Research Topics

Psychosocial rehabilitation for cancer patients

Edited by
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and Guihua Chen

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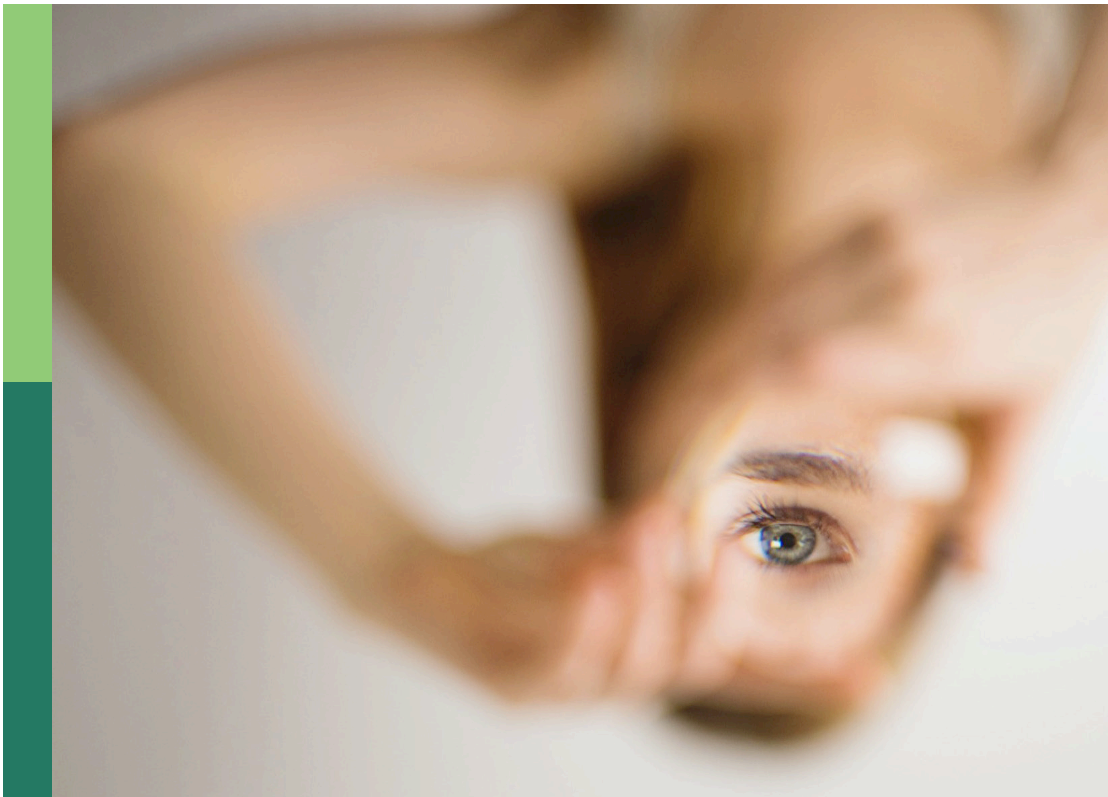

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Psychosocial rehabilitation for cancer patients

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Editorial: Psychosocial rehabilitation for cancer patients

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Editorial on the Research Topic
Psychosocial rehabilitation for cancer patients

Introduction

Cancer has become a major public health issue, as it leads to increased mortality and disability worldwide (Cheatley et al., 2021; Huang et al., 2023). In 2020, there were almost 19.3 million new cancer cases around the world (Sung et al., 2021); however, recent years have seen a rapid rise in the number of cured cancer patients (Miller et al., 2022), which leads to a concomitant upsurge in rehabilitation efforts (Weis, 2003). Rehabilitation is defined as "a process aimed at enabling persons with disabilities to reach and maintain their optimal functional capacity...", while cancer rehabilitation aims at enabling cancer patients to restore their optimal physical, sensory, intellectual, psychiatric, psychological, and/or social function levels (Mikkelsen et al., 2008). Furthermore, psychosocial rehabilitation of cancer patients focuses on how to restore the psychosocial function of cancer populations. It has been proposed that cancer psychosocial rehabilitation should be an integral part of the care plan and that it should enjoy a status equal to that of surgery, radiation, and chemotherapy (Cheville, 2005). The current Research Topic entitled "*Psychosocial rehabilitation for cancer patients*" examined various facets related to the psychosocial rehabilitation for cancer patients, including psychosocial issues of cancer patients, conceptualization of psychosocial issues, early detection of psychosocial issues, potential mechanisms of psychosocial issues, and effective intervention for psychosocial issues.

