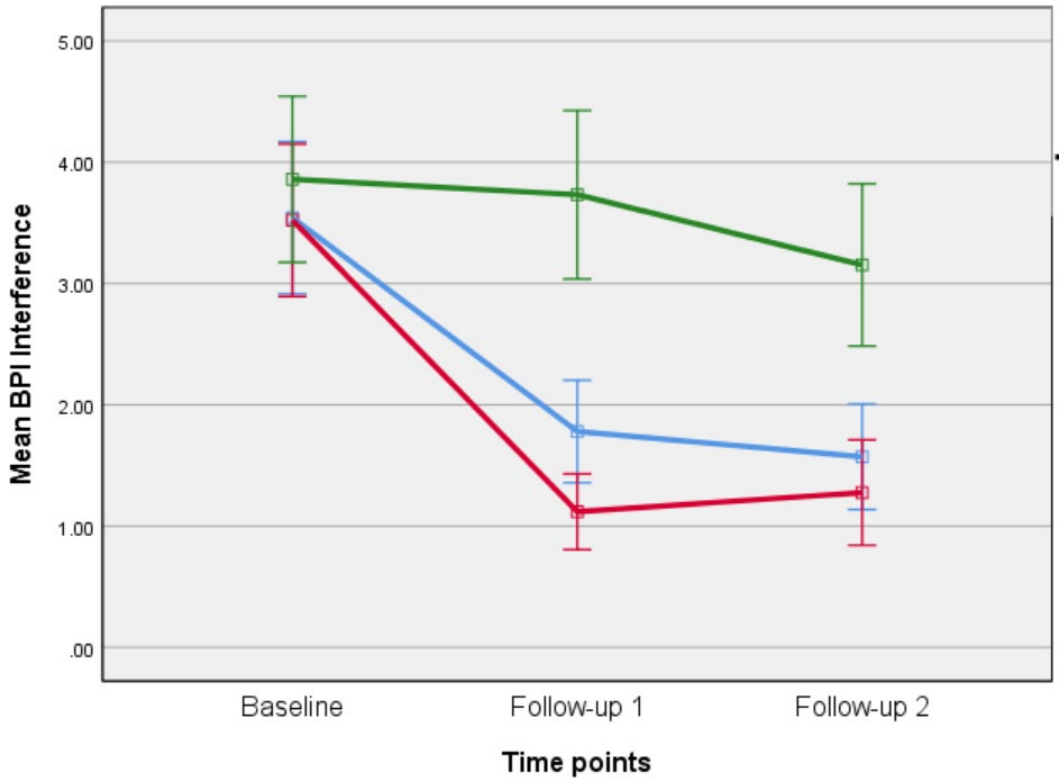


Figure 8.5: Changes in pain interference scores over time

1: Baseline

2: Post-intervention (F1) (after 14 days)

3: Follow-up 2 (after 28 days)

None of the remaining secondary outcomes were significantly impacted by CBM-I training compared to placebo. For physical symptoms, data revealed no significant overall main effect for group or time. There was also no significant interaction effect of time by group ($F = 1.198$, $p = .111$). For anxiety, our LMMR indicated that there were no overall significant main effects of group

or time, nor a time by group interaction (F = .416, p = .79). Similar results were obtained for depression and quality of life, with the interaction effect not being significant (depression: F = .301, p = .87; quality of life: F = .659, p = .62). That is, neither CBM-I condition produced a significant change in physical symptoms, anxiety, depression or quality of life over time.

8.3.5. Mediation Analyses

To investigate if the induced interpretation bias mediated the relationship between intervention group and post-treatment FCR levels, controlling for pre-treatment FCR, a meditation analysis was performed. First, the results of the regression analysis showed that the type of intervention was a significant predictor of interpretation bias [b = 16.59, $t_{(139)}$ = 10.22, p < .001]. Similarly, intervention type was also a significant predictor of FCR scores at post-treatment [b = 3.367, $t_{(138)}$ = 5.067, p < .001].

However, the results of indirect effects based on 5000 bootstrap samples showed that the indirect relationship between type of intervention and FCR levels at post-treatment was not significant [Indirect; a*b = .291, SE = .41, 95%CI (-.525, 1.112)]. In other words, interpretation bias did not mediate the relationship between intervention group and FCR.

8.4. Discussion:

The present study investigated the efficacy of two types of CBM-I interventions (cancer-specific versus pain-related) compared to placebo for people with breast or ovarian cancer. Both CBM-I training programs were associated with changes in how people interpreted ambiguous information. CBM-I demonstrated significantly greater improvements in both co-primary outcomes,

FCR and FoP. These significant improvements were found after the intervention and were maintained two weeks later (28 days). There were no differences in efficacy between the cancer-specific and pain-related CBM-I training programs compared to placebo. Furthermore, both versions of CBM-I were also effective in reducing pain intensity and interference scores at post-treatment and follow-up. However, no other significant effects of CBM-I were observed for other secondary outcomes, and interpretation bias did not mediate the primary treatment effects.

One could argue that this is a relatively small trial of a brief and minimal intervention in which short-term benefits were found without any evidence of long-standing change. The study employed a convenience sample of people with two types of cancer only and therefore how generalizable the study might be is open to question. However, we would disagree for a number of reasons. Firstly, the degree of FCR reported by participants in this study is in the severe range, on average (cut-off FCRI ≥ 21). Over the two-week treatment period, FCR reduces by, on average, 7 points, which corresponds to a very large effect size (Cohen's $d \approx 1$). Changes of this size are larger than those typically found in the FCR literature, even with face-to-face interventions (Cohen's d = 0.38, in Tauber et al., 2019 meta-analysis). Hence, these results are not trivial. Further, we specifically chose two cancers which varied in their prognosis, and CBM was efficacious for both. Moreover, the fact that the more general pain-related CBM-I protocol resulted in large changes means that there is no reason to think this would not generalize to other cancers. Finally, this was a fully automated minimal intervention which required no therapist time, and only 1 hour over 2 weeks of time from the participants to gain benefit. Even if the benefits only last for 2 weeks, there are many times (such as anniversaries, when waiting for scans), when a brief intervention might make a considerable difference to people living with or beyond cancer. Hence, we would argue that

these results mark an important potential minimal intervention that could form part of a stepped care model of psychotherapy for FCR.

The previous chapter proposed model of stepped care for the management of FCR. We proposed that minimal interventions that would have few costs associated with therapist time and could be easily delivered online or through an app would be a good step for those with moderate to severe FCR. However, we pointed out that as yet there are no minimal interventions that have been shown to be efficacious for FCR. This was also the conclusion of a recently published scoping review (Cincidda et al., 2022). Therefore, the demonstrated efficacy of two versions of CBM-I is the first demonstration of a remote intervention with large effects on FCR. It is also important to note that the CBM programs evaluated in this study were also efficacious for pain severity and pain interference. This is, in and of itself, an important finding. Meta-analyses confirm that persistent pain is a problem for nearly 40% of people treated with curative intent, and higher still during treatment (55%) or in advanced disease (66%) (Van Den Beuken-Van et al., 2016). Therefore, if CBM-I can have demonstrated efficacy in improving pain severity and the interference associated with persistent pain, then CBM-I may have broader applications for people living with and beyond cancer.

These results are important and are consistent with the Cancer Threat Interpretation model. That model suggests that, in the presence of physical symptoms – particularly pain – threatening interpretations contribute to severe FCR. Hence, based on that theory, an intervention that modifies these interpretations should reduce FCR. Further, models of chronic pain also indicate that the interpretation of pain as threatening also contributes to pain severity and interference (Vlaeyen et al., 2016; Todd et al., 2015). Indeed, a recent study from our group confirmed the efficacy of the

pain-related CBM-I protocol that was used in this study in a sample of 288 people with chronic pain (Sharpe et al., 2022). It is noteworthy that the effect size in the current study was large at follow-up (Cohen's d = 1.04 vs 0.39 for pain severity).

It was pleasing in this study that we were able to show that CBM induced an interpretation bias across both CBM-I groups but not in the placebo. However, it would be ideal to see that this induced bias mediated the relationship between intervention group and FCR severity, but this was not the case. Hence, we can say that CBM-I did induce an interpretation bias, that it did change FCR and pain outcomes, but we cannot definitively conclude that the change in interpretation bias was the treatment mechanism. A commentary on CBM-I research by MacLeod et al (2009) emphasized the importance of testing for mediation to better understand the mechanisms of treatment efficacy. Despite this, relatively few studies report mediation analysis. A meta-analysis by Cristea and colleagues (2015) assessing the efficacy of CBM in anxiety and depression found that only 11 out of 49 RCTs had conducted a formal mediation analysis and only 4 of these studies confirmed mediation.

8.4.1 Limitations

The findings from the current study should be interpreted in light of the following limitations. Firstly, there has been a debate in the literature about the face validity of these cognitive tasks related to interpretation bias (Beard, 2011). Many authors advocate for consumer input and adaptation of stimuli to different populations (see Hughes et al., 2016). In our study, the cancer-specific CBM-I adopted two sets of stimuli that had been extensively co-developed with people with the two cancers included in this study so that the stimuli could be personalized to the cancer (i.e. ovarian versus breast cancer). The other CBM-I condition, however, focused on the tendency

to interpret ambiguous scenarios as likely to result in pain. This CBM-I training was developed in the laboratory (Jones & Sharpe, 2014) and used pragmatically in this trial. It is encouraging that there were few differences between these two training paradigms. Secondly, we chose two cancers (to allow the training to be personalized). Breast and ovarian cancer differ in respect of prognosis, but both predominantly affect women. Therefore, how these findings might generalize to other cancers, particularly those that predominantly affect men, such as prostrate or testicular cancer, is unknown. The fact that the pain-related CBM-I was as effective as the cancer-specific CBM-I suggests it is likely that CBM might be beneficial in other cancers, but this is an empirical question. Future research could explore this question. Finally, as the study duration was only 28 days, it is still not clear whether these effects are long lasting. However, if 1 hour of training every two weeks could reduce FCR and pain outcomes for the next two weeks, this would nevertheless be clinically meaningful. Future research is needed to assess the long-term outcomes from this intervention and to determine the optimal number of treatment sessions, as well as who might benefit most from intervention.

8.4.2 Clinical Implications

This was the first study to compare the efficacy of two types of CBM-I intervention for reducing FCR in people with breast or ovarian cancer. The strength of this study was that CBM-I was administered entirely online and involved low costs of delivery. This makes the intervention highly scalable and easier for dissemination which could be home-delivered or developed into an app. Hence, CBM-I could form an early step in a much needed stepped-care model to meet the growing number of cancer survivors who fear disease recurrence or progression (Pradhan et al., 2021). This is particularly the case since it was effective both with women with current disease and

those who had been treated with curative intent in our study. Furthermore, CBM-I could be beneficial at particular timepoints to reduce cancer-specific anxiety, such as when scan appointments are due (i.e., to treat 'scanxiety') (Bui et al., 2022). Lastly, the retention rates of this study were fairly high that is, more than 80% and 70% of enrolled participants respectively completed post-treatment assessments and follow-up, which bodes well for implementation.

8.5. Conclusion

In conclusion, as compared to placebo, we found two CBM-I interventions were efficacious in reducing fear of cancer recurrence and progression. These interventions, one of which was cancer-specific and the other which focused on pain-related biases, were equally effective. CBM-I was also effective in reducing the pain-related outcomes of pain intensity and interference. These effects lasted for up to two weeks following intervention and required only an hour of participants' time to achieve these benefits. As FCR remains one of the highest unmet psychosocial needs for those living with and beyond cancers, future research should confirm these benefits with other cancer types. Given that CBM-I was delivered entirely remotely, future research could adapt this online program to a more sophisticated, engaging and smartphone friendly intervention that could be used by people living with and beyond cancer (Sun et al., 2019).

Chapter 9: General Discussion

9.1 Overview of the main findings

In recognition of the growing interest in the role of information processing styles in the development of fear of cancer recurrence/progression (FCR/P), the aim of this thesis was to explore the role of cognitive biases in relation to FCR/P. Specifically, the initial aim was to examine attentional, interpretation and memory biases in cancer patients, and to determine whether they contribute to clinical levels of FCR/P. Hence, the research questions were: (1) Are cognitive biases common in people with cancer? (2) Are these biases associated with FCR/P? And in what ways? And (3) Are we able to harness these processes to reduce FCR/P?

The starting point to answer these questions was a scoping review and meta-analysis described in Chapter 3. The protocol (see Appendix A) focused on biases in attention, interpretation and memory and their role in the context of cancer and its relationship to FCR/P. The review found that there was a small literature that confirmed that people with cancer have attentional biases that are greater than people without cancer, and that distress was associated with attentional biases. However, the review also determined that there were insufficient studies of either interpretation biases or memory biases to be able to include in the review. While the two studies of memory biases showed no evidence of biases in people with cancer that differed from people without cancer, the two studies of interpretation bias both supported a potentially important role of interpretation biases in cancer-related distress (Lam et al., 2018) and FCR/P (Lichtenthal et al., 2017). Therefore, the remainder of the thesis aimed to fill this identified gap in the literature and examine the role of interpretation biases specifically in relation to FCR/P.

The aim of the studies presented in Chapters 4 and 5 was to determine whether people with cancer interpret ambiguous words as health-related more often than people without cancer; and whether this style of interpretation was related to FCR/P in theoretically predicted ways. The empirical studies assessed the role of interpretation bias in a sample of ovarian (Chapter 4) and breast cancer survivors (Chapter 5) and the relationship of interpretation biases to FCR/P. We found evidence that people with ovarian cancer are more likely to interpret ambiguous words as health-related than people without cancer, with a large effect size (*Cohen's d* = 1.28). Further, the interpretation bias was larger for people with clinically significant levels of FCR/P compared to those in the non-clinical range. The relationship between interpreting ambiguous information as health-related and FCR/P was replicated in Chapter 5 in people with breast cancer.

The finding that interpretation bias is associated with FCR/P is consistent with predictions from the Cancer Threat Interpretation model (Heathcote & Eccleston, 2017). However, that model also predicts that interpretation bias will moderate the relationship between pain and FCR/P. Hence, this hypothesis was tested in both studies (Chapter 4 and 5). This hypothesis was supported in the breast cancer sample but was not supported in ovarian cancer sample. That is, interpretation bias did not moderate the relationship between fear of progression and pain (or physical symptoms) in ovarian cancer. However, in breast cancer, interpretation bias did moderate the relationship between pain and FCR, but not fear of progression. Analyses suggested that for people with ovarian cancer, the physical symptoms most strongly associated with FCR/P were gastrointestinal symptoms and fatigue, which are also the most common sign of recurrence. Hence, taken together, these results suggest that symptoms that could potentially indicate a recurrence are unique predictors of FCR, in particular, and to a lesser degree fear of progression.

These findings – particularly in ovarian cancer – indicated that information about the nature of symptoms and fears might be helpful in reducing FCR/P. Butow and colleagues (2018) have argued that clear information about the risk of recurrence, the signs of recurrence, and when to consult a doctor could help to prevent FCR/P becoming clinically significant. One common, and parsimonious method, often used in cancer, is the use of psychoeducational booklets, since these booklets are thought to address the informational needs (Lukens & McFarlane, 2004; Cuthbert et al., 2019). For this purpose, the efficacy and acceptability of a booklet for people with ovarian cancer was examined (Chapter 6). This booklet was developed by Ovarian Cancer Australia, and researchers (Phyllis Butow and Ben Smith). The booklet provided a detailed overview on the nature of FCR/P and its persistence over time. It also suggested 'day-to-day' strategies and techniques that might help survivors to manage this fear based on the existing evidence-based approaches (Butow et al., 2017), and it gave an indication of common symptoms, likelihood of recurrence and how to manage symptoms. The study assessed the FCR/P levels at baseline and one week after reading the booklet. Although this was a basic pre- to post-test study, the results failed to provide any benefit to participants. Although the booklet was acceptable and participants reported high levels of satisfaction, the booklet was clearly insufficient to reduce FCR/P. Given the large number of survivors in Australia alone, and how common moderate levels of FCR/P are (58.8% from a recent meta-analysis by Luigjes-Huizer et al., 2022), there is a pressing need for brief interventions for FCR/P.

In a recent meta-analysis, Tauber et al (2019) found that available treatments are effective for reducing FCR with a small effect size (Hedge's g = 0.33). However, most available interventions are intensive, delivered face-to-face and require specialised therapeutic skills (e.g., ConquerFear; Butow et al., 2017; Herschbach et al., 2010; AFTER intervention by Humphris &

Rogers, 2012). With the large number of cancer survivors that continue to increase with improved survival rates, there is a need for models of care that are accessible to the 20% of people who have had cancer who experience severe FCR/P. There has been no attempt to synthesize the evidence for brief or remotely delivered interventions. Hence, Chapter 7 aimed to examine the currently available literature at all levels of care, with a view to proposing a potential stepped care model for FCR/P. The review found that, although there is evidence for face-to-face intensive psychological intervention (Tauber et al., 2019), emerging evidence for nurse-led approaches (Reb and colleagues, 2020), and preliminary evidence for stepped care approach (FEARLESS; Lynch et al., 2020), there was not a single controlled study that had found a brief or remotely delivered intervention to reduce FCR/P. Therefore, while Chapter 7 advocated for a stepped care approach, it identified the urgent need to develop and evaluate remotely administered brief interventions to reduce FCR/P. The narrative review in Chapter 7, identified two candidate treatments that had shown some promise in that they found that a remotely delivered intervention was effective on at least one subscale of an FCR/P intervention, even though they were not effective on the full scale. These two interventions were cognitive bias modification for interpretation (CBM-I) (Lichtenthal et al., 2017) and a gratitude intervention (Otto et al., 2016).

Given the results of Chapters 4 and 5 that confirmed a strong association between interpretation bias and FCR/P, the final study (Chapter 8) aimed to test two different versions of cognitive bias modification for interpretation (CBM-I): one focusing on encouraging people to interpret ambiguous scenarios as not being painful, and the other focusing specifically on cancer-related scenarios that were personalised to either breast or ovarian cancer. One hundred and seventy-seven individuals with either breast or ovarian cancer were randomized in a double-blind randomized controlled trial to receive either pain-related CBM, cancer-specific CBM or placebo.

The results showed that both versions of CBM were efficacious in reducing FCR and fear of progression (the co-primary outcomes) compared to the placebo with large effect sizes. Further, the CBM groups also showed large reductions in pain severity and pain interference. Other secondary outcomes (such as depression and anxiety) were not improved. These results were maintained two weeks later.

9.2. Methodological and Conceptual Considerations

Methodological limitations of each study have been discussed in detail in each chapter previously. However, there are some over-arching methodological considerations to this area of research that warrant consideration before the major findings are considered in further detail.

9.2.1

Conceptual issues in fear of cancer recurrence or progression

As highlighted in previous chapters, the consensus definition of FCR is "fear, worry or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016, p. 3267). This definition conflates FCR with fear of progression (FoP). That is, the prevailing definition suggest that FCR and FoP are part of the same construct. As a result, FCR/P research has used the constructs of fear or recurrence and fear of progression interchangeably. Nevertheless, most theoretical accounts about the development of FCR have been developed based on a literature that has typically included participants with disease-free, early-stage cancer survivors who have been treated with curative intent (Simonelli et al., 2017; Fardell et al., 2016). Similarly, the majority

of interventions have likewise targeted early stage, good prognosis cancers who currently have no evidence of disease (Tauber et al., 2019; Butow et al., 2019, 2017). Therefore, whether the same theories apply to people with current disease who worry about progression has not been widely addressed, and therefore whether interventions are equally efficacious for groups with advanced disease is unknown.

Conceptually, one would expect that FCR was more relevant to people treated with curative intent who currently have no evidence of disease, as it is understandable that their fear would be of a recurrence of their disease. In contrast, FoP might be expected to be of particular concern to those whose cancer has not been treated with curative intent and who have advanced disease that has metastasized (Greene et al., 2002). Based on this common-sense approach, the studies involving people with a diagnosis of ovarian cancer (Chapter 4 and 6) administered FoP-Q-SF to measure FCR/P. Ovarian cancer is a poor prognosis cancer, with fewer than 50% of individuals diagnosed with ovarian cancer surviving more than five years. In our first study, more than 60% of participants had either Stage III or Stage IV cancer, and the majority had evidence of some disease at the point of recruitment. The FoP-Q-SF was specifically developed for people with advanced cancers (Mehnert et al, 2006) and, with the FCRI, was one of the two favoured instruments in a systematic review of FCR/P measures (Thewes et al., 2012). For the breast cancer study, we included both FCR-I severity subscale and FoP-Q-SF (Chapter 5). Interestingly, our results showed that interpretation bias moderated the relationship between pain and FCR but not pain and FoP. This result was surprising based upon the consensus definition that considers FCR and FoP conceptually overlapping fears.

However, a recent study by our team (Coutts-Bain et al, 2022) (See Appendix J, for published manuscript) explicitly tested the assumption that FCR and FoP are the same construct. This assumption was tested in a large sample (n = 311) of people with breast or ovarian cancer who were administered both the FCR-I and Fear of Progression Questionnaire. The results of the factor analysis revealed that FCR and FoP did not load onto the same construct, but in contrast FCR and FoP loaded onto two distinct, but related factors (Coutts-Bain et al., 2022). Furthermore, using structural equation modelling, it was found that while FCR and FoP were predicted by some common factors, FCR was more strongly associated with perceived risk of recurrence and body threat monitoring than FoP. However, there was no evidence that FoP was more relevant to those with active disease, nor that FCR was more relevant to people with breast compared to ovarian cancer. Indeed, higher levels of both FCR and FoP were evident in people with advanced disease compared to those without current evidence of disease.

Given these results, it is not clear whether the difference in the role of interpretation bias in the ovarian and breast samples is due to the different role of these biases in the two conditions, or because we only measured fear of progression and not FCR in the ovarian cancer sample. In hindsight, it would have been useful to have measured both constructs across all studies. The need to investigate the conceptual clarity of FCR and FoP has been highlighted as one of the research priorities in FCR/P in an Australian (Butow et al., 2019) and an international Delphi study (Shaw et al., 2021).

9.2.2

Measurement issues in fear of cancer recurrence and progression

We opted in the clinical trial of CBM to measure both fear of cancer recurrence and fear of progression and we relied on the two measures that were found to be the most valid and reliable in a systematic review of measurement instruments for FCR (Thewes et al., 2012), namely FCRI severity subscale and FoP-Q-SF. Both of these measures have 'clinical cut-offs' that determine whether individuals have clinically significant fears of recurrence or progression, although what constitutes clinical levels of FCR is still debated. Lebel et al (2016) suggested that clinical levels of FCR should have the following characteristics: "(1) high levels of preoccupation, worry, rumination, or intrusive thoughts; (2) maladaptive coping; (3) functional impairments; (4) excessive distress; and (5) difficulties making plans for the future" (p. 3265). Similarly, Mutsaers and colleagues (2020) conducted a Delphi study and identified the following criteria should be met to consider that an individual has a clinically significant level of FCR: "1) high levels of preoccupation; 2) high levels of worry; 3) that are persistent; and 4) hypervigilance to bodily symptoms" (p. 434). However, these characteristic features are yet to be validated in a clinical interview.

The degree to which currently available questionnaires identify clinically significant FCR is open to debate. Simard & Savard (2015) administered the severity subscale on FCR-I and a structured face-to-face interview adapting DSM-IV criteria to FCR. The authors found optimal sensitivity (88%) and specificity (75%) for clinical FCR at a cut-off score of 13. In our studies, using a cut-off of 13 resulted in the vast majority of the samples falling in the clinical range for FCR (more than 80%; Chapter 5). However, many researchers have argued that the cut-off of 13 is

too low to indicate clinically significant FCR. For example, Fardell and colleagues (2018) proposed a new cut-off score ≥22 based on an receiver operating characteristic analysis. However, this high cut-off on FCRI severity subscale has not been validated yet. Since there is, as yet, a consensus on the most appropriate cut-off point, we reported the results using both cut-offs in our study on breast cancer patients. In line with this, the breast cancer study (Study 3), adopted both of these cut-off scores for FCR (≥22 and ≥13) and interestingly the pattern of results were similar using both these cut-off scores. However, our clinical trial relied on people scoring ≥ 13, because as a minimal intervention we were particularly interested in the impact on moderate levels of FCR/P, not just severe levels.

9.2.3 Measuring Interpretation bias

One of the most important considerations in the field of cognitive bias research is the type of task used to assess a bias. Concerns have been expressed regarding the use of unreliable or invalid tasks, or tasks that have not been individually developed with people with lived experience specifically for the target population (Hughes et al., 2016). For example, for the measurement of attentional bias, the two most common tasks that are used are the Stroop paradigm and the dot-probe task. It has long been accepted that because the Stroop task has a single stimulus presented at one time that it is impossible to disentangle whether slowed responses are due to the stimuli capturing attention or causing a freezing response. The dot-probe task overcomes this problem, by including both a salient and neutral stimulus in each trial. However, the reliability of the dot-probe task has very poor reliability (Dear et al., 2011b; Schmukle, 2005), largely because it is based on difference scores between two highly correlated scores (i.e., reaction times) (See McNally, 2019 for

a comprehensive review). There have recently been some novel paradigms developed (e.g., dual probe task, by Grafton, Teng & MacLeod, 2021) that appear to measure attentional bias more reliably. However, these have yet to be used in the attentional bias and cancer literature. Future research should examine attentional biases, using more reliable tasks or more direct methods of assessment, e.g., eye-tracking.

In the case of interpretation bias, the issue with measuring this bias that is often raised is ensuring that the ambiguous stimuli are ecologically valid. In other words, it is worthwhile noting that previous research in cognitive bias area highlights the importance of tailoring stimuli to disorder or sample-specific concerns (Hughes, Chalder, Hirsch & Moss-Morris, 2017). One way to ensure this is to involve people with lived experience of the phenomena (in this case cancer) to develop stimuli that resonates with them and their experience. In the cancer literature, there were two paradigms only that had been used to examine interpretation biases in cancer. The first used cancer-specific stimuli using the Word Sentence Ambiguous Paradigm (WSAP), Lichtenthal and colleagues (2017) involved patients initially with breast cancer to develop these stimuli and have subsequently developed personalised stimuli for different cancer types, using participant feedback from cancer survivors (Lichtenthal, personal communication). In contrast, the other study by Lam et al. (2018) had used a much simpler task adapted from the pain literature, the ambiguous cues task (Pincus et al., 1994). This simple task has 14 words that can be interpreted in a pain or health-related way or a neutral way. The advantage of the ambiguous cues task is that it is very brief and easily administered. Lam et al. (2018) found that scores on this task predicted persistent distress in cancer survivors.

We initially opted to use the ambiguous cues task, that Lam and colleagues had previously used in people with breast cancer. In our first study (Chapter 4), we found that this task did correlate in expected ways both with symptom burden and FCR/P in sample of women with ovarian cancer, although it did not moderate the relationship. Importantly, the task demonstrated a substantial inter-rater reliability (k = 0.80) (Chapter 4). Hence, we continued to use this task in the breast cancer study, where again the predicted relationships were identified. Nevertheless, when it came to the CBM-I study (Chapter 8), we were unsure whether a generic, pain-related training would be sufficient to change FCR, despite the fact that the same task had previously been used and shown to be efficacious in people with chronic pain (Sharpe et al., 2022). Therefore, we developed a collaboration with Memorial Sloan Kettering Cancer Centre (MSKCC) and Harvard University, to use their iTHRIVE intervention. iTHRIVE is a cancer-specific CBM-I program that has been developed with input from people with lived experience of cancer and to be specific to the type of cancer (in this case, breast or ovarian). It is interesting that in the CBM-I study reported in Chapter 8, both the intervention developed with participant input and specific to the sample did not outperform the more generic training based on training people to make benign rather than pain-related interpretations. Future research should further explore the face validity of such tasks and it may also be beneficial to explore new ways in assessing such biases specifically in cancer population, where there is dearth of such evidence.

9.2.4

The choice of breast or ovarian cancer

Cancer can affect any of the major organs of the body and different types of cancers have very different characteristics in terms of the likelihood of curative treatment, risk of recurrence and longer term prognosis. It is well known that the literature in psycho-oncology has tended to focus on people with good prognosis cancers, such as breast or prostate cancer. In both these cancers, the five-year survival rates are over 90% (AIHW, 2021), and they are both common cancers affecting predominantly women or men, respectively. However, it is then unclear whether the results would apply to those with poorer prognosis cancers. This is particularly the case in an area such as fear of cancer recurrence, where in breast or prostate cancers recurrence rates are low, but in poorer prognosis cancers recurrence rates are higher. It seems intuitively likely that the base rate of recurrence would impact the degree to which people worry about their cancer returning.

For this reason, it was decided in this thesis to focus on two groups of participants: people with breast cancer and people with ovarian cancer. This was a strategic decision for a number of reasons: (1) much of the FCR literature has focused on breast cancer and so including breast cancer would allow us to determine whether our results were consistent with prior research; (2) breast cancer is also common with strong local advocacy groups that support research and hence, recruiting large samples is more feasible; (3) since breast cancer affects predominantly women, it was important to include a poorer prognosis cancer that also predominantly affected women and for this purpose, ovarian cancer was chosen. Hence, choosing two cancers which predominantly affect women, we were able to determine the relevance of interpretation bias to each of these groups.

As a result of this decision, however, the sample in each of our studies consisted entirely of women since both breast and ovarian cancer predominantly affect women and men were explicitly excluded. This raises an important empirical question in terms of individual differences such as gender. That is, while the choice of ovarian and breast cancer allowed us to explore the role of interpretation bias and symptom burden in two cancers that differed in prognosis and likelihood of recurrence, specifically, whether these findings are also applicable to men is not known. In the literature assessing cognitive biases in anxiety disorders, gender has rarely been studied, despite the greater prevalence rates of anxiety in women compared to men (Craske, 2003). A study indicated that attentional bias in males was positively correlated to social anxiety, however this was not the case with females (Zhao, Zhang, Chen, & Zhou, 2014). Hence, the evidence for gender differences in terms of attentional bias suggests that we cannot necessarily apply the results of this study to men.

In relation to interpretation bias, a study by Miers, Blöte, Bögels & Westenberg (2008) found a significant effect of gender in terms of interpreting social situations. They concluded that girls were significantly more likely to endorse negative interpretations (or less likely to endorse positive interpretations) of a social situation. In contrast, there was no evidence of gender-related effects, between anxiety and interpretation biases (Mobach et al., 2019). Both studies had adolescent participants with anxiety (social, separation and spider anxiety), and gender effects were found only for social situations. Gender related effects have rarely been studied in adults and there are no studies in health or cancer-related interpretations.

There have been studies examining the effect of gender on FCR, and these studies have demonstrated that women report greater levels of both FCR and FoP as compared to men (Simard

et al., 2013; Hinz et al., 2015; Pang & Humphris, 2021). In studies of cognitive processes in cancer, only one study included men (Butow et al., 2015). This study did not find significant attentional biases to cancer-related stimuli. Gender did not predict fear of cancer recurrence in this sample, although whether gender impacted attentional bias was not investigated. There have, as yet been no studies of interpretation bias in cancer context that have included men, because all studies to date have included women with breast cancer (Lam et al., 2018; Lichtenthal et al., 2017). Hence, whether interpretation biases are present and contribute to FCR in men with cancer is unclear.

9.2.5

Representativeness of the sample

While the choice of breast and ovarian cancer for this study was, in part, chosen on theoretical grounds, it was also a pragmatic choice. In Australia, there are two patient advocacy group that are very supportive of research: Breast Cancer Network Australia (BCNA) and Ovarian Cancer Australia (OCA), with whom the research team had pre-existing relationships. Participants involved in the series of studies presented in this thesis (Chapter 4, 5, 6 and 8) were primarily recruited from these Cancer Registries. Both of these registries have a large database of people diagnosed with either breast or ovarian cancer. These people have indicated that they are happy to be contacted about research opportunities, and the organisations email them directly to invite survivors to take part.

Because participants have already agreed to be considered for research by virtue of being on these registries, it is likely that they are not truly representative of all people with cancer. Indeed, in

our studies, as one might expect the participants were more likely to be highly educated contributing to the preponderance of research being conducted with WEIRD samples (White, Educated, Industrialised, Rich and Democratic; Henrich, Heine & Norenzayan, 2010). It is also possible that the participants in our studies had already taken part in research studies before. As a result of this familiarity, there may be a possibility of response bias on the questionnaires and interpretation bias assessments as they already have been primed to cancer-related (illness-related primes) stimuli. However, this is entirely speculative. Nevertheless, the extent to which these results would generalize to other women who are not a part of these registries remains to be determined.

It is also worthwhile noting that the ovarian cancer samples volunteered to take part in a study evaluating the booklet (Chapter 6), and their baseline data was presented in Chapter 4. Because the women with ovarian cancer were recruited seeking access to a new resource, they may have higher levels of fear of cancer recurrence than other women with ovarian cancer and therefore not be representative. However, it is also worthwhile noting that the demographic and medical variables are similar to what one would expect in terms of age and cancer status for a representative sample of women with ovarian cancer.

9.2.6

Methodological considerations specific to individual studies

The meta-analysis presented in Chapter 3 was limited largely by the paucity of research in the area of cognitive biases in cancer. It was initially intended to evaluate cognitive biases in attention, memory and interpretation, but a sufficient number of studies to present results was only identified for attentional biases. Even for attentional biases, there were relatively few studies – and

not sufficient to specifically assess the relationship between attentional bias and FCR/P. As a result, most of the planned moderation analyses were not able to be completed. Hence, there remains a clear need for more investigation of attentional processes and their relationship with fear of cancer recurrence.

For the studies presented in Chapters 4 and 5, we tested the central tenet of Cancer Threat Interpretation model. However, the model suggests that the interpretation of ambiguous stimuli as threatening is causally related to the development of severe FCR/P. The studies were limited by their cross-sectional nature and could only therefore provide evidence of the predicted associations, not their causal relevance to FCR/P.

The evaluation of the booklet study presented in Chapter 6 was arguably the weakest study in the program of research presented here. It was a single-arm, pre- post design to evaluate whether there were any effects of a newly developed booklet. While this was a weak design, in that there was no control group, the fact that even in a potentially biased design there was no indication of benefit of the pamphlet is important. The study was powered to identify a medium effect size, and it is possible that a smaller effect may have been missed. However, if a booklet was not effective for people seeking help with FCR in a weak single-arm design, it seems highly unlikely that the booklet would be efficacious using a stronger design and for this reason other intervention options were explored.

The review presented in Chapter 7 was not a systematic review. One of the reasons that we opted not to conduct a systematic review was that a number of systematic reviews and meta-analyses had already been published on treatments with FCR/P (e.g., Tauber et al., 2019; Liu, Butow & Beith, 2019). As such, we aimed to synthesize these results, as well as provide a narrative

synthesis for levels of intervention that had yet to be subject to systematic review (e.g., nurse-led interventions). For many levels of intervention, there were very few interventions and therefore a systematic review would have added little to the narrative review provided. The main aim of this paper was to develop a model of accessible care for the large and increasing number of cancer survivors and to identify gaps for the final study.

Finally, the RCT that was presented in Chapter 8 did overcome some of the challenges of earlier studies. That is, it used a large sample based on a clear analysis. The study was not cross-sectional and was pre-registered. Nevertheless, it can be considered largely a strong proof of concept study. We did not include a lengthy follow-up (follow-up was only 2 weeks) and therefore do not know whether this is the optimal dose of intervention and how long these effects would last are unknown. However, CBM-I clearly warrants future research. We chose four sessions over two weeks based on a similar study in chronic pain (Sharpe et al., 2022).

9.3

Strengths

Despite the conceptual issues outlined in the above section and the observed limitations, the current research has numerous methodological strengths that are worth highlighting. Firstly, it is the first body of research in cancer survivorship literature which aims to assess the role of implicit cognitive processing in terms of development and maintenance of FCR/P. Importantly, the series of studies conducted directly assessed interpretation biases in the context of FCR/P. Although there is previously published research in the field of interpretation biases examined their effect in chronic

conditions such as chronic pain (Schoth & Liossi, 2016), there was only a single study measuring interpretation biases as a function of distress when this program of research was developed (Lam et al., 2018). The present research is therefore highly novel in the area of cancer and fear of cancer recurrence.

The meta-analysis and scoping review reported in Chapter 3 was the first one to establish the existence of attentional biases in the cancer context by comparing attentional biases in people with and without a history of cancer. The meta-analysis reduces the risk of bias from individual studies and enables the pattern of findings across a range of studies to be determined. Meta-analyses are usually the gold-standard in terms of the evidence for an effect. Moreover, the meta-analysis identified significant gaps in the literature – particularly in relation to interpretation biases - and highlighted that the field is still in its nascent stages. It also provided the major impetus for future research in terms of investigating interpretation biases and fear of cancer recurrence.

The empirical studies reported in this thesis recruited participants with both ovarian or breast cancers which deepened the understanding as to how the cognitive processes differ across cancers with varying prognosis. The studies included larger samples than are typical in cognitive bias research, which gives more confidence in the findings. The fact that interpretation biases were found to be associated with FCR in both independent samples of people with ovarian and breast cancer increases our confidence in the results. The randomized controlled trial presented in Chapter 8 is arguably the strongest study in this dissertation. In most psychological intervention trials, neither participants nor researchers are blinded to the condition to which each participant is allocated. However, the trial reported in Chapter 8 was a double-blind randomized controlled trial. The trial had three arms, comparing CBM-I that trained people to interpret ambiguous scenarios as

not being pain related (i.e., not to interpret minor niggles as pain) versus a cancer-specific training that trained people not to interpret cancer-related scenarios as signs of a recurrence. The results confirmed that both CBM interventions changed biases and also primary outcomes (FCR/FoP), as well as pain severity and pain interference. This was a well powered study which produced surprisingly large changes in the short-term and are certainly encouraging for the use of these entirely remotely delivered interventions, although the results fell short of confirming the mechanism of treatment through mediation analyses.

9.4.

Implications and directions for future research

9.4.1

Future research directions for measuring attentional biases in cancer context

The review described in Chapter 3 clearly demonstrated the role of attentional biases in cancer patients. It also explored the impact of task parameters used to assess attentional biases that is, type of task and presentation timings for stimuli. Evidence of attentional bias was found on both Stroop and Dot probe paradigms; however, these tasks did not differ from each other. There was also no difference in terms of stimulus presentation timings (500 ms vs 1000ms). However, there was insufficient information to conduct most of the moderator analysis and so it could not be determined whether these parameters were optimal in detecting a bias. In other words, it was concluded that there was lack of clarity as to which task and type of stimulus would best capture attentional biases. Since this review, there have been two more studies that assessed attentional bias

in the cancer context. A study by Bártolo and colleagues (2021) examined attentional biases towards reproductive-related stimuli in women with breast cancer. The study found evidence of biased attention towards reproductive-related visual cues for women with breast cancer as compared to women without cancer. It is worth noting that the study did not use cancer-specific stimuli, nor did it assess FCR/P. The other study examined the role of attentional biases in FCR/P (Waroquier et al., 2022). The study compared attentional biases to cancer-related words in breast cancer patients with high and low FCR/P. They did not find a difference in bias between those with high vs low FCR/P. However, the study was not sufficiently powered.

Consistent with the above results in cancer patients, the evidence of attentional biases in the area of chronic pain is also less clear than in anxiety. This clearly indicates that there is a need for more research in attentional biases in the context of FCR/P. Therefore, it becomes important to learn from the existing literature that most of these studies have utilised either dot probe or Stroop and future research should consider novel methods (such as visual search or eye tracking) of assessing attentional biases in people with cancer (specifically in relation to FCR/P) in line with chronic pain literature. Furthermore, it is also important to assess the existence of multiple biases (both attentional and interpretation) together as it has already been previously established in previously in social phobia (Hirsch, Clark & Mathews, 2006).

9.4.2

Theoretical Implications

The overall aim of this thesis was to increase our understanding of implicit cognitive processing biases in the context of cancer. As described earlier in Chapter 2, various theoretical models have been proposed to conceptualize clinical levels of FCR/P. The earlier theories such as

the Lee-Jones' (1997) model largely focuses on the content of an individual's worries or concerns. However, more recent theories place a strong emphasis on the cognitive processes as well as the content of these worries. Indeed, these theories specifically highlight the potential role of both attentional (e.g. hypervigilance, cognitive attentional syndrome) and interpretation biases (e.g. threat appraisal, interpretation) as central to the development of FCR/P (Fardell et al., 2016; Heathcote & Eccleston, 2017). The research in this thesis was guided by the Cancer Threat Interpretation Model, which focuses on misinterpretation of physical sensations as signs of recurrence as the putative mechanism that gives rise to severe levels of FCR/P.

Given that there was no evidence to determine whether interpretation biases were related to FCR/P, the empirical studies in Chapters 4 and 5 were developed to determine whether biases differed between those with and without clinical levels of FCR/P, and whether they moderated the relationship between pain and FCR/P, as suggested by the Cancer Threat Interpretation (Heathcote & Eccleston, 2017). The empirical study on breast cancer survivors (Chapter 5) provided support for one of the central tenets of the model, that is, interpretation bias moderated the relationship between pain symptoms and FCR. Specifically, amongst breast cancer survivors, the relationship between pain symptoms and FCR becomes stronger amongst those who are more likely to interpret ambiguous stimuli as threatening. For those with a low propensity to interpret ambiguous words as painful, the relationship between pain and FCR is not significant. While this was not the case for FoP in the breast cancer sample or ovarian cancer sample, interpretation biases nevertheless were associated with FoP in both studies.

Interestingly, the nature of interpretation bias that was measured was the degree to which an ambiguous word was interpreted as health-related. This is not specifically related to the

interpretation of an ambiguous scenario being interpreted as indicating recurrence or bad news. If we assume that the response to word stimuli can index responses to actual somatosensory and real-life situations (see Van Ryckegham et al., 2019 for a full discussion), then this might help us to understand the nature of the bias. That is, the experience of everyday somatic symptoms (aches and pain, tension, dizziness, fatigue etc) is very common in the population and increasingly common amongst people as they age (Beutel et al., 2019). If one feels tight in the chest, the degree to which one views this as pain may well contribute to how threatening the sensation appears. Todd et al. (2015) argue that this "categorization" of physical sensations as "painful" is a form of interpretation bias that triggers other cognitive processes to amplify pain. The ambiguous cues task is most aligned to this form of interpretation bias. Tuman et al. (2021) have recently published the baseline results from the Lichtenthal et al. (2017) trial. They used the WSAP to assess interpretation biases, which is a cancer-specific version of interpretation bias and more akin to interpreting the presence of pain as a sign of recurrence. Their results confirmed that in women with breast cancer who took part in their earlier trial that there was a correlation between interpretation bias and FCR/P.

Taken together, these results suggest that there might be multiple forms of interpretation bias that are associated with FCR/P. The trial presented in Chapter 8 is therefore important in terms of determining whether training a bias to interpret ambiguous sensations as pain-related; and/or to interpret ambiguous situations as specifically cancer-related produces more change in FCR/P. One could have anticipated that training people not to interpret ambiguous sensations as pain-related may reduce pain symptoms, and in doing so reduced FCR/P. In contrast, one might have anticipated that when training people not to interpret scenarios as indicative of a recurrence may have a more direct impact on FCR/P, which may or may not lead to a reduction in pain severity. However, this was not the case. That is, participants had reductions contemporaneously in FCR and pain severity

and pain interference with both forms of interpretation bias compared to controls. Future research could measure pain and FCR more frequently to see whether the mechanisms differ. However, the results to date suggest that both of these types of interpretation bias may be relevant to FCR and that reducing either will result in large changes in both FCR and pain outcomes.

It should be noted that in that in this program of research, the novel empirical work focused exclusively on interpretation bias and attentional bias was not measured. Theoretical accounts also incorporate attentional biases in their models. For example, the Cancer Threat Interpretation model describes the importance of hypervigilance and bodily threat monitoring. While we did measure body threat monitoring in the breast cancer study, which did contribute to the variance in FCR/P (see Chapter 5), it is debatable the degree to which cognitive processes can be reliably reported on using self-report questionnaires. However, in the area of anxiety, it has been acknowledged for some time that cognitive biases most likely operate in concert, which is often described as the combined cognitive hypothesis. The combined cognitive hypothesis was first put forward in relation to social anxiety (Hirsch, Clark, & Mathews, 2006). According to this model, both interpretation and self-imagery (i.e., negative attention directed towards oneself during social interaction) are argued to interact and maintain each other and contribute to the development of social phobia. Others have since noted the interaction of other forms of cognitive bias, such as memory bias, in the context of other disorders, such as depression (Everaert et al., 2012). However, in this study, only interpretation biases were examined.

The interaction between different cognitive biases (attention, interpretation and memory) should be investigated in future research. The combined cognitive hypothesis would suggest that there would be inter-relationships between different biases, which together contribute to FCR/P.

Similarly, future studies should also test the Cancer Threat Interpretation model in other cancers with varying prognosis and particularly in cancers that affect men. Finally, the research assessing the existence of interpretation bias in adolescents and young adults (AYAs) and caregivers of cancer survivors is still lacking. Hence, it becomes clear that further studies replicating these findings would be required to lend further support for these theoretical models.

9.4.3

Clinical Implications

With the improved survival rates, there are now increasing number of people living beyond their cancer diagnosis, and a recent meta-analysis confirmed that one in five of those survivors live with severe fear of recurrence (Luigjes-Huizer et al., 2022). While for some people these fears are manageable and a natural part of surviving cancer, for some of these individuals FCR/P impacts profoundly on their day-to-day functioning and increases the risk of developing other mental health issues including anxiety, depression and post-traumatic stress symptoms (Götze et al., 2019). When severe, this high level of FCR/P can persist over time with little evidence that it spontaneously remits once established (Crist & Grunfeld, 2013). The fear of cancer returning prompts individuals to seek frequent medical tests to rule out a recurrence, thus resulting in an increase in health-care utilization and costs (Williams et al., 2021). Help with FCR/P has commonly been reported as one of the leading survivorship needs (Simard et al., 2013), and despite a large amount of work on developing efficacious treatments, help with FCR/P remains the most common unmet need (Tan et al., 2021).

The biggest challenge of meeting the needs of people with severe FCR is the number of affected individuals. AIHW (2021) estimates that in Australia alone there will be 185,000 cancer survivors by 2031. If 20% of these survivors have severe FCR/P, then this would require services to be available to 37,000 Australians. In the last decade, many interventions for FCR/P have been developed and evaluated, and the largest meta-analysis in this area of 23 studies shows that there is a small to moderate effect of these interventions overall on FCR/P (Tauber et al., 2019). However, the median number of sessions in these interventions that have been studied is six face-to-face sessions. Moreover, most of these interventions include specialised psycho-oncology professionals. For example, ConquerFear included therapists who were either psychiatrists, psychologists or social workers with at least five years post-qualification experience, at least two years of which was in oncology to be a therapist on the trial (Butow et al., 2017). This level of expertise is expensive. Hence, there is a need for brief, efficacious treatments that can be scalable to meet this growing unmet need in oncology settings.

Therapeutic interventions such as CBM-I, have the potential to be included in a stepped care approach as there has been a recent call to develop more scalable interventions for people in sub-clinical range of FCR/P (Chapter 7). Protocols such as CBM-I require minimal time involvement for participants and therapists. That is, four sessions over a time of two weeks, with 15 minutes for each session (Chapter 8). Since the completion rates were high at both follow-up time points, this intervention has a promising potential to be implemented in a busy oncology clinic, where resources such as time is a major issue amongst oncology professionals. Given the fact that such interventions are remotely delivered, future research should investigate more easy, sophisticated and user-friendly technology to disseminate the intervention to people who are in need.

The studies described in Chapters 6 and 8 provides an interesting insight as to what sort of intervention is more applicable across people with varying levels of FCR/P depending on their level of need (Stepped-care approach). In other words, both of these studies evaluated the efficacy of treatments across two levels in a stepped-care approach. Firstly, there is a need to find basic universal interventions (at step 1) that can reduce the likelihood of developing FCR. That is, addressing informational needs should be included in the first step of this approach as it can be delivered to every cancer patient, where FCR/P is a realistic threat. Secondly, scalable remote interventions that can meet the needs of those with moderate-severe levels of FCR (as step 2) so that more intensive methods can be reserved for those who fail to respond to the remotely administered interventions.

Although, there are no evidence-based universal approaches available, however we tested the booklet, and while it was not efficacious, neither did it do any harm – and it was valued by women. Therefore, it may be worthwhile including this type of psychoeducational resource as a first step. One such example of brief intervention is CIFeR, which is a clinician-led intervention to address FCR/P (Liu et al., 2021). Although, this is a single-arm intervention which demonstrated some preliminary efficacy in reducing FCR/P. However, based on CIFeR intervention, training oncologists to give basic information could be part of this solution to meet this increasing need. One major contribution of the present thesis is the evidence base for CBM-I, although now a large-scale phase III trial would be welcome, with longer follow-up time points. In this way, the current research makes a significant contribution to these stepped care models, which are still under researched. Refer to figure 9.1 for a stepped care model where these interventions could be placed.

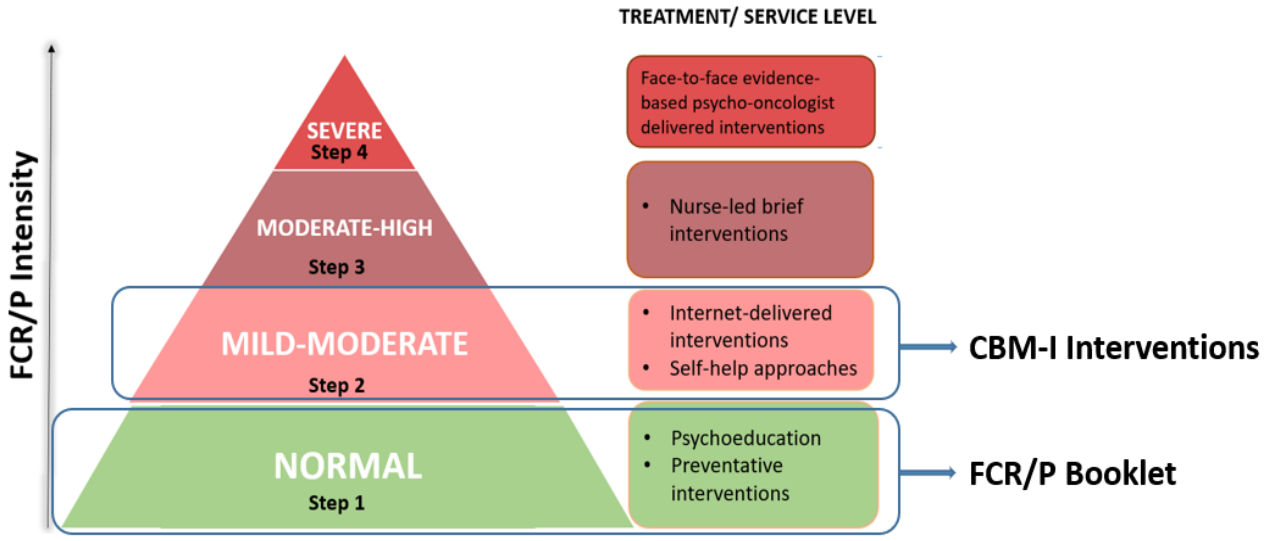


Figure 9.1

Stepped-care approach (Pradhan et al., 2021)

Finally, the results from the ovarian cancer study (Chapter 4), found no association between interpretation bias and overall symptom burden. Post-hoc analyses were conducted to determine those symptoms which were associated with interpretation bias. Based on these post-hoc analyses, it was concluded that symptoms such as fatigue and constipation (and other gastrointestinal symptoms) significantly contributed to unique variance in FCR/P. In ovarian cancer, gastrointestinal symptoms do indicate a recurrence or progression more often than pain (Chapter 4). These results offered critical insights into the importance of symptoms relating to a particular cancer type. Further, these results confirm that patients should be provided with sufficient information from their oncologists about potential signs and symptoms which could be indicative of a recurrence or progression. This has been highlighted by Butow and colleagues (2018) where they emphasize the role of oncologists in terms of screening for FCR/P and further identifying patients with severe FCR/P who may benefit from intensive and evidence-based treatments to reduce this

level. They also highlight the need of providing adequate information on prognosis, behavioural strategies to reduce 'risk reduction', and further 'normalizing' FCR/P by encouraging patients to discuss freely with their oncologists. These recommendations were recently tested in a 'proof-of-concept' study called CIFeR by Liu and colleagues (2021), which was effective in reducing FCR/P severity, as previously mentioned. In other words, the way the clinician communicates with survivors in explaining symptom-cancer link plays a crucial role in terms of manifestation of this cancer-specific anxiety (or FCR/P). For example, a patient who has recently been treated for a breast cancer should be informed that a pain in the bones especially ribs indicate a cancer recurrence, whereas leg pain is unlikely to signify recurrence. Across studies, this type of doctor-patient communication has been argued to help to regulate patient's emotions and facilitating the comprehension of complex information and is therefore the essence of routine clinical practice (Glatzer et al., 2020; Yang et al., 2018; Prip et al., 2018).

9.5.

Concluding remarks

Cancer remains one of the leading causes of death in developed countries but over the past few decades improved survival rates have also led cancer to become one of the most common chronic medical conditions. However, evidence now clearly shows that, even amongst survivors with the best prognosis, a prior diagnosis of cancer leads to a constant fear of the cancer returning – like the Sword of Damocles hanging over the person's head for the remainder of their lives. For this

reason, the most common survivorship concern reported in the literature is the fear of cancer coming back or progressing (FCR/P). While at lower levels, these concerns can serve as an adaptive function by alerting an individual in the context of realistic threat and uncertainty, for many survivors this fear becomes excessive and impairs their quality of life. Increasingly, it has been recognised that when these fears become excessive, there is a cascade of cognitive processes wherein people interpret situations as likely recurrence, ruminate about symptoms, check their bodies and seek reassurance (Heathcote & Eccleston, 2017; Fardell et al., 2016). While these processes are recognised as important, they have been under-researched. Therefore, the aim of this thesis was to investigate the role of cognitive processing biases in the development, maintenance and treatment of FCR/P. After identifying that attentional biases do exist, and are associated with distress in the meta-analysis, we also observed the lack of empirical research on interpretation biases which became the focus of the thesis.

The present research provides a number of important findings to this field of research and proposed future research directions in order to better understand these mechanisms.

1. The meta-analysis presented in Chapter 3 provides strong evidence of greater attentional biases in people who have been diagnosed with cancer compared to those who have not. Further, attentional biases were larger amongst those who were distressed.

2. People with ovarian cancer are more likely to interpret ambiguous words as health-related in comparison to people without ovarian cancer.

3. For both people with breast and ovarian cancer, interpretation biases are larger amongst those who score in the clinical range for FCR/P.

4. For breast cancer, interpretation bias moderates the relationship between pain and FCR, as predicted by the Cancer Threat Interpretation model.

5. There are efficacious face-to-face treatments for FCR/P, however, the majority are intensive and require a highly skilled workforce who will not be able to meet the needs of the ever-increasing number of cancer survivors in our community.

6. A simple booklet containing psychoeducation about FCR/P is insufficient to produce change in FCR, at least for people with ovarian cancer. However, people with ovarian cancer are satisfied with the information provided.

7. A brief, remotely administered cognitive bias modification intervention, either focused on changing pain-related interpretation or cancer-related interpretations, was efficacious in reducing not only FCR/P, but also improving pain severity and pain interference in the short-term. This could be an important solution to stepped care models in providing a highly efficacious treatment requiring few resources, allowing highly trained professionals to manage those individuals for whom this approach does not provide improvement.

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Appendix A

Meta-analysis protocol and Quality Rating scale

Systematic review

Fields that have an asterisk (*) next to them means that they must be answered. Word limits are provided for each section. You will be unable to submit the form if the word limits are exceeded for any section.

Registrant means the person filling out the form.

This record cannot be edited because it has been marked as out of scope

1. * Review title.

Give the title of the review in English

The role of cognitive biases in relation to cancer: a systematic review

2. Original language title.

For reviews in languages other than English, give the title in the original language. This will be displayed with the English language title.

3. * Anticipated or actual start date.

Give the date the systematic review started or is expected to start. **07/01/2019**

4. * Anticipated completion date.

Give the date by which the review is expected to be completed. **31/12/2019**

5. * Stage of review at time of this submission.

This field uses answers to initial screening questions. It cannot be edited until after registration.

Tick the boxes to show which review tasks have been started and which have been completed. Update this field each time any amendments are made to a published record.

The review has not yet started: **Yes**

Review stage	Started	Completed
Preliminary searches	No	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

Provide any other relevant information about the stage of the review here.

6. * Named contact.

The named contact is the guarantor for the accuracy of the information in the register record. This may be any member of the review team.

Poorva Pradhan

Email salutation (e.g. "Dr Smith" or "Joanne") for correspondence:

Miss Pradhan

7. * Named contact email.

Give the electronic email address of the named contact. **ppra9419@uni.sydney.edu.au**

8. Named contact address

Give the full institutional/organisational postal address for the named contact.

Room 450, Brennan Maccallum Building (a18) the University of Sydney Nsw 2006

9. Named contact phone number.

Give the telephone number for the named contact, including international dialling code.
0286277678

10. * Organisational affiliation of the review.

Full title of the organisational affiliations for this review and website address if available. This field may be completed as 'None' if the review is not affiliated to any organisation.

The University of Sydney

Organisation web address:

11. * Review team members and their organisational affiliations.

Give the personal details and the organisational affiliations of each member of the review team. Affiliation refers to groups or organisations to which review team members belong. NOTE: email and country now MUST be entered for each person, unless you are amending a published record.

Miss Poorva Pradhan. The University of Sydney

Professor Louise Sharpe. The University of Sydney

Professor Phyllis Butow. The University of Sydney

12. * Funding sources/sponsors.

Details of the individuals, organizations, groups, companies or other legal entities who have funded or sponsored the review.

None

Grant number(s)

State the funder, grant or award number and the date of award

13. * Conflicts of interest.

List actual or perceived conflicts of interest (financial or academic). **None**

14. Collaborators.

Give the name and affiliation of any individuals or organisations who are working on the review but who are not listed as review team members. NOTE: email and country must be completed for each person, unless you are amending a published record.

15. * Review question.

State the review question(s) clearly and precisely. It may be appropriate to break very broad questions down into a series of related more specific questions. Questions may be framed or refined using PI(E)COS or similar where relevant.

The objective of this systematic review is to summarise the literature on the presence and impact of cognitive biases in cancer survivors and their caregivers. There are three research questions:

1. **Do cancer survivors show attention, interpretation or memory biases in processing cancer-related stimuli as compared to people without cancer?**
2. **Do cancer survivors or their caregivers show attention, interpretation or memory biases in processing cancer-related stimuli as compared to neutral stimuli?**
3. **Are cognitive biases in cancer survivors or their caregivers associated with psychological outcomes namely, fear of cancer recurrence/progression, depression, and anxiety?**

16. * Searches.

State the sources that will be searched (e.g. Medline). Give the search dates, and any restrictions (e.g. language or publication date). Do NOT enter the full search strategy (it may be provided as a link or attachment below.)

Keyword-based searches in the electronic databases PubMed, PsycINFO, Scopus, CINAHL, and Embase

There is no restriction on the publication period. Population related keywords:

Cancer OR Oncology OR Neoplasms

AND

Following keywords will be entered for first search:

1. For Attentional Bias:

Selective attention* Attention* bias* Vigilance Hypervigilance Stroop

Dot probe Probe detection Posner

(Spatial) Cueing or spatial cuing

2. For Interpretation Bias:

Interpret* Bias* Ambiguous cues Homophone

3. For Memory Bias:

Selective recall Memory bias* Recognition

In addition to the electronic search, reference lists from all identified articles will be screened manually for additional relevant papers.

17. URL to search strategy.

Upload a file with your search strategy, or an example of a search strategy for a specific database, (including the keywords) in pdf or word format. In doing so you are consenting to the file being made publicly accessible. Or provide a URL or link to the strategy. Do NOT provide links to your search results.

Alternatively, upload your search strategy to CRD in pdf format. Please note that by doing so you are consenting to the file being made publicly accessible.

Yes I give permission for this file to be made publicly available

18. * Condition or domain being studied.

Give a short description of the disease, condition or healthcare domain being studied in your systematic review.

The review aims to explore cognitive biases (attention, interpretation and memory) in the context of cancer of any type or stage.

19. * Participants/population.

Specify the participants or populations being studied in the review. The preferred format includes details of both inclusion and exclusion criteria.

Studies will need to sample participants who have had or currently have cancer or those who are caregivers of patients who have or have had cancer. We will include participants regardless of age (both children and adults).

20. * Intervention(s), exposure(s).

Give full and clear descriptions or definitions of the interventions or the exposures to be reviewed. The preferred format includes details of both inclusion and exclusion criteria.

Studies will be included if they assessed bias in attention, interpretation or memory. We will include studies that used stimuli that is relevant to the cancer experience including specific cancer-related stimuli, general threat-related stimuli, health or disability related stimuli and symptom related stimuli (e.g. pain, fatigue, nausea). Studies will be eligible for inclusion in the review if they use standard experimental paradigms.

For attention bias such as, dot-probe paradigm, emotional Stroop task, visual search task, spatial cueing task or attentional eyeblink task.

For interpretation biases such as, ambiguous scenarios task, word-sentence association task, ambiguous homophone task.

For memory biases such as, implicit or explicit memory task; free recall or recognition. Self-referent versus other referent conditions will be examined.

21. * Comparator(s)/control.

Where relevant, give details of the alternatives against which the intervention/exposure will be compared (e.g. another intervention or a non-exposed control group). The preferred format includes details of both inclusion and exclusion criteria.

Where possible cognitive biases (attentional, interpretation and memory) in cancer-related groups will be compared to people without cancer. However, it is also of interest whether people in the context of cancer have an absolute bias. That is, do they attend more to experimental words (e.g. cancer-related) than neutral words? Do they interpret ambiguous information in a more threatening compared to benign manner? Do they remember relatively more cancer-related information than neutral information? Therefore, studies will be included even when there is no control group.

22. * Types of study to be included.

Give details of the study designs (e.g. RCT) that are eligible for inclusion in the review. The preferred format includes both inclusion and exclusion criteria. If there are no restrictions on the types of study, this should be stated.

The review will consider all articles that examined cognitive biases using an accepted experimental paradigm to measure interpretation, attention or memory biases in the context of cancer.

23. Context.

Give summary details of the setting or other relevant characteristics, which help define the inclusion or exclusion criteria.

Studies will be included regardless of the location or type of research setting. Studies carried out in clinical and non-clinical settings; via any format (e.g. online or in the clinic) will be included.

24. * Main outcome(s).

Give the pre-specified main (most important) outcomes of the review, including details of how the outcome is defined and measured and when these measurement are made, if these are part of the review inclusion criteria.

Index of cognitive bias with regard to attention, interpretation or memory bias. Measures based on proportion of responses, response time or eye-tracking data will be included.

Measures of effect

Please specify the effect measure(s) for you main outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

25. * Additional outcome(s).

List the pre-specified additional outcomes of the review, with a similar level of detail to that required for main outcomes. Where there are no additional outcomes please state ‘None’ or ‘Not applicable’ as appropriate to the review

Moderators:

Data will be extracted on psychological outcomes and their association with cognitive biases specifically fear about cancer returning or progressing (fear of cancer recurrence/progression), depression, and anxiety.

Measures of effect

Please specify the effect measure(s) for you additional outcome(s) e.g. relative risks, odds ratios, risk difference, and/or 'number needed to treat.

26. * Data extraction (selection and coding).

Describe how studies will be selected for inclusion. State what data will be extracted or obtained. State how this will be done and recorded.

After duplicate studies are removed, titles and abstracts of the identified studies will be screened to identify if they meet the inclusion criteria. Full-text records will be obtained for the eligible studies that are identified as potentially meeting the inclusion criteria. Two

authors (PP and LS) will further review these full records to identify the studies for inclusion. Any disagreements will be resolved by consensus and discussion with a third author (PB) if necessary. Data extracted from the relevant studies will include publication year, location and study, nature of sample (e.g., cancer patient, caregiver), age (adult/child), sample size, type of cancer, type of task, means and standard deviations of cognitive biases (attentional, interpretation and memory) for the cancer-relevant group and any control group, effect size, relationship between cognitive bias and fear of cancer recurrence/progression, anxiety or depression.

27. * Risk of bias (quality) assessment.

State which characteristics of the studies will be assessed and/or any formal risk of bias/quality assessment tools that will be used.

In order to assess quality of included studies, the Modified Downs and Black (1998) Quality Index Scale will be used to assess each of the included studies. The scale consists of 27 yes-no questions that are rated across different criteria: study reporting, external validity, study bias, selection bias and power of the study.

28. * Strategy for data synthesis.

Describe the methods you plan to use to synthesise data. This must not be generic text but should be specific to your review and describe how the proposed approach will be applied to your data. If meta- analysis is planned, describe the models to be used, methods to explore statistical heterogeneity, and software package to be used.

Although we will calculate effect size of biases quantitatively but as we expect limited literature therefore, we will conduct a narrative synthesis of the obtained findings following data extraction and quality assessment.

29. * Analysis of subgroups or subsets.

State any planned investigation of 'subgroups'. Be clear and specific about which type of study or participant will be included in each group or covariate investigated. State the planned analytic approach.

We do not expect that there will be a sufficient number of studies for subgroup analyses.

30. * Type and method of review.

Select the type of review, review method and health area from the lists below.

Type of review Cost effectiveness No

Diagnostic No

Epidemiologic No

Individual patient data (IPD) meta-analysis No

Intervention No

Living systematic review No

Meta-analysis No

Methodology No

Narrative synthesis Yes

Network meta-analysis No

Pre-clinical No

Prevention No

Prognostic No

Prospective meta-analysis (PMA) No

Review of reviews No

Service delivery No

Synthesis of qualitative studies No

Systematic review Yes

Other No

Health area of the review Alcohol/substance misuse/abuse No

Blood and immune system No

Cancer Yes

Cardiovascular No

Care of the elderly No

Child health No

Complementary therapies No

COVID-19; No

Crime and justice: No

Dental No

Digestive system No

Ear, nose and throat No

Education No

Endocrine and metabolic disorders No

Eye disorders No

General interest No

Genetics No

Health inequalities/health equity No

Infections and infestations No

International development No

Mental health and behavioural conditions No

Musculoskeletal No

Neurological No

Nursing No

Obstetrics and gynaecology No

Oral health No

Palliative care No

Perioperative care No

Physiotherapy No

Pregnancy and childbirth No

Public health (including social determinants of health) No

Rehabilitation No

Respiratory disorders No

Service delivery No

Skin disorders No

Social care No

Surgery No

Tropical Medicine No

Urological No

Wounds, injuries and accidents No

Violence and abuse No

31. Language.

Select each language individually to add it to the list below, use the bin icon to remove any added in error. English

There is not an English language summary

32. * Country.

Select the country in which the review is being carried out. For multi-national collaborations select all the countries involved.

Australia

33. Other registration details.

Name any other organisation where the systematic review title or protocol is registered (e.g. Campbell, or The Joanna Briggs Institute) together with any unique identification number assigned by them. If extracted data will be stored and made available through a repository such as the Systematic Review Data Repository (SRDR), details and a link should be included here. If none, leave blank.

34. Reference and/or URL for published protocol.

If the protocol for this review is published provide details (authors, title and journal details, preferably in Vancouver format)

Add web link to the published protocol. Or, upload your published protocol here in pdf format. Note that the upload will be publicly accessible.

Yes I give permission for this file to be made publicly available

Please note that the information required in the PROSPERO registration form must be completed in full even if access to a protocol is given.

35. Dissemination plans.

Do you intend to publish the review on completion?

Yes

Give brief details of plans for communicating review findings.?

36. Keywords.

Give words or phrases that best describe the review. Separate keywords with a semicolon or new line. Keywords help PROSPERO users find your review (keywords do not appear in the public record but are included in searches). Be as specific and precise as possible. Avoid acronyms and abbreviations unless these are in wide use.

Fear of Cancer Recurrence

Fear of Progression

Cognitive Biases

Cancer Survivorship

37. Details of any existing review of the same topic by the same authors.

If you are registering an update of an existing review give details of the earlier versions and include a full bibliographic reference, if available.

38. * Current review status.

Update review status when the review is completed and when it is published. New registrations must be ongoing so this field is not editable for initial submission.

Please provide anticipated publication date

Review_Ongoing

39. Any additional information.

Provide any other information relevant to the registration of this review.

40. Details of final report/publication(s) or preprints if available.

Leave empty until publication details are available OR you have a link to a preprint (NOTE: this field is not editable for initial submission). List authors, title and journal details preferably in Vancouver format.

Give the link to the published review or preprint.

Quality Rating Criteria:

Modified Downs and Black checklist for the assessment of the methodological quality of both randomized and non-randomized studies[1]

Item	Criteria	Possible Answers
Reporting		
1	*Is the hypothesis/aim/objective of the study clearly described?*	Yes = 1 No = 0
2	*Are the main outcomes to be measured clearly described in the Introduction or Methods section?* If the main outcomes are first mentioned in the Results section, the question should be answered no.	Yes = 1 No = 0
3	*Are the characteristics of the patients included in the study clearly described?* In cohort studies and trials, inclusion and/or exclusion criteria should be given. In case-control studies, a case-definition and the source for controls should be given.	Yes = 1 No = 0
4	*Are the interventions of interest clearly described?* Treatments and placebo (where relevant) that are to be compared should be clearly described.	Yes = 1 No = 0

5	*Are the distributions of principal confounders in each group of subjects to be compared clearly described?* A list of principal confounders is provided.	Yes = 2 Partially = 1 No = 0
6	*Are the main findings of the study clearly described?* Simple outcome data (including denominators and numerators) should be reported for all major findings so that the reader can check the major analyses and conclusions. (This question does not cover statistical tests which are considered below).	Yes = 1 No = 0
7	*Does the study provide estimates of the random variability in the data for the main outcomes?* In non-normally distributed data the interquartile range of results should be reported. In normally distributed data the standard error, standard deviation or confidence intervals should be reported. If the distribution of the data is not described, it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0
8	*Have all important adverse events that may be a consequence of the intervention been reported?* This should be answered yes if the study demonstrates that there was a comprehensive attempt to measure adverse events. (A list of possible adverse events is provided).	Yes = 1 No = 0
9	*Have the characteristics of patients lost to follow-up been described?* This should be answered yes where there were no losses to follow-up or where losses to follow-up were so small that findings would be unaffected by their inclusion. This should be answered no where a study does not report the number of patients lost to follow-up.	Yes = 1 No = 0
10	*Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?*	Yes = 1 No = 0
External validity		
11	*Were the subjects asked to participate in the study representative of the entire population from which they were recruited?* The study must identify the source population for patients and describe how the patients were selected. Patients would be representative if they comprised the entire source population, an unselected sample of consecutive patients, or a random sample. Random sampling is only feasible where a list of all members of the relevant population exists. Where a study does not report the proportion of the source population from which the patients are derived, the question should be answered as unable to determine.	Yes = 1 No = 0 Unable to determine = 0
12	*Were those subjects who were prepared to participate representative of the entire population from which they were recruited?* The proportion of those asked who agreed should be stated. Validation that the sample was representative would include demonstrating that the distribution of the main confounding factors was the same in the study sample and the source population.	Yes = 1 No = 0 Unable to determine = 0
13	*Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?* For the question to be answered yes the study should demonstrate that the intervention was representative of that in use in the source population. The question should be answered no if, for example, the intervention was undertaken in a specialist centre unrepresentative of the hospitals most of the source population would attend.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - bias		

14	*Was an attempt made to blind study subjects to the intervention they have received?* For studies where the patients would have no way of knowing which intervention they received, this should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
15	*Was an attempt made to blind those measuring the main outcomes of the intervention?*	Yes = 1 No = 0 Unable to determine = 0
16	*If any of the results of the study were based on "data dredging", was this made clear?* Any analyses that had not been planned at the outset of the study should be clearly indicated. If no retrospective unplanned subgroup analyses were reported, then answer yes.	Yes = 1 No = 0 Unable to determine = 0
17	*In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?* Where follow-up was the same for all study patients the answer should be yes. If different lengths of follow-up were adjusted for by, for example, survival analysis the answer should be yes. Studies where differences in follow-up are ignored should be answered no.	Yes = 1 No = 0 Unable to determine = 0
18	*Were the statistical tests used to assess the main outcomes appropriate?* The statistical techniques used must be appropriate to the data. For example nonparametric methods should be used for small sample sizes. Where little statistical analysis has been undertaken but where there is no evidence of bias, the question should be answered yes. If the distribution of the data (normal or not) is not described it must be assumed that the estimates used were appropriate and the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
19	*Was compliance with the intervention/s reliable?* Where there was non-compliance with the allocated treatment or where there was contamination of one group, the question should be answered no. For studies where the effect of any misclassification was likely to bias any association to the null, the question should be answered yes.	Yes = 1 No = 0 Unable to determine = 0
20	*Were the main outcome measures used accurate (valid and reliable)?* For studies where the outcome measures are clearly described, the question should be answered yes. For studies which refer to other work or that demonstrates the outcome measures are accurate, the question should be answered as yes.	Yes = 1 No = 0 Unable to determine = 0
Internal validity - confounding (selection bias)		
21	*Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?* For example, patients for all comparison groups should be selected from the same hospital. The question should be answered unable to determine for cohort and case-control studies where there is no information concerning the source of patients included in the study.	Yes = 1 No = 0 Unable to determine = 0
22	*Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time? For a study which does not specify the time period over which patients were recruited, the question should be answered as unable to determine.*	Yes = 1 No = 0 Unable to determine = 0
23	*Were study subjects randomized to intervention groups? Studies which state that subjects were randomized should be answered yes except where method of randomization would not ensure random allocation. For example alternate allocation would score no because it is predictable.*	Yes = 1 No = 0 Unable to determine = 0

24	*Was the randomized intervention assignment concealed from both patients and health care staff until recruitment was complete and irrevocable? All non- randomized studies should be answered no. If assignment was concealed from patients but not from staff, it should be answered no.*	Yes = 1 No = 0 Unable to determine = 0
25	*Was there adequate adjustment for confounding in the analyses from which the main findings were drawn? This question should be answered no for trials if: the main conclusions of the study were based on analyses of treatment rather than intention to treat; the distribution of known confounders in the different treatment groups was not described; or the distribution of known confounders differed between the treatment groups but was not taken into account in the analyses. In non-randomized studies if the effect of the main confounders was not investigated or confounding was demonstrated but no adjustment was made in the final analyses the question should be answered as no.*	Yes = 1 No = 0 Unable to determine = 0
26	*Were losses of patients to follow-up taken into account? If the numbers of patients lost to follow-up are not reported, the question should be answered as unable to determine. If the proportion lost to follow-up was too small to affect the main findings, the question should be answered yes.*	Yes = 1 No = 0 Unable to determine = 0

*Item has been modified.

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Appendix B:

Articles included in the review

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Appendix C:

Review Database Search Terms

EMBASE:

1. cancer.mp.

2. oncology/ or oncology.mp.

3. neoplasms.mp. or neoplasm/

4. 1 or 2 or 3

5. cognitive bias*.mp.

6. attention* bias*.mp.

7. selective attention.mp.

8. vigilance.mp.

9. hypervigilance.mp.

10. stroop.mp.

11. dot probe.mp.

12. posner.mp.

13. probe detection.mp.

14. spatial cueing.mp.

15. interpret* bias*.mp.

16. ambiguous cues.mp.

17. homophone.mp.

18. selective recall.mp.

19. memory bias*.mp.

20. word recognition.mp.

21. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 4 and 21

PsycINFO:

1. cancer.mp. or exp Neoplasms/

2. oncology.mp. or exp ONCOLOGY/

3. 1 or 2

4. cognitive bias.mp. or exp Cognitive Bias/

5. attentional bias.mp. or exp Attentional Bias/

6. selective attention.mp. or exp Selective Attention/

7. vigilance.mp. or exp VIGILANCE/

8. hypervigilance.mp.

9. stroop.mp.

10. dot probe.mp.

11. probe detection.mp.

12. posner.mp.

13. spatial cueing.mp.

14. interpretation bias.mp.

15. exp Interpretive Bias/ or interpretive bias.mp.

16. ambiguous cues.mp.

17. homophone.mp.

18. memory bias.mp.

19. selective recall.mp.

20. word recognition.mp. or exp Word Recognition/

21. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20

22. 3 and 21

MEDLINE:

1. cancer.mp. or Neoplasms/

2. oncology.mp.

3. 1 or 2

4. cognitive bias.mp.

5. selective attention.mp.

6. attention* bias*.mp.

7. vigilance.mp.

8. hypervigilance.mp.

9. stroop.mp.

10. dot probe.mp.

11. probe detection.mp.

12. posner.mp.

13. spatial cueing.mp.

14. interpret* bias*.mp.

15. ambiguous cues.mp.

16. homophone.mp.

17. memory bias*.mp.

18. selective recall.mp.

19. word recognition.mp.

20. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19

21. 3 and 20

SCOPUS:

(TITLE-ABS-KEY ("cancer" OR "oncology" OR "neoplasms") AND TITLE-ABS-KEY (cognitive AND bias) OR TITLE-ABS-KEY ("attention* bias*") OR TITLE-ABS-KEY ("vigilance") OR TITLE-ABS-KEY ("hypervigilance") OR TITLE-ABS-KEY (stroop) OR TITLE-ABS-KEY (posner) OR TITLE-ABS-KEY ("dot probe") OR TITLE-ABS-KEY ("spatial cueing") OR TITLE-ABS-KEY ("interpret* bias*") OR TITLE-ABS-KEY ("ambiguous cues") OR TITLE-ABS-KEY (homophone) OR TITLE-ABS-KEY ("memory bias*") OR TITLE-ABS-KEY ("selective recall") OR TITLE-ABS-KEY ("selective attention") OR TITLE-ABS-KEY ("word recognition") OR TITLE-ABS-KEY ("probe detection"))

WEB OF SCIENCE:

TS=("cognitive bias" OR "Selective attention*" OR "Attention* bias*" OR "Vigilance" OR "Hypervigilance" OR "Stroop" OR "Dot probe" OR "Posner" OR "probe detection" OR "spatial cueing" OR "Interpret* Bias*" OR "Ambiguous cues" OR "Homophone" OR "Selective recall" OR "Memory bias*" OR "word recognition")

CINAHL:

#	Query
S1	"cancer"
S2	"oncology"
S3	"neoplasm"
S4	S1 OR S2 OR S3

S5 "cognitive bias*"

S6 "selective attention"

S7 "attention* bias*"

S8 "vigilance"

S9 "hypervigilance"

S10 "stroop"

S11 "dot probe"

S12 "probe detection"

S13 "posner"

S14 "spatial cueing"

S15 "interpret* bias*"

S16 "ambiguous cues"

S17 "homophone*"

S18 "memory bias*"

S19 "selective recall"

S20 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19

S21 S4 AND S21

Appendix D:

Questionnaire Measures

Questionnaire	**Chapters**
Demographics	4, 5, 6
Fear of Cancer Recurrence (Severity Subscale) (FCR-I)	5, 8
Fear of Progression (Short-form) (FoP-Q-SF)	4, 5, 8
Physical Symptoms Inventory	4, 5, 8
Ambiguous Cues Task	4, 5

Demographics:

English

AGE

MARITAL STATUS

- Married
- Widowed
- Divorced
- Separated
- Never married

Number of children

Educational Status

- Did not complete High School
- Completed High School
- Undergraduate degree at University
- Postgraduate degree at University

Are you currently working?

- Yes
- No

Please state the time duration in month or year when you were diagnosed with cancer.

- Please specify:

- Not Known

At what stage was your cancer when you were first diagnosed?

- STAGE 1
- STAGE 2
- STAGE 3
- STAGE 4
- Not Known

What is your current cancer status?

- Currently on treatment
- Active Disease
- In Remission

Have you experienced a recurrence of your cancer?

- Yes
- No

Did you have a surgery for your cancer?

Yes

No

Are you currently receiving any of these treatments now?

Chemotherapy

Radiation therapy

No

If you are currently receiving any other treatment,

Please specify:

No

Fear of Cancer Recurrence (Severity Subscale):

Most people who have been diagnosed with cancer are worried, to varying degrees, that there might be a recurrence of the cancer. **By recurrence, we mean the possibility that the cancer could return or progress in the same place or in another part of the body.** This questionnaire aims to better understand the experience of worries about cancer recurrence. Please read each statement and indicate to what degree it applied to you **DURING THE PAST MONTH** by circling the appropriate number.

0 Not at all	1 A little	2 Somewhat	3 A lot	4 A great deal

9. I am worried or anxious about the possibility of cancer recurrence	0	1	2	3	4
10. I am afraid of cancer recurrence	0	1	2	3	4
11. I believe it is normal to be worried or anxious about the possibility of cancer recurrence	0	1	2	3	4
12. When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family)	0	1	2	3	4
13. I believe that I am cured and that the cancer will not come back	0	1	2	3	4

14. In your opinion, are you at risk of having a cancer recurrence?

0 Not at all at risk	1 A little at risk	2 Somewhat at risk	3 A lot at risk	4 A great deal at risk

15. How often do you think about the possibility of cancer recurrence?

0 Never	1 A few times a month	2 A few times a week	3 A few times a day	4 Several times a day

16. How much time per day do you spend thinking about the possibility of cancer recurrence?

0 I don't think about it	1 A few seconds	2 A few minutes	3 A few hours	4 Several hours

17. How long have you been thinking about the possibility of cancer recurrence?

0 I don't think about it	1 A few weeks	2 A few months	3 A few years	4 Several years

Fear of Progression (Short Form) (FoP-Q-SF):

Short Fear of Progression Questionnaire (FOP 12)

Your Name: _____ **Age :** _____ **Your Location Today:** _____

_____ **Today's Date:** _____

Instructions Below you will see a list of statements that are related to your illness and possible future concerns. Please place a tick "√ " or cross "X" in the appropriate column as the statement pertains to you. Some questions will not apply to you. Please make a mark under "never" in these cases.

		Never	Seldom	Sometimes	Often	Very Often
1.	I become anxious if I think my disease may progress					
2.	I am nervous prior to doctors' appointments or periodic examinations					
3.	I am afraid of pain					
4.	I have concerns about reaching my professional goals because of my illness					
5.	When I am anxious, I have physical symptoms such as a rapid heartbeat, stomach ache or agitation					
6.	The possibility of my children contracting my disease disturbs me					
7.	It disturbs me that I may have to rely on strangers for activities of daily living					
8.	I am worried that at some point in time I will no longer be able to pursue my hobbies because of my illness					
9.	I am afraid of severe medical treatments during the course of my illness					
10.	I worry that my treatment could damage my body					
11.	I worry about what will become of my family if something should happen to me					
12.	The thought that I might not be able to work due to my illness disturbs me					
		Never	Seldom	Sometimes	Often	Very Often

Physical Symptoms Inventory:

During the past **30 days** did you have any of the following symptoms? If you did have the symptom, did you see a doctor about it? **During the past 30 days did you have?**	No	Yes, but I didn't see doctor	Yes, and I saw doctor
1. An upset stomach or nausea			
2. A backache			
3. Trouble sleeping			
4. A skin rash			
5. Shortness of breath			
6. Chest pain			
7. Headache			
8. Fever			
9. Acid indigestion or heartburn			
10. Eye strain			
11. Diarrhea			
12. Stomach cramps (Not menstrual)			
13. Constipation			
14. Heart pounding when not exercising			
15. An infection			
16. Loss of appetite			
17. Dizziness			
18. Tiredness or fatique			

Ambiguous Cues Task (For assessing interpretation bias):

TABLE I.--STIMULI

Ambiguous cues:	Pain responses	Neutral responses
Terminal	illness, growth	bus, train, airport
Needle	injection, shot	cotton
Wheel	chair	car
Plaster	of paris, fracture	walls
Growth	cancer, tumour	children, economy
Wrenching	pain	spanner
Block	nerve	flats, tackle
Back	pain, ache	front
Relief	pain	laugh
Nerve	pain	guts, courage, endings
Bed	ridden	spread
Pound*	pain	coin
Shot*	injection	gun
Attack*	heart	rape, etc.

*Experiment 1 only.

Sourced from:

Pincus, T., Pearce, S., McClelland, A., Farley, S., & Vogel, S. (1994). Interpretation bias in responses to ambiguous cues in pain patients. *Journal of Psychosomatic Research, 38*(4), 347-353. doi: 10.1016/0022-3999(94)90039-6

Appendix E:

Additional materials relevant to Chapter 4

1. Ethics Approval
2. Participant Information Statement
3. Participant Consent Form
4. Key statistical Output
5. Supplementary tables

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Research Integrity & Ethics Administration
HUMAN RESEARCH ETHICS COMMITTEE

Tuesday, 29 January 2019

Prof Louise Sharpe
Psychology; Faculty of Science
Email: louise.sharpe@sydney.edu.au

Dear Louise,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

I am pleased to inform you that after consideration of your response, your project has been approved.

Details of the approval are as follows:

Project No.:	**2018/993**
Project Title:	**Do symptoms and their interpretation affect women's response to a booklet about fear of cancer recurrence/progression?**
Authorised Personnel:	**Sharpe Louise; Pradhan Poorva; Butow Phyllis;**
Approval Period:	**29/01/2019 – 29/01/2023**
First Annual Report Due:	**29/01/2020**

Documents Approved:

Date Uploaded	Version Number	Document Name
10/01/2019	Version 2	Participant Information Statement Version 2
10/01/2019	Version 1	Participant Consent Form v1
10/01/2019	Version 2	Fear of Progression Questionnaire- Short Form (Revised)
25/10/2018	Version 1	List of Ambiguous words
25/10/2018	Version 1	Demographic Information
25/10/2018	Version 1	Satisfaction Questionnaire
24/10/2018	Version 1	Web interface
24/10/2018	Version 1	Physical Symptom Inventory

Condition/s of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.

THE UNIVERSITY OF SYDNEY

- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,

[REDACTION]

Associate Professor Rita Shackel
Chair, Human Research Ethics Committee (HREC 3)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) and the NHMRC's Australian Code for the Responsible Conduct of Research (2007)

THE UNIVERSITY OF SYDNEY

School of Psychology
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FEAR OF RECURRENCE/PROGRESSION RESOURCE

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part in a research study of a new resource to help with fear of cancer recurrence/progression. We want to determine how satisfied you are with the online resource that provides information on Fear of Cancer Recurrence/Progression and whether you would recommend the resource to other people. We will also see whether reading the resource improves your fears and worries.

This Participant Information Statement describes the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about. Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(2) Who is running the study?

The study is being carried out by the following researchers at the University of Sydney:

- Poorva Pradhan, PhD Candidate, School of Psychology
- Professor Louise Sharpe, Professor of Psychology, School of Psychology
- Professor Phyllis Butow, PoCoG & CeMPED, School of Psychology, SoURCe, Institute of Surgery, University of Sydney

Poorva Pradhan is conducting this study as the basis for the degree of Doctor of Philosophy (Psychology) at The University of Sydney. This will take place under the supervision of Professor Louise Sharpe and Professor Phyllis Butow.

There are no Conflicts of Interest to declare.

(3) What will the study involve for me?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will then be asked to:

Complete a 15-20 minutes online questionnaire (before and after reading the resource) which will ask you about the following:

i) Demographic Information (such as your age and marital status)

ii) Information about your ovarian cancer (such as, statements related to your illness and possible concerns about future course of your illness).

iii) What comes to mind when you read about certain symptoms.

The completion of this questionnaire will lead you to the online resource. After reading this resource, you will be again asked to complete the same questionnaire.

(4) Who can take part in the study?

Any person who has been diagnosed with ovarian cancer is able to participate in this study.

(5) Do I have to be in the study? Can I withdraw from the study once I've started?

Your participation in this research is entirely voluntary and you are not under any obligation to give your consent. You are free to withdraw from the survey at any point, without giving a reason. Whatever your decision, please be assured that it will not affect your medical treatment. It will also not affect your current or future relationship with the staff, researchers or anyone else at the University of Sydney.

(6) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study. However, when people think about their future concerns, it is possible that this could cause some distress. If you do become distressed at any time during this study, please let the researcher know and we will ensure that you receive any additional support that might be necessary.

(7) Are there any benefits associated with being in the study?

While we intend that, this study furthers knowledge on the efficacy of the online resource and may improve the scientific understanding on the Fear of Cancer Recurrence/Progression. It may not be of direct benefit to you.

(8) What will happen to information about me that is collected during the study?

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement. Study findings may be published, but you will not be individually identifiable in these publications.

(9) Can I tell other people about the study?

Yes, you are welcome to tell other people about the study.

(10) What if I would like further information about the study?

When you have read this information, Poorva Pradhan will be available to discuss it with you further and answer any questions you may have. If you would like to know more at any stage during the

study, please feel free to contact Poorva Pradhan (ppra9419@uni.sydney.edu.au) or Professor Louise Sharpe (louise.sharpe@sydney.edu.au).

(11) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by answering the relevant question in an online questionnaire. This feedback will be in the form of a one-page summary of the study's results. You will receive this feedback after the study is finished.

(12) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney *[Study Protocol No. :- 2018/993].* As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** human.ethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep.

PARTICIPANT CONSENT FORM

I agree to take part in this research study. In giving my consent I state that:

- I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- The researchers have answered any questions that I had about the study and I am happy with the answers.
- I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.
- I understand that I can withdraw from the study at any time.
- I understand that my questionnaire responses cannot be withdrawn once they are submitted, as they are anonymous and therefore the researchers will not be able to tell which one is mine.
- I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law.
- I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me.

I consent to:

I would like to receive feedback about the overall results of this study YES ☐ NO ☐

If you answered **YES**, please indicate your preferred form of feedback and address:

☐ Postal: _____

_____

☐ Email: _____

I, ..., CONSENT.
PRINT name

Email address:_____

T-Test

Group Statistics

	Participant_Groups	N	Mean	Std. Deviation	Std. Error Mean
AGE	cancer patients	62	56.90	11.642	1.479
	healthy controls	96	43.20	13.874	1.416

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
AGE	Equal variances assumed	11.007	.001	6.448	156	.000	13.705	2.126	9.507	17.904
	Equal variances not assumed			6.695	145.577	.000	13.705	2.047	9.659	17.751

```
CROSSTABS
  /TABLES=Participant_Groups BY Employment_Status
  /FORMAT=AVALUE TABLES
  /STATISTICS=CHISQ
  /CELLS=COUNT
  /COUNT ROUND CELL.
```

Crosstabs

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
Participant_Groups * Are you currently working?	158	99.4%	1	0.6%	159	100.0%

Participant_Groups * Are you currently working? Crosstabulation

Count

		Are you currently working?		
		Yes	No	Total
Participant_Groups	cancer patients	28	34	62
	healthy controls	75	21	96
Total		103	55	158

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	18.038[a]	1	.000		
Continuity Correction[b]	16.615	1	.000		
Likelihood Ratio	17.989	1	.000		
Fisher's Exact Test				.000	.000
Linear-by-Linear Association	17.924	1	.000		
N of Valid Cases	158				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 21.58.

b. Computed only for a 2x2 table

```
*Nonparametric Tests: Independent Samples.
NPTESTS
  /INDEPENDENT TEST (Educational_status) GROUP (Participant_Groups)
  /MISSING SCOPE=ANALYSIS USERMISSING=EXCLUDE
  /CRITERIA ALPHA=0.05  CILEVEL=95.
```

Nonparametric Tests

Hypothesis Test Summary

	Null Hypothesis	Test	Sig.	Decision
1	The distribution of Educational Status is the same across categories of Participant_Groups.	Independent-Samples Mann-Whitney U Test	.000	Reject the null hypothesis.

Asymptotic significances are displayed. The significance level is .05.

NPar Tests

Mann-Whitney Test

Ranks

	Participant_Groups	N	Mean Rank	Sum of Ranks
Educational Status	cancer patients	62	55.65	3450.00
	healthy controls	96	94.91	9111.00
	Total	158		

Test Statistics[a]

	Educational Status
Mann-Whitney U	1497.000
Wilcoxon W	3450.000
Z	-5.753
Asymp. Sig. (2-tailed)	.000

a. Grouping Variable: Participant_Groups

Correlations

		AGE	Educational Status	Are you currently working?	IB
AGE	Pearson Correlation	1	-.344**	.156	.178*
	Sig. (2-tailed)		.000	.050	.025
	N	158	158	158	158
Educational Status	Pearson Correlation	-.344**	1	-.241**	-.298**
	Sig. (2-tailed)	.000		.002	.000
	N	158	158	158	158
Are you currently working?	Pearson Correlation	.156	-.241**	1	.253**
	Sig. (2-tailed)	.050	.002		.001
	N	158	158	158	158
IB	Pearson Correlation	.178*	-.298**	.253**	1
	Sig. (2-tailed)	.025	.000	.001	
	N	158	158	158	158

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Univariate Analysis of Variance

Between-Subjects Factors

		Value Label	N
Participant_Groups	1	cancer patients	62
	2	healthy controls	96

Descriptive Statistics

Dependent Variable: IB

Participant_Groups	Mean	Std. Deviation	N
cancer patients	6.0323	3.26415	62
healthy controls	2.9167	1.70242	96
Total	4.1392	2.86749	158

Tests of Between-Subjects Effects

Dependent Variable: IB

Source	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
Corrected Model	387.212[a]	4	96.803	16.389	.000	.300
Intercept	91.662	1	91.662	15.518	.000	.092
Age	9.486	1	9.486	1.606	.207	.010
Educational_status	6.711	1	6.711	1.136	.288	.007
Employment_Status	6.181	1	6.181	1.046	.308	.007
Participant_Groups	222.188	1	222.188	37.616	.000	.197
Error	903.724	153	5.907			
Total	3998.000	158				
Corrected Total	1290.937	157				

a. R Squared = .300 (Adjusted R Squared = .282)

Regression

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	Symptoms_Total, IB[b]	.	Enter

a. Dependent Variable: FOP_PRE

b. All requested variables entered.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.442[a]	.195	.168	7.77381

a. Predictors: (Constant), Symptoms_Total, IB

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	863.606	2	431.803	7.145	.002[b]
	Residual	3565.491	59	60.432		
	Total	4429.097	61			

a. Dependent Variable: FOP_PRE

(ii)

b. Predictors: (Constant), Symptoms_Total, IB

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	19.986	6.704		2.981	.004	6.572	33.401
	IB	.968	.313	.371	3.096	.003	.342	1.593
	Symptoms_Total	.364	.253	.172	1.438	.156	-.143	.871

a. Dependent Variable: FOP_PRE

Correlations

		IB	FOP_PRE	Symptoms_Total	COMPUTE fatiguepainappetite=Chest_Pain + Heart_Pounding + Loss_of_Appetite + Fatigue	pain
IB	Pearson Correlation	1	.408**	.219	.435**	.133
	Sig. (2-tailed)		.001	.087	.000	.302
	N	158	62	62	62	62
FOP_PRE	Pearson Correlation	.408**	1	.253*	.508**	.088
	Sig. (2-tailed)	.001		.047	.000	.499
	N	62	62	62	62	62
Symptoms_Total	Pearson Correlation	.219	.253*	1	.591**	.649**
	Sig. (2-tailed)	.087	.047		.000	.000
	N	62	62	62	62	62
COMPUTE fatiguepainappetite=Chest_Pain + Heart_Pounding + Loss_of_Appetite + Fatigue	Pearson Correlation	.435**	.508**	.591**	1	.279*
	Sig. (2-tailed)	.000	.000	.000		.028
	N	62	62	62	62	62
pain	Pearson Correlation	.133	.088	.649**	.279*	1
	Sig. (2-tailed)	.302	.499	.000	.028	
	N	62	62	62	62	62

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Reliability

Case Processing Summary

		N	%
Cases	Valid	62	39.2
	Excluded[a]	96	60.8
	Total	158	100.0

a. Listwise deletion based on all variables in the procedure.

Reliability Statistics

Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items	N of Items
.848	.857	12

Crosstabs

Symmetric Measures

		Value	Asymptotic Standard Error[a]	Approximate T[b]	Approximate Significance
Measure of Agreement	Kappa	.802	.014	37.827	.000
N of Valid Cases		2210			

a. Not assuming the null hypothesis.

b. Using the asymptotic standard error assuming the null hypothesis.

```
Run MATRIX procedure:

*************** PROCESS Procedure for SPSS Version 3.4.1 ***************

          Written by Andrew F. Hayes, Ph.D.       www.afhayes.com
    Documentation available in Hayes (2018). www.guilford.com/p/hayes3

**************************************************************************
Model  : 1
    Y  : FOP_PRE
    X  : Symptoms
    W  : IB

Sample
Size:  62

**************************************************************************
OUTCOME VARIABLE:
 FOP_PRE

Model Summary
          R       R-sq        MSE          F        df1        df2
p
      .4421      .1955    61.4353     4.6979     3.0000    58.0000
.0053

Model
              coeff         se          t          p       LLCI       ULCI
constant    17.2025    16.0637     1.0709      .2887   -14.9528    49.3577
Symptoms      .4648      .5843      .7955      .4296     -.7048     1.6344
IB           1.4990     2.7990      .5355      .5943    -4.1039     7.1018
Int_1        -.0189      .0990     -.1910      .8492     -.2171      .1793

Product terms key:
 Int_1    :        Symptoms x        IB

Covariance matrix of regression parameter estimates:
           constant   Symptoms         IB      Int_1
constant   258.0436    -9.2985   -40.6559     1.4431
Symptoms    -9.2985      .3414     1.4439     -.0520
IB         -40.6559     1.4439     7.8344     -.2754
Int_1        1.4431     -.0520     -.2754      .0098

Test(s) of highest order unconditional interaction(s):
       R2-chng          F        df1        df2          p
X*W      .0005      .0365     1.0000    58.0000      .8492

********************** ANALYSIS NOTES AND ERRORS ************************

Level of confidence for all confidence intervals in output:
  95.0000

NOTE: Variables names longer than eight characters can produce incorrect
output.
      Shorter variable names are recommended.

------ END MATRIX -----
```

Table S1: Mean interpretation bias scores between levels of demographic variables for each group (cancer patients vs controls).

		Age		**Educational Status**				**Employment Status**	
		< 50 years	≥ 50 years	1	2	3	4	Yes	No
Mean IB Scores	Ovarian Cancer sample	7.18	5.78	0	5.96	6.68	5.00	5.46	6.5
	Healthy controls	2.92	2.91	0	3.00	3.25	2.8	2.92	2.91

IB: Interpretation Bias

1: Did not complete high school

2: Completed high school

3: Undergraduate degree at university

4: Postgraduate degree at university

Yes: Currently employed

No: Currently not employed

Table S2: percentage of health-related responses by each word type for women with and without cancer.

Ambiguous Words	**Percentage of women with cancer selecting health-related responses**	**Percentage of women without cancer selecting health-related responses**
Terminal	58.1	44.8
Needle	72.6	38.5
Wheel	8.1	0
Plaster	58.1	61.5
Growth	32.3	4.2
Wrenching	48.4	22.9
Block	25.8	3.1
Back	43.5	26

Relief	29	30.2
Nerve	59.7	24
Bed	38.7	7.3
Pound	27.4	0
Shot	40.3	12.5
Attack	33.9	17.7

Table S3: Unadjusted and covariate adjusted descriptive statistics for interpretation bias score between participant groups (cancer patients and healthy controls).

Participant Groups	**Mean Score on IB**	**SE**	**95% CI Lower**	**Upper**	**Unadjusted F**	**p**	**Unadjusted R^2**	**Adjusted F**	**Adjusted R^2**
cancer patients	6.032	.31	5.421	6.643	61.65	.000	.283		
healthy controls	2.917	.25	2.426	3.408				43.67	.281

Table S4: Table showing regression (with interpretation bias and symptom burden as predictors of FCR/P) and moderation analysis (with interpretation bias as a moderating variable).

Predictors	**Unstandardized β**	**SE**	**t**	**p**	**95.0% CI for β**	
					Lower	Upper
IB	.968	.313	3.096	.003	.342	1.593
Symptoms	.364	.253	1.438	.156	-.143	.871
Interaction effect	**R^2 change**	**F**	**df**	**p**		
IB X Symptoms	.0005	.0365	1, 58	.84		

Overall model summary	R^2 change	F	df	p	Adjusted R^2	SE
	.195	7.145	2, 59	.002	.168	7.77

IB: Interpretation bias

Table S5: Table summarizing prevalence of physical symptoms in people with high and low FCR/P.