Psychosocial issues of cancer patients

Due to various reasons, such as cancer diagnosis and subsequent anticancer treatment, most cancer patients may suffer from various psychosocial issues (Lindert et al., 2021), such as psychological distress (Tian et al., 2021a) and social isolation (Liang et al.). For example, endocrine therapy is a standard treatment for hormone positive (HR+) breast cancer (BC) patients (Noordhoek et al., 2021), but the study by Zhao et al. revealed that side effects associated with this treatment significantly increased the risk of anxiety and depression. Psychosocial issues have been confirmed to be associated with increased risk of various adverse consequences, such as interruption of anticancer treatment, prolonged hospitalization stay, poorer quality of life (QoL), and increased mortality (Lindert et al., 2021). A preclinical study even showed that psychological stress can accelerate the growth of tumor cells (Zhang et al., 2020), and Zhang et al. found that psychological distress might increase the risk of incident lung cancer. Undoubtedly, psychosocial issues have become a major challenge in cancer setting given the associated increased risk of adverse consequences caused by these issues (Hyde et al., 2016).

Many efforts have been made to investigate how to effectively manage psychosocial issues of cancer patients (Chambers et al., 2015), as can be seen from the bibliographic analysis performed by Ahmad et al.. In their study, Ahmad et al. analyzed the research productivity and trends in psycho-oncology between 1980 and 2021, and confirmed a significant increase in publications over the past 5 years, with an annual growth rate of 13.9%. Meanwhile, they found that research hotspots mainly include interventions in cancer patients in developed countries, which further emphasizes the importance of paying more attention to psychosocial issues of cancer patients in low-income countries.

Conceptualization of psychosocial issues

Clear and precise conceptual systems is crucial for developing and enriching nursing knowledge (Tofthagen and Fagerstrøm, 2010), which also emphasize that conceptualizing psychosocial issues should be the first step in starting research on how to effectively manage various psychosocial issues in cancer settings. For example, social isolation is not an emerging psychosocial issue (Berkman and Syme, 1979); however, an oncology-specific multidimensional definition of social isolation is yet to be systematically clarified. Liang et al. therefore performed an evolutionary concept analysis to conceptualize social isolation in adult cancer care, and comprehensively documented the antecedents, attributes, and consequences of social isolation, which further provides a basis for developing multidimensional assessment tools and intervention protocols to alleviate social isolation in adults with cancer.

Early detection of psychosocial issues

Psychosocial issues can occur at any stage of cancer patients, and even throughout the entire disease course (Chambers et al., 2013). Early detection of psychosocial issues is the prerequisite of effective intervention; therefore, the development of appropriate tools is critically important (Sharpe et al., 2004; Kadan-Lottick et al., 2005). For example, there is currently no specific tool for lung cancer patients who may be at the high risk of suffering from psychological distress. Tian et al. (2021b, 2023) therefore developed an easy-to-use predictive algorithm to help identifying lung cancer patients at high risk of psychological distress in their subsequent study. Psychological flexibility (PF), an emerging concept in clinical psychology, refers to the ability to stay in contact with the present moment and pursue behavioral goals based on personal values and situational contexts (Cherry et al., 2021). Although many tools are available for measuring PF in non-cancer patients, the PF of cancer patients may differ from that of non-cancer patients, therefore proposing the urgent need of developing a specific instrument to this psychosocial issue. Ou et al. developed the Cancer-related Psychological Flexibility Questionnaire (CPFQ), which helps to reliably measure psychological flexibility in cancer patients and thus facilitate intervention for high-risk patients. However, we also need to realize that the levels of PF may differ between patients with different types of cancer, therefore more studies are still needed to clarify various open problems.