Symptoms	Presence of symptoms	N	Mean FoP Scores	Mean Difference	t	df	Sig	95.0% CI (Mean Difference)	
								Lower	Upper
Nausea	No	30	35.97	.75	.34	60	.73	-3.61	5.11
	Yes	32	35.22						
Backache	No	34	36.85	2.82	1.303	60	.20	-1.51	7.14
	Yes	28	34.04						
Trouble sleeping	No	20	34.5	-1.6	-.69	60	.50	-6.25	3.06
	Yes	42	36.09						
Skin rash	No	50	36.16	2.99	1.09	60	.28	-2.47	8.46
	Yes	12	33.17						
Shortness of breath	No	38	34.74	-2.18	-.98	60	.33	-6.63	2.27
	Yes	24	36.92						
Chest pain	No	51	34.05	-8.58	-3.26	60	.002	-13.84	-3.31
	Yes	11	42.63						
Headache	No	23	35.69	.18	-.081	60	.94	-4.33	4.70
	Yes	39	35.51						
Fever	No	50	35.94	1.86	.68	60	.50	-3.65	7.36
	Yes	12	34.08						
Heartburn	No	33	34.64	-2.02	-.93	60	.36	-6.36	2.32
	Yes	29	36.65						

Eye strain	No	40	34.85	-2.06	-.91	60	.37	-6.59	2.47
	Yes	22	36.91						
Diarrhoea	No	42	34.43	-3.57	-1.56	60	.12	-8.15	1.01
	Yes	20	38.00						
Stomach cramps	No	26	34.62	-1.66	-.76	60	.45	-6.06	2.74
	Yes	36	36.28						
Constipation	No	33	33.39	-4.68	-2.22	60	.03	-8.88	-.47
	Yes	29	38.07						
Heart pounding	No	36	33.22	-5.62	-2.69	60	.009	-9.8	-1.45
	Yes	26	38.84						
Infection	No	54	36.03	3.58	1.09	60	.28	-2.91	9.98
	Yes	8	32.5						
Loss of appetite	No	44	34.16	-4.9	-2.11	60	.04	-9.53	-.26
	Yes	18	39.06						
Dizziness	No	44	34.61	-3.33	-1.41	60	.16	-8.06	1.40
	Yes	18	37.94						
Fatigue	No	9	28.44	-8.35	-2.86	60	.006	-14.16	-2.54
	Yes	53	36.79						

Appendix F:

Additional materials relevant to Chapter 5

1. Ethics Approval
2. Participant Information Statement
3. Participant Consent Form
4. Key statistical Output
5. Supplementary tables

THE UNIVERSITY OF SYDNEY

Research Integrity & Ethics Administration
HUMAN RESEARCH ETHICS COMMITTEE

Monday, 17 February 2020

Prof Louise Sharpe
Psychology; Faculty of Science
Email: louise.sharpe@sydney.edu.au

Dear Louise,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

I am pleased to inform you that after consideration of your response, your project has been approved.

Details of the approval are as follows:

Project No.:	**2019/1042**
Project Title:	**Testing the threat interpretation model of fear of cancer recurrence in women with breast cancer**
Authorised Personnel:	**Sharpe Louise; Butow Phyllis; Pradhan Poorva; Shaw Joanne;**
Approval Period:	**17 February 2020 to 17 February 2024**
First Annual Report Due:	**17 February 2021**

Documents Approved:

Date Uploaded	Version Number	Document Name
31/01/2020	Version 2	Death Anxiety Questionnaire (Clean Copy)
31/01/2020	Version 1	Email for participation
31/01/2020	Version 2	Consent form version 2.0 (Clean Copy)
31/01/2020	Version 2	Participant Information Statement V_2.0 (Clean copy)
27/11/2019	Version 1	Demographic Information
27/11/2019	Version 1	Physical Symptoms Inventory
27/11/2019	Version 1	List of Ambiguous words
27/11/2019	Version 1	Fear of Cancer Recurrence Inventory
27/11/2019	Version 1	Breast Cancer advert
27/11/2019	Version 1	Fear of Progression Questionnaire- Short Form
27/11/2019	Version 1	Impact of Events Scale - Revised
27/11/2019	Version 1	Metacognitions Questionnaire

Special Condition/s of Approval

1. Please ensure the last question of the questionnaire links to the new survey to register for feedback.

2. PIS says 'The data collected will be stored perpetually.' this should read 'the data collected will be stored in perpetuity'. Please revise.

Condition/s of Approval

- Research must be conducted according to the approved proposal.

- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.

- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.

THE UNIVERSITY OF SYDNEY

- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

This letter constitutes ethical approval only.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,

[REDACTION]

Associate Professor Helen Mitchell
Chair
Human Research Ethics Committee (HREC 1)

The University of Sydney of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2007) and the NHMRC's Australian Code for the Responsible Conduct of Research (2007)

THE UNIVERSITY OF SYDNEY

School of Psychology
Faculty of Science

ABN 15 211 513 464

PROFESSOR LOUISE SHARPE
PROFESSOR, SCHOOL OF PSYCHOLOGY, THE UNIVERSITY OF SYDNEY

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Web: http://www.sydney.edu.au/

PREDICTORS OF FEAR OF CANCER RECURRENCE FOLLOWING BREAST CANCER

PARTICIPANT INFORMATION STATEMENT

(13) What is this study about?

You are invited to take part in a research study that aims to understand fear of cancer recurrence following breast cancer. There are numerous reasons that have been proposed to explain why some people become preoccupied by fear of cancer returning. In this study, we are investigating a number of possible predictors, such as physical symptoms, intrusive thoughts about cancer, fears about death, and beliefs about worry. This will help us to better understand fears of cancer recurrence.

This Participant Information Statement describes the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about. Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(14) Who is running the study?

The study is being carried out by the following researchers at the University of Sydney:

- Poorva Pradhan, PhD Candidate, School of Psychology
- Professor Louise Sharpe, Professor of Psychology, School of Psychology
- Professor Phyllis Butow, PoCoG & CeMPED, School of Psychology, SoURCe, Institute of Surgery, University of Sydney
- Dr Joanne Shaw, Chief Executive Officer, PoCoG, School of Psychology, University of Sydney

Poorva Pradhan is conducting this study as the basis for the degree of Doctor of Philosophy (Psychology) at The University of Sydney. This will take place under the supervision of Professor Louise Sharpe and Professor Phyllis Butow.

There are no Conflicts of Interest to declare.

(15) What will the study involve for me?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will then be asked to:

Complete a 30-40 minutes online questionnaire (before and after reading the resource) which will ask you about the following:

iv) Demographic Information (such as your age and marital status)
v) Information about your breast cancer (such as, statements related to your illness and possible concerns about future course of your illness).
vi) What comes to mind when you read about certain symptoms.
vii) Fear of cancer recurrence, beliefs about worry, intrusive thoughts and fears of death.

(16) Who can take part in the study?

Any person who has been diagnosed with breast cancer is able to participate in this study.

(17) Do I have to be in the study? Can I withdraw from the study once I've started?

Your participation in this research is entirely voluntary and you are not under any obligation to give your consent. You are free to withdraw from the survey at any point, without giving a reason. Whatever your decision, please be assured that it will not affect your medical treatment. It will also not affect your current or future relationship with the staff, researchers or anyone else at the University of Sydney.

(18) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study. However, when people think about their future concerns, it is possible that this could cause some distress. If you do become distressed at any time during this study, please let the researcher know and we will ensure that you receive any additional support that might be necessary. OR, if you wish you can directly access Breast Cancer Network Helpline:

BCNA Helpline number- 1800 500 258
Between 9.00 am and 6.00 pm (AEST) Monday to Thursday and 9.00 am to 5.00 pm on a Friday.

(19) Are there any benefits associated with being in the study?

While we intend that, this study furthers knowledge about the Fear of Cancer Recurrence/Progression, It will not be of direct benefit to you.

(20) What will happen to information about me that is collected during the study?

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. However, we will only collect your preferred contact details if you want to receive information about the study later. Your information will only be used for the purposes outlined in this Participant Information Statement. Study findings may be published, but you will not be individually identifiable in these publications. Because this study is anonymous, if you take part and later change your mind, we will not be able to remove your data. The data collected will be stored in perpetuity.

(21) Can I tell other people about the study?

Yes, you are welcome to tell other people about the study.

(22) What if I would like further information about the study?

If you would like to know more at any stage during the study, please feel free to contact Poorva Pradhan (ppra9419@uni.sydney.edu.au) or Professor Louise Sharpe (louise.sharpe@sydney.edu.au).

(23) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by answering the relevant question in an online questionnaire (through a separate link). This feedback will be in the form of a one-page summary of the study's results. You will receive this feedback after the study is finished.

(24) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney *[Study Protocol No. :- 2019/1042].* As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** human.ethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep.

PREDICTORS OF FEAR OF CANCER RECURRENCE FOLLOWING BREAST CANCER

PARTICIPANT CONSENT FORM

I agree to take part in this research study. In giving my consent I state that:

- I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- The researchers have answered any questions that I had about the study and I am happy with the answers.
- I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.
- I understand that I can withdraw from the study at any time.
- I understand that my questionnaire responses cannot be withdrawn once they are submitted, as they are anonymous and therefore the researchers will not be able to tell which one is mine.
- I understand that the data collected will be stored in perpetuity.

- I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law.

- I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me.

If you consent to the above, please press the button below:

I CONSENT.

Metacognitions Questionnaire (MCQ - 30)

Version: 1 MCQ Version Date: 04.01.2010

Patient Identification Number:

This questionnaire is concerned with beliefs people have about their thinking. Listed below are a number of beliefs that people have expressed. Please read each item and indicate how much you generally agree with it by circling the appropriate number. Please respond to all of the items, there are no right or wrong answers.

		Do not agree	Agree slightly	Agree moderately	Agree very much
1	My worrying is dangerous for me	1	2	3	4
2	My worrying could make me go mad	1	2	3	4
3	I have a poor memory	1	2	3	4
4	I cannot ignore my worrying thoughts	1	2	3	4
5	I need to worry in order to remain organised	1	2	3	4
6	I pay close attention to the way my mind works	1	2	3	4
7	I could make myself sick with worrying	1	2	3	4
8	I have little confidence in my memory for places	1	2	3	4
9	I need to worry in order to work well	1	2	3	4
10	I think a lot about my thoughts	1	2	3	4
11	I do not trust my memory	1	2	3	4
12	I have little confidence in my memory for words and names	1	2	3	4
13	I will be punished for not controlling certain thoughts	1	2	3	4
14	It is bad to think certain thoughts	1	2	3	4
15	I am aware of the way my mind works when I am thinking through a problem	1	2	3	4
16	My worrying thoughts persist, no matter how I try to stop them	1	2	3	4
17	I constantly examine my thoughts	1	2	3	4
18	I have little confidence in my memory for actions	1	2	3	4
19	I should be in control of my thoughts all of the time	1	2	3	4
20	Worrying helps me to solve problems	1	2	3	4
21	Worrying helps me to avoid problems in the future	1	2	3	4
22	Worrying helps me cope	1	2	3	4
23	If I did not control a worrying thought and then it happened, it would be my fault	1	2	3	4
24	I am constantly aware of my thinking	1	2	3	4
25	Not being able to control my thoughts is a sign of weakness	1	2	3	4
26	If I could not control my thoughts, I would not be able to function	1	2	3	4
27	My memory can mislead me at times	1	2	3	4
28	Worrying helps me to get things sorted out in my mind	1	2	3	4
29	I monitor my thoughts	1	2	3	4
30	When I start worrying I cannot stop	1	2	3	4

Impact of Events – Revised (Intrusions Subscale) (IES - R)

Below is a list of difficulties people sometimes have after stressful life events. Please read each item, and then indicate how distressing each difficulty has been for you DURING THE PAST SEVEN DAYS with respect to your cancer.
How much have you been distressed or bothered by these difficulties?

	Not at all	A little bit	Moderately	Quite a bit	Extremely
1. Any reminder brought back feelings about it.	○	○	○	○	○
2. I had trouble staying asleep	○	○	○	○	○
3. Other things kept making me think about it	○	○	○	○	○
4. I thought about it when I didn't mean to	○	○	○	○	○
5. Pictures about it popped into my mind	○	○	○	○	○
6. I found myself acting or feeling as though I was back at that time	○	○	○	○	○
7. I had waves of strong feelings about it	○	○	○	○	○
8. I had dreams about it	○	○	○	○	○

Threat Appraisal (Appraisal of Life Events – Threat Subscale)

Please indicate the extent to which each of the following adjectives best describes your perceptions about **having cancer**.

Do this by selecting the appropriate point on the scale.

	Not At All 0	1	2	3	4	Very Much So 5
Fearful	◯	◯	◯	◯	◯	◯
Worrying	◯	◯	◯	◯	◯	◯
Hostile	◯	◯	◯	◯	◯	◯
Threatening	◯	◯	◯	◯	◯	◯
Frightening	◯	◯	◯	◯	◯	◯
Terrifying	◯	◯	◯	◯	◯	◯

		FoP_Total	FCR_Total	Physical_Symptoms_Total	IES_R_Total	Threat_Expectancy_Total	MCQ_SubscalesTotal
FoP_Total	Pearson Correlation	1	.747**	.482**	.760**	.334**	.400**
	Sig. (2-tailed)		.000	.000	.000	.000	.000
	N	147	147	147	147	147	147
FCR_Total	Pearson Correlation	.747**	1	.386**	.700**	.345**	.366**
	Sig. (2-tailed)	.000		.000	.000	.000	.000
	N	147	147	147	147	147	147
Physical_Symptoms_Total	Pearson Correlation	.482**	.386**	1	.514**	.123	.219**
	Sig. (2-tailed)	.000	.000		.000	.138	.008
	N	147	147	147	147	147	147
IES_R_Total	Pearson Correlation	.760**	.700**	.514**	1	.245**	.471**
	Sig. (2-tailed)	.000	.000	.000		.003	.000
	N	147	147	147	147	147	147
Threat_Expectancy_Total	Pearson Correlation	.334**	.345**	.123	.245**	1	.292**
	Sig. (2-tailed)	.000	.000	.138	.003		.000
	N	147	147	147	147	147	147
MCQ_SubscalesTotal	Pearson Correlation	.400**	.366**	.219**	.471**	.292**	1
	Sig. (2-tailed)	.000	.000	.008	.000	.000	
	N	147	147	147	147	147	147

Regression

Descriptive Statistics

	Mean	Std. Deviation	N
FCR_Total	17.7347	6.40668	147
Pain_Sympts	5.6395	1.21038	147
IB_Total_PP	5.8163	3.33109	147

Correlations

		FCR_Total	Pain_Sympts	IB_Total_PP
Pearson Correlation	FCR_Total	1.000	.400	.449
	Pain_Sympts	.400	1.000	.313
	IB_Total_PP	.449	.313	1.000
Sig. (1-tailed)	FCR_Total	.	.000	.000
	Pain_Sympts	.000	.	.000
	IB_Total_PP	.000	.000	.
N	FCR_Total	147	147	147
	Pain_Sympts	147	147	147
	IB_Total_PP	147	147	147

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	IB_Total_PP, Pain_Sympts[b]	.	Enter

a. Dependent Variable: FCR_Total

b. All requested variables entered.

Model Summary[b]

				Std. Error of	Change Statistics				
Model	R	R Square	Adjusted R Square	the Estimate	R Square Change	F Change	df1	df2	Sig. F Change
1	.525[a]	.276	.266	5.48906	.276	27.447	2	144	.000

a. Predictors: (Constant), IB_Total_PP, Pain_Sympts

b. Dependent Variable: FCR_Total

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	1653.961	2	826.980	27.447	.000[b]
	Residual	4338.692	144	30.130		
	Total	5992.653	146			

a. Dependent Variable: FCR_Total

b. Predictors: (Constant), IB_Total_PP, Pain_Sympts

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	5.132	2.169		2.366	.019	.845	9.419
	Pain_Sympts	1.524	.395	.288	3.855	.000	.742	2.305
	IB_Total_PP	.690	.144	.359	4.802	.000	.406	.973

a. Dependent Variable: FCR_Total

```
Run MATRIX procedure:

*************** PROCESS Procedure for SPSS Version 3.4.1 ***************

          Written by Andrew F. Hayes, Ph.D.       www.afhayes.com
    Documentation available in Hayes (2018). www.guilford.com/p/hayes3

**************************************************************************
Model  : 1
    Y  : FCR_Tota
    X  : Pain_Sym
    W  : IB_Total

Sample
Size:  147

**************************************************************************
OUTCOME VARIABLE:
 FCR_Tota

Model Summary
          R       R-sq        MSE          F        df1        df2
p
      .5514      .3040    29.1655    20.8235     3.0000   143.0000
.0000

Model
```

```
              coeff         se          t          p       LLCI       ULCI
constant    14.2502     4.3572     3.2705      .0013     5.6373    22.8631
Pain_Sym      .0245      .7357      .0333      .9735    -1.4297     1.4787
IB_Total    -1.0753      .7487    -1.4361      .1531    -2.5553      .4047
Int_1         .2819      .1175     2.4002      .0177      .0497      .5141

Product terms key:
 Int_1    :        Pain_Sym x        IB_Total

Covariance matrix of regression parameter estimates:
           constant   Pain_Sym   IB_Total      Int_1
constant    18.9853    -3.1252    -2.8124      .4462
Pain_Sym    -3.1252      .5412      .4420     -.0734
IB_Total    -2.8124      .4420      .5606     -.0864
Int_1         .4462     -.0734     -.0864      .0138

Test(s) of highest order unconditional interaction(s):
       R2-chng          F        df1        df2          p
X*W      .0280     5.7610     1.0000   143.0000      .0177
----------
    Focal predict: Pain_Sym (X)
          Mod var: IB_Total (W)

Conditional effects of the focal predictor at values of the moderator(s):

   IB_Total     Effect         se          t          p       LLCI
ULCI
     3.0000      .8702      .4746     1.8336      .0688     -.0679
1.8084
     5.0000     1.4341      .3906     3.6716      .0003      .6620
2.2061
     9.0000     2.5617      .5816     4.4047      .0000     1.4121
3.7114

Data for visualizing the conditional effect of the focal predictor:
Paste text below into a SPSS syntax window and execute to produce plot.

DATA LIST FREE/
   Pain_Sym   IB_Total   FCR_Tota   .
BEGIN DATA.
     4.0000     3.0000    14.5054
     6.0000     3.0000    16.2459
     7.0000     3.0000    17.1161
     4.0000     5.0000    14.6102
     6.0000     5.0000    17.4783
     7.0000     5.0000    18.9124
     4.0000     9.0000    14.8197
     6.0000     9.0000    19.9432
     7.0000     9.0000    22.5049
END DATA.
GRAPH/SCATTERPLOT=
 Pain_Sym WITH     FCR_Tota BY       IB_Total .

************************ ANALYSIS NOTES AND ERRORS ************************

Level of confidence for all confidence intervals in output:
  95.0000

W values in conditional tables are the 16th, 50th, and 84th percentiles.
```

```
NOTE: Variables names longer than eight characters can produce incorrect
output.
      Shorter variable names are recommended.

------ END MATRIX -----
```

```
Run MATRIX procedure:

**************** PROCESS Procedure for SPSS Version 3.4.1 ****************

          Written by Andrew F. Hayes, Ph.D.       www.afhayes.com
    Documentation available in Hayes (2018). www.guilford.com/p/hayes3

**************************************************************************
Model  : 1
    Y  : FoP_Tota
    X  : Pain_Sym
    W  : IB_Total

Sample
Size:  147

**************************************************************************
OUTCOME VARIABLE:
 FoP_Tota

Model Summary
          R       R-sq        MSE          F        df1        df2
p
      .5918      .3503    66.0513    25.6981     3.0000   143.0000
.0000

Model
              coeff         se          t          p       LLCI       ULCI
constant    13.4893     6.5571     2.0572      .0415      .5279    26.4508
Pain_Sym     2.1448     1.1071     1.9373      .0547     -.0436     4.3333
IB_Total      .7282     1.1267      .6463      .5191    -1.4990     2.9555
Int_1         .0814      .1768      .4604      .6459     -.2680      .4308

Product terms key:
 Int_1    :        Pain_Sym x        IB_Total

Test(s) of highest order unconditional interaction(s):
       R2-chng          F        df1        df2          p
X*W      .0010      .2119     1.0000   143.0000      .6459

*********************** ANALYSIS NOTES AND ERRORS ************************

Level of confidence for all confidence intervals in output:
  95.0000
```

```
NOTE: Variables names longer than eight characters can produce incorrect
output.
      Shorter variable names are recommended.

------ END MATRIX -----
```

Regression

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	IB_Total_PP, Pain_Sympts[b]	.	Enter

a. Dependent Variable: FoP_Total

b. All requested variables entered.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.591[a]	.349	.340	8.10493	.349	38.653	2	144	.000

a. Predictors: (Constant), IB_Total_PP, Pain_Sympts

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	5078.174	2	2539.087	38.653	.000[b]
	Residual	9459.336	144	65.690		

	Total	14537.510	146			

a. Dependent Variable: FoP_Total

b. Predictors: (Constant), IB_Total_PP, Pain_Sympts

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
		B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
1	(Constant)	10.857	3.202		3.390	.001	4.528	17.187
	Pain_Sympts	2.578	.584	.313	4.417	.000	1.424	3.731
	IB_Total_PP	1.238	.212	.413	5.837	.000	.819	1.657

a. Dependent Variable: FoP_Total

Correlations

		IB_Total_PP	Pain_Sympts	FCR_Total	FoP_Total
IB_Total_PP	Pearson Correlation	1	.313**	.449**	.511**
	Sig. (2-tailed)		.000	.000	.000
	N	147	147	147	147
Pain_Sympts	Pearson Correlation	.313**	1	.400**	.442**
	Sig. (2-tailed)	.000		.000	.000
	N	147	147	147	147
FCR_Total	Pearson Correlation	.449**	.400**	1	.747**
	Sig. (2-tailed)	.000	.000		.000
	N	147	147	147	147
FoP_Total	Pearson Correlation	.511**	.442**	.747**	1
	Sig. (2-tailed)	.000	.000	.000	
	N	147	147	147	147

**. Correlation is significant at the 0.01 level (2-tailed).

Regression

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	Cancer Status[b]	.	Enter

2	MCQ_SubscalesTotal, Threat_Expectancy_Total, IES_R_Total[b]	.	Enter
3	IB_Total_PP[b]	.	Enter

a. Dependent Variable: FCR_Total

b. All requested variables entered.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change
1	.446[a]	.199	.193	5.75365	.199	36.022	1	145	.000
2	.731[b]	.535	.522	4.42972	.336	34.209	3	142	.000
3	.748[c]	.559	.543	4.32872	.024	7.704	1	141	.006

a. Predictors: (Constant), Cancer Status

b. Predictors: (Constant), Cancer Status, MCQ_SubscalesTotal, Threat_Expectancy_Total, IES_R_Total

c. Predictors: (Constant), Cancer Status, MCQ_SubscalesTotal, Threat_Expectancy_Total, IES_R_Total, IB_Total_PP

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	28.543	1.862		15.327	.000	24.862	32.224
	Cancer Status	-6.305	1.050	-.446	-6.002	.000	-8.381	-4.229
2	(Constant)	12.520	2.369		5.284	.000	7.836	17.203
	Cancer Status	-1.901	.964	-.135	-1.973	.050	-3.807	.004
	MCQ_SubscalesTotal	.028	.053	.036	.534	.594	-.077	.133
	Threat_Expectancy_Total	.206	.070	.179	2.956	.004	.068	.344
	IES_R_Total	.560	.076	.571	7.388	.000	.410	.710

3	(Constant)	9.234	2.600		3.551	.001	4.094	14.375
	Cancer Status	-1.398	.959	-.099	-1.457	.147	-3.294	.498
	MCQ_SubscalesTotal	.064	.053	.082	1.200	.232	-.042	.170
	Threat_Expectancy_Total	.190	.068	.165	2.784	.006	.055	.326
	IES_R_Total	.485	.079	.495	6.148	.000	.329	.640
	IB_Total_PP	.350	.126	.182	2.776	.006	.101	.599

a. Dependent Variable: FCR_Total

Regression

Variables Entered/Removed[a]

Model	Variables Entered	Variables Removed	Method
1	AGE, Cancer Recurrence, Cancer Status[b]	.	Enter
2	Threat_Expectancy_Total, MCQ_SubscalesTotal, IES_R_Total[b]	.	Enter
3	IB_Total_PP[b]	.	Enter

a. Dependent Variable: FoP_Total

b. All requested variables entered.

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate	Change Statistics				
					R Square Change	F Change	df1	df2	Sig. F Change

1	.563[a]	.317	.303	8.33324	.317	22.115	3	143	.000
2	.792[b]	.628	.612	6.21660	.311	38.985	3	140	.000
3	.816[c]	.666	.649	5.91460	.038	15.661	1	139	.000

a. Predictors: (Constant), AGE, Cancer Recurrence, Cancer Status

b. Predictors: (Constant), AGE, Cancer Recurrence, Cancer Status, Threat_Expectancy_Total, MCQ_SubscalesTotal, IES_R_Total

c. Predictors: (Constant), AGE, Cancer Recurrence, Cancer Status, Threat_Expectancy_Total, MCQ_SubscalesTotal, IES_R_Total, IB_Total_PP

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.	95.0% Confidence Interval for B	
		B	Std. Error	Beta			Lower Bound	Upper Bound
1	(Constant)	65.253	4.998		13.055	.000	55.373	75.133
	Cancer Status	-9.561	1.648	-.434	-5.801	.000	-12.819	-6.303
	Cancer Recurrence	-1.848	1.840	-.073	-1.005	.317	-5.484	1.788
	AGE	-.215	.069	-.222	-3.106	.002	-.352	-.078
2	(Constant)	28.679	5.243		5.470	.000	18.314	39.043
	Cancer Status	-4.093	1.387	-.186	-2.951	.004	-6.834	-1.351
	Cancer Recurrence	-.539	1.389	-.021	-.388	.698	-3.286	2.207
	AGE	-.025	.055	-.025	-.449	.654	-.133	.084
	MCQ_SubscalesTotal	.079	.075	.065	1.051	.295	-.069	.227
	IES_R_Total	.892	.110	.585	8.136	.000	.675	1.109
	Threat_Expectancy_Total	.260	.099	.145	2.638	.009	.065	.455
3	(Constant)	21.693	5.291		4.100	.000	11.231	32.154
	Cancer Status	-3.108	1.343	-.141	-2.315	.022	-5.763	-.454
	Cancer Recurrence	-.722	1.323	-.029	-.546	.586	-3.337	1.892
	AGE	-.012	.052	-.013	-.232	.817	-.115	.091
	MCQ_SubscalesTotal	.151	.074	.125	2.051	.042	.005	.297
	IES_R_Total	.748	.110	.490	6.771	.000	.530	.967
	Threat_Expectancy_Total	.233	.094	.129	2.472	.015	.047	.419
	IB_Total_PP	.683	.173	.228	3.957	.000	.342	1.024

a. Dependent Variable: FoP_Total

Supplementary Tables:

Table (S1): t-test values: Difference between clinical and non-clinical FCR (>22) in terms of interpretation bias, physical symptoms, metacognitions, body threat monitoring, threat expectancy and intrusive thoughts.

Psychological measure	Clinical FCR		Non-clinical FCR		$t_{(145)}$
	M	*SD*	*M*	*SD*	
Interpretation Bias	8.58	4.31	4.85	2.24	6.79***
Pain Symptoms	6.24	1.02	5.43	1.20	3.68***
Metacognitions	36.89	7.47	31.71	8.09	3.46**
Body Threat Monitoring	36.68	11.00	21.92	14.43	5.75***
Threat Expectancy	20.45	3.15	17.26	5.96	3.15**
Intrusive Thoughts	14.31	5.30	4.18	4.63	11.18***

FCR: Fear of Cancer Recurrence

**p < .01, ***p <.001

Table (S2): t-test values: Difference between clinical and non-clinical FoP in terms of interpretation bias, physical symptoms, metacognitions, body threat monitoring, threat expectancy and intrusive thoughts.

Psychological measure	Clinical FoP		Non-clinical FoP		$t_{(145)}$
	M	*SD*	*M*	*SD*	
Interpretation Bias	7.11	3.96	4.82	2.32	4.38***
Pain Symptoms	6.03	1.13	5.33	1.19	3.58***
Metacognitions	37.11	8.47	29.93	6.53	5.80***
Threat Expectancy	19.83	3.89	16.73	6.23	3.48**
Intrusive Thoughts	11.53	6.32	3.16	3.82	9.95***

FoP: Fear of progression

**p < .01, *** p <.001

Table (S3): Hierarchical regression showing variables predicting FCR

Step 1	***Adjusted R^2***	***df***	***F change***	***Significance***	
	.193	1, 145	36.02	.000	
Individual predictors	***Unstandardized β***	***Std. Error***	***t statistic***	***Significance***	
Cancer Status	-6.305	1.05	-6.00	.000	-8

Step 2	***Adjusted R^2***	***df***	***F change***	***Significance***	
	.52	3, 142	34.21	.000	
Individual predictors	***Unstandardized β***	***Std. Error***	***t statistic***	***Significance***	
Cancer Status	-1.901	.964	-1.97	.05	-3
Metacognitions	0.3	.053	-.201	.534	-.0
Threat Expectancy	.21	.07	2.95	.004	.0
Intrusions	.56	.076	7.39	.000	.4

Step 3	***Adjusted R^2***	***df***	***F change***	***Significance***	
	.545	1, 140	7.37	.007	
Individual predictors	***Unstandardized β***	***Std. Error***	***t statistic***	***Significance***	
Cancer Status	-1.39	.959	-1.46	.147	-3
Metacognitions	.064	.053	1.2	.23	-.0
Threat Expectancy	.190	.068	2.78	.006	.0
Intrusions	.49	.079	6.15	.000	.3
Interpretation Bias	.35	.126	2.78	.006	.1

Appendix G:

Additional materials relevant to Chapter 6

1. Satisfaction Questionnaire
2. Key statistical output
3. FCR/P Online Booklet

SATISFACTION QUESTIONNAIRE

Please carefully answer each of the following questions by marking the appropriate box of your choice.

NOT AT ALL

COMPLETELY

QUESTIONS	1	2	3	4	5	6	7	8	9	10
1. Do you feel satisfied after reading the resource, in terms of its usefulness in providing all the relevant information on Fear of Cancer Recurrence?										
2. Do you find the resource helpful in managing or improving your worries and concerns about the cancer coming back or progressing?										
3. Will you recommend this resource to other women who have been diagnosed with ovarian cancer?										
4. Do you feel that the severity of your physical symptoms has decreased over the past one week?										

Between-Subjects Factors

		Value Label	N
clinicalFOP	.00	normal range	22
	1.00	clinical range	28

Descriptive Statistics

	clinicalFOP	Mean	Std. Deviation	N
FOP_PRE	normal range	27.9545	5.03774	22
	clinical range	41.3214	5.70285	28
	Total	35.4400	8.58608	50
FOP_POST	normal range	26.8182	4.30544	22
	clinical range	39.5357	7.67624	28
	Total	33.9400	9.00433	50

Tests of Within-Subjects Contrasts

Measure: FoP

Source	time	Type III Sum of Squares	df	Mean Square	F	Sig.	Partial Eta Squared
time	Linear	52.597	1	52.597	2.695	.107	.053
time * clinicalFOP	Linear	2.597	1	2.597	.133	.717	.003
Error(time)	Linear	936.653	48	19.514			

Paired Samples Test

		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference Lower	Upper			
Pair 1	FOP_PRE - FOP_POST	1.50000	6.19167	.87563	-.25965	3.25965	1.713	49	.093


OVARIAN
CANCER
AUSTRALIA
Fear of Cancer Recurrence
A guide for women with ovarian cancer and their families
INTRODUCTION
WHAT DOES 'CANCER RECURRENCE' MEAN?
WHY ARE WOMEN FEARFUL?
TYPES OF FEARS
COMMON WORRY TIMES
DAY-TO-DAY APPROACHES TO MANAGING YOUR FEARS
CARERS' FEELINGS
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Introduction

One of the most common worries women have after finishing cancer treatment is fear of their cancer coming back. You may hear this called 'fear of cancer recurrence' or, for some women, 'fear of cancer progression'.

Having these fears is a natural and expected reaction. And we know a certain amount of worry can help us problem-solve and find ways to move through our concerns. For example, your fear of a recurrence may lead you to seek further useful information from your medical team or to join a support group. Fears may motivate you to take positive actions that help you feel more in control. For some women, though, their fear is so strong that it will interfere with their day-to-day life and relationships. This may make planning for the future difficult.

With time, most women say their fear of the cancer coming back does lessen, although for many it never completely goes. However, many women also say there are things you can do to help manage your fear of recurrence.

This factsheet discusses cancer recurrence and suggests some tips on how to help you manage your fears. It includes:

- What does 'cancer recurrence' mean?
- Why are women fearful?
- Types of fears
- Common worry times
- Day-to-day approaches to managing your fears
- Carers' feelings
- Some techniques for managing the fear of recurrence
- Finding information online
- Further information and support

It is important to remember that not all women with ovarian cancer will have a recurrence. But if you do, there are usually treatments available to help. We encourage women to speak with their specialist doctor about possible recurrence and treatments.

For detailed information about ovarian cancer and its treatment call **Ovarian Cancer Australia** on 1300 660 334 and ask for a copy of our Resilience Kit to be posted out to you.

What does 'cancer recurrence' mean?

Cancer recurrence means cancer that has come back (recurred). This is usually after a period during which you have had no symptoms and the cancer cannot be detected anywhere in your body.

Ovarian cancer may come back:

- in the same place it began (local recurrence)
- in the lymph nodes near to where it began (regional recurrence)
- in another area of your body some distance from the original cancer (tumor). This is called a 'distant recurrence' or 'metastases.' The most common places in the body for ovarian cancer to spread to are the bowel, liver and lungs.

There are several treatments available to treat a recurrence of ovarian cancer, *no matter where it comes back*. Examples include chemotherapy (most common), surgery, biological therapies and radiotherapy.

Will my cancer come back (recur)?

Knowing how likely it is a cancer will come back depends on several factors such as the type of cancer, the stage and grade of the original cancer, and which treatments you have already had. Speak with your cancer specialist as they will know your individual situation the best.

"I am personally in a good spot at the moment as last month I reached the 10-year mark, and that is pretty good going for Stage III, so I am feeling most fortunate. Mind you, I still experience real fear when tests are due. One never really feels safe again."

- Jan

Introduction

How will I know if the cancer has come back?

You and your doctor may suspect your cancer has come back if you begin to have symptoms similar to those you had when you were first diagnosed. Or, you may notice other changes in your health. Your doctor will be able to explain what symptoms to watch out for that might suggest the cancer has come back. It is important you report these to your doctor.

Your doctor may also suspect your cancer has come back based on changes found in your follow-up physical examination, or if your CA125 level has been rising; see **Ovarian Cancer Australia's** factsheet on CA125 for more information. Some women may have signs the cancer has come back even though their CA125 isn't rising. If tests or symptoms suggest your cancer has recurred, it may then be confirmed by an ultrasound or computed tomography (CT) scan.

It is important to know that for some women, the CA125 test result is not an accurate marker for confirming their cancer has come back.

Responding to new symptoms

Many women speak of feeling that any symptom they develop is a sign their cancer has come back. But developing symptoms does not always mean your cancer has come back. Many symptoms have nothing to do with cancer. However, if you have concerns or a symptom is persistent or severe, see your GP or cancer specialist for advice.

Always tell your doctor about any new symptoms or symptoms that have returned.

Remember: Every change is not cause for alarm! For changes that persist, remember to use common sense in taking steps to address them. Managing fear of recurrence is about finding a balance – you don't need to react to everything urgently. But nor do you want to ignore important symptoms. It is about finding that balance and reacting when necessary.

Why are women fearful?

Fear of the cancer coming back is the most common concern in the first year after treatment finishes. Although most women say the fear lessens over time, it can have a huge impact on their day-to-day life at the time, as well as on those around them.

It is well documented that a significant shock in your life, such as a diagnosis of cancer, can cause a deep sense of loss and grief. Even if your cancer is cured or you are in remission, the sense of loss the cancer causes can continue to affect you for a long time. You can be left feeling uncertain about your future.

Uncertainty about the future and having to take 'new steps' in life often creates a space for fear. Considering all this, it is not surprising that the first things women worry about once their treatment is over are:

- What if my cancer comes back?
- How will I cope if it does?
- Is there treatment to help cancer that comes back?
- How will my children, partner and friends cope?
- If it comes back, will it be worse than last time?

These are difficult questions. Unfortunately, not all of them have clear answers. Unanswered questions can leave you feeling scared, lonely, sad, depressed or helpless. You may feel unable to stop thinking about your cancer coming back, see a future or make plans. However, the answers to many of your questions may not be negative. And there are things you can do for yourself, as well as working with professional support, to help you gradually move away from that gnawing fear that your cancer will come back.

Types of fears

When women worry about cancer coming back, they may have fears relating to:

- what this would mean for those close to them – they don't want to cause anyone more stress, especially children (if they have them)
- coping with more treatment – fears of the side effects, possible pain and treatment success
- taking time off work, study or family life again
- attending follow-up appointments and tests
- loss, grief and possibly dying.

There are different feelings surrounding the fear of cancer coming back. How much you worry can depend on:

- your age
- the stage of your cancer
- the level of support you have
- your personality type
- your past experiences
- your individual circumstances with your family, work/studies and general lifestyle.

Research shows some women worry more intensely about their cancer coming back, including:

- women who had a lot of side effects from their initial treatment (e.g. pain, fatigue, depression, nausea and vomiting)
- younger women
- women who feel isolated and may have little or no support
- women who feel they didn't get enough information about their cancer, its treatment and side effects, especially about sexual changes that may happen after treatment
- women who suffered anxiety and/or depression before their cancer diagnosis.

Types of fears

Managing your fears may seem impossible and there may be times when your thoughts feel completely out of control. Enjoying day-to-day life can be difficult if you are constantly worrying about your cancer coming back. Relationships (intimate, work and others) can be affected. You may find it hard to make plans for future events such as holidays, family celebrations (birthdays, birth of a baby, new year celebrations) and children's school activities.

But there are some practical things you can do to help lessen your worries and bring a greater sense of control over your fears. It is important to look after yourself when your treatment is over. Focus on living a healthy lifestyle and asking for the help and support you need. Many women find this difficult but getting help will relieve stress and provide long-term benefits. It can also lessen the time you may worry about your cancer coming back.

We discuss further ideas in 'Day-to-day approaches to managing your fears' and 'Some techniques for managing the fear of recurrence'.

"My biggest fear was I would not see my daughter live her life. Every other fear paled into insignificance."

- Jan

Common worry times

Worrying about your cancer coming back can happen at any time. But some things may trigger the fear more than others, including:

- going to follow-up appointments, and knowing that a follow-up appointment is approaching
- starting anything new – job, fitness class, studies
- anniversary dates such as the date you were diagnosed or finished treatment
- birthdays, holidays and festivals such as Christmas, and other special occasions such as births or weddings
- hearing someone you know has been diagnosed with cancer
- media stories about people with cancer or about deaths from cancer
- developing symptoms that you cannot explain such as headache, abdominal pain or sore throat
- having long-term side effects from your treatment such as fatigue
- any stressful event within your family – marriage break-ups, job changes or financial difficulties.

Day-to-day approaches to managing your fears

At first it may seem impossible to manage your fears. But with time and effort many women say the intensity of their fears lessens and they can move forward. Below are practical tips that may help control your fears of a recurrence. It is important to remember that what works for one person may not work for another. But it is worth trying several things to see what works best for you.

If your feelings of anxiety persist and are affecting your day-to-day life, you may need further help. We address this in 'Further information and support'.

Recognise your triggers and have a plan

Work out what triggers your fears the most. For some, it might be the lead-up to follow-up appointments, scans and blood tests; for others, it may be the anniversary of being diagnosed. These events can cause severe anxiety as they bring up bad memories and overwhelm some women.

"It is not always there on a daily basis but if cancer comes into the news or I am going back for a follow-up test or if I hear about a friend having cancer – then I start to worry about my cancer coming back."

– Jan

Whatever triggers you, have a plan in place to manage the fear. For example, in the few days before your follow-up appointment, plan to do something special every day, like meet a friend for coffee, have a massage or go out to dinner with someone special. On the day of the appointment, plan another activity to 'reward' yourself for getting through the appointment.

Remember – the feelings will pass.

"I used to find it quite confronting when my specialist would say: 'I'll just send you for a scan to rule out …' But now I find it reassuring because if my doctor is vigilant and I do have a recurrence, it will be found early hopefully."

– Jenny

Day-to-day approaches to managing your fears

Challenge unhelpful thoughts

Balancing out your fears against what really is happening or 'might' happen is very important. Thoughts about your cancer coming back are completely normal after you finish treatment. It is important to manage these thoughts and lessen the impact they can have on your daily life. Sometimes thoughts can seem to 'have a mind of their own' and race ahead, generating more and more worry. Being aware these thoughts are not helpful is important.

When unhelpful thoughts come into your head, stop and ask yourself the following questions:

- Am I letting my thoughts get away with me?
- Are my fears reasonable/logical?
- How would I comfort or advise a friend having thoughts about their cancer coming back?

Allowing thoughts to spiral out of control is something we have all felt. In the table we give examples of unhelpful thoughts, and suggest some more realistic or positive thoughts.

UNHELPFUL THOUGHT	MORE BALANCED THOUGHT
"My cancer will come back, and I will never be able to cope with more treatment or pain. It would be impossible a second time around."	"My doctor said my cancer might come back. If I must have more treatment in the future, I got through it last time with the support of my team and my family, I will get through it again."
"This headache I have had for a few days must mean my cancer has come back and spread to my brain."	"I often got tension headaches before I had cancer. It might be just that. If it keeps up for another couple of days I'll see my GP to make sure."
"I feel so tired all the time and cannot seem to motivate myself; I am scared this means my cancer has come back."	"My nurses told me to take it easy and be kind to myself as I have been through a lot and that I may feel very tired for a long time after my treatment."

Day-to-day approaches to managing your fears

Challenging your fears doesn't mean you are ignoring them. It simply means you are finding ways to manage the fear attached to the thoughts.

One woman who has had ovarian cancer described the way she did this very clearly:

"Try to imagine your mind like a big house with lots of rooms and in one room is the cancer and your fear of it coming back, but you don't have to spend all your time in that room. Spend some time in the other rooms, such as those where there are family/friends who love you, or the one where you can make plans. It doesn't mean you can't go back into the room where your cancer and fear of recurrence is, but just remember to go out and close the door on it sometimes. Be in the present."

Challenging unhelpful thoughts is not always easy; read 'Some techniques for managing the fear of recurrence' for other helpful ideas to help address feelings of fear.

Talk about your fears

Many women say talking to others about their fear helps. This may be difficult and make you feel uncomfortable. And some people say they don't talk about their fears as they don't want to worry or burden those close to them. Most people feel valued and pleased if you confide in them. They will want to provide support where they can but might not know the best way to do this. You and your close family and friends may be hiding your fears from each other, to protect each other. Yet you may have similar fears. Sharing your fears with each other can help reduce loneliness and isolation. One research study has shown that not expressing your concerns about your cancer coming back was associated with worrying more.

It is important you feel safe with who you are talking to. Remember to do it in your own time and not feel you must talk if you are not ready.

You may gain support from talking to:

- **friends and family,** who can continue to comfort and support you after your treatment is over – but they may need reminding you still have fears and need to adjust to life after treatment
- **your doctors and nurses**, who can help you understand which of your fears are realistic and which are not

Day-to-day approaches to managing your fears

- **other women who have had ovarian cancer** – join a support group (online, tele-support or face to face) where you can discuss your fears with women who have been through similar experiences to you. Call Ovarian Cancer Australia for further information on 1300 660 334 or see www.ovariancancer.net.au
- **counsellors** who are trained to help people understand and handle fear of cancer recurrence. They can work closely with you to find methods to manage your fears and anxiety. Social workers, psychologists and psychiatrists are all excellent options for counselling. Start by asking your medical team where you are having treatment if there is ongoing counselling support available. You can also talk to your GP about whether you are eligible for some reduced-cost counselling sessions under a GP mental health care plan.

"Family love you and let you know how important you are, and this calms your worry. Without them I would have been so lonely – I can't even go there. Without support it would have just been terrible."

- Jenny

If your fear of recurrence is ongoing and significantly affecting your overall mood, you should speak with your GP or specialist doctor. They may recommend medication to help with your anxiety or feelings of sadness. This is only one of several options along with counselling and other supports. For more information about how to join a support group or seek counselling call **Ovarian Cancer Australia** on 1300 660 334.

"Don't be isolated in this – get involved with Ovarian Cancer Australia, chat to other women who have had a similar experience as no-one else quite understands it like they will. This is such a relief."

- Jan

Jenny

Day-to-day approaches to managing your fears

Don't miss follow-up appointments

Going to follow up appointments can trigger fear about your cancer coming back. But it is important you attend these appointments even if they make you anxious. Regularly attending the appointments gives you the chance to ask your specialist doctors and nurses about your fears and discuss ways to help you feel less anxious. They can link you in with other professionals such as counsellors, dietitians, exercise physiologist and social workers, who can all help with your road to recovery.

Most women say they feel reassured after their follow-up appointment. It is often the build-up to the appointment that is most challenging time. Read 'Recognise your triggers and have a plan' section above for further tips on how to cope with a follow-up appointment.

"I used to always get anxious before a follow-up appointment, but with each positive result, my fears have diminished. At my five years visit I felt like I didn't need to worry anymore." – Jenny

Focus on being healthy and well

It can help to focus on being healthy rather than the possibility of becoming unwell again. As hard as it is, this has been shown to help reduce anxiety and make you feel more in control of your life again. If you feel healthy you will worry less about your cancer coming back. Putting energy into being healthy rather than worrying about a cancer recurrence is well worth it.

Eat a healthy diet with lots of fresh fruit and vegetables. Avoid excessive sugar, red meat, alcohol and fats. Get regular exercise each day. Exercise has been proven to help combat fatigue and make you feel better. You can access an exercise physiologist with a care plan from your GP to help you feel confident about the best type of exercise for your particular needs. This might include walking, riding your bike, or doing a yoga or Pilates class. Meditation helps many women focus and feel calmer and not worry so much about their cancer returning. Other complementary therapies shown to help women reduce their stress level are acupuncture, Tai Chi, massage, music therapy and guided meditations. Others find comfort in prayer.

Other ways proven to help people feel mentally and emotionally healthy is knowing they are contributing to society: being an active member of your local community. Some people find it helps to join a neighborhood group wanting to

Day-to-day approaches to managing your fears

make change in your community or volunteer at your local charity shop for a few hours every month. Being around people who care about others is comforting and a good distraction from our fears.

Many women express the importance of having a laugh where possible despite difficult circumstances. Nurture your hobbies and spend time with those you love most. Let people know what is best for you – talking about your health or doing 'normal' things like going to a movie or meeting for coffee. These can sometimes be the best 'medicine' to help with feeling healthy and well. Establishing what is important to you and prioritizing these activities and people can help in maintaining your emotional wellbeing.

Be kind and patient with yourself

Remember, recovering from cancer treatment takes time. Although it can be difficult, try to be patient and not expect too much too soon. It can be extremely hard to watch others live their busy and full lives while you still feel tired and worried about your cancer coming back. You may have feelings of guilt that you cannot go back to work or study yet, take the children to school or attend to home duties like you used to. You need to be kind to yourself and keep reminding yourself that things often become more tolerable, and the fear of recurrence generally lessens with time. If fear of cancer recurrence continues to persist over time, we recommend you see your GP to ask for help.

Make plans and look ahead – go on that holiday!

Many women feel unable to plan or think about events in the future. These sorts of things can seem very challenging:

- booking a holiday
- planning future changes in your work/business
- planning your retirement
- dreaming about special occasions with your children or grandchildren (births, weddings and special birthday parties)
- starting new intimate relationships
- taking up a new hobby, training course or looking for a new job
- doing volunteer work.

Day-to-day approaches to managing your fears

Some women say they 'no longer feel they will make old bones'. Or they say they feel they are living in a parallel universe and no longer part of ordinary life. If you no longer feel you have a future, it may not seem worth planning ahead, or you may be scared to plan in case you are not around to enjoy it.

Not making plans can mean you stay stuck and lose out on the chance to do things that could give you pleasure. So, make plans around things that matter to you, even if they seem small. It might be something like a special event at the end of next week. You might choose to plan to do something around an activity or hobby you used to enjoy before you had cancer. Others might prefer to start new hobbies or have different goals after their cancer treatment finishes. This is very normal and can give you a new lease on life after a very difficult time.

The important thing is to remind yourself of what is important to you outside your 'world of cancer'. Having something to look forward to, or new to try, gives life a sense of purpose. This can all be an excellent distraction from any negative thoughts about your cancer coming back.

Moving away from the feeling of being a 'cancer patient' and trying to move towards being an active participant in society again can be very healing. Planning events and actively taking part in them will bring new energy and strengthen your ability to believe that you still do have a future.

Carers' feelings

Caring for someone who has been through cancer and its treatment can be very rewarding, but it can also have challenging times. Carers may also have fears about the cancer coming back. But they may find it hard to express their concerns for fear of upsetting or worrying the person they are caring for.

If you can share your fears with someone you trust, it may help ease the burden. Carers may find some of the tips in this factsheet useful. For more information about caring for someone with cancer:

- **Ovarian Cancer Australia** has a brochure for 'Family and Friends'
- **Cancer Council** has a helpful booklet, 'Caring for someone with cancer'
- **Carers Australia** works with carers' associations in each state and territory to help improve the lives of carers. These associations provide counselling, advice, education and advocacy on behalf of carers (www.carersaustralia.com.au or 1800 242 636).

Some techniques for managing the fear of recurrence

Scientists all over the world are carrying out research studies into the prevention, screening, diagnosis and treatment of ovarian cancer and management of its side effects. While these studies are important, researchers are also aware of the huge impact a cancer diagnosis can have on your emotional wellbeing. This has led to an increase in research in this area, including studies into the fear of recurrence and ways to manage these fears.

For example, researchers at the University of Sydney tested techniques to help people with cancer address the fear of their cancer coming back, including:

- attention training technique
- detached mindfulness
- postponing worry

We describe each technique below.

Because it is normal, and in some ways helpful, to have a realistic concern about your cancer coming back, these techniques don't try to get rid of your fears, but rather try to help you stop getting too caught up in always worrying about your cancer coming back.

"I found it incredibly helpful to work out how mind and emotions are connected." – Jenny

ATTENTION TRAINING TECHNIQUE (ATT)

When someone gets anxious or stressed, they tend to direct their attention in particular ways. For example, they may think over and over about something they did that they regret, or about something they heard that worries them. Or they may focus on how awful or unfair their situation is, and how it is stressing them.

Using up our attention on these things sets up a cycle of self-focused attention. This only serves to increase worry and stress, maintain low mood and promote unhelpful behaviour, such as going to the GP for extra tests, which may provide short-term relief but ultimately only serve to make someone feel more under threat. The more we focus on a problem, the more sensitive we become to it and the more it grows. For example, the more we focus our attention on a dripping tap in the middle of the night, the more irritating it becomes.

These thoughts may feel impossible or beyond your control to change. However, increasing scientific evidence suggests people can train their attention, and in doing so they become less likely to suffer high levels of worry and unpleasant emotions.

Some techniques for managing the fear of recurrence

ATT involves using simple techniques to give you better attention control. ATT is designed to help people put their attention where they want to, rather than where it goes automatically. ATT helps people decrease their tendency to brood over a problem. It can help people to shift their attention more flexibly when unwanted thoughts about cancer recurrence happen.

To get the most out of ATT, it is recommended that you practise for 15 minutes each day for a month. It is like going to a 'gym' for your attention! That is, the attention training exercises are just like using gym equipment – the more you exercise your attentional muscles, the more you build them up, and the more ability you develop.

You may find it helpful to listen to this video on ATT:

► Attention Training Technique

"At first, I thought ATT was a bit weird, but the more I did it, the more I enjoyed feeling like I was in control over what I thought about, not my brain!"

– Susan

DETACHED MINDFULNESS

Detached mindfulness has been described as being aware of internal events (e.g. thoughts or feelings) without any attempt to judge, react or suppress them. Detached mindfulness is not aiming to suppress your thoughts, as doing this uses up a lot of energy and means you will actually think about your worries more. Try this thought suppression experiment to better understand how this might work:

For three minutes try to avoid all thoughts about a blue giraffe. Don't allow yourself to have any thought connected with it, try to push it away. What did you notice? Did you think of a blue giraffe?

Now let your mind roam freely for three minutes and if you have thoughts of blue giraffes watch them in a passive way as part of an overall landscape of thoughts, much like you would watch passing clouds in the sky. What do you notice? How important are any thoughts about a blue giraffe the second time around?

As you might notice, actively trying not to think about these things can sometimes only serve to increase your thoughts about them.

Some techniques for managing the fear of recurrence

Detached mindfulness means being more aware or mindful of your thinking. It involves learning to:

- step back and become an observer of your own thoughts
- understand that the self is much greater than just the content of our thoughts
- see thoughts and feelings as just passing internal events
- accept your thoughts and feelings for what they are and observe them without judging them, reacting to them or trying to get rid of them.

You can think of detached mindfulness as similar to the way you might manage a child playing up when you are out shopping. You could pay a great deal of attention to the child and try to control the child's behaviour. But if the child craves attention, this response could make things worse. It is usually better not to actively engage with the child but to keep a passive/caring watch over the child without doing anything.

Your negative thoughts and beliefs are like that child. If you pay them a great deal of attention, if you control them or use punishment, they misbehave even more. It is better not to try and control or actively engage with them, just keep an awareness of everything. As you do this, try to be aware of yourself as an observer of these things.

The aim of detached mindfulness is not to get rid of worries about cancer recurrence but to help you become less involved with them.

You can learn to view your worries not as truths but as individual passing internal events – like leaves floating down a stream or clouds passing in the sky. If you can view your thoughts like this, they will cause you much less distress, or the distress that they cause can be reduced.

There are many detached mindfulness exercises; here we outline three you may like to practise at home. Once you have got the hang of them, you can use them the next time you have a troubling thought about cancer recurrence: for example, watch the thought, just like you watched the cloud or the tiger in the examples below. Watch and react without noticing or engaging with it.

TIGER TASK

With your eyes closed, form an image of a tiger. Do not attempt to influence or change the image in any way. Just watch the image and the tiger's behaviour. The tiger may move, but don't make it move. It may blink, but don't make it blink.

Some techniques for managing the fear of recurrence

The tiger may wag its tail, but don't make it do that. Watch how the tiger has its own behaviour. Do nothing, but simply watch the image, see how the tiger is simply a thought in your mind, that it is separate from you and it has a behaviour all of its own. After the practice, notice whether you made the tiger move – or did it happen spontaneously?

If you can experience the movement as spontaneous, this is a state of detached mindfulness. You can apply this form of observation to thoughts or images of a negative kind and see what happens with them. Do they change?

CLOUDS METAPHOR

One way to understand detached mindfulness and what it requires is to consider experiencing your thoughts as you would experience clouds passing in the sky. The clouds are part of the earth's weather system, and it would be impossible and unnecessary to try and control them. Try to treat your thoughts and feelings like you would treat passing clouds and allow them to occupy their own space and time in the knowledge that they will eventually pass you by.

WORRY POSTPONEMENT

Worry, like fear of cancer coming back, can be useful, in that it can trigger you to do something to solve a problem. But worry can often happen without you even being aware of what triggered it. Because of this, worry can interfere in our daily life. One way of dealing with this is to only allow yourself to worry at a particular time – create a 'worry period'. By learning to postpone your worry successfully it will:

- mean your worries are less intrusive in your life
- allow you to manage your worry effectively
- give you a feeling of better self-control.

This is similar to the example earlier about imagining your mind as a big house in the 'Challenge unhelpful thoughts' section. Another example is to imagine someone who is self-employed. If the mobile rings during work, the choice is to answer it and disrupt the current work or to let the caller leave a message and return the call later. It is about choosing when to think about things rather than responding to every thought as it appears.

Below we outline the steps you can take to postpone your worry. Be prepared to practise this approach repeatedly. It takes time and patience.

Some techniques for managing the fear of recurrence

1. **Create a worry period:** Choose a time, place and length of time for worrying. Make sure you are comfortable and free from distractions. The duration should be no more than 20 minutes, and at the same time and place each day and more than two hours before bedtime.
2. **Postpone your worry:** During the day when you worry, tell yourself you will postpone each worry to the worry period. Write down each worry as it comes into your head but then put it away. Be firm with yourself and keep reminding yourself you will have time to focus on your worry later. This can help you to return to whatever it is that is important or enjoyable for you to focus on in that moment.
3. **Come back to your worries at the designated worry period:** When your worry period comes around, settle yourself down at the place you had planned and take some time to reflect on the worries you had during the day. If you have any worries after your worry period, just write them down for the next day.

To begin with many people, say worry postponement feels strange and is an effort to put in practice. But with time and practice and sticking to the 'rules' it can work. People are often surprised by how they can postpone their worries and have a greater sense of self.

But remember: It is not compulsory to use up your worry time – if you do not get back to it, don't be hard on yourself – you can always do it tomorrow. And with time you may find you do not even need the worry postponement time at all.

Finding information online

The internet has an enormous amount of information about ovarian cancer and fear of recurrence. Try not to use online information as a substitute for the information from your doctor and other members of your healthcare team. Not all information online is accurate or will be suitable for you.

"I remember spending a lot of time searching the internet for information and scaring myself to death. I would advise anyone with cancer, especially when you first find out, not to look on the internet."

- Jenny

While there are some very good websites, some sites provide wrong or biased information. If you want to search online, focus on websites from reputable cancer organisations and universities. You will find plenty of these sites throughout our Resilience Kit and on our website (www.ovariancancer.net.au).

When you are unwell, it can be overwhelming to try and sort through information. But you could ask a family member or friend to help if you are feeling unable to do this.

Further information and support

If you have continuous feelings of sadness, anxiety and fear of your cancer coming back, we strongly advise you to seek medical help. Asking your medical team for a referral to a psychologist can also help with controlling your fears of cancer recurrence.

Call **Ovarian Cancer Australia** on **1300 660 334** for further information about support groups and networks that can help you connect with other women in similar circumstances. They can also suggest how you can connect you with counsellors and psychologists who specialise in helping people with cancer.

Acknowledgements

Writer: Annie Angle

Editor: Rosemary Moore

This resource has been reviewed by several expert health professionals.

Reviewed December 2018.

REVIEWERS

- Nadia Addabbo
- Jan Anthony
- Jennifer Kennedy
- Dr Ben Smith, Translational Research Fellow, Centre for Oncology Education and Research Translation, Ingham Institute and University of New South Wales
- Professor Phyllis Butow, AM, University of Sydney
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- Assoc. Professor Orla M. McNally, Consultant Gynaecological Oncologist, Royal Women's Hospital

Ovarian Cancer Australia would like to acknowledge the University of Sydney for the use of handouts from the ConquerFear study which were adapted in collaboration with Professor Phyllis Butow and Dr Ben Smith to form the "Techniques" section of this resource. Authors of the original ConquerFear materials are Afaf Girgis – (University of New South Wales), Belinda Thewes – (School of Psychology, University of Sydney), Cathy Mihalopoulos – (Deakin University), Jane Beith – (Central Sydney Area Health Service), Jemma Gilchrist – (Macquarie University), Louise Sharpe – (School of Psychology, University of Sydney), Margaret Turner – (University of Queensland, Melanie Bell – (School of Psychology, University of Sydney), Phyllis Butow – (School of Psychology, University of Sydney).

Appendix H:

Additional materials relevant to Chapter 7

Studies reviewed in Chapter 7

1. Arch JJ, Mitchell JL. An acceptance and commitment therapy (ACT) group intervention for cancer survivors experiencing anxiety at re-entry. Psycho-oncology. 2016. 25:610-615.
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Appendix I:

Additional materials relevant to Chapter 8

1. Ethics Approval
2. Risk Assessment Outcome
3. ANZCTR trial registration
4. Participant Information Statement
5. Participant Consent Form
6. Additional Questionnaires (Demographics, Brief Pain Inventory, HADS, Quality of Life)
7. Key statistical Output

THE UNIVERSITY OF SYDNEY

Research Integrity & Ethics Administration
HUMAN RESEARCH ETHICS COMMITTEE

Monday, 25 January 2021

Prof Louise Sharpe
Psychology; Faculty of Science
Email: louise.sharpe@sydney.edu.au

Dear Louise,

The University of Sydney Human Research Ethics Committee (HREC) has considered your application.

After consideration of your response to the comments raised your project has been approved.

If your research project is a clinical trial and is being sponsored by the University or is to be conducted on a University of Sydney site, you must comply with additional University governance requirements prior to commencing your Clinical Trial.

Protocol Number:	**2020/835**
Protocol Title:	**Cognitive bias modification for interpretation (CBM-I) in management of fear of cancer recurrence/progression in women with breast and ovarian cancer**
Sites Approved:	**Conducted entirely online (researchers are based at The University of Sydney)**
Authorised Persons:	**Sharpe Louise; Butow Phyllis; Pradhan Poorva; Todd Jemma;**
Approval Period:	**25 January 2021** to **25 January 2025**
First Annual Report Due:	**25 January 2022**

Documents Approved:

Date Uploaded	Version Number	Document Name
13/01/2021	Version 2	Participant Information Statement Version 2 (Clean copy)
13/01/2021	Version 2	Debrief sheet Version 2 (Clean Copy)
20/11/2020	Version 1	Study Advert
20/11/2020	Version 1	Physical Symptoms Inventory
20/11/2020	Version 1	Brief Pain Inventory
20/11/2020	Version 1	Participant Consent Form
20/11/2020	Version 1	Hospital Anxiety and Depression Scale (HADS)
20/11/2020	Version 1	CBM-I Study Protocol
20/11/2020	Version 1	Participation email
20/11/2020	Version 1	Fear of Cancer Recurrence Inventory
20/11/2020	Version 1	Fear of Progression Questionnaire- Short Form
20/11/2020	Version 1	Quality of Life Questionnaire

Special Conditions of Approval for Clinical Trials

- **This letter constitutes ethical approval only.** This project cannot proceed at any site until the necessary research governance authorisation is obtained. If your study is sponsored by the University or is to be conducted on a University of Sydney site you may need to comply with additional University governance requirements prior to commencing. Please contact the Clinical Trials Governance Office at clinical-trials.research@sydney.edu.au

- Clinical Trials must be registered on a clinical trials registry that complies with the International Committee of Medical Journal Editors (ICMJE). For trials conducted in Australia or New Zealand registration should be on the Australian New Zealand Clinical Trial Registry before recruitment of the first subject (http://www.anzctr.org.au/).

THE UNIVERSITY OF SYDNEY

Condition/s of Approval

- Research must be conducted according to the approved proposal.
- An annual progress report must be submitted to the Ethics Office on or before the anniversary of approval and on completion of the project.
- You must report as soon as practicable anything that might warrant review of ethical approval of the project including:
  - Serious or unexpected adverse events (which should be reported within 72 hours).
  - Unforeseen events that might affect continued ethical acceptability of the project.
- Any changes to the proposal must be approved prior to their implementation (except where an amendment is undertaken to eliminate *immediate* risk to participants).
- Personnel working on this project must be sufficiently qualified by education, training and experience for their role, or adequately supervised. Changes to personnel must be reported and approved.
- Personnel must disclose any actual or potential conflicts of interest, including any financial or other interest or affiliation, as relevant to this project.
- Data and primary materials must be retained and stored in accordance with the relevant legislation and University guidelines.
- Ethics approval is dependent upon ongoing compliance of the research with the *National Statement on Ethical Conduct in Human Research*, the *Australian Code for the Responsible Conduct of Research*, applicable legal requirements, and with University policies, procedures and governance requirements.
- The Ethics Office may conduct audits on approved projects.
- The Chief Investigator has ultimate responsibility for the conduct of the research and is responsible for ensuring all others involved will conduct the research in accordance with the above.

Please contact the Ethics Office should you require further information or clarification.

Sincerely,

[REDACTION]

Associate Professor Helen Mitchell
Chair
Human Research Ethics Committee (HREC 1)

The University of Sydney HRECs are constituted and operate in accordance with the National Health and Medical Research Council's (NHMRC) National Statement on Ethical Conduct in Human Research (2018) and the NHMRC's Australian Code for the Responsible Conduct of Research (2018).

Poorva Pradhan

From: Services Team <research.support@sydney.edu.au>
Sent: Friday, 11 June 2021 4:51 PM
To: Louise Sharpe
Cc: Clinical Trials Risk And Governance; CDIP Clinical Trials Agreements; Poorva Pradhan
Subject: Risk assessment – Cognitive bias modification for interpretation (CBM-I) in management of fear of cancer recurrence/progression in women with breast and ovarian cancer. PI Professor Louise Sharpe

Risk assessment – Cognitive bias modification for interpretation (CBM-I) in management of fear of cancer recurrence/progression in women with breast and ovarian cancer. PI Professor Louise Sharpe Study contact Poorva Pradhan

Dear Professor Sharpe,

Thank you for your submission to the Clinical Trials Support Office (CTSO). The outcome of the risk assessment is provided below.

Risk rating: Minor.

Action required: No further action is required based on the risk rating.

Insurance: This clinical trial has been listed, with the University role as sponsor.

Submission details:

Title	Cognitive bias modification for interpretation (CBM-I) in management of fear of cancer recurrence/progression in women with breast and ovarian cancer
Principal Investigator	Professor Louis Sharpe
Contact	Poorva Pradhan
Sponsor	University of Sydney
Site(s)	This study is being conducted on line and there are no sites.
HREC approval	Approval by University of Sydney HREC Reference: 2020/835
Date of submission	Initial:05-Mar-2021 Final:11-Jun-2021
Documents reviewed	1. Clinical Trial Risk and Site Assessment Form signed by Head of School 03-Mar-2021 2. Protocol (Version 1 dated 18-Nov-2020) 3. HREC approval letter dated 25-Jan-2021 4. CV – Professor Sharpe

Please review the information below (updated as of 12 November 2020):

1. This clinical trial cannot commence unless approval is granted by the responsible Human Research Ethics Committee (HREC) and if applicable, the Research Governance Offices and/or delegated authorities of each site.

2. In accordance with COVID-19 physical distancing requirements, trials may require written approval to initiate recruitment or continue with face-to-face participant visits. Please refer to advice provided by the Australian Government Department of Health and to COVID-19 updates on the Clinical Trials Support Office (CTSO) Intranet: Clinical trials at the University of Sydney. Contact the CTSO for further advice via clinical-trials.research@sydney.edu.au or the Research Services Portal.

3. Please address any outstanding matters before commencing this trial:

   a. Contact the CTSO regarding Site-Specific Assessment (SSA) for trials conducted at University of Sydney sites and/or Clinical Trial Notification (CTN) for trials sponsored by the University of Sydney.

b. Contact the CDIP Clinical Trials Agreements via cdip.ct-agreements@sydney.edu.au regarding contractual arrangements for trials involving the University of Sydney.

4. Please refer to the Ongoing reporting responsibilities on the CTSO Intranet: Risk and Governance. For trials sponsored by and/or conducted at University of Sydney sites, please comply with reporting requirements for changes to the trial and HREC approval status, annual reports, safety monitoring and reporting, serious breaches and end of study reports.

5. Please retain this email as a record of the risk assessment. Please notify the CTSO in case of circumstances which could impact the validity of this risk assessment.

Please do not hesitate to contact the CTSO should require any further assistance. I wish you all the very best in your research.

Best wishes

Pauline

Dr Pauline Hanrahan | Risk and Governance Manager Clinical Trials Support Office
The University of Sydney
Office of the Pro-Vice Chancellor (Research), Research Portfolio

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Please note that Research Portfolio staff are working in a hybrid mode, both remotely and on campus. Please include a Zoom option in all proposed meetings. Thank you.

Poorva Pradhan

From: info@actr.org.au
Sent: Thursday, 27 May 2021 3:02 PM
To: Poorva Pradhan
Cc: Louise Sharpe
Subject: Your ACTRN (registration number): ACTRN12621000634875

Dear POORVA PRADHAN and Louise Sharpe,

Re: Cognitive bias modification for fear of cancer recurrence/progression

Thank you for submitting the above trial for inclusion in the Australian New Zealand Clinical Trials Registry (ANZCTR).

Your trial has now been successfully registered and allocated the ACTRN: ACTRN12621000634875

Web address of your trial: https://www.anzctr.org.au/ACTRN12621000634875.aspx
Date submitted: 18/03/2021 2:44:32 PM
Date registered: 27/05/2021 3:01:55 PM
Registered by: POORVA PRADHAN
Principal Investigator: Louise Sharpe

If you have already obtained Ethics approval for your trial, please send a copy of at least one Ethics Committee approval letter to info@actr.org.au or by fax to (+61 2) 9565 1863, attention to ANZCTR.

Note that updates should be made to the registration record as soon as any trial information changes or new information becomes available. Updates can be made at any time and the quality and accuracy of the information provided is the responsibility of the trial's primary sponsor or their representative (the registrant). For instructions on how to update please see https://www.anzctr.org.au/Support/HowToUpdate.aspx.

Please also note that the original data lodged at the time of trial registration and the tracked history of any changes made as updates will remain publicly available on the ANZCTR website.

The ANZCTR is recognised as an ICMJE acceptable registry (http://www.icmje.org/about-icmje/faqs/clinical-trials-registration/) and a Primary Registry in the WHO registry network (https://www.who.int/ictrp/network/primary/en/index.html).

If you have any enquiries please send a message to info@actr.org.au or telephone +61 2 9562 5333.

Kind regards,
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THE UNIVERSITY OF SYDNEY

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COGNITIVE BIAS MODIFICATION (CBM) FOR FEAR OF CANCER RECURRENCE/PROGRESSION

PARTICIPANT INFORMATION STATEMENT

(25) What is this study about?

You are invited to take part in a research study looking at a novel intervention for fear of cancer recurrence or progression (FCR), known as Cognitive Bias Modification (CBM). FCR is natural and common amongst cancer survivors, and leads people living beyond cancer to interpret many situations in light of their experience (a potential threat of recurrence or progression). CBM is an intervention that is administered online and trains people not to interpret ambiguous situations in a threatening way. By doing so, people reduce their anxiety. CBM has been shown to be helpful in a range of populations including in people with anxiety and depression. However there is only one pilot study in people living beyond breast cancer. That study achieved promising results, and we aim to test CBM in a larger trial to see if CBM does reliably reduce FCR, and if the results extend to women with ovarian cancer.

This Participant Information Statement describes the research study. Knowing what is involved will help you decide if you want to take part in the research. Please read this sheet carefully and ask questions about anything that you don't understand or want to know more about. Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

You will be given a copy of this Participant Information Statement to keep.

(26) Who is running the study?

The study is being carried out by the following researchers at the University of Sydney:

- Professor Louise Sharpe, Professor of Psychology, School of Psychology
- Professor Phyllis Butow, PoCoG & CeMPED, School of Psychology, SoURCe, Institute of Surgery, University of Sydney

- Dr Jemma Todd, Lecturer, Clinical Psychology Unit, School of Psychology, The University of Sydney

Poorva Pradhan is conducting this study as the basis for the degree of Doctor of Philosophy (Psychology) at The University of Sydney. This will take place under the supervision of Professor Louise Sharpe.

There are no Conflicts of Interest to declare.

(27) What will the study involve for me?

If you agree to participate in this study, you will be asked to agree to the Participant Consent Form page.

This study is a double-blind, randomised, placebo controlled trial. If you choose to participate in this study, you will firstly be asked to complete a series of questionnaires which will take around 30-35 minutes. If your answers indicate that this treatment might be suitable for you, then you will be invited into the trial.

As part of the trial, you will be randomly allocated into a treatment or placebo group, like the toss of a coin. Neither you, nor the researchers will know which group you have been allocated to. Neither you nor the researchers can choose which group you are in – it is decided completely by chance. There are two groups in this study:

A: Cognitive Bias Modification (CBM)

In this group, you will be presented with a series of sentences and words and asked to determine if they are associated. The training itself takes between 10-15 minutes. You will be asked to complete another 3 online training sessions over the course of the next 2 weeks. Each subsequent training session (x3) will take approximately 10-15 minutes.

B: Placebo

If you are allocated to the placebo condition, you will receive a similar online training program to the one above, and you will not know that the training you receive is not the active treatment. Each training session will take approximately 10-15 minutes to complete and the time commitment will be the same as that described above.

<u>If you are allocated to the placebo group and wish to complete the CBM training, it will be made available to you free of charge when the study is complete, as long as we find that the CBM training is beneficial as we hope.</u>

(28) How much of my time will the study take?

The study will be conducted over 4 weeks in total. The first stage of the study is estimated to take up to 45 - 60 minutes. The three subsequent training sessions are estimated to take you –10-15 minutes each. The initial follow-up set of questionnaires are estimated to take up to 30 - 35 minutes, and the second follow-up set of questionnaires two weeks after are estimated to take up to 30 -35 minutes. Therefore, your total maximum participation in hours across 4 weeks would be approximately 3 hours.

(29) Who can take part in the study?

Women who has been diagnosed with breast or ovarian cancer can participate in this study, unless they are receiving palliative care. To participate in this study, you must be able to use the computer and you must have access to the internet over the course of the 4 week period. You also must be fluent in English. This is because the training is delivered online and requires a good understanding of the written content.

(30) Do I have to be in the study? Can I withdraw from the study once I've started?

Your participation in this research is entirely voluntary and you are not under any obligation to give your consent. You are free to withdraw from the survey at any point, without giving a reason. Whatever your decision, please be assured that it will not affect your medical treatment. It will also not affect your current or future relationship with the staff, researchers or anyone else at the University of Sydney or with the association from whom you heard about the study.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by emailing the research team.

If you decide to withdraw from the study, we will not collect any more information from you unless you agree to complete the questionnaires again, which you are not obliged to do. Because this is a clinical trial, we will retain the information that you have already contributed since we must account for all people in the study to ensure that we do not overestimate any benefit the treatment appears to give.

(31) Are there any risks or costs associated with being in the study?

Aside from giving up your time (for which we are very grateful), we do not expect that there will be any risks or costs associated with taking part in this study. There is no evidence that the questionnaires in the study will cause distress nor that the training involved in this study would pose a risk to you. However, when people think about their future concerns, it is possible that this could cause some distress. If you do become distressed at any time during this study, please let the researcher know and we will ensure that you receive any additional support that might be necessary. OR, if you wish you can directly access Breast Cancer Network or Ovarian Cancer Australia Helpline:

BCNA Helpline number- 1800 500 258
Between 9.00 am and 6.00 pm (AEST) Monday to Thursday and 9.00 am to 5.00 pm on a Friday.

Ovarian Cancer Australia Helpline number - 1300 660 334
Between 9.00 am to 5.00 pm AEST, Monday to Friday

(32) Are there any benefits associated with being in the study?

While we intend that, this study furthers knowledge about the Fear of Cancer Recurrence/Progression, It will not be of direct benefit to you. We also believe the results of this study may inform future treatments for Fear of cancer recurrence/progression.

(33) What will happen to information about me that is collected during the study?

All information that you provide in the questionnaires, training and email contact is strictly confidential. Electronic records will be kept on a password protected server owned by the University

of Sydney that is only accessible to members of the research team. Qualtrics, an external online survey host, will be used for initial data collection. Your survey responses are also password protected and again, only accessible by the research team. All electronic records will be stored in perpetuity, but any personal details will be deleted after 5 years. In the interest of transparency, fully anonymised data may be stored indefinitely for the purposes of open-access practice.

Your email address will be used for the sole purpose of distributing the training sessions and questionnaires. Similarly, we will only contact your via telephone if you have indicated high levels of distress in the questionnaires and we are concerned about you. After you have completed the study, you will not receive any contact from the research team, unless you have elected to receive a summary of the findings via email after the project is complete or if you have indicated you would be happy to take part in future research. However, you are welcome to contact the investigators at any time during the trial or afterwards.

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement. Your information will be stored securely and your identity/information will be kept strictly confidential, except as required by law.

Study findings may be published, but you will not be individually identifiable in these publications.

(34) What will happen to my treatment when the study is finished?

At the end of the study, we will contact you to let you know which group you were in. As previously mentioned, if you are allocated to the placebo group and wish to complete the CBM training, it will be made available to you as long as we found it to be beneficial for those who received it during the study. If you are allocated to the CBM group, you will already have completed the relevant treatment in this study.

(35) Can I tell other people about the study?

While we are happy for you to talk about being part of this study with others. Please don't talk to other people about the details of the training you receive who are likely to participate in the study (i.e. have breast or ovarian cancer), as it may affect their responses.

(36) What if I would like further information about the study?

When you have read this information, Poorva Pradhan will be available to discuss it with you further and answer any questions you may have. Also, if you would like to know more at any stage during the study, please feel free to contact her.

Poorva Pradhan, PhD Candidate, The University of Sydney
Phone (02) 8627 7678 or email: poorva.pradhan@sydney.edu.au

(37) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by answering the relevant question in an online questionnaire. This feedback

will be in the form of a one-page summary of the study's results. You will receive this feedback after the study is finished. We will also send a copy of the outcomes to organisations from whom we recruit, and they may circulate these or post them on their Facebook pages.

(38) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney *[Project number: 2020/835].* As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** human.ethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

COGNITIVE BIAS MODIFICATION (CBM) FOR FEAR OF CANCER RECURRENCE/PROGRESSION

PARTICIPANT CONSENT FORM

I agree to take part in this research study. In giving my consent I state that:

- I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- The researchers have answered any questions that I had about the study and I am happy with the answers.
- I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.
- I understand that I can withdraw from the study at any time.
- I understand that my questionnaire responses cannot be withdrawn once they are submitted, as they are anonymous and therefore the researchers will not be able to tell which one is mine.
- I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law.
- I understand that the results of this study may be published, and that publications will not contain my name or any identifiable information about me.

If you consent to the above, please press the button below:

I CONSENT

If you do not wish to consent to the above, please press the button below:

I DO NOT CONSENT

THE UNIVERSITY OF SYDNEY

School of Psychology
Faculty of Science

ABN 15 211 513 464

PROFESSOR LOUISE SHARPE
PROFESSOR, SCHOOL OF PSYCHOLOGY, THE UNIVERSITY OF SYDNEY

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COGNITIVE BIAS MODIFICATION (CBM) FOR FEAR OF CANCER RECURRENCE/PROGRESSION [HREC reference no.: 2020/835]

DEBRIEF

Background of the study:

Fear of cancer recurrence or progression (FCR) is the most prominent and persistent psychosocial concern reported by cancer survivors. FCR affects from most of cancer survivors to some degree, and is completely understandable. However, for some people FCR becomes preoccupying and causes a lot of distress and a difficulty in planning for their future.

Fortunately there are now a number of effective face-to-face treatments to help people manage FCR. However, as prognosis for cancer improves, and there are an increasing number of survivors, meeting that need is becoming increasingly difficult with scarce resources. Our previous findings also suggest that people with moderate levels of FCR perhaps do not need an intensive face-to-face treatment. And so a brief intervention that produces improvements in FCR would help to meet the needs of cancer survivors whose FCR is affecting their quality of life, but is not necessarily severe.

One such intervention is the intervention that was tested in the current study, namely Cognitive Bias Modification (CBM). CBM has been found to be effective for anxiety disorders in large studies that have synthesized the results of many trials. But there was only one prior study of CBM for people with cancer. Although it showed some promising results, it was limited to breast cancer and produced relatively small reductions in FCR.

In this study, we allocated people to one of three groups, although originally you would have been informed that it was one of two groups. This is because two of those three groups are essentially CBM-I training but differ in terms of their stimulus content. The first training group is a standard CBM-I which constitutes generic cancer-related scenarios while the second group is a personalised CBM-I training with scenarios reflecting the concerns of the individual participant. This design would enable us to determine whether a personalised or non-personalised version of CBM-I would be more effective in managing FCR.

If you were allocated to the control group, we appreciate that it may seem disappointing that you did not receive active training, but we would like to assure you that your participation in this study has been incredibly important. Control conditions allow researchers to assess whether variables such as time, practice effects and expectations are responsible for any changes observed during treatment. Without control conditions, there is no way of knowing whether the intervention actually worked, or whether improvements in outcomes are largely due to these other variables. We would like to offer you a link to the CBM training as soon as the study has finished assuming that we find that the treatment is effective. You will then be able to access the active intervention if you wish.

It is important you do not discuss the specifics of this study with any potential participants so our results are not influenced.

If you wish to contact the research team to discuss any of the information, please email poorva.pradhan@sydney.edu.au

DEMOGRAPHIC INFORMATION:

1. Age
2. Marital Status
3. Number of children
4. Educational Status
5. Are you currently working?

i. YES
ii. NO

6. Please state the time duration in month or year when you were diagnosed with cancer.

7. At what stage was your cancer when you were first diagnosed?

i. Stage 1
ii. Stage 2
iii. Stage 3
iv. Stage 4
v. Not known

8. What is your current cancer status?

i. Currently on treatment
ii. Active Disease
iii. In Remission

9. Have you experienced a recurrence of your cancer?

i. Yes
ii. No

10. Did you have a surgery for your cancer?

i. Yes
ii. No

11. Are you currently receiving any of these treatments now?

i. Chemotherapy
ii. Radiation therapy
iii. No

Brief Pain Inventory (Short Form)

Study ID# _____ Hospital # _____

Do not write above this line.

Date: _____

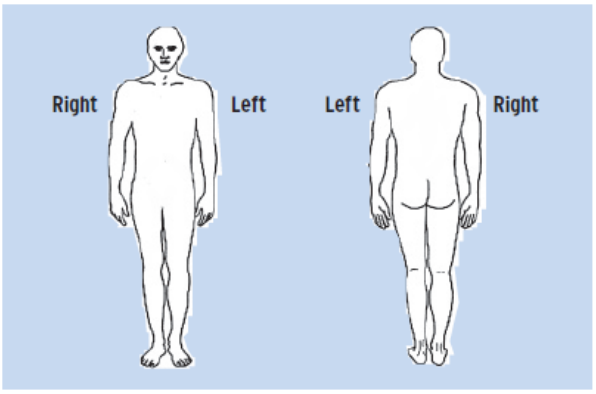
Time: _____

Name: _____
Last First Middle Initial

1) Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

○ 1. yes ○ 2. no

2) On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3) Please rate your pain by circling the one number that best describes your pain at its **WORST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

4) Please rate your pain by circling the one number that best describes your pain at its **LEAST** in the past 24 hours.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

5) Please rate your pain by circling the one number that best describes your pain on the **AVERAGE**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

6) Please rate your pain by circling the one number that tell how much pain you have **RIGHT NOW**.

0 1 2 3 4 5 6 7 8 9 10
No Pain — Pain as bad as you can imagine

7) What treatments or medications are you receiving for your pain?

_____

8) In the past 24 hours, how much **RELIEF** have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%
No Relief — Complete Relief

9) Circle the one number that describes how, during the past 24 hours. **PAIN HAS INTERFERED** with your:

A. General Activity:

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

B. Mood

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

C. Walking Ability

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

D. Normal work (Includes both work outside the home and housework)

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

E. Relation with other people

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

F. Sleep

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

G. Enjoyment of life

0 1 2 3 4 5 6 7 8 9 10
Does not Interfere — Completely interferes

Hospital Anxiety and Depression Scale (HADS)

Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Quality of Life:

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

		Not at All	A Little	Quite a Bit	Very Much
1.	Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2.	Do you have any trouble taking a long walk?	1	2	3	4
3.	Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4.	Do you need to stay in bed or a chair during the day?	1	2	3	4
5.	Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

		Not at All	A Little	Quite a Bit	Very Much
6.	Were you limited in doing either your work or other daily activities?	1	2	3	4
7.	Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8.	Were you short of breath?	1	2	3	4
9.	Have you had pain?	1	2	3	4
10.	Did you need to rest?	1	2	3	4
11.	Have you had trouble sleeping?	1	2	3	4
12.	Have you felt weak?	1	2	3	4
13.	Have you lacked appetite?	1	2	3	4
14.	Have you felt nauseated?	1	2	3	4
15.	Have you vomited?	1	2	3	4
16.	Have you been constipated?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

T-Test

Group Statistics

	Baseline Questionnaires completion	N	Mean	Std. Deviation	Std. Error Mean
AGE	Not Completed	49	62.02	12.156	1.737
	Completed	174	58.49	10.334	.783

Independent Samples Test

		Levene's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
AGE	Equal variances assumed	1.196	.275	2.027	221	.044	3.526	1.739	.098	6.954
	Equal variances not assumed			1.851	68.734	.068	3.526	1.905	-.275	7.327

NPar Tests

Mann-Whitney Test

Ranks

	Baseline Questionnaires completion	N	Mean Rank	Sum of Ranks
Educational Status	Not Completed	49	109.21	5351.50
	Completed	174	112.78	19624.50
	Total	223		
At what stage was your cancer when you were first diagnosed?	Not Completed	49	101.24	4961.00
	Completed	174	115.03	20015.00
	Total	223		

Test Statistics[a]

	Educational Status	At what stage was your cancer when you were first diagnosed?
Mann-Whitney U	4126.500	3736.000
Wilcoxon W	5351.500	4961.000
Z	-.360	-1.366
Asymp. Sig. (2-tailed)	.719	.172

a. Grouping Variable: Baseline Questionnaires completion

T-Test

Group Statistics

	Baseline Questionnaires completion	N	Mean	Std. Deviation	Std. Error Mean
FCRI Screening	Not Completed	59	9.6780	9.49308	1.23589
	Completed	174	21.6494	4.95740	.37582
FoP Screening	Not Completed	59	13.5932	15.49874	2.01776
	Completed	174	36.5977	9.49714	.71998
COMPUTE BPI_Int_Baseline_Total=(BPI_B_Int_1 + BPI_B_Int_2 + BPI_B_Int_3 + BPI_B_Int_4) / 4	Not Completed	9	1.4167	2.50312	.83437
	Completed	174	2.3032	2.03360	.15417
COMPUTE BPI_Intf_Baseline_Total=(BPI_B_Intf_5 + BPI_B_Intf_6 + BPI_B_Intf_7 + BPI_B_Intf_8 + BPI_B_Intf_9 + BPI_B_Intf_10 + BPI_B_Intf_11) / 7	Not Completed	8	2.3929	2.63166	.93043
	Completed	174	3.6379	2.44865	.18563
	Not Completed	8	9.1250	1.80772	.63913

COMPUTE HADS_ANX_Total_Baseline= HADS_ANX_1_B + HADS_ANX_2_B + HADS_ANX_3_B + HADS_ANX_4_B + HADS_ANX_5_B + HADS_ANX_6_B + HADS_ANX_7_B	Completed	174	9.7759	4.19073	.31770
COMPUTE	Not Completed	7	5.8571	2.79455	1.05624
HADS_DEP_Total_Baseline= HADS_DEP_8_B + HADS_DEP_9_B + HADS_DEP_10_B + HADS_DEP_11_B + HADS_DEP_12_B + HADS_DEP_13_B + HADS_DEP_14_B	Completed	174	7.3621	4.58206	.34737
COMPUTE	Not Completed	5	29.8000	7.98123	3.56931
QOL_Functg_Total_Baseline =QOL_1 + QOL_2 + QOL_3 + QOL_4 + QOL_5 + QOL_6 + QOL_7 + QOL_21 + QOL_22 + QOL_23 + QOL_24 + QOL_20 + QOL_26 + QOL_25 + QOL_27	Completed	174	30.7529	8.05486	.61064
COMPUTE	Not Completed	11	5.8182	3.18805	.96123
PhysicalSympts_Total_Baseline=Upset_stomach_nausea + Backache + Trouble_Sleeping + Skin_Rash + Shortness_of_Breath + Chest_Pain + Headache + Fever + Heartburn + Eye_strain + Diarrhoea + Stomach_Cramps + Constipation + Heart_Pounding + Infection + L	Completed	174	14.8333	10.17027	.77101

		t-test for Equality of Means					
		t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confider Difference Lower
	Equal variances assumed	12.405	231	.000	11.97146	.96503	13.87285
	Equal variances not assumed	9.267	69.024	.000	11.97146	1.29177	14.54846
	Equal variances assumed	13.504	231	.000	23.00448	1.70352	26.36091
	Equal variances not assumed	10.738	73.311	.000	23.00448	2.14237	27.27391
l=(BPI	Equal variances assumed	1.261	181	.209	.88649	.70304	2.27371
_2 + _Int_4)	Equal variances not assumed	1.045	8.555	.325	.88649	.84850	2.82125
	Equal variances assumed	1.402	180	.163	1.24507	.88807	2.99745
al=(BPI f_6 + _Intf_8	Equal variances not assumed	1.312	7.568	.228	1.24507	.94877	3.45488
	Equal variances assumed	.436	180	.663	.65086	1.49115	3.59324
aseline=	Equal variances not assumed	.912	10.860	.382	.65086	.71373	2.22425
	Equal variances assumed	.861	179	.390	1.50493	1.74766	4.95359
seline=	Equal variances not assumed	1.353	7.365	.216	1.50493	1.11189	4.10795
	Equal variances assumed	.261	177	.795	.95287	3.65288	8.16168

seline= L_3 + L_6 + OL_22 +	Equal variances not assumed	.263	4.237	.805	.95287	3.62117	10.78848
Baselin ea + eeping e + + ction +	Equal variances assumed	2.924	183	.004	9.01515	3.08301	15.09797
	Equal variances not assumed	7.316	26.376	.000	9.01515	1.23224	11.54631

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	165.514	4689.595	.000
Intervention_Cond	2	165.503	26.417	.000
Time_Points	2	143.443	43.157	.000
Intervention_Cond * Time_Points	4	143.436	17.193	.000

a. Dependent Variable: FCRI Total.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	21.691895	.661393	137.174	32.797	.000	20.384050	22.999740
[Intervention_Cond=1.00]	-7.068918	.908513	135.967	-7.781	.000	-8.865563	-5.272274
[Intervention_Cond=2.00]	-4.983538	.929594	137.212	-5.361	.000	-6.821721	-3.145355
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	-.209752	.776417	158.821	-.270	.787	-1.743185	1.323681
[Time_Points=2]	1.414148	.757403	135.644	1.867	.064	-.083697	2.911993
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	7.520109	1.070109	157.124	7.027	.000	5.406453	9.633764
[Time_Points=2] * [Intervention_Cond=1.00]	-.178469	1.049537	133.735	-.170	.865	-2.254309	1.897370
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	5.018636	1.090507	159.056	4.602	.000	2.864895	7.172378
[Time_Points=2] * [Intervention_Cond=2.00]	-2.122053	1.069282	136.396	-1.985	.049	-4.236569	-.007537
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: FCRI Total.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	17.472	.477	164.140	16.529	18.414
Generic	18.075	.487	167.080	17.114	19.037
Placebo	22.093	.493	165.253	21.119	23.067

a. Dependent Variable: FCRI Total.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	21.644	.378	171.000	20.898	22.390
Follow-up 1	18.322	.398	142.596	17.535	19.108
Follow-up 2	17.674	.373	136.414	16.937	18.412

a. Dependent Variable: FCRI Total.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	21.933	.643	171.000	20.664	23.203
	Follow-up 1	15.859	.684	142.913	14.507	17.211
	Follow-up 2	14.623	.623	134.512	13.391	15.855
Generic	Baseline	21.517	.654	171.000	20.226	22.809
	Follow-up 1	16.000	.691	142.844	14.634	17.367
	Follow-up 2	16.708	.653	137.250	15.417	18.000
Placebo	Baseline	21.482	.666	171.000	20.168	22.796
	Follow-up 1	23.106	.693	142.027	21.737	24.476
	Follow-up 2	21.692	.661	137.174	20.384	23.000

a. Dependent Variable: FCRI Total.

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	167.593	4727.670	.000
Intervention_Cond	2	167.590	27.319	.000
Time_Points	2	151.505	46.512	.000
Intervention_Cond * Time_Points	4	151.761	15.031	.000

a. Dependent Variable: FoP Total.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	36.263616	.949839	141.939	38.179	.000	34.385957	38.141275
[Intervention_Cond=1.00]	-13.011333	1.307428	140.175	-9.952	.000	-15.596161	-10.426506
[Intervention_Cond=2.00]	-7.190337	1.335038	141.969	-5.386	.000	-9.829459	-4.551215
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	.361384	1.307275	163.949	.276	.783	-2.219881	2.942649
[Time_Points=2]	1.409397	.959379	132.515	1.469	.144	-.488280	3.307075
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	12.903000	1.808073	161.912	7.136	.000	9.332555	16.473446
[Time_Points=2] * [Intervention_Cond=1.00]	.971281	1.327270	130.765	.732	.466	-1.654420	3.596982
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	7.220509	1.835225	164.289	3.934	.000	3.596841	10.844177
[Time_Points=2] * [Intervention_Cond=2.00]	-1.982739	1.354808	133.184	-1.463	.146	-4.662463	.696985
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: FoP Total.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	28.467	.798	166.926	26.891	30.043
Generic	31.409	.813	168.686	29.804	33.015
Placebo	36.854	.825	167.145	35.225	38.482

a. Dependent Variable: FoP Total.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	36.599	.724	171.000	35.169	38.029
Follow-up 1	30.602	.566	145.365	29.484	31.720
Follow-up 2	29.530	.536	140.805	28.469	30.590

a. Dependent Variable: FoP Total.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	36.517	1.233	171.000	34.082	38.951
	Follow-up 1	25.633	.971	145.991	23.714	27.552
	Follow-up 2	23.252	.898	138.105	21.476	25.029
Generic	Baseline	36.655	1.254	171.000	34.179	39.131
	Follow-up 1	28.500	.982	145.772	26.559	30.441
	Follow-up 2	29.073	.938	141.999	27.219	30.928
Placebo	Baseline	36.625	1.276	171.000	34.105	39.145
	Follow-up 1	37.673	.986	144.336	35.724	39.622
	Follow-up 2	36.264	.950	141.939	34.386	38.141

a. Dependent Variable: FoP Total.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	165.580	766.055	.000
Intervention_Cond	2	165.578	.671	.513
Time_Points	2	144.387	37.020	.000
Intervention_Cond * Time_Points	4	144.372	1.918	.111

a. Dependent Variable: Physical Symptoms.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	8.380231	.731682	131.903	11.453	.000	6.932881	9.827580
[Intervention_Cond=1.00]	-.202144	1.008741	129.422	-.200	.841	-2.197901	1.793612
[Intervention_Cond=2.00]	-1.404010	1.028821	131.820	-1.365	.175	-3.439145	.631126
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	6.012627	1.484340	164.986	4.051	.000	3.081877	8.943376
[Time_Points=2]	1.176202	.637385	127.338	1.845	.067	-.085035	2.437439
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	.292620	2.059654	163.790	.142	.887	-3.774277	4.359517
[Time_Points=2] * [Intervention_Cond=1.00]	-1.402228	.877577	126.731	-1.598	.113	-3.138829	.334374
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	2.631842	2.082491	165.294	1.264	.208	-1.479870	6.743554
[Time_Points=2] * [Intervention_Cond=2.00]	-1.590471	.899646	128.053	-1.768	.079	-3.370567	.189624
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: Physical Symptoms.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	10.204	.629	165.004	8.962	11.447
Generic	9.720	.641	166.501	8.454	10.985
Placebo	10.777	.650	165.217	9.492	12.061

a. Dependent Variable: Physical Symptoms.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	14.832	.775	171	13.303	16.361
Follow-up 1	8.023	.366	142.047	7.301	8.746
Follow-up 2	7.845	.414	130.213	7.026	8.663

a. Dependent Variable: Physical Symptoms.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	14.483	1.319	171	11.880	17.086
	Follow-up 1	7.952	.628	142.535	6.711	9.193
	Follow-up 2	8.178	.694	126.601	6.804	9.552
Generic	Baseline	15.621	1.341	171	12.973	18.268
	Follow-up 1	6.562	.635	142.504	5.308	7.816
	Follow-up 2	6.976	.723	131.736	5.546	8.407
Placebo	Baseline	14.393	1.365	171	11.699	17.087
	Follow-up 1	9.556	.637	141.111	8.297	10.816
	Follow-up 2	8.380	.732	131.903	6.933	9.828

a. Dependent Variable: Physical Symptoms.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	165.801	393.017	.000
Intervention_Cond	2	165.790	19.298	.000
Time_Points	2	150.067	3.493	.033
Intervention_Cond * Time_Points	4	150.136	6.140	.000

a. Dependent Variable: BPI Intensity.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	3.019988	.240904	135.015	12.536	.000	2.543555	3.496422
[Intervention_Cond=1.00]	-1.603734	.331029	133.537	-4.845	.000	-2.258471	-.948996
[Intervention_Cond=2.00]	-1.865170	.338636	134.994	-5.508	.000	-2.534888	-1.195452
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	-.578024	.314886	158.301	-1.836	.068	-1.199944	.043896
[Time_Points=2]	.235983	.257151	127.067	.918	.361	-.272870	.744835
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	1.353436	.434828	156.176	3.113	.002	.494533	2.212339
[Time_Points=2] * [Intervention_Cond=1.00]	-.285227	.355551	125.233	-.802	.424	-.988894	.418440
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	1.707688	.442146	158.566	3.862	.000	.834433	2.580944
[Time_Points=2] * [Intervention_Cond=2.00]	-.409982	.362963	127.803	-1.130	.261	-1.128177	.308213
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: BPI Intensity.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	1.658	.173	164.363	1.317	1.999
Generic	1.473	.176	167.319	1.125	1.821
Placebo	2.906	.179	165.650	2.554	3.258

a. Dependent Variable: BPI Intensity.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	2.306	.155	171.000	2.000	2.612
Follow-up 1	1.868	.133	141.651	1.605	2.131
Follow-up 2	1.864	.136	134.035	1.595	2.132

a. Dependent Variable: BPI Intensity.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	2.192	.264	171.000	1.671	2.712
	Follow-up 1	1.367	.229	141.976	.915	1.819
	Follow-up 2	1.416	.227	131.776	.967	1.865
Generic	Baseline	2.284	.268	171.000	1.755	2.814
	Follow-up 1	.981	.231	141.933	.524	1.438
	Follow-up 2	1.155	.238	134.971	.684	1.625
Placebo	Baseline	2.442	.273	171.000	1.903	2.981
	Follow-up 1	3.256	.232	141.039	2.798	3.714
	Follow-up 2	3.020	.241	135.015	2.544	3.496

a. Dependent Variable: BPI Intensity.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	168.331	534.698	.000
Intervention_Cond	2	168.321	18.996	.000
Time_Points	2	155.491	31.085	.000
Intervention_Cond * Time_Points	4	156.574	5.223	.001

a. Dependent Variable: BPI Interference.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	3.258237	.258337	133.752	12.612	.000	2.747282	3.769192
[Intervention_Cond=1.00]	-1.688411	.354785	132.472	-4.759	.000	-2.390188	-.986634
[Intervention_Cond=2.00]	-1.974202	.363162	133.732	-5.436	.000	-2.692485	-1.255919
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	.601457	.374174	168.491	1.607	.110	-.137217	1.340131
[Time_Points=2]	.456656	.278461	131.825	1.640	.103	-.094175	1.007486
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	1.371574	.517228	166.441	2.652	.009	.350401	2.392747
[Time_Points=2] * [Intervention_Cond=1.00]	-.270685	.384877	130.218	-.703	.483	-1.032105	.490736
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	1.636676	.525258	168.826	3.116	.002	.599755	2.673596
[Time_Points=2] * [Intervention_Cond=2.00]	-.602920	.393000	132.613	-1.534	.127	-1.380281	.174440
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: BPI Interference.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	2.289	.193	166.992	1.908	2.671
Generic	1.981	.197	169.798	1.592	2.371
Placebo	3.611	.200	168.139	3.216	4.006

a. Dependent Variable: BPI Interference.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	3.642	.186	171.000	3.274	4.010
Follow-up 1	2.203	.143	143.184	1.921	2.485
Follow-up 2	2.037	.146	132.903	1.749	2.326

a. Dependent Variable: BPI Interference.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	3.543	.317	171.000	2.916	4.169
	Follow-up 1	1.756	.245	143.555	1.271	2.240
	Follow-up 2	1.570	.243	130.932	1.089	2.051
Generic	Baseline	3.522	.323	171.000	2.885	4.159
	Follow-up 1	1.138	.248	143.467	.648	1.627
	Follow-up 2	1.284	.255	133.711	.779	1.789
Placebo	Baseline	3.860	.328	171.000	3.211	4.508
	Follow-up 1	3.715	.248	142.524	3.224	4.206
	Follow-up 2	3.258	.258	133.752	2.747	3.769

a. Dependent Variable: BPI Interference.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	166.934	886.704	.000
Intervention_Cond	2	166.931	2.205	.113
Time_Points	2	140.271	32.616	.000
Intervention_Cond * Time_Points	4	140.284	.416	.797

a. Dependent Variable: Anxiety.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	8.184347	.593579	150.125	13.788	.000	7.011500	9.357194
[Intervention_Cond=1.00]	-1.355817	.817555	148.428	-1.658	.099	-2.971366	.259733
[Intervention_Cond=2.00]	-1.633283	.833935	150.296	-1.959	.052	-3.281032	.014467
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	2.047796	.575180	141.318	3.560	.001	.910727	3.184864
[Time_Points=2]	.699278	.617490	134.260	1.132	.259	-.521989	1.920545
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	.907007	.791721	139.548	1.146	.254	-.658311	2.472326
[Time_Points=2] * [Intervention_Cond=1.00]	.152951	.856396	132.062	.179	.859	-1.541079	1.846980
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	.728726	.808196	141.446	.902	.369	-.868979	2.326431
[Time_Points=2] * [Intervention_Cond=2.00]	-.043049	.872126	134.880	-.049	.961	-1.767860	1.681761
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: Anxiety.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	8.098	.474	166.332	7.161	9.034
Generic	7.695	.483	168.068	6.741	8.650
Placebo	9.100	.490	166.384	8.133	10.068

a. Dependent Variable: Anxiety.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	9.781	.318	171.000	9.152	10.410
Follow-up 1	7.924	.376	149.482	7.181	8.667
Follow-up 2	7.188	.335	149.131	6.526	7.850

a. Dependent Variable: Anxiety.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	9.783	.542	171.000	8.713	10.853
	Follow-up 1	7.681	.645	150.303	6.406	8.955
	Follow-up 2	6.829	.562	146.453	5.717	7.940
Generic	Baseline	9.328	.551	171.000	8.239	10.416
	Follow-up 1	7.207	.653	149.892	5.918	8.497
	Follow-up 2	6.551	.586	150.468	5.394	7.708
Placebo	Baseline	10.232	.561	171.000	9.125	11.340
	Follow-up 1	8.884	.656	148.258	7.588	10.179
	Follow-up 2	8.184	.594	150.125	7.012	9.357

a. Dependent Variable: Anxiety.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	166.780	534.968	.000
Intervention_Cond	2	166.773	2.067	.130
Time_Points	2	145.539	14.835	.000
Intervention_Cond * Time_Points	4	145.544	.301	.877

a. Dependent Variable: Depression.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	5.683451	.586171	140.888	9.696	.000	4.524623	6.842279
[Intervention_Cond=1.00]	-.169186	.805452	139.629	-.210	.834	-1.761644	1.423272
[Intervention_Cond=2.00]	-.902941	.823734	140.943	-1.096	.275	-2.531411	.725530
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	1.941549	.660971	147.093	2.937	.004	.635323	3.247774
[Time_Points=2]	1.268225	.680548	124.482	1.864	.065	-.078719	2.615169
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	.427519	.910552	145.178	.470	.639	-1.372131	2.227170
[Time_Points=2] * [Intervention_Cond=1.00]	-.208644	.943916	122.193	-.221	.825	-2.077191	1.659903
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	-.153094	.928381	147.282	-.165	.869	-1.987763	1.681575
[Time_Points=2] * [Intervention_Cond=2.00]	-.812953	.960821	125.156	-.846	.399	-2.714514	1.088608
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: Depression.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	6.657	.464	165.815	5.740	7.574
Generic	5.528	.474	168.128	4.593	6.464
Placebo	6.753	.480	166.356	5.806	7.701

a. Dependent Variable: Depression.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	7.359	.347	171.000	6.675	8.044
Follow-up 1	6.254	.378	148.313	5.506	7.001
Follow-up 2	5.326	.331	140.106	4.672	5.980

a. Dependent Variable: Depression.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	7.883	.590	171.000	6.718	9.049
	Follow-up 1	6.574	.649	148.966	5.291	7.857
	Follow-up 2	5.514	.552	138.125	4.422	6.607
Generic	Baseline	6.569	.600	171.000	5.384	7.754
	Follow-up 1	5.236	.657	148.635	3.938	6.534
	Follow-up 2	4.781	.579	140.998	3.636	5.925
Placebo	Baseline	7.625	.611	171.000	6.419	8.831
	Follow-up 1	6.952	.659	147.332	5.649	8.255
	Follow-up 2	5.683	.586	140.888	4.525	6.842

a. Dependent Variable: Depression.