Potential mechanisms of psychosocial issues

We must recognize that elucidating the mechanisms of psychosocial issues is critically important for developing precise intervention protocols. Emotional self-care (Mesurado et al., 2018), psychological distress (Osmani et al., 2023), and fear of cancer recurrence (FCR) (Luigjes-Huizer et al., 2022) have been showed to be important psychological issues during anticancer treatment. However, due to the lack of elucidation of the underlying mechanisms of these issues, there is still controversy over how to accurately target these issues to improve anti-cancer effects. In this Research Topic, three studies did efforts to investigate the influencing factors of different psychosocial issues or elucidate the possible associations between different psychosocial variables related to a certain one of these three psychological issues. Sebastian et al. used qualitative method to identify eight influencing factors related to emotional self-care, and also explained how different factors influence emotional self-care practices. Tian, Tang et al. revealed that mindfulness may alleviate psychological distress of lung cancer patients by reducing the level of illness perception and perceived stress. Yu et al. reported that good social support can directly mitigate FCR among Chinese breast cancer survivors, while illness uncertainty can play a mediation role between social support and FCR. These three studies provide an evidence basis for developing intervention protocols, and also provide an optional methodological framework for elucidating the mechanisms of other psychosocial issues in cancer patients.

Effective intervention for psychosocial issues

Effective intervention is crucial for managing cancer patients who may experience or be experiencing psychosocial issues. There are two ways to choose intervention protocols, one is to conduct evidence-based evaluation of existing interventions, and another is to develop new intervention protocols. From the perspective of feasibility and economy, the first one should be preferentially considered. Crow et al. systematically evaluated the role of psychosocial interventions in reducing cortisol among BC patients, and reported that certain types of psychosocial interventions reduce cortisol (indicator of chronic stress) in BC patients. These findings also indicate that different types of psychosocial interventions may have different potential in addressing different psychosocial issues in different cancer patients. Therefore, Tian, Yi et al. separately evaluated the effectiveness of the mindfulness-based stress reduction (MBSR) program on psychological states and QoL in lung cancer patients, and suggested that the MBSR approach should be recommended as a part of the rehabilitation program for lung cancer patients. However, under certain special conditions, such as COVID-19 pandemic, the second way may be better for effectively managing psychosocial issues. Notably, it is difficult to deliver MBSR program in in-person approach during COVID-19 pandemic. With the popularization of the Internet in the healthcare field (Oh et al., 2005), mixed intervention models targeting the psychosocial issues of cancer patients have been widely recognized (Peng et al., 2007). Chang et al. developed an internet-delivered MBSR (iMBSR) program, and also evidenced that iMBSR improve mental health, body image, and self-efficacy in BC patients. Baussard et al. found that, although both hypnosis and cognitive behavioral therapy have been applied in cancer settings, they are still understudied on the symptom of fatigue in the colorectal cancer (CRC), and such programs have never been evaluated in Europe. Therefore, these authors developed hypnosis and cognitive behavioral therapy with online sessions, and designed a prospective, single-center, randomized interventional feasibility study to evaluate the role of this program in reducing fatigue in patients undergoing chemotherapy for a metastatic CRC. It is reasonable to believe that, after the formal study accomplishment, these authors will let us know the barriers/facilitators to the implementation of the program and the relevance of the program to the patients, and will generate hypotheses for a randomized control trial.

Conclusion

Undoubtedly, current Research Topic provides valuable insights into the psychosocial rehabilitation of cancer settings, but also reveal some knowledge gaps that require further investigation. First, with the advancement of artificial intelligence technology, conventional psychosocial issues screening tool should be transformed into intelligent models. In addition, the forms of intervention should also be updated, but we must emphasize the challenges of implementing eHealth on an individual, environmental and technical level (Schreiweis et al., 2019). Second, more studies are required to deeply elucidate the possible psychosocial mechanisms of the most common psychosocial issues to develop precise intervention protocols. Finally, although it's recommended to manage psychosocial issues of cancer patients through psychosocial interventions (Riba et al., 2019), the role of traditional Chinese medicine (TCM) in managing these issues cannot be ignored (Tan et al., 2022). However, to promote TCM intervention protocols in clinical practice, further efforts are needed to standardize TCM intervention protocol.

Author contributions

XT: Writing—original draft, Writing—review and editing. MJ-H: Conceptualization, Supervision, Writing—review and editing.

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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ORIGINAL RESEARCH
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Social Support and Fear of Cancer Recurrence Among Chinese Breast Cancer Survivors: The Mediation Role of Illness Uncertainty

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Objective: To examine the relations between social support, illness uncertainty (IU), and fear of cancer recurrence (FCR).

Methods: Using data from a convenience sample of 231 breast cancer survivors in China to perform structural equation modeling with bootstrapping estimation. Participants were recruited from a general hospital in Shenyang, China. Participants completed the Perceived Social Support Scale, Mishel Uncertainty in Illness Scale, and Fear of Cancer Recurrence Inventory- Shorter Form.