Fixed Effects

Type III Tests of Fixed Effects[a]

Source	Numerator df	Denominator df	F	Sig.
Intercept	1	165.817	5014.122	.000
Intervention_Cond	2	165.810	1.361	.259
Time_Points	2	148.029	29.235	.000
Intervention_Cond * Time_Points	4	148.164	.659	.621

a. Dependent Variable: Global QOL.

Estimates of Fixed Effects[a]

Parameter	Estimate	Std. Error	df	t	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Intercept	10.195665	.310089	140.633	32.880	.000	9.582626	10.808705
[Intervention_Cond=1.00]	.123216	.426535	139.085	.289	.773	-.720114	.966546
[Intervention_Cond=2.00]	.287983	.435896	140.638	.661	.510	-.573773	1.149740
[Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=1]	-1.767094	.387224	156.903	-4.563	.000	-2.531938	-1.002249
[Time_Points=2]	-.717310	.322413	137.399	-2.225	.028	-1.354843	-.079777
[Time_Points=3]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=1.00]	.248212	.534715	154.842	.464	.643	-.808065	1.304489
[Time_Points=2] * [Intervention_Cond=1.00]	.649373	.446006	135.767	1.456	.148	-.232644	1.531390
[Time_Points=3] * [Intervention_Cond=1.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=2.00]	.128273	.543806	157.190	.236	.814	-.945837	1.202383
[Time_Points=2] * [Intervention_Cond=2.00]	.587598	.455268	138.105	1.291	.199	-.312599	1.487795
[Time_Points=3] * [Intervention_Cond=2.00]	0[b]	0	.	.	.	.	.
[Time_Points=1] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=2] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.
[Time_Points=3] * [Intervention_Cond=3.00]	0[b]	0	.	.	.	.	.

a. Dependent Variable: Global QOL.

b. This parameter is set to zero because it is redundant.

Estimated Marginal Means

1. Intervention type[a]

Intervention type	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Personalization	9.790	.233	164.745	9.330	10.250
Generic	9.894	.237	167.170	9.426	10.363
Placebo	9.368	.240	165.488	8.893	9.842

a. Dependent Variable: Global QOL.

2. Time points[a]

Time points	Mean	Std. Error	df	95% Confidence Interval	
				Lower Bound	Upper Bound
Baseline	8.691	.186	171.000	8.323	9.059
Follow-up 1	10.028	.185	144.887	9.662	10.393
Follow-up 2	10.333	.175	139.625	9.987	10.679

a. Dependent Variable: Global QOL.

3. Intervention type * Time points[a]

Intervention type	Time points	Mean	Std. Error	df	95% Confidence Interval	
					Lower Bound	Upper Bound
Personalization	Baseline	8.800	.317	171.000	8.174	9.426
	Follow-up 1	10.251	.318	145.431	9.623	10.879
	Follow-up 2	10.319	.293	137.243	9.740	10.898
Generic	Baseline	8.845	.323	171.000	8.208	9.482
	Follow-up 1	10.354	.321	145.266	9.719	10.989
	Follow-up 2	10.484	.306	140.641	9.878	11.089
Placebo	Baseline	8.429	.328	171.000	7.780	9.077
	Follow-up 1	9.478	.322	143.965	8.841	10.115
	Follow-up 2	10.196	.310	140.633	9.583	10.809

a. Dependent Variable: Global QOL.

Stimuli used in Word Sentence Association Paradigm:

Stimuli for ovarian cancer

sentence	related_word	unrelated_word
Your abdomen seems bloated for a few hours.	Gas	Cancer recurrence
Your vulva (folds outside the vagina) feels dry and flaky.	Dehydrated	Cancer recurrence
You feel more fatigued than usual for a few hours.	Not enough sleep	Cancer recurrence
You are tired lately.	Not enough sleep	Cancer
You feel nauseated for a few hours.	Ate too much	Cancer
You lose your appetite for a few hours.	Nervous	Cancer spread
Someone asks if you lost weight.	Healthy	Cancer spread
You feel a pain on your side for a few hours.	Cramp	Cancer spread
You feel a pain in your back for a few hours.	Strained muscle	Cancer spread
You experience hot flashes.	Menopause	Cancer recurrence
You experience a burning sensation when urinating.	Infection	Cancer spread
Your back aches for a couple of hours.	Mattress	Cancer spread
You run a low-grade fever.	Virus	Cancer spread
You are more forgetful than usual.	Aging	Brain metastases
You have trouble focusing.	Distracted	Brain metastases
It is difficult to focus on any task lately.	Overwhelmed	Brain metastases
You find it difficult to concentrate.	Busy	Brain metastases
You have trouble sleeping.	Stressed	Cancer spread
You wake up tired.	Not enough sleep	Recurrence
You feel sleepier than usual.	Busy	Cancer spread
You wait longer than usual for your appointment.	Busy clinic	Bad news
The doctor seems anxious.	Distracted	Bad news
The technician needs to repeat your scan.	Inconvenience	Suspicious mass
The technician needs to take additional scans.	Thorough	Suspicious mass
The doctor does not smile while examining you.	Unfriendly	Suspicious finding
You have a nervous feeling after your appointment.	Natural	Bad news
The nurse sounds worried in their message.	Busy day	Bad news
You see signs everywhere about cancer.	Common	Recurrence
You have a nightmare about dying.	Normal	Bad sign
The doctor calls with the results.	Normal	Bad news
The nurse leaves a message asking you to come in.	Standard practice	Bad news
The doctor does not return your call.	Busy	Bad news
The nurse does not return your call.	Busy	Bad news
The doctor recommends a new specialist.	Caring	Suspicious results

The technician takes a long time to perform ultrasound imaging.	Thorough	Suspicious mass
Your doctor suggests genetic testing.	Standard practice	High risk
Your doctor asks about cancer history in your family.	Standard practice	High risk
The doctor orders to repeat the bloodwork.	Error	Bad news
You have a stomachache for a couple of hours.	Gas	Cancer recurrence
You're constipated for a day.	Medication side effects	Cancer recurrence
You gain weight.	Steroids	Higher risk
You have a headache for a few hours.	Migraine	Metastases
You do not hear back from the doctor.	Busy	Bad news
The doctor sends you for a scan.	Routine	Malignancy
You use your dilator and see a pink tinge.	Infection	Cancer recurrence
You see a pinkish discharge.	Dry vaginal tissue	Cancer recurrence
Your CA-125 went up one point.	Infection	Cancer
Your partner seems worried about you.	Caring	Bad sign
People at work avoid you.	Busy	Bad sign
Friends do not call you.	Busy	Bad sign
Sex is more painful than it used to be.	Nervous	Cancer recurrence
Sex is not as satisfying as it used to be.	Low libido	Cancer recurrence
You do not look the same as you used to.	Aging	Cancer

Stimuli for Breast cancer

Scenarios	related_word	Unrelated_word
Your breast seems swollen for a few hours.	Period	Recurrence
Your breasts look uneven since surgery.	Need new bra	Cancer
The nipple of your unaffected breast looks different.	Cold	New tumor
You had lumpectomy, and your breast looks uneven.	Normal	Cancer
Your nipple feels sore.	Period	Cancer
You see a spot that looks bruised.	Fall	Metastases
Your breast is more sensitive than usual.	Period	Tumor
Your skin feels dry and flaky.	Winter	Recurrence
You feel more fatigued than usual for a few hours.	Not enough sleep	Recurrence
You have less energy lately.	Need more sleep	Cancer
You are tired lately.	Not enough sleep	Cancer
You feel nauseated for a few hours.	Ate too much	Cancer
You lose your appetite for a few hours.	Nervous	Metastases
Someone asks if you lost weight.	Healthy	Cancer spread
You feel a pain on your side for a few hours.	Cramp	Metastases
You feel a pain in your back for a few hours.	Strained muscle	Metastases
You experience hot flashes.	Menopause	Recurrence
You experience a stinging sensation.	Cut	Cancer spread
Your back aches for a couple of hours.	Mattress	Metastases
You run a low grade fever.	Virus	Metastases
You are more forgetful than usual.	Aging	Brain metastases
You have trouble focusing.	Distracted	Brain metastases
It is difficult to focus on any task lately	Overwhelmed	Brain metastases
You find it difficult to concentrate.	Busy	Brain metastases
You have trouble sleeping.	Stressed	Metastases
You wake up tired.	Not enough sleep	Recurrence
You feel sleepier than usual.	Busy	Metastases
Sleeping on your stomach feels uncomfortable.	Bloated	Tumor
You wait longer than usual for your appointment.	Busy clinic	Bad news
The doctor seems anxious.	Distracted	Bad news
The technician tells you that you need to have your mammogram repeated.	Inconvenience	Suspicious mass
The technician needs to repeat your scan.	Inconvenience	Suspicious mass

The doctor does not smile while examining you.	Unfriendly	Suspicious mass
You feel nervous after your mammogram appointment.	Natural	Bad news
The nurse sounds worried in their message.	Busy day	Bad news
You see signs everywhere about breast cancer.	Common	Recurrence
You have a nightmare about dying.	Normal	Bad sign
The doctor calls with the results.	Normal	Bad news
The nurse leaves a message asking you to come in.	Standard practice	Bad news
The doctor does not return your call.	Busy	Bad news
The nurse does not return your call.	Busy	Bad news
The doctor recommends a new specialist.	Caring	Suspicious mass
The technician needs to take additional scans.	Thorough	Suspicious mass
Your doctor suggests genetic testing.	Standard practice	High risk
Your doctor asks about cancer history in your family.	Standard practice	High risk
The doctor orders to repeat the bloodworK.	Error	Bad news
You have a stomachache for a couple of hours.	Gas	Recurrence
Your partner seems worried about you.	Caring	Bad sign
People at work avoid you.	Busy	Bad sign
Friends do not call you.	Busy	Bad sign
Sex is more painful than it used to be.	Nervous	Recurrence
Sex is not as satisfying as it used to be.	Low libido	Recurrence
You have a headache for a few hours.	Migraine	Metastases
You do not hear back from the doctor.	Busy	Bad news
The doctor sends you for a scan.	Routine	Malignancy
You have a nervous feeling after your appointment.	Natural	Bad news
You do not look the same as you used to.	Aging	Cancer

Appendix J

Published manuscripts

Received: 27 July 2020 | Revised: 12 November 2020 | Accepted: 26 November 2020

DOI: 10.1002/pon.5617

WILEY

REVIEW

The role of attentional biases in the context of cancer: A systematic review and meta-analysis

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Abstract

Objective: Little is known about the role of attentional processes in the context of cancer. This systematic review aimed to (1) synthesize the literature on attentional biases in cancer survivors; and (2) assess if these biases are associated with indicators of psychological distress.

Method: Studies were identified through a systematic search in PsycINFO, Medline, Scopus, CINAHL, Web of Science and Embase databases. We included studies that examined attentional biases using an accepted experimental paradigm (Dot-probe or Stroop) in cancer survivors.

Results: Of 4105 papers identified, 18 met inclusion criteria. Cancer survivors had a greater attentional bias towards salient stimuli (cancer/negative stimuli) as compared to controls (Hedge's $g = 0.82$). Survivors who were more distressed had greater attentional biases (Hedge's $g = 0.27$). It was unclear whether the nature of stimuli was important in driving these effects (e.g., cancer-specific vs. negative).

Conclusion: These results demonstrate that cancer survivors have an attentional bias towards cancer-related (typically words) or negative stimuli (typically facial expressions), and that bias is greater for those with higher levels of distress.

KEYWORDS
attention, cancer, cognitive biases, fear of cancer recurrence, neoplasms, oncology, psycho-oncology

1 | INTRODUCTION

Although most people cope well following cancer treatment, a small but important minority develop clinically significant levels of anxiety, depression or fear of cancer recurrence.[1–4] These psychosocial sequelae are known to impair the quality of life of cancer survivors.[5,6] One factor thought to contribute to a vulnerability to anxiety and depression is attentional bias towards threatening or negative stimuli.[7–9] Attentional biases refer to the tendency of individuals to have their attention drawn to threatening (personally salient) stimuli, and have difficulty disengaging from those stimuli.

A systematic review[10] of theoretical models on the development of cancer-related anxiety found that recent models specified a role for attentional biases in the development of anxiety in the cancer context. Historically, models focused on the content of beliefs, such as appraisals of threat (e.g.,[11,12]), illness representations (e.g.,[13,14]) or beliefs about death and dying (e.g.,[12]). However, more recent models also emphasised cognitive processing, such as attentional bias (e.g.,[11,15]). However, contemporary models suggest that it is not just the content of beliefs, but also the way people attend to potentially threatening information, such as focusing on intrusive thoughts, physical symptoms or other cancer-related cues (attentional biases), which contribute to the development and maintenance of anxiety.[11,16,17]

However, investigation of attentional biases in relation to cancer-related cues is sparse. Furthermore, findings of the studies conducted to date are mixed, with some studies finding attentional biases amongst people with cancer compared to controls,[18,19] others

finding biases only amongst people with cancer who are distressed[20] and some finding no biases in cancer survivors.[21] Different results likely reflect differences in methodology, such as different paradigms, valence of stimuli, type of stimuli and different stimulus presentation timings.

While little is yet known about attentional biases in relation to cancer, it is important to synthesise the literature at this early stage to guide future research. Therefore, the aims of this review were to summarise the literature on: (a) the presence of attentional biases in cancer survivors, and (b) the relationship between attentional biases and cancer-related distress; and (c) to make recommendations for future research. We proposed three specific research questions.

- Do cancer survivors show attentional biases in processing cancer-related and/or negative (i.e., salient) stimuli as compared to people without cancer?
- Do cancer survivors show attentional biases in processing salient stimuli as compared to neutral stimuli?
- Are attentional biases in cancer survivors associated with distress, such as fear of cancer recurrence (FCR), depression or anxiety?

2 | METHOD

The protocol of the review was preregistered with PROSPERO (ID CRD42019117140).

2.1 | Search strategy

Comprehensive searches were conducted up until May 2020 in six online databases: PsycINFO, Medline, Web of Science, Scopus, Embase and CINAHL. Key search terms were related to cognitive bias; "attention* bias*, interpret* bias*, memory bias*". These were combined with cancer population related keywords "cancer or neoplasm" (see Supporting Information Material 1 for complete search string). The reference lists of selected articles were manually screened to identify additional papers.

2.2 | Selection of studies

Titles and abstracts were screened according to inclusion and exclusion criteria (PP) and 10% were reviewed by another author (LS) with almost perfect[22] interrater agreement of $k = 0.83$. All full-text article screening and data extraction were conducted by two authors (Poorva Pradhan and Louise Sharpe). Disagreements were resolved by consensus.

The following inclusion criteria were applied.

- Studies using standard experimental paradigms to measure attentional biases with and without control group were included. Experimental paradigms typically use reaction time to determine whether individuals respond more quickly to salient stimuli than neutral stimuli (or probes that replace salient stimuli), such as the Dot-Probe or Stroop task (see Supporting Information Material 2 for a description).[23]
- Participants who have had or currently have cancer of any type or stage.
- Studies that were published as a peer-reviewed journal article or dissertation thesis.

2.3 | Data extraction

The following data points were extracted from included studies: publication year, nature of sample(s) (cancer survivor; control), mean age, sample size, type of cancer, type of task used to assess attentional biases, means and standard deviations for attentional biases for cancer survivors and controls and the relationship between attentional biases and distress. The attentional bias index scores on the dot probe task were calculated by subtracting mean reaction times to probes appearing in the same location as neutral stimuli from mean reaction times to probes appearing in the same location as salient stimuli. The Stroop interference effect was calculated by subtracting mean reaction time on neutral stimuli from mean reaction time on salient stimuli. A positive bias index indicates attention towards salient stimuli. Hence, a positive effect size indicates evidence of attentional bias towards salient stimuli.[23]

Where data were not available, we contacted the authors. If unavailable, we used other statistical information to calculate an effect size, wherever possible. Where multiple stimuli were used, we used the stimuli that we considered most salient to cancer survivors. Hence, we prioritised stimuli in following order: cancer-related stimuli (if differently valenced, we opted for negative cancer-related stimuli), over health-related stimuli, over negative stimuli (often facial expressions of fear or sadness) and finally threat stimuli. Where multiple presentation times were used in a single study, we prioritised 500 ms over 1000 ms over subliminal presentation. Only one study used a subliminal presentation time and, therefore, subliminal attention was not assessed in this meta-analysis. To investigate distress, studies included different measures, including measures of FCR, anxiety or general distress. Where multiple assessments of distress were included, we included the relationship according to the order above.

2.4 | Quality assessment

For assessing the methodological quality of included studies, a modified version of Downs and Black[24] quality index checklist was used. The modified checklist has 18 items relating to five criteria: reporting, external validity, internal validity (bias), selection bias and power of the study, where a higher score indicates

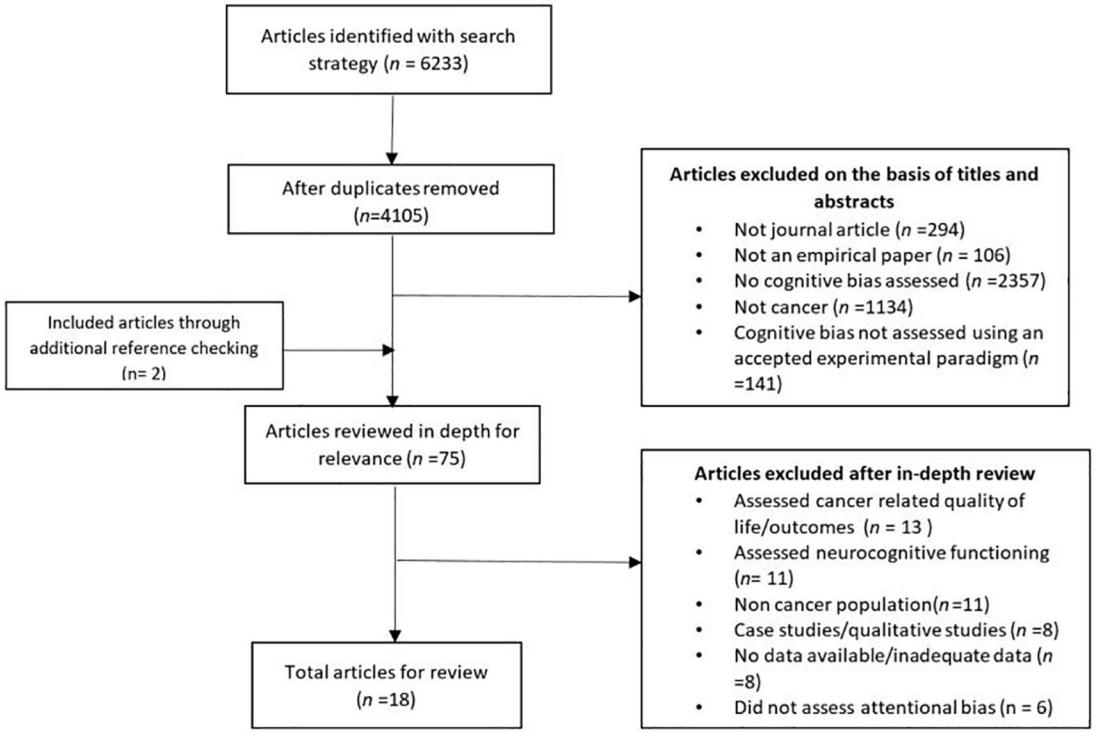

FIGURE 1 Prisma flow diagram depicting the selection process of final included articles

higher quality. Two reviewers (PP; LS) performed quality ratings for each article. Interrater reliability was $k = 0.86$, indicating almost perfect reliability.[22] Discrepancies were resolved through discussion.

2.5 | Statistical analysis

The analyses were performed with the Comprehensive Meta-analysis software (version 3). We report Hedge's g as the effect size. We pooled these effect sizes for individual studies to calculate whether the attentional bias was larger for people who had cancer compared to people with no personal or family history of cancer (*between-subjects analysis*). We then examined all studies that investigated attentional bias in people with cancer, to determine whether people with cancer exhibited more attention to salient than neutral stimuli (*within-subjects analysis*). Finally, we examined studies where distress (e.g., FCR, anxiety, depression) was measured to determine whether distressed people with cancer had greater attentional biases than those who were not distressed. Study characteristics, including, type of paradigm (Dot-probe or Stroop), type of stimuli (words or faces) and exposure duration (500 or ≥1000 ms) were used as moderator variables. As suggested by Cohen,[25] the following conventions were used to interpret effect sizes: 0.2 represents a small, 0.5 represents a medium and 0.8 represents a large effect size.

All analyses used random-effects models, which allow more weight to be given to studies with larger samples.[26] To determine heterogeneity, we assessed Cochran's Q and I^2 statistic which is an estimate of heterogeneity across studies. Increasing values indicate increasing heterogeneity. A p value of less than 0.05 was considered statistically significant for all analyses.

To assess for publication bias, we tested the asymmetry of the funnel plot and used Egger's test to determine overall symmetry. We conducted Duval–Tweedie trim and fill analysis, which provides an estimate of missing studies and recalculates the adjusted effect size. Finally, Rosenthal fail-safe N was also computed to determine how many additional studies would need to be unpublished for the p-value to become nonsignificant.[27]

2.6 | Differences from the published protocol

We intended to review studies for all cognitive biases (including interpretation and memory biases) and investigate cognitive biases in caregivers. However, there were insufficient data to meta-analyse these outcomes.

3 | RESULTS

The search strategy yielded 6233 articles, 4105 after removal of duplicates (see Figure 1). Titles and abstracts of the 4105 results were screened and 75 full-text articles were retrieved. Details of the reason for exclusion are listed in Figure 1. Eighteen studies met our inclusion criteria.

3.1 | Study characteristics

Study characteristics are presented in Table 1. All 18 included studies recruited adult participants ($n = 1273$). Eleven studies utilized the Dot-probe paradigm[42] and seven used the Stroop paradigm.[43] Thirteen studies used linguistic stimuli and five studies used pictorial or face stimuli. Stimuli presentation time for the Dot-probe ranged from 500 to 1250 ms. The average sample size for cancer survivors was 71 ($SD = 33.9$) and their mean age was 56.07.

3.2 | Meta-analytic results

Research Question 1 Do cancer survivors show attentional biases to cancer-related stimuli as compared to people without cancer?

Only six studies included a comparison of cancer survivors and a control group. There was a significant bias towards salient stimuli for people with cancer compared to those without, with a large effect size ($k = 6$, Hedge's $g = 0.82$, 95% CI [0.081, 1.568], $p < 0.001$; see Figure 2). There was significant heterogeneity ($Q = 98.24$, $p < 0.001$). There was asymmetry evident in the Funnel plot upon visual inspection, with one study falling far to the right of the distribution and two studies falling to the left. However, Egger's regression was not significant ($t = 0.0178$, $p = 0.99$), nor was Begg and Mazumdar's rank correlation ($\tau = 0.33$, $p = 0.34$). Duval and Tweedie's trim and fill analysis did not indicate that any studies needed to be trimmed, supporting an absence of publication bias effects. The fail-safe n was 6, although this may simply indicate the small number of available studies. Removing one outlying study in a sensitivity analysis, confirmed a significant difference on salient stimuli between people with and without cancer, but with a small effect size (Hedge's $g = 0.378$, $p < 0.0005$).

Research Question 2 Do cancer survivors show attentional biases to cancer-related or negative stimuli as compared to neutral stimuli?

Data were available for attentional biases towards salient stimuli in 12 studies. Within-group analysis indicated a small attentional bias towards salient compared to neutral stimuli in cancer patients ($k = 12$, Hedge's $g = 0.50$, 95% CI [0.223, 0.779], $p < 0.001$). There was significant heterogeneity ($Q = 155.142$, $p < 0.001$). The funnel plot appeared to be symmetrical and Egger's regression was not significant ($t = 1.35$, $p = 0.196$) nor was Begg and Mazumdar's rank correlation ($\tau = 0.26$, $p = 0.15$). Duval and Tweedie's trim and fill indicated that no studies needed to be trimmed and the fail-safe n was 408.

Both cancer-related ($k = 10$, Hedge's $g = 0.54$, 95% CI [0.157, 0.929], $p = 0.006$) and negative stimuli ($k = 7$, Hedge's $g = 0.435$, 95% CI [0.029, 0.841], $p = 0.036$) resulted in a significant effect and did not differ from each other ($t = 0.144$, $p = 0.71$).Overall, there was a significant attentional bias on the Dot-probe paradigm ($k = 10$, Hedge's $g = 0.33$, 95% CI [0.081, 0.572], $p = 0.009$) and Stroop paradigm ($k = 7$, Hedge's $g = 0.71$, 95% CI [0.126, 1.301], $p = 0.017$) and no difference between the tasks ($t = 1.418$, $p = 0.234$). There was no difference between studies where trials were presented for 500 ms compared to those with more than 1000-ms presentation ($k = 10$, $t = 0.00$, $p = 0.988$)

Research Question 3 Are attentional biases in survivors associated with distress?

There were 10 studies that reported effect sizes relevant to this question. There was a significant bias towards salient stimuli in people who were distressed that was significantly larger than for people who were not distressed with a small effect size ($k = 10$, Hedge's $g = 0.31$, 95% CI [0.031, 0.576], $p = 0.001$). There was no asymmetry evident in the Funnel plot upon visual inspection and Egger's regression was not significant ($t = 0.66$, $p = 0.53$), nor was Begg and Mazumdar's rank correlation ($\tau = 0.08$, $p = 0.75$). Duval and Tweedie's trim and fill indicated that no studies needed to be trimmed. The fail-safe n was 24, which likely indicates the early stage of research in this area. As in previous analyses, there was significant heterogeneity ($Q = 24.19$, $p = 0.002$), therefore we conducted moderator analyses using stimuli (cancer vs. negative) as the moderator. The moderator analysis for stimuli did not show a difference between cancer-specific and other negative stimuli ($t = 0.109$, $p = 0.742$).

3.3 | Study quality

Quality scores on attentional bias studies ranged from 2 to 15 (out of 19). The quality of reporting was good in most studies (14/17). There was insufficient data to rate one study for quality, so ratings were available for 17/18 studies. External validity was of poorer quality with 11 studies being either unclear or low quality. Similarly, for internal validity only three studies were scored as high quality. Only six studies clearly reported power analysis.

4 | DISCUSSION

The results of the meta-analysis demonstrate that cancer patients exhibit a greater attentional bias towards salient stimuli than people without cancer and a greater bias towards salient stimuli compared to neutral stimuli. The difference between people with and without cancer was smaller following sensitivity analyses, confirming that the large effect could be an overestimate. Nevertheless, we can be confident that those living with and beyond cancer have attentional biases towards salient stimuli. Importantly, our results also confirm an association between distress and attentional bias to salient compared to neutral stimuli.

People who are more anxious are known to be more likely to attend towards threatening stimuli,[9] and that bias towards stimuli is greater when the stimuli is specific to their concerns.[44] Indeed, there is evidence from both prospective studies and studies in which

TABLE 1 Study characteristics and effect sizes of included studies for meta-analysis

Study	Nature of sample	Sample size	Type of cancer	Type of task	Duration of trials/stimuli	Type of stimuli	Effect size (Hedge's *g*)	95% CI	Quality index scores (max score = 19)
Aramaki et al.[28]	Cancer patients	17	Multiple cancers	Stroop task		Words	0.401	(−0.262, 1.065)	3
Bakhshaie et al.[29]	Cancer patients	123	Multiple cancers	Stroop task		Words	0.005	(−0.244, 0.254)	11
Balandin[18]	Cancer survivors controls Caregivers	Cancer survivors: 100 controls: 100 caregivers: 100	Breast cancer	Stroop task		WORDS	2.372*	(2.011, 2.733)	12
Boyle et al.[30]	Cancer survivors	91	Breast cancer	Dot probe task	1000 ms	Faces	1.056*	(0.587, 1.525)	9
Butow et al.[21]	Cancer survivors	63	Breast and prostate cancer	Dot probe task	500 ms	Words	0.099	(−0.394, 0.592)	12
Carpenter et al.[31]	Cancer survivors Controls	Cancer survivors: 61 controls: 54	Breast and ovarian cancer	Stroop task		Words	0.201	(−0.163, 0.565)	15
Chan et al.[32]	Cancer patients	56	Breast cancer	Dot probe task	1000 ms	Faces	0.619*	(0.041, 1.198)	7
Cobeanu[33]	Cancer patients	30	Breast cancer	Dot probe task	500 ms	Words	0.275	(−0.466, 1.016)	6
Custers et al.[19]	Cancer survivors and Controls	Cancer survivors: 67 Controls: 40	Breast cancer	Stroop task		Words	High versus low FCR: 0.136 cancer patients versus controls: 0.509*	High versus low FCR: (−0.338, 0.611) Cancer patients versus Controls: (0.114, 0.903)	11
Glinder et al.[34]	Cancer patients	127	Breast cancer	Dot probe task	20 ms, 1000 ms	Words	0.491*	(0.131, 0.852)	6
Koizumi et al.[35]	Cancer patients	27	Hematopoietic tumour patients	Dot probe task	500 ms	Faces	N/A		4

(Continues)

TABLE 1 (Continued)

Study	Nature of sample	Sample size	Type of cancer	Type of task	Duration of trials/stimuli	Type of stimuli	Effect size (Hedge's *g*)	95% CI	Quality index scores (max score = 19)
Lam et al.[20]	Cancer patients	140	Breast cancer	**Attentional bias**: dot probe task **interpretation bias**: Ambiguous cues task	500 and 1250 ms	Words	500 ms: 0.222	500 ms: (−0.176, 0.620)	12
Lautenbacher et al.[36]	Cancer patients	58	Multiple cancers	Dot probe task	500 ms	Words	0.245	(−0.281, 0.770)	7
Lichtenthal et al.[37]	Cancer survivors	110	Breast cancer	**Attentional bias**: dot probe task **interpretation bias**: word-sentence association paradigm (WSAP)	Dot probe: 500 ms WSAP: 500 ms	Dot probe: words WSAP: word-sentence pairings	0.319	(−0.051, 0.688)	11
Naidich & Motta[38]	Cancer patients and controls	Cancer patients: 31 Controls: 31	Breast cancer	Stroop task		Words	0.436	(−0.062, 0.933)	5
Shi et al.[39]	Cancer patients and controls	Cancer patients: 54 Controls: 52	Multiple cancers	Dot probe task	500 ms, 1250 ms	Faces	500 ms: 1.184*	500 ms: (0.590, 1.779)	N/A
Sullivan-Singh et al.[40]	Cancer patients and controls	Cancer patients: 85 Controls: 49	Breast cancer	**Attentional bias**: Dot probe task **memory bias**: Recognition task	1000 ms	Faces	0.252	(−0.101, 0.604)	11
Taylor et al.[41]	Cancer patients	33	Multiple cancers	Stroop task		Words	0.295	(−0.378, 0.967)	2

*$p < 0.05$.

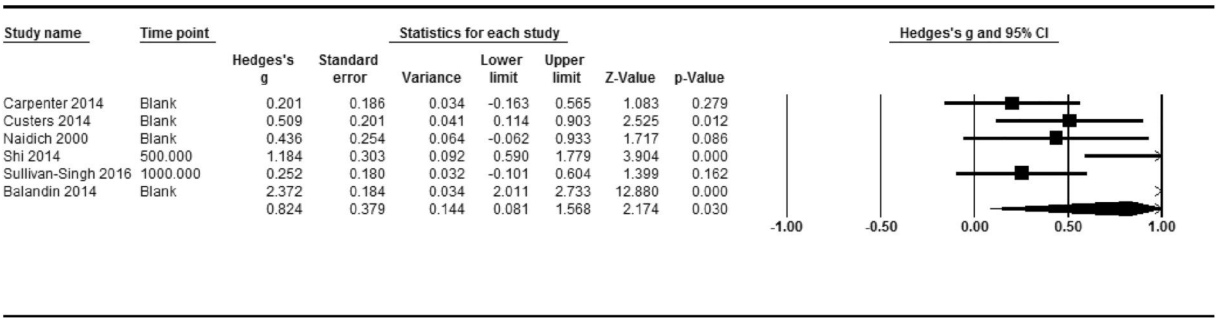

FIGURE 2 Forest plot for attention biases between those who have had cancer and those who have not

attentional biases are manipulated, that attentional bias has a likely causal role in the development of anxiety.[45] For these reasons, theoretical models that attempt to explain why some people develop clinically significant anxiety in the context of cancer, have also focused on the way that people process or attend to information.[9] It is proposed that survivors who are anxious are vigilant to cues of cancer in the environment and are unable to disengage from these cues. It is these attentional biases that the experimental paradigms aim to identify, and therefore we would expect that cancer survivors who are distressed would have greater attentional biases to salient stimuli than those who are not distressed.

In anxiety disorders, there is evidence that this bias is particular to disorder-specific stimuli.[44] However, in none of our analyses was the difference between cancer-specific stimuli and other negative stimuli (typically faces) significant. One possible explanation is the nature of cancer-specific versus negative stimuli. Most negative stimuli were facial expressions, while most cancer-specific stimuli were words. It may be that cancer-specific stimuli that were pictorial might produce larger effects. Alternatively, since studies varied in how they categorised distressed participants, biases to negative stimuli may be due to general anxiety and/or depression and it may be cancer-specific anxiety, such as FCR, that is linked to cancer-specific stimuli. These explanations are speculative and the results may simply reflect insufficient power.

4.1 | Limitations

The main limitation of this meta-analysis is the paucity of current research on attentional biases in the context of cancer. There was considerable heterogeneity between studies in relation to stimuli, presentation time and measures of distress used to characterise the samples. Furthermore, there were no studies that used more direct measures of attentional bias, such as eye tracking methodology. There was only one study that assessed attentional biases subliminally (i.e., at presentation times too short for participants to be aware of the stimuli) and so we can draw no conclusions about subliminal presentations. Studies used different measures of "distress" and we collapsed these. Furthermore, we had intended to include other cognitive biases, such as interpretation and memory biases but there were too few studies to do so.

The conclusion of this review is that cancer survivors have attentional biases towards salient stimuli, and this bias is greater amongst those who are more distressed. Nevertheless, the review raises more questions than it answers due to the limitations in the literature. We make eight recommendations that stem from these findings (see Table 2).

- Given the lack of clarity surrounding what stimuli are associated with an attention bias in the cancer context, we recommend that authors include at least negative and cancer-related stimuli. Furthermore, researchers should develop stimuli specific to the cancer type, since one might expect that mastectomy may elicit more of a response in breast cancer survivors than other tumour groups (see[46] for a discussion).
- All studies of attentional bias used reaction time measures, that are known to be unreliable.[47] Future research would benefit from measuring gaze behaviour more directly.
- The inclusion of well-matched control groups is important because many measures of attentional bias are influenced by factors, such as age or education.
- There were only two studies of interpretation bias[20,37] and memory bias.[40,48] More research of these constructs in the context of cancer.
- Ideally research would investigate multiple cognitive biases within the same sample, as it has been argued that cognitive biases interact, known as the "combined cognitive bias hypothesis."[49]
- Only two studies specifically examined FCR, which is the leading psychosocial unmet need of cancer survivors.[50] Recent FCR theories have all emphasized cognitive processes as important to the development or maintenance of FCR (e.g.,[11,16,17]).
- From the broader emotion research, we would expect attention and interpretation bias to be the primary biases involved in constructs like FCR, whereas memory biases have been more implicated in depressive mood.[51] Therefore, it would be important for research to investigate the impact of depressed mood on memory biases in the cancer context.
- Much of the research was pragmatic, rather than theoretically driven. Future research should be designed to try and test relevant theories of the role of attentional biases in the cancer experience.

TABLE 2 Identified gaps in the literature and recommendations for future research

Identified gaps	Recommendations for future research
Studies have not developed stimuli specific to the relevant sample	At least, cancer-related *and* negative stimuli should be included in studies
No studies of eye gaze behaviour	More direct methods of assessment, such as eye tracking methods are needed
Few studies comparing people with and without cancer, caregivers versus controls	Need to include appropriate control groups
Only two studies of interpretation biases, and memory biases	Need more research into interpretation and memory biases
Only two studies assessing attention and interpretation bias in one study	Important to measure more than one cognitive bias to determine interactions
Relatively few studies specific to FCR, despite theories emphasizing cognitive biases	Need to assess specifically in relation to fear of cancer recurrence
No studies of implicit memory, no studies linking memory bias to depression	Need to examine memory in relation to depressive symptoms
Studies were rarely theoretically driven	Need to develop studies to test the role of cognitive biases, not just their presence

4.2 | Clinical implications

Further research into attentional biases is important because procedures have been developed to modify cognitive biases and use these for interventions (cognitive bias modification [CBM]). In a systematic review of meta-analyses of CBM, Jones and Sharpe[52] concluded that CBM for interpretation biases (CBM-I) reduced *anxiety symptoms*, while CBM for attentional biases (CBM-A) reduced *stress vulnerability* (i.e., how anxious people felt in a stressful situation). The only study of CBM applied to cancer found that combined CBM (for attention and interpretation) modified negative interpretations (but did not change attentional bias) and reduced one subscale of Concerns about Recurrence Scale.[37] These results are consistent with the anxiety literature, where we would expect CBM-I to be efficacious for worry-type symptoms. In the cancer context there are many stressful situations, in that CBM-A may be particularly suited to reducing the increase in anxiety associated with particular situations, such as prior to regular scans.[53,54] However, in order for such interventions to be developed and tested, we first need to characterise the nature of cognitive biases in the context of cancer and their relation to distress and other constructs.

5 | CONCLUSION

In conclusion, our meta-analysis provides evidence for attentional biases towards cancer-specific and/or negative stimuli amongst cancer survivors. Importantly, the results also suggest survivors who are distressed have larger attentional biases those who are not distressed. Overall, there is a need to expand research in this area by including appropriate stimuli, more direct measures of cognitive processes, appropriate control groups and more research on other cognitive biases, particularly in the same sample. Currently, little of the research is theoretically driven. Examining cognitive biases using a theoretical framework will undoubtedly help us better understand the role of cognitive biases in the context of cancer, and their clinical potential.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Pradhan P, Sharpe L, Butow P. The role of attentional biases in the context of cancer: A systematic review and meta-analysis. *Psycho-Oncology*. 2021;30:649–658. https://doi.org/10.1002/pon.5617

Received: 13 January 2021 | Revised: 3 May 2021 | Accepted: 14 May 2021

DOI: 10.1002/pon.5748

WILEY

ORIGINAL ARTICLE

The role of interpretation biases and symptom burden in fear of cancer recurrence/progression among ovarian cancer survivors

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Abstract

Background: Models of fear of cancer recurrence or progression (FCR/P) suggest that the way in which people interpret ambiguous physical symptoms is an important contributor to the development and maintenance of FCR/P, but research has not investigated this claim. The aim of this study is to fill that gap.

Methods: This was a cross-sectional study. Sixty-two women with ovarian cancer reported completed measures of FCR/P, an interpretation bias task and a symptom checklist. The healthy control group ($n = 96$) completed the interpretation bias task.

Results: Women with ovarian cancer were more likely to interpret ambiguous words as health-related compared to healthy women ($p < 0.001$; Cohen's $d = 1.28$). In women with cancer, FCR/P was associated with overall symptom burden ($r = 0.25$; $p = 0.04$) and interpretation bias score ($r = 0.41$; $p = 0.001$), but interpretation bias and symptom burden were not related ($r = 0.22$; $p = 0.09$). Interpretation bias did not moderate the relationship between symptoms and FCR/P.

Conclusions: We found that women with ovarian cancer interpreted ambiguous words as health related more often compared to women without cancer, and this bias was greater for women with higher FCR/P. Symptom burden was also associated with FCR/P. However, interpretation bias did not moderate the relationship between physical symptoms and FCR/P. Hence, the central tenet of the Cancer Threat Interpretation model was not supported in women with ovarian cancer.

KEYWORDS
cancer, cancer survivorship, cognitive biases, fear of cancer recurrence/progression, interpretation bias, oncology, ovarian cancer

1 | INTRODUCTION

Ovarian cancer is the 10th most commonly diagnosed cancer among Australian women, with a poorer prognosis than more common cancers. Only 46% of women diagnosed with ovarian cancer are expected to survive to 5 years. Consequently, women with ovarian cancer live with a significant risk of cancer recurrence or progression and have high symptom burden, making fear of cancer recurrence or progression (FCR/P) an important survivorship issue.[1] FCR/P is defined as the "fear, worry, or concern about the cancer returning or progressing".[2] FCR/P was recently found to be the highest unmet need for women with ovarian cancer in a large Australian survey.[3]

While some degree of FCR/P is natural and even adaptive, severe levels of FCR/P compromise quality of life for an important minority of cancer survivors,[4] and are associated with depressive, anxiety, and post-traumatic stress symptoms.[5,6] FCR/P has also been associated

with impairment in future planning[6–8] and for some survivors, increased visits to doctors, and oncology services, thus increasing healthcare costs.[9,10] FCR/P tends not to resolve over time and hence, individuals experiencing clinically significant levels of FCR/P often require specialized psychological support and intervention.[11]

Most recent models of FCR/P have focused on cognitive or metacognitive processes, an increased focus on physical sensations and increased misinterpretation of these symptoms. For example, Fardell et al.'s[12] cognitive processing model proposes that individuals who believe that worry is either helpful, harmful, or uncontrollable, attribute significance to intrusive thoughts and worries. This increases anxiety which leads to the "cognitive attentional syndrome", that is, characterized by worry, rumination, and focus on threat (including physical symptoms), which in turn perpetuates FCR/P.[13] Similarly, Simonelli et al.[14] emphasize that cues such as physical symptoms trigger FCR/P-related cognitive schemas that lead to an avoidant response toward these cues as a method for protecting the self from threat. This results in cognitive emotional processing whereby these cues are interpreted as threatening. When danger appraisals are made, less adaptive coping outcomes, such as hypervigilance, symptom checking, and suppression emerge, which creates a vicious cycle leading to increased FCR/P. Similarly, the Cancer Threat Interpretation model,[15] focuses on the ambiguous nature of physical symptoms such as pain or other symptoms, which, on the one hand, are common in daily life, but in the context of cancer, could signal recurrence. The model suggests that those patients highly anxious about recurrence interpret these symptoms (specifically pain) as a sign of recurrence, and become hypervigilant, monitor excessively, and seek reassurance, all of which further reinforces FCR/P through the immediate reduction of anxiety, but increase FCR/P in the longer term.

In the anxiety literature, cognitive processes have been the subject of a large body of literature which suggests that the tendency to interpret ambiguous situations as threatening (interpretation bias) and biases in attention allocation to threatening situations (attentional bias) play a key role in the development and maintenance of maladaptive anxiety.[16,17]

In the cancer context, a recent meta-analysis has confirmed the presence of *attentional* biases to cancer-related or negative stimuli in cancer patients as compared to controls and that these biases were larger in patients who were highly distressed.[18] However, only two studies have measured interpretation biases in cancer patients, both in breast cancer populations,[19,20] and neither included a control group who had not had cancer. Lichtenthal et al.[20] recruited women with a history of breast cancer who scored in the clinical range for FCR/P. Participants completed attention and interpretation bias measures before they were randomized to either receive cognitive bias modification (CBM) or placebo. The CBM procedure trained people to interpret information in a non-threatening way and to attend to neutral rather than threatening stimuli. Participants made more threat-related interpretations than benign interpretations when interpreting ambiguous sentences before the intervention but there was no control group. Following CBM, participants were less likely to interpret ambiguous sentences as threatening, but attention biases were not reliably changed compared to placebo. There were also changes on the health worries subscale of the concerns about recurrence scale (although not on the full scale) in the CBM group compared to placebo. These results were interpreted to suggest that changes in interpretation bias were likely to have driven the observed symptom changes, although the authors did not present mediation analyses. Likewise, Lam et al.[19] did find that breast cancer survivors with high levels of anxiety showed more interpretation bias than those with low levels of anxiety, but did not specifically assess FCR/P. These results are suggest that interpretation biases could be relevant to increased worry in the cancer context and may contribute to clinical levels of FCR/P, but more research is needed.

The current study aims to fill this gap and test the central tenet of Heathcote and Eccleston's[15] threat interpretation model of FCR/P, that interpretation bias moderates the relationship between the severity of symptoms (e.g., pain, fatigue) and FCR/P in a sample of women with ovarian cancer. It is hypothesized that

1. Women with ovarian cancer will be more likely to interpret ambiguous words with an illness-related meaning than women without cancer.
2. Greater interpretation bias will be associated with more severe levels of FCR/P.
3. Interpretation biases will moderate the relationship between symptoms and FCR/P.

2 | METHODS

2.1 | Participants

One hundred and fifty-eight participants volunteered for the study. Sixty-two women diagnosed with ovarian cancer were compared with 96 women who constituted the control group. Eligibility criteria for the cancer group were aged over 18 years of age, and English speaking; women could be on active treatment or have completed treatment. Women with ovarian cancer were recruited online through Ovarian Cancer Australia when they sought access to a newly developed resource about FCR/P. Those without cancer were recruited online through social media announcements requesting volunteers. In order to participate in the study, the healthy individuals were required to be female, over 18 years of age, without a personal or family history of cancer and fluent in English.

Informed consent was obtained from all participants and they were free to withdraw from the study at any time. Ethics approval was provided by the University of Sydney's Human Research Ethics Committee (HREC) (Project no. 2018/993).

2.2 | Procedure

A cross-sectional study was conducted and participants were invited to follow the link to an online survey, which displayed the participant

information and consent forms. After giving consent, women were asked to complete some demographic and medical information followed by a measure of interpretation bias (ambiguous cues task). Clinical data such as cancer stage, cancer status (active disease and in remission), history of recurrence, treatment, and surgery for cancer were self-reported and were collected via self-report, through a web-based platform, Qualtrics. The ambiguous word task was administered prior to questionnaires on symptoms or FCR/P to ensure these did not prime participants' responses. Women with ovarian cancer were asked to respond to questionnaires assessing FCR/P and the presence of various symptoms and were asked whether they experienced any pain in the past month.

2.3 | Materials

2.3.1 | Interpretation bias assessment

Illness-relevant interpretation bias was assessed through participants' response to a set of 14 ambiguous words which have both an illness-related and non-illness related meanings.[21] In this task, participants are instructed to write down the first word that comes into their mind when they read each (e.g., "needle" or "terminal"). The responses were then categorized into health-related (e.g., needle-injection or terminal-death) or neutral (e.g., needle-sewing or terminal-bus). Participants' responses were independently coded by two researchers (LS and PP) as illness-related "1" or not "0." Inter-rater reliability between the two raters was substantial (kappa = 0.80) and discrepancies were resolved through consensus.

2.3.2 | Fear of cancer recurrence/progression

The Fear of Progression Questionnaire—Short Form (FoP-Q-SF)[22] was administered to assess FCR/P. It consists of 12 items, with response options of never (1), rarely (2), sometimes (3), often (4), and very often (5). Thewes et al.[23] reviewed measures of FCR/P and concluded that the Fear of Cancer Recurrence Inventory (FCRI) and FoP-Q-SF were the most psychometrically sound measures and we chose the FoP-Q-SF because many women with ovarian cancer have active disease and therefore "recurrence" is arguably less relevant. Total FoP scores range from 12 to 60. A score of 34 is recommended as the clinical cut-off for clinically significant levels of FCR/P.[23] The reliability index of Lambda-2 in the current sample was 0.86.[24]

2.3.3 | Symptom checklist

The physical symptoms inventory[25] is an 18-item questionnaire where participants indicate whether or not they experience each symptom (during the past 30 days) and if they did, whether they had sought medical attention. Symptoms are scored as absent (0), present (1), and needed to seek medical attention (2). Items are summed. The Guttman's Lambda-2 for this scale was found to be 0.67 in the current ovarian cancer sample.

2.4 | Data analysis

All statistical analyses were conducted in SPSS version 26. Preliminary analyses investigated differences between participants with and without cancer on demographic variables, using Mann–Whitney *U*-tests for categorical variables and *t*-tests for continuous variables. Spearman's correlation was conducted to examine the association between interpretation bias and ordinal variables such as education and employment status. Demographic variables (age, education, and employment status) differing between cancer and control groups that were also associated with the dependent variable (i.e., interpretation bias), were included as covariates. An ANCOVA analysis was conducted to compare women with and without cancer in illness-related interpretation bias. Although no study has previously compared interpretation biases of people with and without cancer, a meta-analysis of studies in another health group (chronic pain) found an effect size of Cohen's $d = 0.67$ between people with and without chronic pain on interpretation bias.[26] Assuming a similar effect size, we needed at least 118 participants to have 95% power to detect this difference between groups with an alpha set at 0.05.

In the cancer group, we tested Heathcote and Eccleston's[15] Cancer Threat Interpretation model. We first conducted Pearson product–moment correlation analyses between continuous variables such as interpretation biases, symptom burden, and FCR/P. We tested whether interpretation bias moderated the relationship between symptom burden and fear of cancer progression, using the Hayes[27] PROCESS macro in SPSS. The PROCESS program determines whether symptom burden and FCR/P independently contribute to variance in FCR/P and then tests whether the interaction term also predicts variance in FCR/P in a hierarchical regression.

3 | RESULTS

3.1 | Preliminary analyses

Participant demographic characteristics are displayed in Table 1. Ten women (16%) reported being diagnosed with Stage I cancer, 11 (18%) Stage II, 30 (47%) Stage III, and 9 (15%) Stage IV. The majority of women reported they were currently in remission ($n = 42$; 67%), with 18 (29%) currently receiving active treatment. Just over one-third of the women ($n = 22$; 35%) had experienced a cancer recurrence.

On average, women with cancer fell within the clinical range on the Fear of Progression Questionnaire (FoP-Q) ($M = 35.58$, $SD = 8.52$). Based on the clinical cut-off score of 34, 35 (56%) women reported clinically significant levels of FoP. A high level of symptom burden on the Physical Symptoms Inventory was reported ($M = 26.77$, $SD = 4.03$), which was, on average, one standard deviation above the mean in the normative sample.[25]

TABLE 1 Demographic and clinical characteristics of the sample

	Cancer patients ($n = 62$)		Controls ($n = 96$)	
Variable	**Mean**	**Standard deviation**	**Mean**	**Standard deviation**
Age (years)	56.9	11.64	43.2	13.87
Time since diagnosis (years)	3.45	3.29		
	Frequency (percentage)		**Frequency (percentage)**	
Marital status				
Married	41 (65.45%)		50 (52.08)	
Widowed	2 (3.64)		1 (1.04)	
Divorced	9 (14.55)		10 (10.42)	
Separated	3 (5.45)		3 (3.13)	
Never married	7 (10.71)		32 (33.33)	
Children				
None	13 (20.97)		49 (51.04)	
One	9 (14.52)		13 (13.54)	
Two	32 (51.61)		19 (19.79)	
More than two	8 (12.9)		15 (15.62)	
Education level				
Did not complete high school	0 (0)		0 (0)	
Completed high school	24 (38.18)		10 (10.42)	
Undergraduate degree at university	22 (36.36)		20 (20.83)	
Postgraduate degree at university	16 (25.45)		66 (68.75)	
Employment status				
Currently employed	28 (45.16)		75 (78.13)	
Currently unemployed	34 (54.83)		21 (21.88)	
Stage at diagnosis				
Stage 1	10 (16.36)			
Stage 2	11 (18.18)			
Stage 3	30 (47.27)			
Stage 4	9 (14.53)			
Not known	2 (3.64)			
Current cancer status				
Currently on treatment	18 (29.09)			
Active disease	2 (3.64)			
In remission	42 (67.27)			
Cancer recurrence				
Yes	22 (36.36)			
No	40 (63.64)			
Surgery				
Yes	1 (1.12)			
No	61 (98.88)			

TABLE 1 (Continued)

	Frequency (percentage)	Frequency (percentage)
Treatment type		
Radiotherapy	0 (0)	
Chemotherapy	46 (74.19)	
Hormonal therapy	12 (19.35)	
No treatment	4 (6.45)	
CA-125 testing		
Yes	60 (96.23)	
No	2 (3.77)	
Not known	0 (0)	

On average, women with cancer were older (M = 56.9; SD = 11.64) than women in the control group (M = 43.2; SD = 13.87) ($t_{(1,156)} = 6.45$, $p < 0.0005$, mean difference [MD] = 13.71, 95% CI of MD [9.51, 17.9]). Control participants were more highly educated (U = 1497, $p < 0.001$) and more likely to be employed ($\chi^2_{(1, 158)} = 18.04$, $p < 0.001$). A greater interpretation bias score was associated with participants who were older (r = 0.21, p = 0.008), employed (r = 0.20, 0.01), and had received less education (r = −0.31, $p < 0.0005$) (see Table S1 for interpretation bias mean scores for each group of demographic variables). We controlled for all three variables in our main analyses.

3.2 | Between group comparisons (women with and without cancer)

We conducted an ANCOVA across participant groups (with and without cancer), controlling for age, educational status, and employment status, with interpretation bias scores as the dependent variable. Between-group comparisons indicated no significant effect of age ($F_{(1,153)}$ = 1.61, p = 0.21), educational level ($F_{(1,153)}$ = 1.14, p = 0.29), or employment status ($F_{(1,153)}$ = 1.05, p = 0.31), on interpretation bias scores. However, there was a significant effect of cancer status on interpretation bias score ($F_{(1,153)} = 37.62$, $p < 0.001$; Cohen's d = 1.28; 95% CI = 0.92–1.62), indicating that women with ovarian cancer had higher levels of illness-related interpretation bias compared to women without cancer (refer to Tables S2 and S3, respectively, for percentage of health-related responses for women with and without cancer and unadjusted and adjusted descriptives for interpretation bias score).

Correlational analyses revealed a moderate association between interpretation bias score and FCR/P in women with ovarian cancer ($r = 0.41$, $p = 0.001$), and a small relationship between total symptom burden and FCR/P (r = 0.25, p = 0.04), as predicted. However, no significant association was found between interpretation bias score and symptom burden (r = 0.22, p = 0.09). To test Heathcote and Eccleston's[15] model, we conducted moderation analyses to determine whether interpretation biases moderated the relationship between total symptom burden and FCR/P. The overall model was significant ($F_{(2, 59)} = 7.15$, $p = 0.002$). While symptom burden did not predict FCR/P ($\beta = 0.36$, $t = 1.44$, $p = 0.16$, 95% CI [−0.143, 0.871]), interpretation bias independently did predict FCR/P (β = 0.97, $t = 3.09$, $p = 0.003$, 95% CI [0.342, 1.593]). The interaction term was not significant ($F_{(1, 58)} = 0.0365$; p = 0.84), indicating that interpretation bias did not moderate the relationship between symptom burden and FCR/P. Refer to Table S4.

3.3 | Post-hoc analyses

We extrapolated from Heathcote and Eccleston's[15] model to indicate that those with higher levels of symptom burden would have higher levels of FCR/P, which would be moderated by interpretation biases, because in ovarian cancer, the most common symptoms of recurrence are not pain, but gastrointestinal symptoms or fatigue.[28,29] However, the model nominates that it is pain rather than overall symptom burden which contributes to fear of progression. Therefore, we conducted additional exploratory analyses to test this assertion. First, we computed the total of all items on the symptom burden checklist that related to pain. There was no correlation between pain and FCR/P (r = 0.09, p = 0.50) or between pain and interpretation bias score (r = 0.13, p = 0.30). Therefore, the inclusion of other symptoms could not explain the results.

Since interpretation biases have been rarely studied in this area, we conducted additional exploratory analyses to determine whether there were particular symptoms that were associated with both interpretation bias and FCR/P as the model predicts. We examined each symptom (whether present or not) and its association with FCR/P using independent t-tests and Spearman Rho correlations. While there were 18 symptoms, and therefore, we had multiple comparisons, we decided against adjusting for these, since this was an exploratory analysis and the need to be cautious did not arise. There were no effects of nausea, back pain, insomnia, rash, breathlessness, fever, infection, eye strain, diarrhea, heartburn, cramps, dizziness, or headache on FCR/P. There was a significant difference in FCR/P for those experiencing chest pain (t = 3.258, p = 0.002),

constipation (t = 2.224, p = 0.03), a pounding heart (t = 2.693, p = 0.009), loss of appetite (t = −2.111, p = 0.039), and fatigue (t = −2.875, p = 0.006). We therefore conducted a hierarchical regression (see Table 2) analysis where we added demographic variables to predict FCR/P in step 1 of the model, interpretation bias in step 2, and the five symptoms for which there was a significant difference in step 3. We conducted this analysis to determine which symptoms contributed unique variance to FCR/P when controlling for other known predictors. The results showed that demographic variables added 13% to the explanation of variance in FCR/P (F = 2.854, p = 0.045), interpretation bias another 10% (F = 7.495, p = 0.008), and the five symptoms added an additional 18% of the variance in FCR/P (F = 3.299, p = 0.012). The individual symptoms that added to the variance were constipation (p = 0.045) and fatigue (p = 0.028). Table S5 summarizes the prevalence of physical symptoms in women with high and low FCR/P.

4 | DISCUSSION

The aim of the present study was to examine whether interpretation bias was associated with FCR/P and symptom burden. Consistent with predictions, the results showed that controlling for demographic factors (age, education, and working status), women with ovarian cancer were more likely to interpret ambiguous words as health related compared to women without cancer. Furthermore, the higher

TABLE 2 Hierarchical regression table showing individual variables predicting FCR/P

Step 1	**Adjusted R^2**	**df**	***F* change**	**Significance**		
	0.084	3, 58	2.854	0.045		
Individual predictors	**Unstandardized β**	**Std. error**	***t*-Statistic**	**Significance**	**95% CI for β**	
					Upper	**Lower**
Age	−0.26	0.09	−2.77	0.008	−0.454	−0.073
Educational status	−1.471	1.4	−1.050	0.298	−4.27	1.33
Employment status	3.044	2.18	1.4	0.17	−1.32	7.41
Step 2	**Adjusted R^2**	**df**	***F* change**	**Significance**		
	0.176	1, 57	7.495	0.008		
Individual predictors	**Unstandardized β**	**Std. error**	***t*-Statistic**	**Significance**	**95% CI for β**	
					Upper	**Lower**
Age	−0.198	0.093	−2.15	0.039	−0.385	−0.011
Educational status	−1.057	1.337	−0.791	0.432	−3.734	1.619
Employment status	1.783	2.117	0.842	0.403	−2.458	6.023
I.B.	0.873	0.319	2.738	0.008	0.234	1.511
Step 3	**Adjusted R^2**	**df**	***F* change**	**Significance**		
	0.314	5, 52	3.299	0.012		
Individual predictors	**Unstandardized β**	**Std. error**	***t*-Statistic**	**Significance**	**95% CI for β**	
					Upper	**Lower**
Age	−0.129	0.094	−1.370	0.177	−0.336	0.055
Educational status	−0.063	1.273	−0.049	0.961	−3.353	1.759
Employment status	0.870	1.996	0.436	0.665	−3.324	4.963
I.B.	0.847	0.343	2.470	0.017	0.006	1.399
Chest pain	4.433	2.592	1.710	0.093	0.236	8.472
Constipation	4.315	2.100	2.055	0.045	−1.218	5.729
Pounding heart	−1.461	2.344	−0.623	0.536	−4.465	3.615
Loss of appetite	1.139	2.132	0.534	0.596	−1.762	5.078
Fatigue	6.356	2.814	2.258	0.028	−1.090	5.945

Abbreviations: FCR/P, fear of cancer recurrence or progression; FoP, fear of progression, IB, interpretation bias.

the levels of FCR/P women with ovarian cancer reported, the more likely they were to interpret ambiguous words as illness related. Women with higher symptom burden were also more likely to make more illness-related interpretations. We also predicted that interpretation biases would moderate the relationship between symptom burden and FCR/P; however, that hypothesis was not supported. Hence, the threat interpretation model was not supported.

Nevertheless, these results clearly show that individuals with cancer exhibited a greater interpretation bias than those without cancer and this difference was robust, resulting in large effect size (Cohen's $d = 1.28$). It is worthwhile noting that the groups with and without cancer were not ideally matched. That is, women in the control group were younger, more highly educated, and more likely to be employed. This could potentially have contributed to the size of the difference, given that this is considerably larger than the effect sizes that have been seen in people with other health problems. For example, Schoth and Liossi[26] found that people with chronic pain exhibited an interpretation bias toward illness-related information more than those without pain, but with a moderate effect size (Cohen's $d = 0.67$). However, in a recent meta-analysis, the attentional bias exhibited by those with cancer was greater than those without cancer and the estimated effect size was also large (Cohen's $d = 0.82$),[18] and again compared to attentional biases reported between those with and without chronic pain (Cohen's $d = 0.2$),[30] the effect size amongst cancer survivors was much larger. Hence, taken together, these results do suggest that a history of ovarian cancer is associated with interpretation biases and the effect is larger than that observed in other conditions where these have been more thoroughly researched.

Clearly, the propensity to interpret otherwise ambiguous stimuli as illness related is affected by cancer, which is hardly surprising given the ramifications of a diagnosis of cancer, its treatment, and ongoing risk. Indeed, one could argue that not only is it normal for people with cancer to interpret ambiguous stimuli as illness related, but potentially adaptive. That is, survivors need to remain somewhat vigilant to bodily cues, and to notice changes that could indicate recurrence.[31] The finding that those cancer survivors with higher levels of FCR/P are more likely to interpret ambiguous information as illness related is important, indicating that these biases are associated with cancer-specific anxiety. Interpretation biases have been found to be associated with a range of emotional disorders, such as social anxiety,[32,33] generalized anxiety disorder,[34] and depression.[35] Indeed, the moderate to large effect size of the correlation observed here is at least comparable to the effect size observed in meta-analysis of interpretation biases in depression (Cohen's $d = 0.72$). Our results are also consistent with Lam and colleagues'[19] finding that higher levels of anxiety among breast cancer survivors were associated with greater interpretation biases.

The moderate correlation between interpretation biases and FCR/P is consistent with the recent emphasis placed on cognitive processes in recent theories of FCR/P[12,14,15] and cancer-related anxiety.[36] In this study, we aimed to test one of the central predictions of the threat interpretation model.[15] Although the predicted relationships between symptom burden and FCR/P and interpretation bias and FCR/P were found, interpretation bias did not moderate the relationship between symptom burden and FCR/P. However, a number of reasons may explain this finding. First, our measure of symptom burden used a range of symptoms, whereas the model specifically indicated pain. However, we conducted post-hoc analyses to determine whether this could account for the failure to find moderation effects and it did not. Second, it would make sense if the specific symptoms that might be open to interpretation differ among those with different cancer types, depending on what survivors had been told could be indicative of a recurrence. We tested this hypothesis using post-hoc analyses and did find some evidence that the primary symptoms associated with FCR/P in this sample were fatigue, constipation, and loss of appetite, which are also the cardinal symptoms of a recurrence in women with ovarian cancer.[28,37–39] Our results indicated that two of these three cardinal symptoms of recurrence were associated with FCR/P, and one with interpretation bias. This finding should, however, be treated cautiously since it was post-hoc and we conducted a large number of correlations without controlling for multiple comparisons. Future research could test the threat interpretation model with specific symptoms nominated a priori that are both common and associated with recurrence in a particular cancer type.

Interestingly, the other symptoms associated with FCR/P were heart pounding and chest pain. These did not contribute independently to FCR/P in the regression analysis, but it is worthwhile noting that these are two common symptoms of anxiety. Indeed, all the symptoms that were either associated with FCR/P or interpretation bias were either key symptoms associated with recurrence in ovarian cancer or symptoms attributable to anxiety. Future research is needed to determine how these symptoms and interpretation biases contribute to persistent FCR/P and anxiety in cancer survivors.

4.1 | Study limitations

A number of methodological limitations should be noted while interpreting results from the study. First, our control group was not well matched to the cancer group, and this could have contributed to the very large effect observed when comparing people with and without cancer. Nevertheless, we did control for confounders, and the effect appears robust and unlikely attributable to these differences. It is also true that women with ovarian cancer were recruited when accessing a resource for FCR/P and therefore may not be representative of all women with ovarian cancer. Of note, however, it is the findings related to FCR/P that are arguably of most interest and these are not affected by the control group, nor the representativeness of the ovarian cancer sample. Second, the sample size for the cancer group could have limited the detection of small effects or the association between interpretation bias and overall symptom burden. Power issues are particularly relevant to the moderation analysis, which should be considered to be less conclusive than other analyses. Finally, this is a cross-sectional study and therefore causal

relationships cannot be established, and measures could have been related to a number of external variables, such as the timing of medical appointments.

4.2 | Clinical implications

These limitations notwithstanding the findings of the present study confirm a potential role of interpretation biases in the development and/or maintenance of FCR/P, which means that interpretation biases could be a useful target for intervention. Lichtenthal et al.[20] conducted a pilot study to investigate the potential therapeutic use of modifying cognitive biases, such as interpretation biases, to reduce FCR/P. They randomized participants to receive placebo or cognitive bias modification that trained participants to interpret ambiguous information in a benign (rather than threatening) manner and to attend less to threatening information. The manipulation check confirmed that participants had learned to interpret ambiguous information as more benign compared to the placebo group, although participants had not learned to attend less to threatening information. The intervention also reduced the health worries subscale of the Concerns about Recurrence scale,[40] although not the total score. This is consistent with a large body of literature showing that cognitive bias modification is an effective intervention for anxiety symptoms (see Jones and Sharpe[41] for a review of meta-analyses). Future studies should confirm whether interventions such as cognitive bias modification can help to manage FCR/P.

5 | CONCLUSIONS

Overall, there were three main findings that should be highlighted. First, the results clearly show that women with ovarian cancer are more likely to interpret ambiguous words as illness related compared to women without cancer. Second, the results show a moderate relationship between the tendency to interpret ambiguous information as illness related and FCR/P. Third, although we did not find that interpretation biases moderated the relationship between symptom burden and FCR/P. In our exploratory analysis, gastrointestinal symptoms seemed associated with fear of recurrence in ovarian cancer, or well-known symptoms of anxiety. The field would benefit from future research to confirm these exploratory results.

ACKNOWLEDGMENTS

We would like to acknowledge Ovarian Cancer Australia for their support with this research, as well as to all the women who took part in this study for their time.

This project was an unfunded study.

DATA AVAILABILITY STATEMENT

Data is available from the authors on request.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Pradhan P, Sharpe L, Butow P, Russell H. The role of interpretation biases and symptom burden in fear of cancer recurrence/progression among ovarian cancer survivors. *Psycho-Oncology*. 2021;1–9. https://doi.org/10.1002/pon.5748

frontiers in Psychology

ORIGINAL RESEARCH
published: 25 February 2021
doi: 10.3389/fpsyg.2021.634136

Is a Brief Online Booklet Sufficient to Reduce Fear of Cancer Recurrence or Progression in Women With Ovarian Cancer?

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Background: Fear of cancer recurrence or progression (FCR/P) is a common challenge experienced by people living with and beyond cancer and is frequently endorsed as the highest unmet psychosocial need amongst survivors. This has prompted many cancer organizations to develop self-help resources for survivors to better manage these fears through psychoeducation, but little is known about whether they help reduce FCR/P.

Method: We recruited 62 women with ovarian cancer. Women reported on their medical history and demographic characteristics and completed the Fear of Progression Questionnaire-Short Form (FoP-Q-SF). They then read a booklet on FCR specifically created for Ovarian Cancer Australia by two of the authors (ABS and PB). One week after reading the booklet, 50/62 women (81%) completed the FoP-Q-SF and answered questions about their satisfaction with the booklet.

Results: More than half of the women (35/62; 56.5%) scored in the clinical range for FCR/P at baseline. Of the completers, 93% said that they would recommend the booklet to other women. Satisfaction with the booklet was relatively high (75.3/100) and more than two-thirds of women rated it as moderately helpful or better. However, FCR/P did not change significantly over the week following reading the booklet [$t_{(49)} = 1.71$, $p = 0.09$]. There was also no difference in change in FCR/P between women in the clinical vs. non-clinical range on the FoP-Q. Women high in FCR/P rated the booklet as less helpful in managing FCR/P ($r = -0.316$, $p = 0.03$), but overall satisfaction with the booklet was not associated with degree of FCR/P ($r = -0.24$, $p = 0.10$).

Conclusions: These results suggest that a simple online FCR booklet is acceptable to women with ovarian cancer and they are satisfied with the booklet, but, it was insufficient to change in FCR/P levels. These results suggest that such resources are valued by women with ovarian cancer, but more potent interventions are necessary to reduce FCR in this population.

Keywords: cancer, oncology, neoplasm, fear of cancer recurrence, fear of cancer progression, ovarian cancer, psychoeducation

OPEN ACCESS

Edited by:
Imad Maatouk, Heidelberg University Hospital, Germany

Reviewed by:
Christine Maheu, McGill University, Canada
Laura Inhestern, University Medical Center Hamburg-Eppendorf, Germany

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Specialty section:
This article was submitted to Psycho-Oncology, a section of the journal Frontiers in Psychology

Received: *27 November 2020*
Accepted: *03 February 2021*
Published: *25 February 2021*

Citation:
Pradhan P, Sharpe L, Butow PN, Smith AB and Russell H (2021) Is a Brief Online Booklet Sufficient to Reduce Fear of Cancer Recurrence or Progression in Women With Ovarian Cancer? Front. Psychol. 12:634136. doi: 10.3389/fpsyg.2021.634136

INTRODUCTION

Ovarian cancer is the leading cause of death among gynecological cancers with a 46% 5-year survival rate, as the disease is often diagnosed at an advance stage (Australian Institute of Health and Welfare, 2020). Approximately 70% of women with ovarian cancer are expected to experience recurrence of their cancer, particularly when diagnosed at later stages (Ovarian Cancer Research Alliance, 2020). Not surprisingly given this high recurrence rate, fear of cancer recurrence or progression (FCR/P) is one of the most common psychosocial concerns reported by this population (Matulonis et al., 2008; Kyriacou et al., 2017). FCR/P, defined as "fear, worry, or concern about the cancer returning or progressing" (Lebel et al., 2016, p. 3267), continues to be the most cited unmet need for ovarian cancer survivors (Tan et al., 2020). In a systematic review of FCR/P in ovarian cancer, Ozga et al. (2015) confirmed that FCR/P was prevalent amongst ovarian cancer survivors, and that women with ovarian cancer felt that there was insufficient support for managing FCR/P. Moreover, in a large prospective study of heterogeneous cancer survivors, those with advanced disease or who had experienced a recurrence had higher levels of FCR (Savard and Ivers, 2013).

Studies have identified that higher levels of FCR/P are associated with reduced quality of life (Hart et al., 2008), increased anxiety and depressive symptoms (Humphris et al., 2003; Koch et al., 2014) as well as post-traumatic stress symptoms (Mehnert et al., 2009). In addition to psychological symptoms, FCR/P is also characterized by increased healthcare costs (Thewes et al., 2012) and frequent reassurance seeking, such as through additional oncology appointments and increased medication use (Lebel et al., 2013). Therefore, individuals experiencing high levels of FCR often require specialized psychological support and intervention (Butow et al., 2018).

Despite clear evidence that high FCR/P is associated with poorer psychological outcomes and additional medical costs, specific interventions to manage FCR/P are still relatively scarce. In a meta-analysis of RCTs, Tauber et al. (2019) found over 23 controlled trials that had examined the efficacy of a psychological intervention and measured FCR, however, only 8 of these had specifically targeted FCR/P. The majority of those evaluated face-to-face interventions (e.g., ConquerFear, Butow et al., 2018) or blended interventions where treatments were administered partially online and partially face-to-face (e.g., SWORD, van de Wal et al., 2017). Both of these interventions required highly trained therapists and considerable time commitment (minimum of four sessions). In that meta-analysis, there were only two trials of a self-administered approach (i.e. minimal intervention). The study by Otto et al. (2016) found that such self-guided gratitude training interventions promoted well-being leading to a decrease in death-related FCR. The other intervention used Cognitive Bias Modification (CBM), an approach than aims to change implicit cognitive processes, such as interpreting ambiguous situations in a threatening way and preferentially attending to threatening information. The CBM approach was associated with reductions in health-related worries compared to placebo (Lichtenthal et al., 2017). One other randomized controlled trial, by Dieng et al. (2016), with melanoma survivors combined psychoeducational materials, as well as three telephone consultations with a psychologist, and found improvements in FCR/P, which were maintained at 12 month follow-up (Dieng et al., 2019). However, the telephone support still required specialist psycho-oncology skills. Given the number of survivors, and the fact that help with FCR/P remains a leading unmet psychosocial need, most services do not have the capacity to support all survivors with elevated levels of FCR/P.

Consequently, researchers are investigating other ways to increase access to information that might reduce or prevent persistent FCR/P. For example, brief interventions led by health professionals who manage the medical needs of survivors (most commonly nurses) have been developed. A recent systematic review of these approaches found that evidence to support their use is still lacking (Liu et al., 2019). Similarly, there has been interest in developing internet-delivered interventions specifically targeting FCR. Most of these are either in early stages of development (Smith et al., 2020) or currently being tested (e.g., Lyhne et al., 2020) and the only online intervention which specifically targeted FCR/P produced largely null results (van Helmondt et al., 2020).

Self-help materials have been used for other survivorship issues, including to reduce anxiety and depression and/or to improve quality of life. Cuthbert et al. (2019) identified 41 studies of self-help interventions that had been evaluated in randomized controlled trials. The results were largely mixed, with some showing short-term benefits and others showing little improvement in outcomes. None of these studies targeted FCR/P.

However, even in the absence of evidence, several non-profit organizations such as, Cancer Council Australia, National Breast Cancer Foundation, Breast Cancer Network Australia and Lymphoma Australia have developed online booklets or leaflets for addressing concerns related to cancer coming back or progressing. Whether these self-help materials attenuate FCR/P has not been the subject of research. Lynch et al. (2020) have recently completed a preliminary evaluation of a stepped care approach for survivors of melanoma who were treated with novel immunotherapies. The first step in their "FearLESS" program was a self-help intervention. Of those who scored in the sub-clinical range and were offered self-help, 90% did not feel the need for referral to individual therapy at the end of the study (Lynch et al., 2020). However, the authors did not evaluate whether changes in FCR/P were significant for those who received the self-management approach.

The evidence examining informational needs of cancer survivors suggests that most patients want to receive as much information as possible about their disease and its consequences (Shea–Budgell et al., 2014; Fletcher et al., 2017). A systematic review of 10 studies that assessed a range of patient outcomes in RCTs of educational resources specific to cancer, found that the provision of psychoeducation was associated with better outcomes for satisfaction, symptom management and anxiety and depressive symptoms (McPherson et al., 2001). However, we could not identify a purely psychoeducational resource that had been developed specifically for FCR/P which had been evaluated in terms of its acceptability and effect on FCR/P.

Therefore, we (PB & ABS) developed a simple online booklet that (a) outlined the nature of FCR/P, (b) provided information about how FCR/P becomes persistent, (c) suggested strategies (based on evidence-based treatments) that might help survivors to better manage FCR/P; and (d) provided links to where survivors can find additional help. The aims of this study were to determine whether (i) the booklet was acceptable to survivors (ii) survivors were satisfied with the booklet and would recommend it to others; and (iii) the booklet reduced levels of FCR/P.

It was hypothesized that

- Women with ovarian cancer will be satisfied with the booklet and would recommend it to other survivors.
- Women with ovarian cancer will have lower levels of FCR/P a week after reading the booklet compared to baseline.
- The booklet will lead to a greater reduction in FCR/P for women with low to mild FCR/P.

METHOD

Design

Women with ovarian cancer completed measures of FCR before and 1 week after reading an online psychoeducational booklet about FCR/P. In addition, a measure of satisfaction was given 1 week after women accessed the booklet.

Participants

Women who had been diagnosed with ovarian cancer, were over 18 years of age, and fluent in English were eligible to take part in the study. Participants were recruited online through Ovarian Cancer Australia (OCA) (see below). Ethical approval was provided by the University of Sydney's Human Research Ethics Committee (Project no.: 2018/993). Informed consent was obtained from all participants online, and they were free to withdraw from the study at any time.

Procedure

The new online FCR booklet developed by the authors was released through OCA and advertised to its members. When women indicated they would like to access the booklet, a pop-up window asked whether they would like the option of taking part in some research to evaluate the impact of the booklet on FCR/P. Women who chose not to do so, were directed immediately to the booklet, while those who indicated their interest in taking part in the research were invited to follow a link which described the study in more detail. Unfortunately, we were unable to get information from women who chose not to take part. After providing consent, participants were directed to an online questionnaire including some demographic and medical information and a measure of FCR/P[1]. On completion, women were given access to the booklet. One week later participating women were sent an email and asked to complete measures of FCR/P and satisfaction with the FCR/P booklet. We chose 1 week as a time frame because we suspected that any impact on FCR/P would be short-term, consistent with the systematic review on psychoeducational approaches (Cuthbert et al., 2019).

[1]Measures of interpretation bias and physical symptoms were included, the results of which are presented elsewhere.

TABLE 1 | List of contents in Fear of Recurrence booklet.

1. What does "cancer recurrence" mean?
2. Why are women fearful?
3. Types of fears
4. Common worry times
5. Day-to-day approaches to managing your fears
6. Carers' feelings
7. Some techniques for managing the fear of recurrence
8. Finding information online
9. Further information and support

Fear of Cancer Recurrence Booklet

The booklet was developed in conjunction with OCA and input from oncology health writer in terms of translating information from ConquerFear study suitable for women with ovarian cancer. It aims to provide information on FCR/P, which is identified as a significant survivorship issue for women with ovarian cancer (Kyriacou et al., 2017), and also suggest strategies to manage these fears. The techniques to manage FCR in this booklet were adapted from the ConquerFear program by Butow et al. (2017). See **Table 1** for the list of contents in the booklet (online link to the booklet: https://www.ovariancancer.net.au/page/94/support-resources).

Materials

Satisfaction Questionnaire

The satisfaction questionnaire has three items that assess: satisfaction with the information provided in the booklet; helpfulness for managing the concerns about cancer coming back or progressing; and whether women would recommend it to another woman diagnosed with ovarian cancer. The participants rated each item on a 10-point scale, from 1 (not at all) to 10 (completely). A higher score indicates that women are more satisfied with the booklet. Women completed this questionnaire 1 week after reading the booklet.

Fear of Cancer Recurrence/Progression

The 12-item Fear of Progression Questionnaire- Short Form (FoP-Q-SF; Herschbach et al., 2005) was administered to assess the level of FCR/P. Responses options ask how often a particular symptom of FCR/P is experienced on a five-point scale from 1 (never) to 5 (very often) (5). Thewes et al. (2012) conducted a systematic review of assessment measures for FCR/P and recommended the use of the Fear of Cancer Recurrence Inventory (Simard and Savard, 2009) and the FoP-Q-SF for assessing FCR/P. We opted to use the FoP-Q-SF because for women with ovarian cancer, many of whom have already experienced a recurrence, fear of recurrence is less relevant than fear of progression. Scores on FoP-Q-SF range from 12 to 60 and a score of 34 and above is taken to indicate a clinical level of FoP (Herschbach et al., 2010). The Cronbach's alpha for the current sample was 0.85.

Data Analysis

All statistical analyses were conducted in SPSS version 26. Preliminary analyses compared those women that completed the study vs. those who accessed the booklet but did not complete questionnaires after reading the booklet. For continuous variables, we used independent *t*-tests and for other variables we used Mann Whitney U tests (categorical variables) or Chi-square (dichotomous).

Mean scores and frequencies were examined for satisfaction ratings. For FCR/P, a paired samples *t*-test was used to compare the level of FCR/P before and after reading the booklet. Using the cut-off of 34 on the FoP-Q, we identified women with clinically significant levels of FCR/P vs. those who scored in the normal range to determine whether clinical FCR/P affected the impact of the booklet. To investigate the impact of clinical status, we conducted a mixed-model 2 (FCR/P: Clinical range vs. within normal range) x 2 (time: before vs. after reading the pamphlet) ANOVA. Finally, we conducted correlations between FCR/P and satisfaction ratings to determine whether level of FCR/P affected the satisfaction that women reported after reading the booklet.

RESULTS

Participant Characteristics

Sixty-two women diagnosed with ovarian cancer were recruited for the study. Participants had a mean age of 56.9 years. In terms of stage of disease, relatively few women had Stage I ($n = 10$; 16%), or Stage II ($n = 11$; 18%) disease, with 47% ($n = 30$) reporting Stage III and 9 (15%) reporting stage IV cancer. See **Table 2** for demographic and medical details. Of the 62 participants who commenced the study, 50 (19% attrition rate) completed the questionnaires again a week after reading the pamphlet.

Between group comparisons revealed that there was no significant difference between participants who completed the study and those who did not for age [$t_{(60)} = 1.13$, $p = 0.26$], education ($U = 216$, $p = 0.11$), cancer stage ($U = 276$, $p = 0.65$), number of children ($U = 289.5$, $p = 0.84$), marital status ($U = 284$, $p = 0.73$), cancer status [$\chi^2_{(1,62)} = 1.06$, $p = 0.33$] or employment status [$\chi^2_{(1,62)} = 0.14$, $p = 0.76$]. Likewise, there were no significant differences between participants in terms of FCR/P scores [$t_{(60)} = -0.26$, $p = 0.79$].

Satisfaction With the Booklet

Almost 75% (37/49) of the respondents rated the booklet to be relevant to people with ovarian cancer and indicated it provided the needed information about FCR/P (as indicated by ratings > 80/100). Only 1 woman indicated that the booklet was not at all relevant. More than two thirds of women (32/49) rated the booklet as at least moderately helpful (ratings > 50/100) in managing their worries about cancer coming back or progressing. Of those, 14/49 reported that it was completely helpful, and only 3/49 thought it was not helpful at all. Importantly, 93% (41/44 women) of the participants would recommend the booklet to other women.

TABLE 2 | Demographic and clinical characteristics of the sample.

	Cancer patients ($n = 62$)
Variable	**Mean**
Age	56.9 (11.64)
Time since diagnosis	3.45 (3.29)
	Frequency (percentage)
Marital status	
Married	41 (65.45%)
Widowed	2 (3.64)
Divorced	9 (14.55)
Separated	3 (5.45)
Never married	7 (10.71)
Children	
None	13 (20.97)
One	9 (14.52)
Two	32 (51.61)
More than two	8 (12.9)
Education level	
Did not complete high school	0 (0)
Completed high school	24 (38.18)
Undergraduate degree at university	22 (36.36)
Postgraduate degree at university	16 (25.45)
Employment status	
Currently employed	28 (45.16)
Currently unemployed	34 (54.83)
Stage at diagnosis	
Stage 1	10 (16.36)
Stage 2	11 (18.18)
Stage 3	30 (47.27)
Stage 4	9 (14.53)
Not known	2 (3.64)
Current cancer status	
Currently on treatment	18 (29.09)
Active disease	2 (3.64)
In remission	42 (67.27)
Cancer recurrence	
Yes	22 (36.36)
No	40 (63.64)
Surgery	
Yes	1 (1.12)
No	61 (98.88)
Treatment type	
Radiotherapy	0 (0)
Chemotherapy	46 (74.19)
Hormonal therapy	12 (19.35)
No treatment	4 (6.45)
CA-125 testing	
Yes	60 (96.23)
No	2 (3.77)
Not known	0 (0)

FCR/P Results

Self-reported outcomes on the FoP-Q indicated that, on average, women with ovarian cancer fell within the clinical range ($M = 35.58$, $SD = 8.52$). Based on the cut-off score on the FoP-Q of 34, 56% ($n = 35/62$) of the participants reported clinically significant levels of FCR/P and the remainder (44%; $n = 27/62$) reported FCR/P scores within the normal range.

Overall, significant differences were not observed in the FoP-Q scores before ($M = 35.4$, $SD = 8.59$) compared to 1 week after reading the booklet ($M = 33.94$, $SD = 9.00$) [$t_{(49)} = 1.71$, $p = 0.09$; Cohen's $d = 0.17$; 95% CI −0.22 – 0.55], indicating that the booklet did not change levels of FCR/P. In considering whether the booklet had a differential impact based on level of FCR/P, we conducted a 2 × 2 mixed-model ANOVA. Consistent with the *t*-test reported above, there was no significant main effect of time [$F_{(1,48)} = 2.69$, $p = 0.11$] on FCR/P scores. There was a significant main effect of FCR/P level indicating that women scoring in the clinical range had higher levels of FCR/P throughout the study [$F_{(1,48)} = 81.96$, $p > 0.001$]. The interaction between time and FCR/P level indicated that clinical status did not impact the effect of time on FCR/P scores [$F_{(1,48)} = 0.13$, $p = 0.72$].

Finally, we performed Pearson product-moment correlations to investigate the relationships between FCR/P and ratings of satisfaction. There was no significant correlation between ratings of satisfaction of the booklet in terms of providing sufficient information and level of FCR/P ($r = -0.24$, $p = 0.10$). However, correlations indicated that women with higher levels of FCR rated the booklet as less helpful in managing their worries about FCR/P ($r = -0.316$, $p = 0.03$).

DISCUSSION

The aim of this study was to determine whether an online booklet about FCR/P led to reductions in FCR/P and whether women were satisfied with the resource. The results demonstrated that there were high levels of satisfaction, and that most women would recommend the booklet to others. However, the booklet did not significantly improve levels of FCR/P, nor did it worsen them. The impact of the booklet on FCR did not differ for women in the clinical range for FCR/P compared to those with lower levels of FCR/P, although women with higher FCR/P rated the booklet as less helpful. Taken together, these results suggest that women believed that the booklet provided relevant information and was helpful, but the booklet was insufficient to reduce FCR/P.

These results are not entirely inconsistent with the previous literature and there are a number of potential reasons that might account for the failure to find an effect of this online resource. Firstly, Cuthbert et al. (2019) found mixed effects of self-help interventions, with some studies finding an effect and others not. They noted that very few self-help resources included specific behavior change techniques (e.g., Michie et al., 2011) and this could account for the failure of some interventions to affect change. This is true of the online resource in this study, which did not specifically include behavior change techniques.

Secondly, Cuthbert et al. (2019) described that in many self-help resources, there was an absence of a theoretical basis for the information provided. The information in the current booklet was adapted from the ConquerFear program (Butow et al., 2017), which was based on Fardell et al. (2016) model of the development of persistent FCR/P. This was the same model that was used as the first stage of the stepped care package developed by Lynch et al. (2020) for melanoma survivors who had responded to immunotherapy. However, in that study, the authors also included exercises as well as information, and there were three brief telephone conversations. Nevertheless, results on the FoP-SF-Q in the FearLESS study were similar to our results. Lynch et al. (2020) did not report the significance of their results for the 21 people that completed the self-help component, but the Cohen's d was similarly small ($d = 0.02$, 95% CI −0.59 – 0.62). Thus, even though both interventions were based on a theoretical model, neither appeared able to change FCR/P significantly and therefore this does not appear to explain the lack of effect observed here.

Thirdly, it has been suggested that some level of FCR/P is adaptive for people following cancer (Butow et al., 2018). This is because for all people who have been diagnosed with cancer, a recurrence is possible. For those in our study, with ovarian cancer, this is particularly the case since up to 70% of women with ovarian cancer will have a recurrence. According to this argument, FCR/P can provide the motivation to adhere to surveillance and therefore identify when a recurrence occurs. While this explanation cannot be excluded, it should be noted that in the Tauber et al. (2019) meta-analysis, there was no effect of cancer stage on the efficacy of interventions for FCR/P. Nevertheless, the bulk of the research on FCR/P involved patients whose cancer has been treated with curative intent and are currently disease-free. More research is needed to determine whether FCR/P is similar in patient groups with poorer prognosis to determine whether similar approaches are indicated. It may be in samples with advanced disease and high risk of relapse that distress and/or QOL are more relevant outcomes than FCR/P.

Finally, it is likely that the simple static FCR/P booklet, available in a PDF, was not sufficient to bring about change for the women who accessed it through this study who had high levels of FCR/P. FCR/P levels that were demonstrated by women in this study can be persistent and very distressing. It is perhaps unsurprising that a brief resource would not be sufficient to reduce FCR/P when one considers that even amongst the 8 available RCTs of psychological interventions with FCR as primary target, the effects were relatively small (Cohen's $d = 0.44$) (Tauber et al., 2019). However, it does pose a problem. With the increasing number of survivors, the small psycho-oncology workforce and the high levels of FCR/P, how can we meet the needs of survivors for help managing FCR?

We urgently need to focus on research that can develop cost-effective interventions that can be implemented in practice. Both the ConquerFear and SWORD studies (Butow et al., 2017; van de Wal et al., 2017) were shown to be cost effective, in that they had reasonable willingness to pay thresholds. However, we also need to consider stepped care models, such as FearLESS (Lynch et al., 2020), which have less time intensive interventions (such as self-management components that can be delivered via internet or telehealth) and/or utilize other members of the

oncology workforce. Liu et al. (2019) in their review, concluded that there was insufficient evidence to support the delivery of interventions by non-specialists. However, there have been successful applications of nurse-led approaches, or clinician-driven interventions (Humphris and Ozakinci, 2008; Davidson et al., 2018; Reb et al., 2020). This needs to be a priority for research, particularly as patients themselves are more likely to take up the offer of therapy with nurses than with psychologists or psychiatrists (Brebach et al., 2016).

Study Limitations

A number of methodological limitations are to be noted in the current study. Firstly, we did not recruit participants from clinical services and so relied on self-report regarding medical details. We did not take into account specific anxiety provoking situations such as oncology or scanning appointments. Studies have consistently shown that the time period when scan results are due can trigger significant anxiety in some patients (Feiler, 2011). This was not assessed and may have impacted the levels of FCR/P for some participants. Secondly, we are uncertain as to how much the booklet was read prior to the follow-up survey and the time was 1 week, and it might take longer for women to process apply the information, or it may have had immediate effects that tapered over time. The levels of motivation and engagement of the participants with the material could vary and could possibly provide a partial explanation for the results. Unfortunately we were unable to get data on how often women downloaded the booklet or how long they used it for. We did not have the pamphlet assessed formally by experts, which may have improved the resource and led to higher satisfaction. Further, our sample included all English-speaking participants and we were unable to get information about women that chose not to take part, therefore, the generalizability of this online resource across people from diverse backgrounds is unknown. The study would have benefitted from a formal power analysis since the study only had sufficient power to detect a moderate effect size (Cohen's $d = 0.33$). Finally, we developed a satisfaction scale for the study rather than using a previously validated scale.

Implications

Findings of the present study suggest that we need to develop brief interventions that are scalable to try and help manage the demand for support for FCR. Stepped care models, such as the FEARLESS (Lynch et al., 2020) approach are likely to be important, but we need evidence to support the efficacy of the first step. Internet-delivered approaches would be an obvious first step, however, the first of these to be trialed produced null findings (van Helmondt et al., 2020), and the only other reported intervention, iConquerFear (Smith et al., 2020) is in the process of being evaluated (Lyhne et al., 2020). In the most recent meta-analysis of treatment for FCR (Tauber et al., 2019), only two minimal interventions were identified. One of these, gratitude training improved well-being and had an impact on some aspects of FCR (Otto et al., 2016). The other intervention trailed was cognitive bias modification (CBM). CBM has been found to be effective in anxiety (Jones and Sharpe, 2017) and has shown some promise in managing some aspects of FCR/P (Lichtenthal et al., 2017). To be able to meet the growing needs of survivors to help them manage FCR/P, there is an urgent need to develop minimal interventions that are efficacious. If effective minimal interventions can be developed, they could be a useful addition to a stepped care approach in reducing FCR/P.

CONCLUSION

In conclusion, the online resource developed for women with ovarian cancer was rated as helpful. Women reported high levels of satisfaction and almost all women reported that they would recommend the resource to a friend. Despite these positive findings, the online resource did not lead to reductions in FCR/P and importantly it was those women with the highest levels of FCR/P who found the resource least helpful. Future research needs to investigate ways in which interventions can be delivered to the large number of cancer survivors who need help to deal with FCR/P.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by University of Sydney's Human Research Ethics Committee (Project No: 2018/993). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

PP, LS, and HR conceived the idea for the present study. PP wrote the first draft of the manuscript and performed the data analysis. PB and AS contributed in developing the online booklet. HR contributed to the participant recruitment. All authors discussed the results and contributed to the final manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REVIEW

Towards a Stepped Care Model for Managing Fear of Cancer Recurrence or Progression in Cancer Survivors

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Background: Fear of cancer recurrence or progression (FCR) is common amongst cancer survivors and an important minority develop clinically significant levels of FCR. However, it is unclear how current clinical services might best support the growing numbers of cancer survivors.

Purpose: The aim of this study is to develop recommendations for future research in the management of FCR and propose a model of care to help manage FCR in the growing population of cancer survivors.

Methods: This is a narrative review and synthesis of empirical research relevant to managing FCR. We reviewed meta-analyses, systematic reviews and individual studies that had investigated interventions for FCR.

Results: A recent, well-conducted meta-analysis confirmed a range of moderately effective treatments for FCR. However, many survivors continued to experience clinical levels of FCR after treatment, indicating a clear need to improve the gold standard treatments. Accessibility of interventions is arguably a greater concern. The majority of FCR treatments require face-to-face therapy, with highly skilled psycho-oncologists to produce moderate changes in FCR. With increasing numbers of cancer survivors, we need to consider how to meet the unmet need of cancer survivors in relation to FCR. Although there have been attempts to develop minimal interventions, these are not yet sufficiently well supported to warrant implementation. Attempts to help clinicians to provide information which might prevent the development of clinically significant FCR have shown some early promise, but research is needed to confirm efficacy.

Conclusion: The next decade of research needs to focus on developing preventative approaches for FCR, and minimal interventions for those with mild-to-moderate symptoms. When evidence-based approaches to prevent FCR or manage moderate levels of FCR are available, stepped care approaches that could meet the needs of survivors could be implemented. However, we also need to improve existing interventions for severe FCR.

Keywords: cancer, oncology, fear of cancer recurrence, fear of progression, FCR interventions

Introduction

Improved methods for early cancer detection and more effective treatment have significantly decreased cancer mortality rates.[1] As a result, there is a growing number of cancer survivors who are faced with a wide range of survivorship issues. The most prominent and persistent concern revealed by cancer survivors is the fear of cancer recurrence or progression.[2–5] According to the recent consensus definition, FCR is the "fear, worry or concern relating to the possibility that cancer will come back or progress".[6] FCR has been identified as one of the most common

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Received: 21 June 2021
Accepted: 7 November 2021
Published: 1 December 2021

concerns of survivors and help with FCR is amongst the most cited unmet needs of cancer survivors.[5]

Following a cancer diagnosis and its treatment, it is normal and potentially adaptive for survivors to be concerned about the possibility that their cancer may recur. Such concerns can motivate the adoption of a healthy lifestyle, vigilance towards potential signs and symptoms of recurrence and promote adherence to medical follow-up.[7,8] For this reason, it is unsurprising that FCR is common and research shows that almost 73% of cancer survivors across different cancers report some degree of FCR. Importantly, nearly half of all survivors (49%) report a moderate to high degree of concern about FCR with approximately 7% reporting a severe level of FCR.[5] Amongst those with moderate to severe concerns, FCR can become chronic and cause a range of negative consequences, even when the risk of recurrence of disease is low.[5,9,10] Clinically significant levels of FCR are characterized by persistent worry, preoccupation with bodily checking for signs of cancer, and the frequent need for reassurance from hospital services.[11,12] As a result of reassurance seeking, clinically significant levels of FCR are typically associated with increased health-care costs.[13,14]

In addition to the costs, higher levels of FCR have consistently been associated with increased depressive, anxiety and post-traumatic stress symptoms,[15–17] as well as the experience of psychiatric disorders.[3] Since clinical levels of FCR do not appear to dissipate over time, individuals often require specialized psychological support and intervention to manage symptoms of FCR.[18]

A survey conducted in 2014, however, showed that there was little agreement about the best approach to managing FCR. Thewes et al[19] conducted a survey amongst 141 oncology health-care workers (77 health professionals and 64 psycho-oncologists) about their current approaches to managing FCR. The respondents reported that more than half of the survivors whom they saw in their practice had an issue with FCR. Amongst the health professionals, only 21% reported referring survivors with FCR to psycho-oncologists. Further, while psycho-oncologists used a range of interventions to manage FCR, all bar one of the respondents wanted additional training to help manage FCR. Thewes et al[19] highlighted the need for the development of effective, theoretically driven treatments for FCR and, since the publication of that survey, there have been randomized controlled trials (RCTs) of different approaches for the management of FCR.

Evidence-Based Approaches to FCR

While FCR has been an outcome in RCTs of psychosocial interventions that generally aim to reduce distress,[20–22] there have been fewer interventions that have explicitly targeted FCR, as a primary outcome. The earliest approaches used a cognitive behavioural approach, likely due to the fact that the prevailing model of FCR was based on the self-regulation theory.[23] This model argued that FCR is a multidimensional construct comprised cognitive and emotional components. According to this model, an emotion (eg, fear) results when one misinterprets neutral bodily sensations. That is, it is those individuals who believe that cancer is likely to recur, who become anxious and then behave in ways to reduce the anxiety, such as checking or avoiding hospital appointments, which leads to increased fear responses over time. However, these approaches had modest success. For example, Herschbach et al[24] found that CBT was more effective than a (non-randomized) no treatment control group, but not a non-directive supportive control group. Similarly, the AFTER intervention[25] showed some evidence of improvement in FCR following treatment in oral cancer patients, but the median number of sessions attended was two, indicating less than ideal attendance. However, with a proliferation of new theoretical models (eg, cognitive processing model[7]), so too followed a number of interventions based on those theories (eg, ConquerFear[26]).

In the most comprehensive meta-analysis to date, Tauber et al[27] evaluated 23 controlled trials (21 of them were randomised controlled trials) of a psychological intervention where FCR was measured as an outcome. Their results confirmed that psychological treatments are effective for FCR; however, the effect is small (Hedge's $g = 0.33$). The quality of the evidence overall led the authors to be moderately confident of the estimate of their effect size using the GRADE criteria.

Tauber et al[27] also examined a range of moderators, including type of therapy (contemporary or traditional CBT), cancer type, FCR as primary or secondary target, intervention format (group or individual) and delivery (face to face or other). The type of therapy did give rise to different treatment effects. Specifically, Tauber et al[27] categorised interventions into traditional CBT which focused on challenging beliefs and changing behaviours (10 interventions) and contemporary CBT which focused on cognitive processes and encourages people to accept negative beliefs and emotions based on more recent

theoretical views of FCR (9 interventions). The results showed a difference between traditional and contemporary CBTs that favoured contemporary CBT (Hedge's g = 0.42) as compared to traditional CBTs (Hedge's g = 0.24). However, these benefits were only observed at post-treatment. Interestingly, only 8 of the interventions included in the meta-analysis included FCR as a primary outcome. It is also worthwhile noting that majority of the FCR-specific interventions were face to face (for example, ConquerFear,[26] CBT[24]) or adopted a blended approach that is combined online with face to face (eg, van de Wal et al[28]). The 19 face-to-face interventions in the Tauber et al[27] meta-analysis involved between 1 and 15 sessions, with a median of 6 sessions. Further, interventions that were not face-to-face, did not result in significant change in total FCR when considered alone. Hence, the results of this meta-analysis suggest that even reasonably intensive interventions that are administered by highly trained psycho-oncology professionals give rise to modest effects. Further, a number of gaps were evident in the literature, more than half of the included trials were in early-stage breast cancer treated with curative intent, and the majority of trials were with survivors who were currently disease free. Given the recent efficacy of novel interventions including immunotherapies and personalised medicine that are leading survivors to live long lives with disease in many cases (see Thewes et al[29]), we need more trials in other cancer types, particularly those with advanced disease.

While Tauber et al's[27] meta-analysis confirmed the efficacy of available interventions, it also highlighted a number of important limitations to the literature. Given the estimated and growing unmet need for management of FCR, it will be impossible to implement the intensive face-to-face approaches with established efficacy to all participants with moderate to severe FCR. Instead, there is a need to develop a model of care where we stratify care to the level of severity with increasingly intensive interventions reserved for those with the most serious or severe difficulties. However, to have an optimal stepped care model, we need to (a) prevent the development of clinically significant levels of FCR, where possible; (b) develop effective minimal interventions for FCR; (c) upskill non psychology health-care professionals in managing FCR; and (d) develop more efficacious treatments for a greater range of survivors. See Table 1 for a detailed account of these studies.

Can Clinically Significant Levels of FCR Be Prevented?

Most models of FCR identify that a survivor's knowledge of the realistic likelihood of recurrence and likely signs of recurrence contribute to clinically significant levels of FCR.[7,23] That is, a lack of information about prognosis and signs of recurrence increases the likelihood that people will experience a clinically significant level of FCR. As such, it is possible that good doctor-patient communication about these topics at the end of treatment may help reduce the chance of developing clinically significant levels of FCR. Butow et al[18] recommended that all members of the oncology team should consider FCR to be a topic of relevance to their care of the patient.

The literature on potential preventative programs is in its infancy. A systematic review by Liu et al[30] identified only five trials of non-psychologist delivered (four of them were nurse led) communication. Only three of the trials had a control arm (the remainder were Phase I pilot interventions), hence these trials were at a high risk of bias. One intervention (the AFTER intervention: Adjustment to the Fears, Threat and Expectation of Recurrence[25]) consisted of 6 weekly sessions with a nurse. This intervention comprised CBT, relaxation and patient-centred approach and reduced FCR levels at post-intervention, but not follow-up. The second trial was a single-session nurse-led coaching intervention, where nurses coached survivors to communicate more with their oncology team about recurrence.[31] Although participants were satisfied with the intervention, there were no impacts on FCR. However, the study had only 44 participants and so was likely under-powered. According to Liu et al,[30] some approaches have shown feasibility and a lack of harm in early trials. The most common strategies were allowing participants to discuss their fears, and providing reassurance and normalisation. More recently, Liu et al[32] also conducted a single-arm study of an oncology delivered intervention that normalised FCR, provided personal prognostic information, educated survivors about symptoms of recurrence and gave advice about managing FCR worries and information about referral, where necessary. This intervention was only 8 minutes long, on average, which was considered to be feasible. FCR did improve over the trial, although whether this is as a result of the intervention is unclear. As such, there remains insufficient data to recommend widespread adoption of these approaches.

Table 1 Study Characteristics and Results of Included Papers

	Sample Size	Type of Cancer	No. of Arms	Delivery Mode	Intervention	Outcomes	Effect Size
							Cohen's d (Time of Assessment)
I.Psychoeducation and preventative interventions							
Pradhan et al (2021)[38]	62	Ovarian Cancer	Single-arm	Online: Psychoeducational booklet	Psychoeducation: Online PDF booklet.	No effect on fear of progression	0.17 1 week
Liu et al (2021)[32]	61	Breast Cancer	Single-arm	Face-to-face	Oncologist delivered preventative intervention	FCR reduced	0.39 (1 month) 0.68 (3 months)
Dieng et al (2016)[40]	164	Melanoma	Two	Psychoeducational booklet 3 Telephone sessions	Psychoeducation plus psychodynamic-based psychotherapy	FCR reduced	0.5 (1 month) 0.3 (6 months)
Sterba et al (2015)[83]	92	Breast Cancer	Two	Mixed	In-person video sessions and educational booklets	No effect on cancer-related worries	−0.22
II.Self-help and internet-delivered interventions							
Otto et al (2017)[42]	67	Breast Cancer	Two	Online	Positive psychology: Gratitude intervention	No effect on FCR	0.21 (1 month) 0.1 (3 months)
Lichtenthal et al (2017)[43]	110	Breast Cancer	Two	Online	Cognitive Bias Modification (Interpretation and Attention)	No effect of Cancer Worry Scale	0.35 Post-treatment 0.54 (3 months)
van Helmondt et al, (2020)[49]	262	Breast Cancer	Two	Online	Cognitive behaviour therapy	No effect on FCR	Not reported
Omidi et al (2020)[39]	105	Breast Cancer	Three	Face to face Online	Group and social network-based self-management education on lymphedema	No effect on FCR	Group education: 0.21 Social Network-based education: 0.06 (3 months)
Dirkse et al (2019)[54]	86	Multiple	Two	Face to face Online	Cognitive behaviour therapy	Reduction in FCR	0.93–0.85 (1 month)
Lengacher et al (2018)[76]	15	Breast Cancer	Single-arm	Online	Mobile-based Mindfulness Stress Reduction for Breast Cancer	Improvements in fear of recurrence at 6 weeks follow-up	0.74
Germino et al (2012)[71]	313	Breast Cancer	Two	Self-directed	Traditional CBT	No significant improvement in FCR was reported.	Not reported
III.Health-care professionals led interventions							
Humphris & Rogers (2012)[25]	90	Head and Neck	Two	Face to face, nurse-led	Cognitive behavioural therapy	FCR reduced during treatment, improvement not maintained	0.56 (3 months)
Shields et al (2010)[31]	44	Breast Cancer	Two	Single session, tele-coaching	Encourage patients to raise top 3 concerns with oncologist	No effect on FCR	−0.13
Reb et al (2020b)[34]	31	Gynaecology Lung Cancer	Single-arm	In person and online	Contemporary CBT, hybrid online and face-to-face	Reduction in FoP at 8 and 12 weeks after intervention.	1.3 (8 weeks)

(*Continued*)

Table 1 (Continued).

	Sample Size	Type of Cancer	No. of Arms	Delivery Mode	Intervention	Outcomes	Effect Size
							Cohen's d (Time of Assessment)
IV.Intensive specialist care							
Herschbach et al (2010)[24]	265	Multiple	Three	Face to face	CBT and SET (based on personal experiences)	Reduction in FoP scores after 12 months for both intervention groups.	CBT: 0.61
							SET: 0.56 (12 months)
Butow et al (2017)[26]	222	Multiple	Two	Face to face	Contemporary CBT and relaxation training	Improvements in both total FCR-I and severity subscale	0.33 (3 months)
							0.39 (6 months)
Van de Wal et al (2017)[28]	88	Multiple	Two	Mixed: Face-to-face and online sessions	Blended cognitive behaviour therapy	Improvements in FCR at 3 months post intervention.	0.76
Bannaasan et al (2015)[64]	59	Breast Cancer	Two	Face-to-face	Buddhist doctrine-based practice	Reduction in FCR scores after 1 month.	1.38 (1 month)
Tomei et al (2018)[84]	25	Multiple	Two	Face to face	Traditional CBT	Reduction in FCR at post-intervention	0.28
Cameron et al (2007)[66]	154	Breast Cancer	Two	Face to face	Contemporary CBT for emotional regulation and adjustment	Decrease in cancer recurrence worries after 4 months, not maintained after 6 and 12 months.	0.59
Lengacher et al (2009)[22]	84	Breast Cancer	Two	Face to face	Mindfulness-based stress reduction	Improvement in FCR after 6 weeks.	0.6
Crane-Okada et al (2012)[68]	49	Breast Cancer	Two	Face to face	Mindful movement program intervention	Decrease in FCR at 6 weeks	0.57
Heinrichs et al (2012)[22]	72	Breast and Gynaecological cancer	Two	Face to face	Couple based coping intervention	Decrease in FoP for intervention participants	0.57
Bower et al (2015)[65]	71	Breast Cancer	Two	Face to face	Mindfulness-based intervention	Improvements in FCR at 3 month follow-up in intervention group	1.39
Dodds et al (2015)[70]	33	Breast Cancer	Two	Face to face	Meditation-based program called CBCT	Reduction in FCR in intervention group	−1.38
Lengacher et al (2016)[75]	322	Breast Cancer	Two	Face to face	Mindfulness-Based Stress Reduction for Breast Cancer	Improvements in FCR at 6 and 12 week follow-up	0.3 (6 weeks)
							0.28 (12 weeks)
Merckaert et al (2016)[78]	159	Breast Cancer	Two	Face to face	CBT and hypnosis	Reduction in FCR severity post intervention	0.33
Manne et al (2017)[77]	352	Gynaecological Cancer	Three	Face to face and 1 telephone session	Communication-enhancing intervention (CCI) and supportive counselling (SC)	No effect on FCR	0.11
Victorson et al (2016)[85]	43	Prostate	Two	Face to face	Mindfulness Based Stress Reduction	Reduction in recurrence fears	0.15

(*Continued*)

Table 1 (Continued).

	Sample Size	Type of Cancer	No. of Arms	Delivery Mode	Intervention	Outcomes	Effect Size
							Cohen's d (Time of Assessment)
Gonzalez-Hernandez et al (2018)[72]	56	Breast Cancer	Two	Face to face	Compassion-based intervention	Reduction in FCR related stress at post-intervention and 6 mth follow-up	0.68 (post-intervention)
							0.46 (6 months)
Chambers et al (2012)[67]	19	Prostate	Single-arm	Face to face	Mindfulness-based cognitive therapy group intervention	Reduction in FCR	0.28
Lebel et al (2014)[74]	56	Breast and ovarian cancer	Single-arm	Face to face	Cognitive-existential (CE) group intervention	Reduction in FCR	0.73
Seitz et al (2014)[81]	20	Multiple cancers	Single-arm	Online	Traditional CBT	Decrease in FoP	0.48
Smith et al (2015)[82]	8	Multiple cancers	Single-arm	Face to face	Contemporary CBT	Reduction in overall FCR scores and severity subscale at 2-month follow-up	FCR Severity: 1.9
							FCRI-Total: 1.8
Arch & Mitchell (2015)[63]	42	Multiple cancers	Single-arm	Face to face	ACT	FCR decreased at post intervention, but 1 mth follow-up	0.66 (post-treatment)
							0.11 (1 month)
Momino et al (2017)[79]	40	Breast	Single-arm	Face to face	Collaborative care and need-based intervention	No effect on FCR	0.15
				Telephone sessions			
Savard et al (2018)[80]	33	Multiple cancers	Single-arm	Face to face	Group-based CBT	Significant decrease in FCR at post-treatment	Not reported
Davidson et al (2018)[69]	16	Breast Cancer	Single-arm	Telephonic sessions	Intervention based on CBT	Decrease in FCR after 1 week follow-up	0.8
Johns et al (2019)[73]	91	Breast Cancer	Three	Face to face	Group-based ACT and Survivorship education	Significant decrease in FCR severity in ACT group	0.61 (6 months)
Stepped care							
Lynch et al (2020)[56]	61	Melanoma	Single-arm	Mixed	Three step intervention: (1) Treatment as usual; (2) Self-management intervention (3) Individual therapy: contemporary CBT.	Contemporary CBT reduced FCR and FoP.	Self-management -0.11 for FCR
							0.02 for FoP
							Individual therapy
							0.64 FCR
							0.4 FOP

Abbreviations: ACT, Acceptance and Commitment Therapy; AFTER, adjustment to the fear expectation or threat of recurrence; bCBT, blended cognitive behavioural therapy; CAREST, cancer recurrence self-help training; CAU, care as usual; CBT, cognitive-behavioral group therapy; CBCT, Cognitively–Based Compassion training; FCR, fear of cancer recurrence; FoP, fear of progression; MCT, meta-cognitive therapy; SET, supportive-experiential therapy; S-REF, Self-Regulation of Executive Function.

Up-Skilling Health Professionals to Deliver Psychosocial Interventions

Whilst the systematic review of Liu et al[30] confirmed that it was premature to confirm the efficacy of clinician-based interventions designed to prevent FCR, there were some indications that nurse-delivered interventions could be efficacious. As described previously, Humphris & Rogers[25] trained nurses to administer a CBT-based intervention to reduce FCR amongst head and neck cancer patients. There was evidence for efficacy of this intervention compared to a control in the short-term, showing strong proof of concept that nurses can be trained to use CBT to help survivors manage FCR. In a similar vein, researchers have attempted to adapt the ConquerFear program as a nurse-led intervention.[33] The ConquerFear program was based on Fardell et al's[7] model of FCR and combined components of acceptance commitment therapy, meta-cognitive therapy and behavioural strategies based on self-regulation theory. The ConquerFear program was used with patients with early-stage breast or colorectal cancer or melanoma, who had been treated with curative intent and were in the clinical range on FCR Inventory.[26] In a phase I trial, in 33 survivors with advanced lung or gynaecological cancer, Reb et al[34] found significant improvements in fear of progression for 21 participants who completed the ConquerFear program in a mixed (zoom/face to face) approach. As an uncontrolled trial, this study was at a high risk of bias; however, the effect sizes that were achieved when ConquerFear was adapted to more advanced disease and administered by nurses were roughly similar to those achieved in the ConquerFear arm in the original study, which is extremely encouraging.[34] There is considerable evidence that patients show a preference for receiving supportive care from nurses, in comparison to psychologists or psychiatrists,[35] however, it is only recently that psychological interventions for FCR have been nurse-led. Given the larger nursing workforce in comparison to the psycho-oncology workforce, the ability of nurses to achieve similar outcomes could begin to bridge the gap between effective treatments being available and accessible. Although given the number of survivors, making help with FCR available to all survivors for whom this is an issue will likely require effective minimal interventions.

Minimal Interventions

Minimal intervention is an umbrella term for interventions that do not require large amounts of therapist time and are typically delivered remotely (eg, telephone, online, a booklet), which allows these interventions to be scalable for a very common problem, where the available workforce cannot meet the needs of the population. These interventions require less time commitment, expertise and resources to achieve an improvement in a particular outcome.[36] FCR amongst cancer survivors can be seen as an area in which minimal interventions may be necessary to ensure that help with FCR does not remain the leading unmet survivorship needs.

The most minimal of interventions are self-help materials, such as pamphlets, information sheets and online resources. While many cancer organisations internationally have developed their own FCR resources to provide some information and support around FCR/P, these have rarely been evaluated. The efficacy of self-help resources in general was extensively evaluated in a systematic review by Cuthbert et al,[37] which included 41 randomised trials with psychoeducational self-help component for cancer survivors. The results of this review were mixed across studies, indicating that while some self-help approaches can produce positive outcomes, many fail to and some even produce unintended negative impacts. However, none of the 41 included trials targeted FCR. Only recently has there been research evaluating the efficacy of brief online FCR resources. In one study, an online self-help pamphlet was developed by Ovarian Cancer Australia and its effect on FCR was evaluated. The pamphlet provided information about FCR and suggested strategies to better manage FCR.[38] These results were consistent with another RCT conducted of information provided either via social media or in group face to face. Omidi et al[39] found that there was a significant impact of group education (but not social media information) on quality of life, compared to a control group. However, the provision of information did not have an impact on FCR. As such, it seems unlikely that the provision of simple information will be sufficient to meet the needs of survivors with elevated FCR levels.

In the Tauber et al[27] meta-analysis, there were only three minimal interventions that were included. For example, an intervention by Dieng et al[40] consisted of a psychoeducational pamphlet and three 15-minute telephone-based psychotherapy sessions by a psychodynamic therapist. It was concluded that this blended intervention

was effective in improving the levels FCR in early-stage melanoma survivors. These results were maintained at a 12-month follow-up.[41] The telephone sessions in this intervention, however, require specialist skills. It is, however, unclear whether the self-help resources would be efficacious without that input. The intervention by Otto et al[42] involved an online self-directed gratitude training on overall FCR and death-related FCR. The intervention produced an improvement in reducing death-related FCR and promoting well-being in the gratitude intervention group, but there was no impact on FCR total severity. Similarly, Lichtenthal et al[43] used a novel Cognitive Bias Modification (CBM) to reduce FCR amongst 120 women with early-stage breast cancer compared to a placebo. CBM is a novel approach which directly aimed to modify implicit cognitive processing biases such as attention or interpretation.[44] The intervention consisted of 8 personalised treatment sessions that were computerized over the span of 4 weeks. Their intervention was successful in modifying interpretation bias and produced an improvement in the health worries subscale of concerns about recurrence scale as compared to a placebo group. However, the total score for worries about cancer was not significantly improved compared to the placebo group. Therefore, while these approaches showed some promise, more research is definitely needed.

Despite the proliferation of internet-delivered interventions in other areas of psychology,[45–48] the FCR literature has been somewhat slow to develop and evaluate online versions of the face to face interventions. For instance, Van de Wal et al.'s[28] SWORD study ("Survivors' Worries of Recurrent Disease") also known as blended cognitive behavioural therapy (bCBT) or partly online. Participants in the intervention condition received 5 individual face to face sessions in combination with three e-consultations. The intervention successfully reduced the severity of FCR on Cancer Worry Scale as compared to control group. SWORD does, of course, have evidence for efficacy – suggesting that at least part of the intervention could be offered online. However, stand-alone internet delivered interventions thus far have failed to show clear evidence of efficacy. The only one to be evaluated in an RCT so far is CAREST.[49] CAREST was a carefully developed intervention based on psychoeducation and CBT principles for FCR. The trial was relatively large (n = 262), but failed to show any difference between women who received CAREST or treatment as usual. This was despite reasonable completion rates: 83% at post-treatment and 70% at follow-up. This trial therefore questions whether an unsupported, stand-alone intervention will be efficacious when delivered online.

There are, however, a number of other internet-delivered interventions that have been developed. For example, iConquerFear has been co-designed by adapting ConquerFear to an online platform.[50] It is currently being evaluated.[51] Akechi et al[52] have developed a smartphone intervention, in the SMILE trial, which is currently underway and will deliver a combination of problem-solving therapy and behavioural activation in an attempt to lessen FCR/P. Finally, the FORTitude study[53] developed an eHealth intervention based on treatments for anxiety disorders but applied to FCR/P. The three active strategies included in the program were relaxation, cognitive restructuring and scheduled worry time. The trial was designed to be able to comment on the relative efficacy of each of these strategies, however, to date the results have not been published. Interesting, a recent study has compared a generic online treatment (Wellbeing after cancer) with and without support and included FCR as an outcome. Dirkse et al[54] found that there was a moderate sized effect for reducing FCR of this program, even without support, which shows that internet-delivered interventions have the capacity to be efficacious for FCR.

Stepped-Care Approaches

There are over 2 million cancer survivors currently living in Australia alone [AIHW, 2020]. Nearly half of all survivors will have moderate levels of FCR[5] and in some groups (such as young women with breast cancer), up to 79% have clinically significant levels of FCR.[13] Without specific effective minimal interventions, there will be no realistic way in which to meet the needs of cancer survivors to manage FCR. Most oncology services have limited resources to support all survivors with elevated FCR, and thus there seems to be an urgent need to develop evidence-based approaches with different levels of intervention. Although stepped care is often described as any model of service provision with different levels of care, there are three main models for how to determine the flow of patients through services.[55] True "stepped care" approaches propose that a simple, inexpensive intervention be tried first for all survivors. If the survivor continues to have clinically significant levels of FCR, then a more complex intervention is tried, and so the process continues as the steps become more complex. The second model is stratified care. These approaches tailor FCR interventions, based on the severity of FCR or other known risk factors

for poor prognosis. Those survivors deemed to have mild, but still bothersome, levels of FCR are referred to minimal interventions, such that more intensive interventions (requiring high professional skills) are reserved for people with clinical FCR who are unlikely to benefit from minimal interventions. The final type of stepped care approach is matched care. Matched care, like stratified care, assesses survivors at baseline, and determines not only the intensity of intervention, but also the nature of intervention based upon different presenting risk factors.

To date, there has been a single stepped care approach described in the literature, the 'FearLESS' program.[56] FearLESS was developed for advanced melanoma survivors who had responded to immunotherapies, and as a result had a large degree of uncertainty in relation to the potential for recurrence or progression. The FearLESS program was a stratified version of stepped care where those survivors who scored in the normal range received treatment as usual. Those scoring in the sub-clinical range for FCR were directed to a self-help intervention, supported with phone calls and screened again five weeks later. In contrast, those who scored in the clinical range for FCR were provided with individualised therapy sessions based on ConquerFear.[26] The FearLESS model holds some promise, as the results showed that participants engaged with the intervention offered and the majority of those assigned to self-help indicated that they did not want further intervention (90%). Although 13 of the 21 completers in the self-help condition reported numerical decreases in their FCR scores, the effect size was very small (Cohen's d = 0.11).[56] The individual therapy resulted in larger changes (Cohen's d = 0.7), which were similar to the within-group effects in the ConquerFear trial, suggesting that the approach is likely suited to more advanced patients. Nevertheless, this was a study with a high risk of bias given the absence of a control group, and the absence of evidence-based minimal interventions makes the provision of effective stepped care approaches challenging.

In order to develop an effective stepped care approach, or to determine the nature of a stepped care approach that might be most suited to FCR, we need more research. If a brief oncologist delivered intervention at the end of treatment, such as that developed by Liu et al[32] was to prove efficacious in RCTs, this would potentially be an easily delivered universal step. That is, an oncologist-based intervention could be incorporated into routine care of all survivors with the hope of preventing clinically significant levels of FCR. Currently, we desperately need to evaluate the available internet-delivered minimal interventions specific to FCR which could then be used as a second step in the stepped care program. We have effective individual face-to-face interventions that produce modest changes in FCR/P. There are few moderation studies of who benefits most, but we know that the relative benefit of ConquerFear was greater for those with higher baseline levels of FCR.[57] This would suggest that a matched approach to stepped care might be most useful. However, it would be important to demonstrate that those with higher FCR/P did not also benefit most from minimal interventions.

One could envisage a model of stepped care, where on a first, universal step, oncologists were encouraged to normalise FCR/P, provide reassurance and accurate prognostic information, as well as specifying the likely symptoms associated with FCR/P to all their patients (eg, Liu et al;[30] See Figure 1). Survivors might then be screened at routine

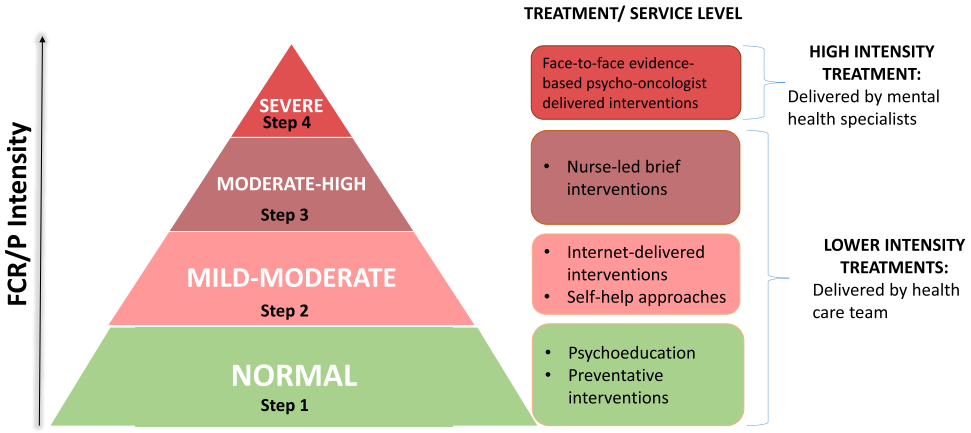

Figure 1 Stepped care model to fear of cancer recurrence/progression in oncology services.

follow-up appointments. Those who developed a "sub" clinical level of symptoms might be encouraged to engage with an efficacious minimal intervention, while those with moderate symptoms might be referred for brief nurse-led interventions. This would reserve specialist psycho-oncologists to work with those survivors with the most severe levels of FCR/P. However, we should also be investigating ways to improve the outcome of existing treatments, which continue to leave a large proportion of survivors in the sub-clinical and clinical range for FCR/P.

Maximising Existing Interventions

Although existing face-to-face interventions are effective, the effect sizes of treatments are small, on average, and the majority of participants still score in at least the sub-clinical range following treatment (e.g.[26,28]). Future research should focus on how to further improve outcomes for survivors with severe FCR and for those with advanced disease (refer to Table 2 for recommendations for future research). There are a number of ways in which to address the problem of finding more efficacious treatments. Firstly, one can examine mediators of treatments that work, which can indicate the likely treatment mechanism and increase the focus on intervention strategies that target those factors. For example, changes in metacognitions and intrusions were found to moderate the relative efficacy of ConquerFear versus relaxation training.[57] Hence, focusing more on metacognitive therapy,[20] or interventions (such as the worst case scenario[58]) may increase the efficacy of existing approaches. Secondly, it is possible that if both traditional and contemporary CBT approaches are both effective, that together they might be more efficacious. A recent case series of a combined approach for transdiagnostic anxiety (including FCR/P) showed that 65% of patients with advanced disease no longer scored in the clinical range following treatment,[59] but again as a case series this study is at risk of bias. Finally, theoretical models can be used to guide the development of improved interventions, such as focusing on modifying interpretation biases, argued to drive FCR in the threat interpretation model[60] or focusing on death anxiety[61] which is seen as central in Simonelli et al's[62] model of FCR. While improving treatments will require more research, the existence of moderately effective psychological treatments should be seen as a starting point for further improving approaches to manage FCR.

There is no doubt that over the past ten years, numerous efficacious psychological treatments for FCR/P have been developed and evaluated. However, these are associated with small to moderate effects with most survivors who complete treatment remaining in either the clinical or sub-clinical range. It may be that combining efficacious treatments, targeting factors that are associated with FCR or increasing the dose of effective treatment components would result in larger improvements. However, research is needed to determine this. Despite a range of efficacious treatments, there is simply not the workforce available to make these treatments available to all survivors with moderate to severe FCR. Furthermore, based on the past literature, we still do not have evidence-based interventions to be able to implement a stepped care approach for FCR. Therefore, we desperately need evidence-based minimal interventions that can be developed for use as part of a stepped care model, as well as good preventative approaches, to meet the needs of the growing number of cancer survivors who fear recurrence or progression.

Table 2 Recommendations to Guide Future Research

Recommendations for Future Research
1. Development and evaluation of universal minimal interventions (eg clinician-delivered, psychoeducational interventions, informational resources, apps) designed to help prevent FCR.
2. Development and evaluation of minimal interventions (eg internet-delivered treatments) that are targeted for those with mild to moderate FCR
3. Up-skilling oncology professionals to deliver interventions targeting FCR in routine clinical practice.
4. Research to improve existing interventions for severe FCR.
5.Adapting available evidence-based FCR interventions for those with advanced disease.
6. Testing models of stepped care to develop the most efficacious and highly implementable service model.

Disclosure

The authors report no conflicts of interest in this work.

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Received: 19 December 2021 | Revised: 3 April 2022 | Accepted: 10 April 2022

DOI: 10.1002/pon.5944

WILEY

ORIGINAL ARTICLE

Are fear of cancer recurrence and fear of progression equivalent constructs?

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Funding information
Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

Abstract

Background: The predominant definition of fear of cancer recurrence (FCR) conflates FCR with fear of progression (FOP). However, this assumption has never been tested. Importantly, if FCR and FOP are distinct and have different predictors, existing interventions for FCR may not be equally effective for survivors who fear progression rather than recurrence of their disease. The present study aimed to determine whether FCR and FOP are empirically equivalent; and whether they are predicted by the same theoretically derived variables.

Methods: Three hundred and eleven adults with a history of breast or ovarian cancer were analysed (n = 209, 67% in remission). Exploratory factor analysis was conducted on the items of the FCR Inventory severity subscale and short-form FOP Questionnaire together. Structural equation modelling was conducted to predict FCR and FOP and determine whether theoretical models accounted equally well for both constructs, and whether models were equally relevant to those with and without current disease.

Findings: The factor analysis demonstrated that the FCR Inventory severity subscale and the short-form FOP Questionnaire loaded onto distinct, but related, factors which represented FCR and FOP. Structural modelling indicated that risk perception and bodily threat monitoring were more strongly associated with FCR than FOP. However, both FCR and FOP were associated with metacognitions and intrusions.

Interpretation: These findings suggest that whilst FCR and FOP are related with some overlapping predictors, they are not the same construct. Hence, it is necessary to ensure that in clinical practice and research these constructs are considered separately.

KEYWORDS
breast cancer, cancer, cognition, fear of cancer recurrence, fear of progression, intrusions, metacognitions, oncology, ovarian cancer, perceived risk, survivorship

Despite advances in cancer treatment, many cancer survivors are confronted with the possibility that their cancer will return. Fear of cancer recurrence (FCR) is a common experience, with one review indicating approximately 73% of cancer survivors have some degree of FCR, and 49% report moderate to high FCR.[1] Even when the objective risk of recurrence is low, FCR remains stable and high for years after treatment.[1,2] FCR is defined as 'fear, worry or concern relating to the possibility that cancer will come back or progress'[3] and may be adaptive by motivating engagement with positive health behaviours.[4] However, FCR can become highly distressing, chronic, and disabling, and is associated with negative health outcomes including depression and anxiety[1,5,6] and generalised anxiety disorder.[6,7] Multiple reviews identify help with FCR as among the most commonly reported unmet needs of cancer survivors.[1,8,9] In addition, FCR has been found to predict several important health behaviours, including: increased use of psychotherapeutic medication,[10] increased health care use,[10-12] and complementary medicine use, and decreased use of mammograms.[11]

Several models to understand FCR and related anxieties have been developed, for example,[13-16] Further, effective psychological interventions for FCR have been developed and evaluated and have been shown to reduce FCR.[16,17] Such interventions are a cost-effective way to reduce the financial burden of FCR, according to a recent systematic review.[18] However, most psychological interventions for FCR have been evaluated with disease-free, early-stage cancer patients previously treated with curative intent.[17,19-22] Conceptually, FCR seems most relevant to those who have entered remission but fear their cancer returning. Increasingly, those with metastatic cancer are living longer with ongoing active disease, and their fears would logically seem less about cancer returning and more about their fear of the cancer progressing.[1] Additionally, those whose cancer has already recurred cannot, by definition, fear recurrence, although many fear progression. The fact that the literature has not distinguished between those with and without current active disease or whether they fear recurrence and/or progression reflects the consensus definition of FCR, as a fear that 'cancer will come back *or* progress'.[3] This definition conflates FCR and fear of progression (FOP) and assumes they represent the same latent construct, although this assertion has never been tested.

The current study aims to determine if FCR and FOP are empirically equivalent, as proposed,[3] and whether FCR and FOP can be accounted for by the same theoretical model. We aim to test Fardell et al's cognitive processing model,[13] which suggests that distressing thoughts and emotions are a normal response to cancer. However, when a cancer survivor believes those worries are helpful, harmful or uncontrollable, (i.e., has unhelpful metacognitions), they will experience a cascade of responses marked by worry, rumination, and bodily threat monitoring that drive FCR-related thoughts.[13] We chose Fardell's model, because there is an evidence-based intervention, ConquerFear,[23] which has been shown to be efficacious, that targets these causal factors. Moreover, reductions in FCR in that study were partially mediated by a decrease in unhelpful metacognitions and intrusive thoughts, confirming their likely role as treatment mechanisms.[24]

This study has two phases. In phase I, we analyse measures of FCR and FOP to explore empirical overlap between the two questionnaires. In phase II, we evaluate the major tenets of the novel cognitive processing model of FCR, to determine whether FCR and FOP can be predicted by the same theoretical model.

1 | METHOD

1.1 | Participants

Three hundred and fifty-four adults with a diagnosis of breast or ovarian cancer accessed an online survey circulated by Ovarian Cancer Australia (OCA) or Breast Cancer Network Australia (BCNA). Recruitment occurred between the 11th of June and 11th of September 2020. Participants were included in analyses when they provided complete data for phase I (n = 304) and phase II (n = 278), see Appendix 1.

1.2 | Procedure

Participants were recruited via the e-mailing lists of two cancer organisations, namely BCNA and OCA. Additionally, OCA advertised the study on social media. Eligible participants consented and then completed the 20–30-min survey. This study was approved by the University of Sydney's Human Research Ethics Committee.

1.3 | Measures

Participants responded to demographic and medical history questions and reported their cancer status in terms of current treatment, and whether they had active disease or were in remission. We were particularly interested in these constructs amongst those with evidence of current disease compared to those without evidence of current disease. All measures possessed high internal consistency (see Appendix 2A for additional descriptive statistics and more information about the scales).

1.4 | Fear of cancer recurrence & fear of progression

FCR was assessed with the Fear of Cancer Recurrence Inventory (FCR-I) severity subscale,[5] a validated screening tool for clinical FCR. Higher scores indicate greater FCR and a score ≥22 indicates clinically significant FCR.[25] FOP was assessed with the short-form Fear of Progression Questionnaire (FoP-Q-SF).[26] The short-form has been validated in cancer samples. Higher scores indicate greater FOP. Scores ≥34 indicate an elevated degree of FOP, and have been proposed as a marker of clinically significant FOP warranting treatment in clinical trials.[27,28] Both questionnaires were administered to all participants irrespective of disease status. FCRI does instruct participants to interpret FCR as referring to the fear of cancer returning or progressing.

1.5 | Intrusive thoughts

Intrusive thoughts about cancer were assessed with the Impact of Event Scale-revised (IES-R) intrusions subscale.[29] This subscale has been validated for assessing intrusive thoughts about cancer in cancer patients.[30] Higher scores indicate greater severity of intrusive thoughts.

1.6 | Metacognitions

Metacognitions were assessed with an 18-item subset of the short-form Metacognitions Questionnaire (MCQ-SF).[31] We included the positive beliefs, negative beliefs, and need for control MCQ-SF subscales as these subscales are most often associated with FCR.[32,33] Higher scores indicate more maladaptive metacognitions.

1.7 | Body threat monitoring scale (BTMS)

The 19-item Bodily Threat Monitoring Scale (BMTS) was used to assess the degree to which participants monitor their body for signs of a recurrence. Validation of the BMTS is in progress. The items were generated through qualitative interviews with cancer survivors, and the scale has good psychometric properties.[34] Higher scores indicate greater propensity to monitor the body for threatening signs and symptoms (body threat monitoring; BTM).

1.8 | Subjective risk perception

Subjective belief in recurrence or progression was assessed with a single item from the short form Concern About Recurrence Questionnaire.[6] Participants indicated their certainty that their cancer would recur or progress on a sliding scale that displayed a value from 0% to 100%.

1.9 | Analyses

In phase I, all 21 items from the FCR-I severity subscale and FoP-Q-SF were entered into an exploratory factor analysis (EFA) in SPSS. Factors were extracted using principal axis factoring (PAF) and rotated with the direct oblimin method. The number of factors to extract was determined based on convergence of evidence from scree plot analysis, parallel analysis,[35] and a minimum average partial (MAP) test.[36,37] In phase II, structural equation modelling was conducted in AMOS, where the analytic method was contingent on the results of phase I. Based on the observed results, the core tenets of the novel cognitive processing model were tested by predicting FCR and FOP.

2 | RESULTS

2.1 | Participant characteristics

Of the 354 participants who accessed the survey, there was a 78·5% completion rate. Little's Missing Completely at Random test demonstrated that data was missing completely at random and not systematically biased (χ^2 = 182·251, *df* = 169, *p* = ·230). Analyses were based on 311 people aged between 22 and 81 (*M* = 58·53, *SD* = 11·41). Demographic and medical history frequencies are reported in Table 1.

People with breast and ovarian cancer differed on several medical factors, as would be expected (see supplementary material).

Based on clinical cut-offs for the FCR-I severity subscale, 36.7% a clinical degree of FCR, whereas 42% of participants were in the elevated FOP range. Rates of elevated FOP did not differ by cancer type, but those with ovarian cancer were more likely to be in the clinical FCR range than those with breast cancer. Those with active disease were more likely to have both clinically significant levels of FCR (χ^2 = 30.105, df = 1, $p < 0.001$), and elevated FOP (χ^2 = 7.197, df = 1, p = 0.007). See Appendix 2B for rates of clinical and non-clinical FCR and elevated FOP status.

2.2 | Phase I: Exploratory factor analysis

Parallel analysis of the 21 FCR and FOP items based on the 95th percentile of random eigenvalues,[35] the MAP test using the original decision-making criteria,[36] and the scree-plot all indicated a two-factor structure. Although the updated MAP test criteria suggested a third factor,[38] convergence of evidence from three of four methods, and lack of a theoretical basis for three factors, suggested a two-factor solution was most appropriate.

A two-factor EFA was conducted using PAF extraction and direct oblimin rotation (Table 2; Figure 1). Cross-loadings were observed for items 1, 2, and 16. However, all other items loaded exclusively with their respective measure. Hence, factor one was comprised largely of FoP-Q-SF items, which loaded positively, and

TABLE 1 Demographics and medical history frequencies

	Full sample *N* (%)
Marital status	
Never married	51 (16·4)
Married	187 (60·1)
Separated	11 (3·5)
Divorced	47 (15·1)
Widowed	15 (4·8)
Education	
Below highschool	24 (7·7)
Highschool	103 (33·1)
Undergraduate	90 (28·9)
Postgraduate	94 (30·2)
Currently working	136 (43·7)
Children[a]	221 (71·1)
Cancer stage at first diagnosis	
I	84 (27)
II	63 (20·3)
III	106 (34·1)
IV	32 (10·3)
Not known	26 (8·4)
Metastatic disease	84 (27·0)
Past cancer recurrence	81 (26)
Past surgery for cancer	303 (97·4)
Current treatment	
Chemotherapy	46 (14·8)
Radiotherapy	1 (·3)
Other current drugs	
Tamoxifen	17 (5·5)
Other HT[b]	34 (10·9)
Olaparib	14 (4·5)
Other non-HT[b] or unclear	34 (10·9)
Cancer status	
Active	18 (5·8)
In treatment	84 (27)
In remission	209 (67·2)
Cancer type	
Breast	132 (42·4)
Ovarian	179 (57·6)

[a]indicates the participant had at least one child.

[b]HT = hormone therapy. Tamoxifen and Olaparib use were reported separately from other drugs given their high frequency relative to the other reported pharmacotherapies.

factor two was comprised largely of FCR-I severity subscale items, which loaded negatively. This indicates factor one is describing FOP, whilst factor two is describing the negative pole of FCR, that is, no fear of recurrence. These factors accounted for 38·81% and 9·30% of variance respectively, thus 48·11% of variance in participants' response was accounted for. The two factors were negatively correlated ($r = -576$). In this case, factor 2 describes the negative pole of FCR, thus the finding that factor 1 and 2 are negatively correlated indicates that FCR and FOP are positively associated.

2.3 | Phase II: Structural equation modelling

See Figure 2. Bodily threat monitoring significantly predicted FCR but not FOP. Intrusions significantly predicted bodily threat monitoring, FCR, and FOP, intrusions had a significant indirect effect on FCR ($\beta = 0.038$, $p = 0.004$), but not FOP ($\beta = 0.027$, $p = 0.119$), thus threat monitoring partially mediates the effect of intrusions on FCR. Metacognitions significantly predicted bodily threat monitoring and FOP, but not FCR. Since bodily threat monitoring predicts FCR but not FOP, threat monitoring is a full mediator of the effects of metacognitions on FCR ($\beta = 0.061$, $p = 0.005$) but does not mediate the relationship between metacognitions and FOP ($\beta = 0.044$, $p = 0.132$). Risk perception significantly predicted FCR and FOP. Lastly, this model accounted for 40·6% of variance in bodily threat monitoring, 51·9% of variance in FOP, and 59·6% of variance in FCR.

If the direct effects of a variable on FCR and FOP are both significant, differences in the predictive power of either effect can be assessed by checking for overlap in the associated confidence intervals. This is a valid, but conservative, means of identifying a significant difference in effect magnitude.[39] The 95% confidence intervals (CIs) of the direct effect of risk perception on FCR and FOP did not overlap, indicating that risk perception is a stronger predictor of FCR than FOP. All other confidence interval pairs overlapped, indicating that predictors were equally strong for FCR and FOP (Appendix 3).

3 | DISCUSSION

Our study is the first to test the prevailing assumption that FCR and FOP represent a single construct. Our results challenged this assumption. The factor analysis demonstrated that items from the FCR-I severity subscale and FoP-Q-SF loaded on separate, albeit related, factors. This confirms that fear of the cancer returning and progressing should not be treated synonymously.

Given that FCR and FOP were highly correlated and predicted by some of the same constructs, one might ask whether the fact that they represent different constructs is important? We would argue that this is crucial to providing optimal care, particularly to

TABLE 2 Results of the EFA of FoP-Q-SF and FCR-I severity subscale items

Items		Factor loadings				
		Factor 1	Factor 2	h^2	*M*	*SD*
1	I Become anxious if I think my disease may progress	**·505**	**−378**	·618	3·03	1·10
2	I Am nervous prior to doctors' appointments or periodic examinations	**·318**	**−364**	·367	3·45	1·19
3	I Am afraid of pain	**·483**	−024	·247	2·72	1·02
4	I Have concerns about reaching my professional goals because of my illness	**·629**	·034	·373	1·98	1·26
5	When I am anxious, I have physical symptoms such as a rapid heartbeat, stomachache or agitation	**·526**	−028	·295	2·82	1·15
6	The possibility of my children contracting my disease disturbs me	**·357**	−051	·151	2·30	1·40
7	It disturbs me that I may have to rely on strangers for activities of daily living	**·659**	·115	·360	2·49	1·28
8	I Am worried that at some point in time I will no longer be able to pursue my hobbies because of my illness	**·660**	−064	·488	2·56	1·21
9	I Am afraid of severe medical treatments during the course of my illness	**·751**	−044	·604	2·79	1·19
10	I Worry that my treatment could damage my body	**·627**	−028	·414	2·91	1·18
11	I Worry about what will become of my family if something should happen to me	**·540**	−155	·412	3·00	1·32
12	The thought that I might not be able to work due to my illness disturbs me	**·661**	·096	·373	2·23	1·34
13	I Am worried or anxious about the possibility of cancer recurrence	·168	**−769**	·769	2·17	1·34
14	I Am afraid of cancer recurrence	·186	**−710**	·691	2·26	1·18
15	I Think it's normal to be anxious or worried about the possibility of cancer recurrence	·039	**−546**	·324	2·66	·89
16	When I think about the possibility of cancer recurrence, this triggers other unpleasant thoughts or images (such as death, suffering, the consequences for my family)	**·418**	**−425**	·560	2·24	1·23
17	I Believe that I am cured and the cancer will not come back	−034	**−521**	·253	2·84	1·22
18	In your opinion, are you at risk of having a cancer recurrence?	−055	**−669**	·409	2·34	1·16
19	How often do you think about the possibility of cancer recurrence?	−001	**−794**	·629	1·63	1·05
20	How much time per day do you spend thinking about the possibility of cancer recurrence?	·023	**−778**	·627	1·18	·90
21	How long have you been thinking about the possibility of cancer recurrence?	−040	**−327**	·093	2·65	1·39

Note: Extraction based on principal axis factoring and direct oblimin rotation. Items 1–12 belong to the FoP-Q-SF, whilst items 13–21 belong to the FCR-I severity subscale. Factor loadings greater than ·30 are bolded. Communalities are indicated by h^2. $n = 304$.

the increasing number of survivors living with advanced disease. To date, the literature has assumed that FOP and FCR are interchangeable and therefore our theoretical understanding of FCR and FOP, as well as our understanding of how to treat these concerns, are built on a conflation of these two constructs. However, in practice, it is fears of progression that are poorly understood. In a 2013 systematic review of quantitative research on FCR included only 18 studies out of 130 (13%) that assessed FOP.[1] Similarly, a meta-analysis of randomised controlled trials for the treatment of FCR included only 3 of 23 (13%) studies which measured FOP as the outcome.[17] Hence, the current literature provides considerably more information about FCR than FOP, particularly in disease-free survivors. As a result, considerably less is known about fears of progression or how to treat them. Given some of the recent advances in personalised medicine, it is likely that an increased number of survivors will present with fears of progression, rather than recurrence.[40] Hence, there is a crucial need to understand the similarities and differences between FCR and FOP.

Our results provide some important information to confirm that the difference between these constructs is not trivial. In relation to FCR, the major tenets of the cognitive processing model were supported. That is, FCR was predicted directly by risk perception, bodily threat monitoring and intrusions. Metacognitions predicted bodily threat monitoring, and was an indirect predictor of FCR severity, as the theory suggests. However, for FOP, the cognitive processing model was only partially supported. That is, both intrusions and metacognitions predicted FOP directly. Risk perception was also associated with FOP, although the relationship was significantly smaller than for FCR, suggesting that high perceived risk does not contribute as much to fears of progression. Another finding was that bodily threat monitoring did not predict FOP, as it did in FCR. This suggests that the degree to which one fears progression of their disease does not predict how vigilant they are towards somatic symptoms, as in FCR.

One speculative account that may explain these findings is that FCR is a form of experiential avoidance. When a cancer survivor

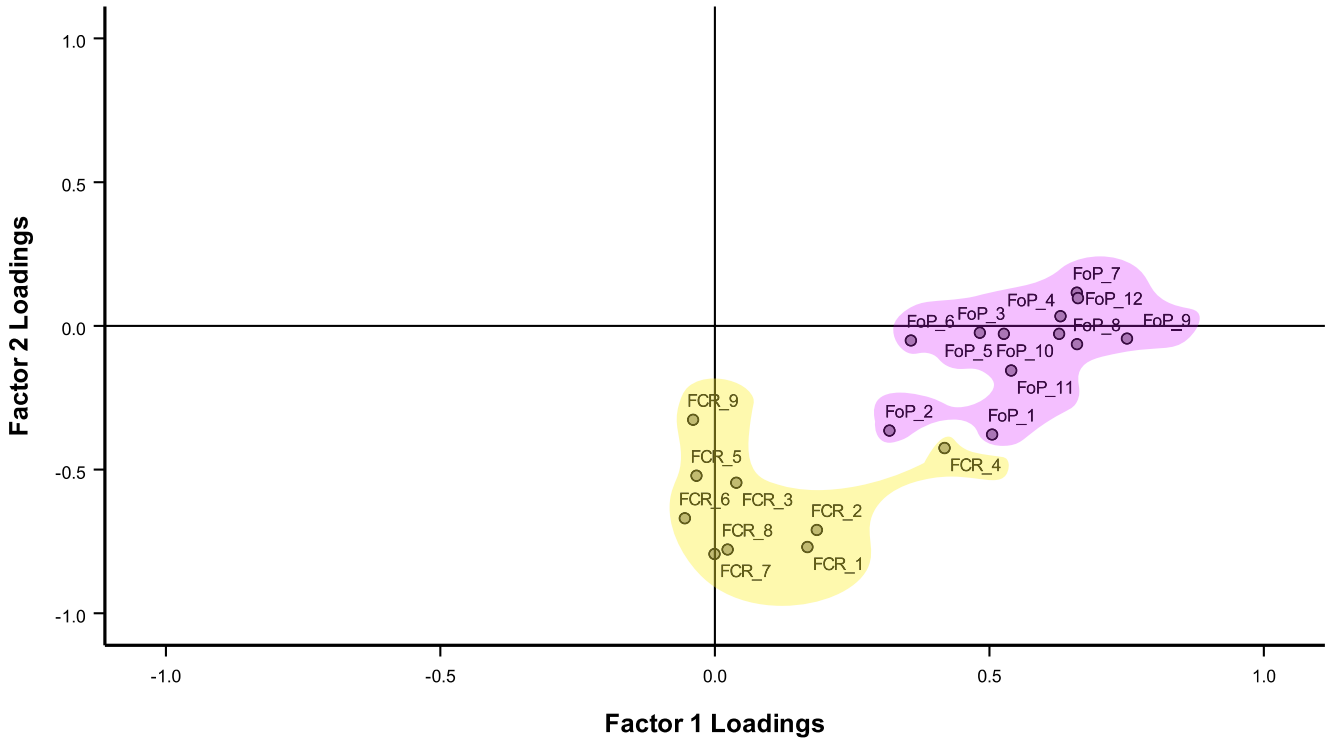

FIGURE 1 Visual Plot of Factor Loadings in Rotated Factor Space. *Note*. The yellow shading highlights FCR-I severity subscale items, whilst the purple shading highlights FoP-Q-SF items. Each item is numbered according to its order in its respective questionnaire. FoP_1, FoP_2, and FCR_4 were cross-loading items

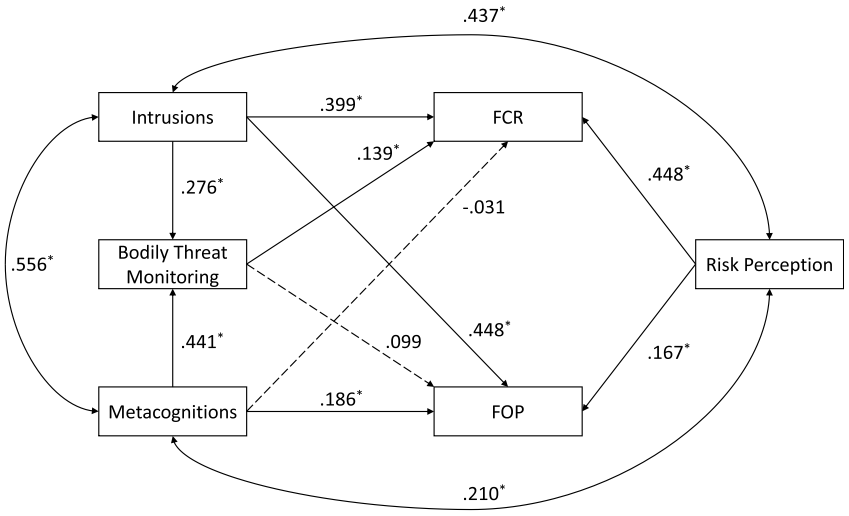

FIGURE 2 Combined model predicting FCR and FOP in all participants. *Note*. Straight paths represent standardised regression weights (β). Curved paths represent correlations. $^{*}p \leq 0{\cdot}01$. Dashed paths are non-significant ($p > 0.05$). $N = 278$

worries about recurrence, a discrete diagnostic event, they may focus on somatic sensations and other information, such as perceived risk, rather than underlying concerns. Consequently, this may avoid mental imagery and anxiety associated with the consequences of recurrence, namely progression of their disease leading to death. If FCR represents cognitive avoidance of FOP, then it would be expected that only FCR is predicted by worry about present somatic sensations, and that risk perception would be more closely related to FCR, and the concerns underlying FOP may be more existential. This could also account for the correlation between FCR and FOP, and the finding that both fears tend to be strongest in people with active disease (see supplementary materials).

3.1 | Clinical implications

These results have important clinical implications. The most comprehensive meta-analysis of psychological interventions for FCR included studies that used either FCR or FOP as an outcome, had only 3 studies that focused on FOP. The results of that meta-analysis

found that contemporary forms of cognitive behavioural therapy (CBT; e.g. acceptance commitment therapy, mindfulness) led to greater reductions in FCR than traditional CBT.[17] However, two of the three studies that assessed FOP were included in the traditional CBT group ($k = 9$). In contrast, all of the contemporary CBT trials measured FCR. Therefore, it is possible that the smaller effects observed for CBT were due to the inclusion of trials for FOP.

The major difference between contemporary and traditional CBT is that traditional CBT includes strategies that attempt to challenge people's beliefs, such as the perceived risk of recurrence. Our results demonstrate that the perceived risk of recurrence is more strongly associated with FCR than FOP. Therefore, it is likely that challenging perceived risk of recurrence would be less effective for FOP than FCR. It is possible that the conflation of FOP and FCR may provide suboptimal recommendations for clinical practice by drawing conclusions about one construct which do not apply to the other. While this remains speculative, it is essential that future studies distinguish between FOP and FCR, since our research clearly shows that they are not the same construct, nor are they associated with the same psychological variables. Therefore, it would not be surprising if different psychological interventions were optimal for each. The development of such optimised interventions will be critical in addressing the significant impact of these fears on those impacted by cancer.

3.2 | Study limitations

Despite careful consideration of the methodology, the present study must be qualified by some limitations. Firstly, we only included two types of cancer that predominantly affect women: ovarian and breast cancer. Therefore, whether these results generalise to men or those impacted by other cancers is unclear. Secondly, we tested a simplified version of Fardell et al.'s cognitive processing model.[13] It is unclear whether other constructs that have been theorised to contribute to FCR and/or FOP are associated with either or both constructs (e.g. interpretation biases[14]; death anxiety).[15] Future research is needed to test these different constructs and their relevance to FCR and FOP. Lastly, the FCR-I instructs participants that items about cancer recurrence refer to 'the possibility that the cancer could return or progress'.[5] These instructions were maintained to ensure our findings were relevant to the existing literature. Consequently, our results may reflect the different aspects of FCR and FOP that are measured by the FCR-I severity subscale and FoP-Q-SF. Yet if this were the case, since both measures are the most popular measures of FCR and FOP, and are used interchangeably, our results would still demonstrate an important distinction between what these questionnaires measure.

3.3 | Conclusions

The present study is the first to demonstrate that fear of the cancer returning or progressing are not synonymous. This study shows that the conflation of FCR and FOP is not warranted. This novel exploration of construct equivalence has demonstrated that whilst FCR and FOP are related, they are clearly distinct constructs, which contradicts the predominant understanding of FCR. The fact that FCR and FOP are different constructs is far from trivial. While some predictors common to FCR and FOP were identified, namely metacognitions, intrusions and, to a lesser extent, perceived risk of recurrence, other differences emerged. The propensity to monitor one's body for threat by checking and reassurance seeking was uniquely associated with FCR and not FOP. Moreover, bodily threat monitoring was a strong predictor of FCR. If theoretical models differ, it is likely that interventions based on those theories will also be differentially effective for FCR and FOP. Therefore, future research needs to separate these constructs, and more research specifically for FOP is needed to ensure that psycho-oncology services can provide optimally effective treatments for survivors with FCR and/or FOP.

ACKNOWLEDGEMENTS

Daelin Coutts-Bain, Louise Sharpe and Daniel Costa developed the concept for this study. Daelin Coutts-Bain and Poorva Pradhan collected the data. Daelin Coutts-Bain, Louise Sharpe, and Daniel Costa analysed the data. Daelin Coutts-Bain, Louise Sharpe, Poorva Pradhan, Hayley Russell, Lauren C. Heathcote, and Daniel Costa contributed to the interpretation of the data. Daelin Coutts-Bain wrote the first draft of the manuscript and Louise Sharpe, Poorva Pradhan, Hayley Russell, Lauren C. Heathcote, and Daniel Costa made critical revisions. Daelin Coutts-Bain, Louise Sharpe, Poorva Pradhan, Hayley Russell, Lauren C. Heathcote, and Daniel Costa have approved the final version of the manuscript.

Open access publishing facilitated by The University of Sydney, as part of the Wiley - The University of Sydney agreement via the Council of Australian University Librarians.

CONFLICT OF INTEREST

The authors have no conflicts of interest to report.

DATA AVAILABILITY STATEMENT

Individual, but deidentified participant data and a data dictionary will be made available from publication upon request to researchers who aim to use the data in secondary analyses.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Coutts-Bain D, Sharpe L, Pradhan P, Russell H, Heathcote LC, Costa D. Are fear of cancer recurrence and fear of progression equivalent constructs? *Psychooncology*. 2022;31(8):1381-1389. https://doi.org/10.1002/pon.5944

PAIN Publish Ahead of Print
DOI: 10.1097/j.pain.0000000000002784

A double-blind phase II randomized controlled trial of an online Cognitive Bias Modification for Interpretation program with and without psychoeducation for people with chronic pain

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Keywords: chronic pain, cognitive bias, randomized controlled trial, cognitive bias modification, interpretation, threat appraisal

Introduction

Most models of chronic pain recognize the pivotal role of interpretation biases in the development and maintenance of chronic pain[19,20,41,48,51-53]. Interpretations of pain as threatening drive preferential attending to ambiguous or painful sensations, fear of movement and (re)injury and prioritization of pain reduction over other life goals. This vicious cycle exacerbates pain and disability. Evidence confirms people with chronic pain[45] and chronic headache[40] have biases towards pain-related interpretations compared to controls.

Cognitive Bias Modification for interpretation (CBM-I) is an intervention that targets implicit interpretation biases[36]. Participants resolve ambiguous stimuli (e.g. sentences, pictures) in line with their training condition. Therapeutic use trains participants to interpret stimuli in a benign rather than disorder-salient manner (e.g. threatening in anxiety). CBM-I is efficacious in the management of anxiety according to a number of meta-analyses[11,12,22,24,31,38].

A systematic review of meta-analyses revealed that while efficacious for anxiety symptoms overall, CBM-I was not efficacious when delivered remotely[31]. Further, CBM-I is associated with only small effects for anxiety compared to placebo[22]. Therefore, CBM-I's potential relies on the fact that it could be administered remotely and, as a result, be highly scalable. If online CBM-I was efficacious for chronic pain, it could prove useful for combatting chronic pain.

Studies reveal that only 25–45% of participants correctly guess their assignment to CBM-I vs placebo[3,18,43]. If treatments lack face validity, people may not adhere to or concentrate on the training and as a result the efficacy of CBM-I could be compromised. Given that the task is identical in the laboratory and remotely, there is no reason if people adhere to the program that it should be less effective remotely. Therefore we proposed that explaining the rationale would increase plausibility and face validity which we expected to increase expectancy. In turn we expected psychoeducation to improve adherence and efficacy. Only one study provided psychoeducation with CBM-I. 75% of participants correctly identified receipt of CBM-I[4]. Results showed that credibility and expectancy ratings of CBM-I were associated with reductions in social anxiety.

In pain, only two studies have explored CBM-I, both face-to-face. Findings of both studies support a potential role for CBM-I. The first study[32] used healthy participants and found that training benign interpretations reduced behavioural avoidance of an acute experimental pain task compared to training pain-related interpretations. Furthermore, induced interpretation bias mediated the relationship between training (CBM-I pain vs CBM-I benign) and avoidance. The second study[1] used a chronic pain sample and found CBM-I changed negative emotional responses to pain. The authors did not measure pain-related symptoms. Consequently, no studies have assessed the therapeutic benefit of CBM-I in reducing pain-specific symptoms in patients with chronic pain.

We hypothesized that CBM-I would result in greater reductions in the primary outcomes of pain intensity and pain interference compared to placebo. We also expected similar benefits in secondary outcomes, including fear of (re)injury, catastrophizing, anxiety, depression and stress. Finally, we predicted that the benefits of training would be greater for those who received psychoeducation.

Methods

Design

This was a randomized, double-blind, placebo-controlled trial. There were two experimental manipulations, training condition (CBM-I or placebo) and psychoeducation (psychoeducation [+PE] vs no psychoeducation [-PE]), which resulted in four training conditions (CBM-I +PE, CBM-I -PE, placebo +PE, placebo -PE).

Participants

Two hundred and eighty-eight people with chronic pain were recruited for this study via social media, advertisements, and a participant recruitment company (TrialFacts) from October 2019 to October 2020. A $5 donation was made for all participants who completed and who were recruited through advertisements to their nominated patient advocacy group (e.g. Arthritis & Osteoporosis WA, Australian Pain Management Association, Chronic Pain Australia, Musculoskeletal Australia, Pain Australia). Eligibility was assessed based on the following inclusion criteria: 1) aged over 18 years, 2) pain present on more days than not over the past 3 months or longer, and 3) access to the internet over the 1-month study period. Participants self-selected and were advised they could initiate their participation at a time that suited them.

Procedure

The study was approved by the University of Sydney Human Research Ethics Committee and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12618001374257). All participants were told that the aim of the study was to assess a novel intervention for chronic pain. All the questionnaires and training components were delivered via an external survey host, Qualtrics. Participants were randomized using simple randomization which was allocated automatically using a computer algorithm in Qualtrics. Participants remained blind to the training group allocation until the end of the study. Researchers were also blind to participant allocation as all training and follow-up components were automated. For each participant the study duration was 28 days and comprised 4 stages: pre-training, training, post-training and

follow-up (See Figure 1). The maximum cumulative estimated time across the 4 stages for participants was 2.5 hours, of which 1 hour was the 4 x 15 minute training sessions.

FIGURE 1 NEAR HERE

Pre-Training

Participants accessed the participant information statement and their unique link to commence the study via email, after their eligibility had been established. They could therefore start the study at any time that was suitable to them. After providing consent, participants completed the baseline questionnaires (see below: BPI, DASS-21, PCS, TAMPA, ACS) and were presented with the generic information about CBM-I. Following this, participants were randomized, using a simple 1:1 randomization schedule, to receive either the psychoeducation or no psychoeducation condition. Those who were allocated to the psychoeducation condition watched the 5-minute video and then completed the expectancy questionnaire. Those in the no psychoeducation condition were directed immediately to the expectancy questionnaire. This stage took approximately 25 minutes for those randomized to the psychoeducation condition.

Training

Immediately following completion of the pre-training, participants were re-randomized using a simple 1:1 randomization schedule to one of two training conditions (CBM-I or placebo) and were directed to commence the first training session, which took approximately 10-15 minutes. For those who were also randomized to the psychoeducation condition, they saw the psychoeducation video before the first training, as described in the pre-training section above.

Three days after completion of the initial training session (day 4), participants were sent a link via email to access training session 2.

All participants were asked to complete the BPI prior to commencing the training. Those in the psychoeducation condition watched the second video prior to commencing the training, whereas those in the no psychoeducation group immediately proceeded to training after completing the BPI. Each of the four training sessions were identical. Participants were asked to complete the training within 2 days. This training session was not mandatory and whether or not the participants completed training 2, they were still sent links for the remaining training sessions.

Training session 3 was sent to participants on day 7 (three days after training session 2). As for training session 2, participants were emailed a link to access training session 3, and completed the BPI prior to commencing the training. Participants were asked to complete the training within 2 days and the session was not compulsory.

One week after training session 3 (day 14), participants were emailed a link to access the final training session. Immediately after the training session, the follow-up measures were presented. Hence, participants who completed per protocol completed 4 training sessions over 14 days but unless participants dropped out, they were required to complete a minimum of 2 sessions.

Post-training

As explained above, participants were emailed a link to complete the final training session and post-treatment questionnaires (BPI, DASS-21, PCS, TAMPA). After the questionnaires,

participants were asked to complete the recognition and homograph response tasks to assess their interpretation biases. Both the recognition and homograph tasks were only presented once (i.e. post training) as their validity relies on the novelty of stimuli for ambiguity, and as such is vulnerable to training effects[29]. Participants were then asked to nominate which training condition they thought they were assigned to, to assess for the success of blinding. Completion of the final training session and post-training questionnaires took approximately 45 minutes.

Follow-up

Exactly 2 weeks after post-training (day 28), participants were emailed the final link for the study. They were asked to complete the same questionnaires (BPI, DASS-21, PCS, TAMPA), which took approximately 10-15 minutes. Participants were then directed to the debrief information, which advised them of their training allocation.

Self-report measures

Brief Pain Inventory (BPI)

The primary outcome measure for the study was the BPI[10]. The BPI is a self-report measure with two subscales: pain intensity (4 items) and pain interference with daily living (7 items). An 11-point Likert scale is used for each question, with 0 indicating no pain intensity or interference and 10 indicating the worst pain imaginable and complete interference. In the current study, both the intensity ($\alpha = 0.86$) and interference ($\alpha = 0.90$) subscales were found to have good internal consistency.

TAMPA Scale of Kinesiophobia

The TAMPA scale aims to assess fear of movement/ (re) injury via 17 self-report items[39]. A 4-point Likert scale is used for each question, with a rating of 1 indicating strong disagreement and 4 indicating strong agreement. The TAMPA showed acceptable internal consistency in the current study ($\alpha = 0.70$).

Pain Catastrophizing Scale (PCS)

The PCS is used to measure pain catastrophizing, which can be thought of as negative attitudes, interpretations, and distress related to the experience of pain[48]. A 5-point Likert scale is used to record responses, with ratings from (0) not at all to (4) all the time. The PCS can be interpreted by its 3 subscales of ruminating, helplessness and magnification, or as a total score. The total score was selected for this study, and internal consistency was strong ($\alpha = 0.94$)

Depression Anxiety Stress Scale -21 (DASS-21)

The DASS-21[35] is a 21 item scale that measures self-reported negative emotional symptoms of depression, anxiety and stress. Participants are asked to rate how much (0 - did not apply to me at all, to 3 – applied to me very much, most of the time) each statement relates to their experience over the past week on a 4-point Likert scale. In the current study, all three subscales showed good internal consistency (depression: $\alpha = 0.92$, anxiety: $\alpha = 0.77$, stress: $\alpha = 0.89$).

Attentional Control Scale (ACS)

The Attentional Control Scale[16] is a 20-item self-report measure that consists of 2 subscales: attentional focusing and attentional shifting. Each item is scored on a 4-point Likert scale

ranging from 1 (almost never) to 4 (always). The total score was used in this study, with acceptable internal consistency ($\alpha = 0.67$). This measure was used at baseline only.

Intervention

Participants in all conditions had access to a total of 4 training sessions during their participation, with 2 training sessions (session 1 and session 4) being mandatory for completers to allow for pre-post comparisons. Each training session was identical in content within groups. There is not good evidence on which to base decisions about the appropriate dosage and spacing for CBM studies. In Cristea and colleagues' meta-analysis[11], they identified 49 studies and in 21 of those studies, the treatment dose was a single session. The range was between 1 and 15 sessions and therefore 4 sessions over two weeks seemed appropriate, as this was close to the median of that distribution. Further, some meta-analyses had suggested that longer training sessions are associated with fatigue, and in our own prior studies, we have found 12-15 minutes to be optimal (see [31,32]).

Cognitive Bias Modification for Interpretation (CBM-I)

The Ambiguous Scenarios paradigm[32] was used as the active CBM-I intervention. The interpretation bias literature in the area of pain is limited, though the most recent meta-analysis and systematic review[45] recommended the Ambiguous Scenarios Task to measure interpretation biases in people with chronic pain. This task is used commonly in the anxiety literature with robust results and was adapted in an earlier study from our laboratory[32] for use in a pain context.

Pain/illness related word stimuli were adapted from an earlier pain study[50] that piloted the accessibility of the stimuli and then employed a lexical decision task to measure interpretation bias. It has been shown participants' ability to imagine themselves in the scenarios influences positively training potency[30]. In our previous study, 80% of participants were able to easily imagine themselves in the scenarios described.

Training conditions presented participants with 30 ambiguous scenarios between 1 – 2 lines in length which end with a word fragment that the participant is required to solve. One sentence is "You find that your eyes are sore and swollen. They are so puffy you can barely open them. This is because you have been cr_i_g". Participants were instructed to imagine they were the character being described and to complete the final word fragment based on their understanding of the paragraph. The meaning of the paragraph remained ambiguous until solution of the word fragment, where it was always revealed to be a benign, rather than pain or health-related outcome. Following each scenario, the participants were asked to answer a question relating to the previous scenario that gave a benign or pain-related interpretation. Participants were given feedback, such that benign interpretations were correct and pain-related interpretations were incorrect. Scenarios were presented in a single block in a randomized order for each participant. A full list of scenarios is available in supplementary materials. (see Supplementary materials).

Placebo Training

The format and structure of the placebo training was identical to that described above for the CBM-I condition; however, the content was different. The scenarios in the placebo condition

were borrowed from the original Ambiguous Scenarios Task in the anxiety literature[37]. Specifically, we used the filler scenarios that did not require any emotional interpretation, nor any resolution of ambiguity. See supplementary materials for an example.

Psychoeducation Manipulation

We wanted to assess whether providing a rationale for why CBM-I should be effective and how it worked would enhance the efficacy of a remotely delivered paradigm. We thought that by explaining the theoretical rationale underlying the application of CBM-I, participants would develop a greater expectancy for efficacy, which would in turn drive adherence and improve outcomes. All participants, regardless of their subsequent randomization, viewed the following paragraph:

> *"The intervention you will receive over the course of this study is called Cognitive Bias Modification (CBM). Cognitive Bias Modification (CBM) has had promising results in previous research, reducing symptoms of depression and anxiety in both healthy and clinical populations. It has also been helpful in reducing fears about dying from cancer, therefore reducing anxiety in people with cancer. In a study from our laboratory, CBM significantly reduced the amount of time university students spent avoiding a painful task. However, CBM has not been trialled with people experiencing chronic pain. Due to the success of CBM in other populations, we believe CBM will be helpful for you. It is a novel, promising intervention, and you are the first ones to have the opportunity to try it."*

Psychoeducation

Then, participants who were randomized to the psychoeducation condition viewed a 5-minute animated video with a voice over, explaining the basic mechanisms and theory behind the development of chronic pain, and the central role of interpretation biases. This video was based on the fear-avoidance model of pain[51-53]. At the start of training session 2 (day 4), participants were asked if they watched a video in the initial session. If they replied no (and were in the psychoeducation group), they were automatically re-directed to watch the original 5-minute video again. If they responded affirmatively, they answered a multiple-choice question about the definition of interpretation bias. If they answered the question correctly, they were automatically directed to watch a condensed 1.5-minute video that reviewed the rationale for the CBM-I intervention. If they responded incorrectly, they were re-directed to watch the original 5-minute video. This was to ensure that participants understood the rationale for CBM-I.

No Psychoeducation

Participants allocated to the no psychoeducation condition did not view either of the psychoeducation videos and were directed immediately to start the training.

Manipulation Checks

Interpretation Bias (Recognition Task)

The recognition task was used to measure interpretation bias alongside the ambiguous scenarios task. The version in this study was adapted from the anxiety literature[37] to include pain and illness relevant information[32]. Interpretation bias was assessed by the extent to which new ambiguous situations are interpreted as pain/illness related or not.

The task comprised two sections. The first section individually presented 10 ambiguous situations that are identifiable by a title (e.g. “The Thriller Movie”) in a random order. Each situation contained a final word fragment that required solving, although in contrast to the ambiguous scenarios task, solution in this case did not disambiguate the meaning of the paragraph. After solution of each paragraph participants answered a (yes/no) comprehension question to check understanding. Examples of scenarios are provided in Table S2. A filler task then followed, which in this study was the DASS-21 questionnaire as part of the post-training questionnaire battery. In the second section of the task, participants are asked to rate 4 alternative endings to each ambiguous scenario for how similar they were to the original. For each scenario the identifying title is displayed, and participants rate each alternative ending on a 4-point Likert scale from (1; very different in meaning) to (4; very similar in meaning). Two of the alternative endings are intended to convey an interpretation bias for pain/illness related threat and the other two are intended to be neutral. The alternate endings are also characterized by their relevance to a pain/illness-related interpretation bias, such that targets are most relevant, and foils are considered more generally threatening outcomes.

Interpretation Bias (Homographic Response Task)

A second interpretation bias measure was included in order to assess near transfer effects to a different measure of interpretation bias. ‘Near-transfer’ refers to when the process of CBM-I is reflected on measures of interpretation bias, whereas ‘far transfer’ refers to when CBM-I influences clinical outcomes[28]. Typically the impact of CBM is assessed on the same or a similar

task to that used in the training. However, to demonstrate complete 'near transfer', training should impact other tasks that are purported to measure the same construct. As such, we adopted a second measure of interpretation bias: The homographic response task. The homographic response task[42] involved presentation of 14 ambiguous cues that can be interpreted in either a pain-related or neutral manner (e.g. *plaster* – broken bone, craft; *needle* – injection, sewing). Participants read each word cue individually and are asked to write down the first word that comes to mind. These responses are later categorized as pain-related or neutral. In the present study, more than 50% of responses were independently coded by two raters with good agreement (k = 0.81).

Psychoeducation (Credibility/Expectancy Questionnaire)

The 6-item credibility/expectancy questionnaire[17] is designed to measure the degree to which participants believe the treatment they will receive will help to improve their lifestyle and functioning. It assesses participants' expectations of the intervention and the credibility of the rationale provided to them. The questionnaire has 2 components: 1) what the participant thinks about treatment success (cognitively based credibility) and 2) what they feel about the likely success of the treatment (affectively based expectancy). An expectancy score was obtained by standardizing the first three item scores and then summing these scores, and a credibility score was obtained via the same method for the last three items.

Blinding

Following completion of the post-training questionnaires, participants were asked to select whether they thought they received the CBM-I intervention or placebo in order to assess for whether participants remained blind to their allocated condition.

Data Analysis

Based on effect sizes in previous pain-related studies of interpretation bias (Cohen's $d = 0.35$)[32], power analyses[21] were calculated. Based on G-power calculations, we needed a sample size of 110 participants per training group (CBM-I or placebo) (total n = 220) to find a more conservative effect with 80% power with alpha set at 0.05.

To determine whether baseline variables were equally distributed across groups, preliminary analyses involved a series of 2 (training) x 2 (psychoeducation) ANOVAs performed on all baseline questionnaire and demographic variables. Any significantly different variables would have been included as covariates in the main analyses to ensure the difference did not impact on results.

To assess whether the experimental manipulations successfully modified the targeted variables (i.e. interpretation bias and expectancy), manipulation checks were undertaken. In line with previous research[32], a bias index for the recognition task was determined by deducting the average no pain target score from the average pain target score for each participant. A positive score is therefore representative of a bias towards pain, and a negative score indicates a bias away from pain. For the homograph response task, a bias score was calculated by summing the number of pain/illness-related items endorsed. Similarly, higher scores indicate a bias towards pain and lower scores indicate a bias away. To measure the effect of CBM-I vs placebo on interpretation bias, a 2 (training) x 2 (psychoeducation) ANOVA was run on the recognition task

and homograph bias scores. Similarly, to determine whether psychoeducation increased participants' expectation for CBM-I efficacy, a 2 (training) x 2 (psychoeducation) ANOVA was run on the 2 expectancy subscales. In cases where an interaction effect was detected, post-hoc pairwise comparisons were run to determine group differences.

The primary analyses were interested in the degree to which CBM-I training impacted pain, and whether participants' expectancy of the training influenced the efficacy of CBM-I. Primary outcomes were pain intensity and pain interference. Linear mixed models were used to examine the effect of time (pre-treatment; post-treatment; follow-up), treatment group (CBM-I vs placebo) and psychoeducation (psychoeducation vs no psychoeducation), and their interactions. Linear mixed models were used to provide imputation of missing data in order to conduct intention to treat analyses. A first order auto-regression correlation structure was utilized, and random effects were employed for individual participants. Where the interaction of time x treatment group; time x psychoeducation or time x psychoeducation x treatment group interactions were significant, we conducted follow-up tests to identify the source of the observed differences. We also report effect sizes, using Cohen's *d*, with the following conventions: 0.2 = a small effect size; 0.5 = moderate or medium effect size; 0.8 = a large effect size.

A series of multiple hierarchical regression analyses were planned to establish predictors for pain outcomes on which a significant effect of CBM-I or an interaction with psychoeducation or time was observed. To assess whether interpretation bias played the hypothesized mediating role, we planned to use the PROCESS macro[25] in cases where interpretation bias significantly predicted a pain outcome in the regression model. We also investigated attentional control as a potential

moderator of treatment efficacy of CBM-I. The key aim of the moderator analysis was to assess if baseline levels of attention control moderated efficacy for those participants who completed at least two training sessions. Therefore, in order to test those assumptions, we were interested only in participants who completed the intervention for this analysis.

Results

Participant characteristics

Two-hundred and ninety-two participants consented to take part in the study, and 288 participants completed the baseline questionnaires and were randomized. Of these, 147 were randomized to CBM-I and 141 were randomized to placebo. Similarly, 147 participants were randomized to psychoeducation and 141 were randomized to no psychoeducation. Hence, the number of participants randomized to each group was as follows: CBM-I + PE (n = 73), CBM-I – PE (n = 74), placebo + PE (n = 74), placebo – PE (n = 67). See PRISMA Figure (Figure 1) for details.

Of the 288 participants who were randomized, 185 completed post-treatment assessments (64% completion rate) and 162 completed follow-up (56% completion rate). Of those allocated to CBM-I, 102 completed post-treatment assessments (44 in CBM-I +PE and 58 in CBM-I – PE) compared to 83 who completed in the placebo group (40 in placebo+PE and 43 in placebo-PE). Similarly, 85 of those allocated to CBM-I completed the follow-up (36 in CBM-I+PE and 49 in CBM-PE) and 77 completed placebo (38 in placebo+PE and 39 in placebo-PE).

Participants on average were 49.44 years (Standard Deviation [SD] = 13.7) and had experienced their pain for, on average, 5.6 (SD = 0.90) years. Eighty-two (28.5%) participants reported more than one pain condition. Participants reported a wide variety of different conditions, the most common chronic pain condition reported was back pain (n = 52, 18%) , 41 (14%) reported fibromyalgia, 41 reported arthritis (14%), 23 (7%) reported lower limb pain, 12 (4%) reported chronic regional pain syndrome and 11 (4%) reported neuropathic pain. All other sources of pain were reported by fewer than 10 participants.

Analyses revealed that there were no differences between completers and drop-outs for gender, age, pain duration, pain intensity or pain interference. However, those who did not complete reported higher symptoms of depression ($t = 3.024$, $p = 0.003$), anxiety ($t = 3.704$, $p < 0.0005$), stress ($t = 3.566$, $p < 0.0005$), fear of (re)injury ($t = 2.132$, $p = 0.034$) and catastrophizing ($t = 3.389$, $p = 0.001$). Importantly, participants who completed treatment were *more likely* to be allocated to CBM-I ($X^2 = 6.668$, $p = 0.036$) but, surprisingly, *less likely* to receive psychoeducation ($X^2 = 9.390$, $p = 0.009$). See Table S3 for means and standard deviations of those who completed the study versus those that did not.

Participant characteristics by psychoeducation and training groups are shown in Table 1. We conducted 2 (treatment group: CBM-I) x 2 (psychoeducation) ANOVAs to determine whether there were baseline differences between the groups. There were no significant group differences or interaction effects for any of the baseline variables, indicating randomization was successful. Therefore, the need to control for baseline characteristics in the main analysis did not arise.

TABLE 1 NEAR HERE

Manipulation checks

Interpretation bias

We conducted a 2 (treatment group) x 2 (psychoeducation) between-subjects ANOVA to examine differences in interpretation bias for those who completed the training. On the recognition task, participants who were allocated to CBM-I (M = -5.91, SD = 5.71) had fewer pain-related interpretation bias than those allocated to placebo (M = -3.27, SD = 5.35) following the intervention phase ($F_{(1,181)}$ = 11.074, p = 0.001). This indicates the intervention impacted interpretation biases as intended, with a small effect size (*d* = 0.48; 95% CI 0.18-0.77). There was no significant main effect of psychoeducation ($F_{(1,181)}$ = 1.287, p = 0.258), nor was the training x psychoeducation interaction effect significant ($F_{(1,181)}$ = 0.492, p = 0.484).

We included a second interpretation bias task, the ambiguous homographs task, to assess the near transfer effects of CBM-I. Unlike the recognition task, there were no significant main effects of training ($F_{(1,181)}$ = 0.570, p = 0.45), nor psychoeducation ($F_{(1,181)}$ = 0.001, p = 0.981) on the homograph bias score. The interaction effect between training and psychoeducation was also not significant ($F_{(1,181)}$ = .689, p = 0.408), indicating that the CBM-I training effects observed on the training task did not transfer to a novel task of interpretation bias.

Psychoeducation

There were no significant main effects of psychoeducation on expectancy ($F_{(1,278)}$ = 0.905, p = 0.342) nor of treatment group on expectancy ($F_{(1,278)}$ = 1.768, p = 0.185). The interaction

between treatment group and psychoeducation was also not significant ($F_{(1,278)}$ = 1.684, p = 0.195). This result indicates that the psychoeducation manipulation failed to influence expectancy.

"What is an interpretation bias?"

Of participants in the psychoeducation condition who were asked the definition of an interpretation bias before the second training, only 26.8% of participants answered correctly (25% chance of correct guesses). Results indicated training condition did not significantly impact accuracy (χ^2 (1, N = 28) = 0.23, p = 0.63), demonstrating a failure to learn the psychoeducation information in both CBM-I and placebo groups.

Success of Blinding

Most participants (73%) guessed that they were in the placebo group, this was 75% in the placebo group and 70% I the CBM-I group (X^2 = 0.436, p = 0.501). Hence, participants were more likely to guess that they received the placebo, and this did not differ between treatment groups, indicating that blinding was successful.

Primary outcome measures

Pain Intensity

All means and standard deviations for the outcome measures are reported in Table 2. We conducted linear mixed model regressions to investigate the effect of time (5 time-points) by treatment group, psychoeducation and the interaction of treatment group and psychoeducation on

pain intensity. Data revealed a significant effect of time by treatment group favouring those allocated to the CBM-I group ($F_{(1,1008)}$ =12.365, p < 0.0005), but no main effect of psychoeducation ($F_{(1,1008)}$ = 1.328, p = 0.250), nor was the training by psychoeducation interaction significant ($F_{(3,1008)}$ = 1.61 p = 0.202). Follow-up analyses demonstrated that the groups were not different at baseline or following the first two training sessions (All t's > 1.055, all ps < 0.295), however, pain intensity did differ between groups by training session 3 (t = 2.223, p= 0.027; Cohen's *d* = 0.35; 95% CI 0.05-0.64), at post-treatment (t = 2.024, p = 0.040; Cohen's *d* = 0.29; 95%CI 0.01-0.56) and one month later (t = 2.469, p = 0.015; Cohen's *d* = 0.39; 95% CI 0.09-0.68). This represented a significant reduction between pre-treatment pain levels and pain intensity at training session 3 (t = 2.296, p = 0.024), and between pre-treatment and follow-up (t = 2.456, p = 0.024), but not at post-treatment (p = 0.20). The placebo group also made significant gains between pre-treatment and training session 3 (t = 2.143, p= 0.035), but not other time points.

TABLE 2 NEAR HERE

Pain Interference

For pain interference, the linear mixed regression confirmed a significant interaction effect of time x treatment group favouring those allocated to CBM-I ($F_{(1,1000)}$ = 4.212, p = 0.04). In addition, a significant time x psychoeducation interaction effect was evident favouring those allocated to receive psychoeducation ($F_{(1.1000)}$ = 9.177, p = 0.003). However, the three-way

interaction between time x treatment x psychoeducation failed to reach significant ($F_{(1.1000)}$ = 3.112, p = 0.078).

We conducted post-hoc 2 x 2 ANOVAs for pain interference at each time point, which failed to confirm significant main effects between pain interference between the CBM-I group and the placebo group at any time point. There was a main effect between those who received psychoeducation and those who did not, favouring psychoeducation at post-treatment but not at other assessments (t = 4.205, p = 0.042). However, the effect size was very small (Cohen's *d* = 0.15). Post-hoc analyses demonstrated that t-tests showed that the CBM-I group improved significantly between pre-treatment and each training session (all ts > 3.466, all ps ≤ 0.001), as did the placebo group (all ts > 2.187, all ps ≤ 0.031).

Secondary outcome measures

TAMPA

We conducted a linear mixed model regression over three time-points (before and after treatment and follow-up). We found a significant effect of time by treatment ($F_{(1,572)}$ = 4.388, p = 0.037), indicating that those who received CBM-I experienced greater changes over time in fear of (re)injury than those who received placebo. There was no effect of time by psychoeducation ($F_{(1,572)}$ = 2.920, p = 0.088), nor an effect of time by treatment x psychoeducation ($F_{(1,572)}$ = 2.696, p = 0.10). Follow-up analyses, showed that there were no significant differences between the CBM-I group and the placebo group at any time point, (all ps < 0.115, Cohen's *d* = 0.25, 95% CI -0.04 - 0.54). However, for CBM-I group alone there was a significant reduction between baseline and post-treatment scores (t = 3.697, p < 0.0005) and baseline and follow-up (t

= 3.500, p = 0.001), indicating improvement in fear of (re)injury over treatment that were maintained at follow-up. No significant changes were observed in the placebo group (all ps > 0.113). See Table 3.

TABLE 3 NEAR HERE

Depression, Anxiety and Stress

For depression, our linear mixed model regression indicated that there were no significant effects of time by treatment ($F_{(1,631)}$ = 0.615, p = 0.433), no impact of time by psychoeducation ($F_{(2,631)}$ = 0.006, p = 0.936) and no three-way interaction effect ($F_{(1,625)}$ = 1.983, p = 0.160). Similar results were found for anxiety. That is, there was no significant time by treatment effect ($F_{(1,625)}$ = 1.835, p = 0.176), no effect of time by psychoeducation ($F_{(2,625)}$ = 1.692, p = 0.194) nor any three-way interaction effect ($F_{(1,625)}$ = 1.983, p = 0.160). For stress, there were no training by time ($F_{(1,629)}$ = 0.040, p = 0.842) or psychoeducation by time effects ($F_{(2,629)}$ = 0.846, p = 0.358). However, there was a significant three-way interaction of time by training by psychoeducation ($F_{(1,629)}$ = 6.390, p = 0.012). This finding indicated that there were improvements in stress but only for the group that received both psychoeducation and CBM-I. Post-hoc analyses confirmed that there were no significant differences between those who received psychoeducation or not in the placebo groups (all ts < 0.014, all ps > 0.559). However, amongst those who received CBM-I, those who received psychoeducation were significantly different from those who did not, with those who received psychoeducation having better outcomes (t = 2.705, p =0.008 at post-treatment; t = 2.003, p = 0.048). However, CBM-I groups did not differ from each other significantly, in either condition at any time (all ps > 0.07). See Table 4.

TABLE 4 NEAR HERE

Pain catastrophising

There were no effects of time by treatment found on pain catastrophising ($F_{(1,630)} = 0.456$, $p = 0.50$), no impact of time by psychoeducation ($F_{(2,630)} = 0.02$, $p = 0.97$; $F_{(2,64)} = 0.36$, $p = 0.70$) and no three-way interaction effect ($F_{(1,630)} = 0.002$, $p = 0.967$). See Table 5.

TABLE 5 NEAR HERE

Adverse Events

No participants reported adverse events in either arm (although we did not specifically collect information about adverse outcomes), although two participants did express dissatisfaction with the program via email. Both were in the CBM-I plus psychoeducation group.

Treatment adherence

There were no significant main effects of training ($F_{(1, 85)} = 2.43$, $p = 0.12$) or psychoeducation ($F_{(1, 85)} = 0.58$, $p = 0.45$) on treatment adherence. A significant interaction effect of training x psychoeducation was detected ($F_{(1, 85)} = 4.25$, $p = 0.04$). Follow-up analyses revealed that in the placebo group, those who received psychoeducation completed more training sessions relative to no psychoeducation ($F_{(1, 37)} = 4.29$, $p = 0.04$), however, for the CBM-I group there was no difference in adherence between those who received psychoeducation and those who did not ($F_{(1, 48)} = 0.84$, $p = 0.36$).

Correlations and mechanism of change

No significant correlations between any of the manipulation checks (recognition test, homographic response task, credibility and expectancy questionnaire) and the outcome variable difference scores (pre to post training) were found. As such, the planned regression and mediation analyses were not conducted.

A significant correlation was found between interpretation bias measured by the homographic response task and participant expectancy, such that less expectation in the training efficacy was associated with a greater interpretation bias towards pain ($r = -0.23$, $p = 0.04$). Reductions in pain interference were significantly associated with reductions in pain intensity ($r = 0.54$, $p < 0.001$), fear of movement ($r = 0.30$, $p = 0.007$) and pain catastrophising ($r = 0.40$, $p < 0.001$). Further, reductions in pain catastrophising were associated reduced fear of movement ($r = 0.38$, $p < 0.001$). Surprisingly, attentional control was unrelated to any outcomes (all $ps > 0.05$) See Table 3 for correlations.

Clinical Significance

The results described above confirm that CBM-I had statistically significant benefits in the two primary outcomes. However, the effect sizes were small and the fact that they differed significantly does not attest to the clinical significance of the outcomes. To address this point, we conducted post-hoc analyses in two ways to try to determine whether the results are clinically meaningful. Firstly, we calculate the proportion of participants at each time point who were allocated to CBM-I versus placebo that reported a moderate-severe level of pain, according to the BPI (i.e. BPI pain intensity ≥ 4). Secondly, we calculated the proportion of people in CBM-I

versus placebo at time 2 who had experienced a minimal clinically important difference in the BPI score. Although there is not a universal agreement about the minimally important difference, Wong et al[55] suggested that 0.5 SD was a reasonable cut-off and in this study the SD in different groups was ≈ 2, therefore we used a cut-off of a change score as ≥ 1 as indicating clinically meaningful deterioration or benefit.

Our results indicated that at baseline 18% of those in placebo and 17% of those in CBM-I scored < 4 on BPI. These proportions were largely unchanged in the placebo group (17% at post-treatment and 21% at follow-up). In the CBM-I group, 30% of the sample reported pain in the mild-moderate range (< 4) at post-treatment and this proportion was the same at follow-up. These results were supported by the findings examining the proportion of patients who experienced a minimal clinically important difference. That is, in the placebo group, approximately 20.5% of participants reliably deteriorated and the same proportion experienced a reliable benefit. In the CBM-I group, only 15% deteriorated and 30% benefitted over the course of the intervention period. Hence, overall, 5% of people who one may have expected to deteriorate in a clinically meaningful way did not, while 10% of those you would expect not to improve in a clinically meaningful way improved.

5.4 Discussion

The present study investigated the efficacy of online CBM-I vs placebo with and without psychoeducation for people with chronic pain. The CBM-I intervention successfully manipulated interpretations on a task similar to the training task, but not a near-transfer task. Expectancy ratings indicated that the psychoeducation manipulation was not effective. Participants answered a knowledge question no better than chance and those who received psychoeducation were more

likely to drop out. Nevertheless, CBM-I was efficacious on both primary outcomes, with small effects. People receiving CBM-I experienced greater decreases in pain intensity and interference than those who received placebo, and these appeared to lead to clinically meaningful outcomes for approximately 15-20% of people in the CBM-I. Those who received CBM-I were also less likely to drop out. For pain-related fear, CBM-I significantly reduced fear of movement relative to placebo. There were no other effects of CBM-I on secondary outcomes except that those in the CBM group who received psychoeducation improved significantly more on stress than those who did not receive psychoeducation.

Improvements over time in pain intensity and interference were demonstrated for the CBM-I group compared to placebo, irrespective of psychoeducation. There was a trend towards a three-way interaction for pain interference, but this was not in the direction that psychoeducation improved CBM-I, and so we can be confident that psychoeducation did not facilitate the efficacy of CBM-I. CBM-I was also effective at reducing fear of (re)injury relative to placebo, with the effect remaining at 2-week follow-up. It is not surprising that of the secondary outcomes, fear of (re)injury was impacted by CBM-I. The fear avoidance model[13,51-53], predicts a direct relationship between fear that pain signifies further harm and interference with daily activities. The relationship between fear of (re)injury and pain interference is robust[54] and these results are consistent with the importance placed on pain-related fear in theoretical models[13,50-52]. The reduction in fear of (re)injury is also consistent with prior CBM research that has found CBM-I most effective at reducing anxiety symptomatology[31]. It is perhaps more surprising that catastrophizing did not change as well, given its role in fear avoidance models[31]. However,

catastrophizing is also highly associated with depression, for which CBM has been found to be less effective[31].

Nevertheless, our findings provide some support for the causal role of interpretation biases in pain, demonstrating that modifying interpretation biases away from pain changes interpretations ***and*** reduces pain intensity, pain-related fear and pain interference. However, CBM-I changed interpretation bias only on a task similar to the training task, and not another interpretation bias task. Further, induced interpretation biases were uncorrelated with treatment-related changes. As such, we cannot confirm the proposed treatment mechanism.

Further, receiving psychoeducation did not increase expectancy. While that was unexpected, participants correctly answered the knowledge question no better than chance, and the majority of participants guessed that they received placebo. These data confirm that the psychoeducation manipulation was unsuccessful. Despite this, there was benefit in pain interference for those who received psychoeducation compared to those who did not, and in stress for those allocated to CBM-I and psychoeducation, compared to those who received CBM-I but no psychoeducation. One of the major barriers to the widespread adoption of CBM-I is its lack of face validity. In this study psychoeducation did not improve expectancy. Nearly 50% of participants in the present study failed to complete all assessments, although those who received CBM-I were more likely to complete than those allocated to placebo. Surprisingly, people that received the psychoeducation were actually more likely to drop-out. Therefore, researchers and clinicians need to develop other methods to better engage people with CBM-I. We did not involve people with lived experience in co-designing the intervention, and using a co-design approach could

lead to more engaging versions of CBM-I. In attention bias modification (ABM), researchers have tried to gamify CBM protocols[55] and these would be a useful future directions for CBM-I research.

Most previous CBM interventions in pain have manipulated attention bias. The results of the literature are mixed with some studies finding an beneficial effect (e.g. Carleton et al.[8]; Sharpe et al.[46]) and others failing to find a significant effect (e.g. Carleton et al.[7]; Heathcote et al[26]). However, even those studies that have found large clinical effects (Study 2, Sharpe et al[46]) failed to find that the ABM task modified attention biases. To be certain that changes in interpretation bias are the treatment mechanism, we need to show (1) the training modifies cognitive biases; (2) that bias is associated with outcomes; and (3) the induced bias mediates the impact of treatment. In this study, CBM-I modified interpretation biases on the recognition task but were not associated with outcomes and did not mediate treatment changes.

In our study, near-transfer was successful with the recognition task that closely mimicked the CBM-I training format but not a less similar task. Failure of CBM-I to generalize between different measures of interpretation bias is common[23,44]. One explanation is that CBM-I that requires imagining scenarios affects processes distinct from the process assessed by the homograph task, limiting transfer-appropriate processing[27,36]. It is apparent that both automatic and controlled cognitive processing are involved in CBM, though their roles are not well understood[29]. Exploration of the contexts producing the strongest transfer effects is an important future research question.

This was the first study to assess the efficacy of CBM-I on pain-specific outcomes in people with chronic pain in a double-blind RCT. One strength was the online delivery of CBM-I, which is an optimal format for any treatment that produces small effects but could be highly scalable. Indeed, even if clinically meaningful benefits were observed for only 15% of those who used it, this could make an enormous contribution to improving pain outcomes as part of a stepped care approach[47]. Methodological decisions about the optimal format for CBM-I were made with reference to a systematic review[31]. We included instructions to imagine scenarios, used a multi-session format, asked participants to solve word fragments to increase engagement and provided feedback. Another strength was the inclusion of a placebo with neutral resolutions rather than a negative control condition, which could worsen pain outcomes and might partially account for therapeutic benefit. Participants could not correctly identify their training allocation better than chance, indicating successful blinding and ensuring that placebo effects cannot account for the results.

However, there were limitations. Firstly, the benefits of CBM-I occurred in the context of improvements on some outcomes for all participants. In some disorders (e.g. PTSD), the placebo condition for ABM appears to have clear and replicable therapeutic impact [2, 15, 33] and it is possible that this may also be the case in pain[14]. Therefore, a no treatment control might be useful in future research. Retention rates were not optimal, although are broadly comparable with other multi-session CBM studies[6,18,34]. Moreover, the retention rate for CBM-I at post-treatment without psychoeducation was high (78%). Nevertheless, compared to those who completed the study, those who did not reported higher depression, anxiety, stress, fear of (re)injury and catastrophizing at baseline. The results also suggested that psychoeducation increased drop-out.

It is possible that, since 70% of people thought that they received the placebo, that those who received psychoeducation were more disappointed. However, this explanation is speculative. It is also important to note that this study assessed short-term outcomes, with a two-week treatment period and two-week follow-up. Longer term outcomes need to be assessed in future research, and as a result, this study might be best conceived as a proof of concept study. Finally, the participants in this study were recruited online. Levels of pain interference were roughly comparable with patients presenting at tertiary pain clinics, but their pain severity was slightly lower, as were their levels of psychopathology, which may have led to floor effects. In an oversight, we did not collect data on the ethnicity of participants and so we do not know how generalizable the current findings are.

In conclusion, compared to placebo, CBM-I resulted in fewer pain-related interpretation biases, and improved pain severity, pain interference and pain-related fear in people with chronic pain. These benefits were maintained over two weeks. The effects were small, but small effects are typical for psychological interventions[54] and medications[9] in the management of pain. Therefore, given that CBM-I ran automatically, it has the potential to be highly scalable. One in five people experience chronic pain, and access to intensive psychological interventions is a major problem[5]. There was little evidence that receiving psychoeducation changed participants' expectancy. Despite improving outcomes for pain interference and for stress amongst those who also received CBM-I, psychoeducation actually increased drop-out, although those who continued did complete more sessions. Nevertheless, these preliminary results suggest potential clinical utility of CBM-I for chronic pain.

Acknowledgements and Conflict of Interest

The completion of this study was supported, in part, by an Australian Research Council Grant to LS, BC and JT. We have no other conflicts of interest to declare. We thank the participants who gave their time to take part in this study.

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Figure 5.1 PRISMA flow diagram of participants through the study

Table 1 Participant characteristics by group

Psychoeducation	Psychoeducation		No Psychoeducation	
Training	CBM-I	Placebo	CBM-I	Placebo
Age	49.34 (14.96)	49.93 (13.92)	48.68 (13.30)	49.52 (13.38)
Sex	Male = 13	Male = 13	Male = 8	Male = 9
Years with pain	12.68 (9.02)	14.36 (11.97)	14.91 (11.53)	13.96 (13.57)
Pain intensity	5.54 (1.93)	5.61 (1.96)	5.19 (1.62)	5.57 (1.91)
Pain interference	6.17 (2.11)	6.32 (2.61)	6.51 (2.04)	6.54 (2.23)
Depression	9.23 (6.47)	9.09 (6.10)	9.62 (6.06)	7.87 (5.49)
Anxiety	6.36 (4.89)	6.76 (4.29)	6.49 (4.40)	6.93 (4.94)
Stress	9.82 (5.63)	10.23 (5.04)	10.31 (5.19)	9.27 (5.00)
PCS	24.88 (13.11)	25.34 (14.04)	25.41 (12.57)	25.21 (13.57)
TAMPA	40.88 (9.15)	40.66 (8.90)	41.50 (7.99)	43.97 (7.82)
Attentional Control	49.82 (8.91)	50.77 (9.92)	50.62 (10.32)	49.36 (8.81)
N	73	74	74	67

Standard deviations in parentheses. PCS: Pain Catastrophizing Scale; TAMPA: TAMPA Scale of Kinesiophobia; N: Number of participants. *Significant group differences, p<.05

Table 2 Pain intensity and pain interference scores

Psychoeducation	Psychoeducation		No Psychoeducation	
Training	CBM-I	Placebo	CBM-I	Placebo
Pre intensity	5.54 (1.93)	5.61 (1.96)	5.19 (1.62)	5.57 (1.91)
Post intensity	5.31 (1.90)	5.59 (2.21)	4.84 (1.85)	5.67 (1.92)
Follow-up intensity	4.78 (2.05)	5.38 (1.99)	4.91 (1.90)	5.82 (1.71)
Pre interference	6.17 (2.11)	6.32 (2.61)	6.51 (2.04)	6.54 (2.23)
Post interference	5.57 (2.25)	5.45 (2.49)	5.56 (2.27)	6.71 (2.18)
Follow-up interference	5.37 (2.22)	5.39 (2.58)	5.52 (2.45)	6.30 (2.39)

Table 3 TAMPA scores

	CBM-I	Placebo
Pre	41.19 (8.56)	42.23 (8.53)
Post	37.08 (12.28)	38.70 (13.90)
Follow-up	37.94 (9.42)	40.23 (8.99)

Table 4 DASS scores

Psychoeducation	Psychoeducation		No Psychoeducation	
Training	CBM-I	Placebo	CBM-I	Placebo
Pre depression	9.23 (6.47)	9.09 (6.10)	9.62 (6.06)	7.87 (5.49)
Post depression	7.55 (6.68)	7.93 (6.59)	8.71 (5.59)	7.47 (6.04)
Follow-up depression	6.67 (6.42)	7.74 (6.19)	7.63 (6.09)	7.76 (5.20)
Pre anxiety	6.36 (4.89)	6.76 (4.29)	6.49 (4.40)	6.93 (4.94)
Post anxiety	4.70 (4.61)	6.50 (5.80)	6.78 (5.16)	5.93 (5.18)
Follow-up anxiety	4.17 (4.29)	6.23 (5.20)	6.39 (4.67)	5.95 (4.20)
Pre Stress	9.82 (5.63)	10.23 (5.04)	10.31 (5.19)	9.27 (5.00)
Post stress	7.36 (4.82)	8.90 (6.25)	10.10 (5.24)	8.14 (5.58)
Follow-up stress	6.50 (4.90)	8.59 (5.51)	8.63 (4.81)	8.61 (4.55)

Table 5 PCS Scores

	CBM-I	Placebo
Pre	25.14 (12.80)	25.28 (13.78)
Post	22.83 (13.96)	22.70 (15.02)
Follow-up	19.16 (12.89)	21.60 (14.57)