Results: The majority of breast cancer survivors have FCR (67.5%). FCR was significantly negatively associated with social support, and was significantly positively associated with IU (both $P < 0.01$). Moreover, IU was found to mediate the relationship between social support and FCR (standardized indirect effect = –0.18; bias-corrected 95% confidence interval: –0.255, –0.123).

Conclusion: The findings support the final model. Good social support can directly mitigate FCR, while illness uncertainty can play a mediation role between social support and FCR. Further studies should be conducted to explore effective interventions for social support and IU to ultimately mitigate FCR in cancer survivors.

Keywords: breast cancer, fear of cancer recurrence, illness uncertainty, social support, structural equation model

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INTRODUCTION

Cancer is a major public health problem worldwide. Among all types of cancer, breast cancer not only leads the number of women with cancer but also has surpassed lung cancer as the most common cancer. In 2020, the number of new cases of breast cancer in China exceeded 410,000, accounting for approximately 9.1% of all new cancer diagnoses in China and 19.9% of new cancer diagnoses in Chinese women. In other words, breast cancer is diagnosed in 1 out of every 5 newly diagnosed cancer cases in women (Sung et al., 2021). Fortunately, with increased public health awareness, early diagnosis through the mammogram, and improved treatment. The mortality rate for women with breast cancer today is down 42% compared to 1989, and the 5-year relative survival rate for women diagnosed with breast cancer is as high as 90%, resulting in a huge number of breast cancer survivors (Siegel et al., 2022). The psychological problems of breast cancer survivors cannot be ignored, and among them, fear of cancer recurrence (FCR) is the most commonly reported concern and the most frequently recognized unmet need.

Fear of cancer recurrence is defined as the "fear, worry, or concern about cancer returning or progressing (Lebel et al., 2016)." In a study of 240 breast cancer survivors in China, a total of 159 breast cancer survivors (76.81%) were found to have experienced high levels of FCR, characterized by lower functional and overall health than survivors with a low FCR (Peng et al., 2019). According to Schapira et al.'s (2022) study of breast cancer survivors' FCR trajectories confirmed that although some breast cancer survivors' FCR improves over time, approximately one-third of breast cancer survivors' FCR remains severe, even within 5 years of diagnosis. Cancer survivors experiencing FCR primarily present with hypervigilance to changes in physical symptoms and may lead to increased healthcare utilization, resulting in increased personal financial burden and waste of public healthcare resources (Vachon et al., 2021). In addition, FCR has been demonstrated in previous studies to be strongly associated with the development of negative emotions such as anxiety and depression, which without timely intervention may affect the psychological functioning of cancer survivors, resulting in reduced quality of life and even an increased risk of suicide (Zhang et al., 2021).

The mechanisms of FCR triggering and formation are not yet conclusive, and terror management theory (TMT) seems to provide an informed framework for the study of FCR (Simonelli et al., 2017). The core idea of TMT is that human beings have higher cognitive functions and are aware of the finiteness of their lives, thus the survival instinct and mortality consciousness create a unique existence dilemma for human beings, anxiety and fear of existence and death arise when they suffer from death-related stimulation. As a serious life-threatening disease, cancer has the potential to recur even after aggressive treatment. Therefore, based on TMT, we speculated that cancer survivors' heightened vigilance against cancer recurrence may awaken their sense of mortality eventually leading to FCR. High vigilance for cancer recurrence is mainly reflected in cancer survivors' over-examination, over-stress and over-attention to changes in physical symptoms, and certain physical symptoms such as pain and chest tightness are considered to be signs of cancer recurrence (Savard and Ivers, 2013). The reason why cancer survivors are overly concerned about physical symptoms may be that, unlike other diseases, the growth and development of cancer cells in the body is usually insidious and not easily detected and controlled, resulting in a strong sense of illness uncertainty (IU) among cancer survivors. IU is a common psychological reaction to the experience of cancer. It is defined as "the inability to determine the meaning of illness-related events" and accurately anticipate or predict health outcomes (Mishel, 1988; Zhang, 2017). However, few studies have been conducted on the relationship between IU and FCR in cancer survivors, which may lead to a lack of direction in FCR intervention programs. Therefore, based on the current state of research, we believe it is necessary to investigate the relationship between IU and FCR to clarify the interaction between each other.

In addition, psychological problems of cancer survivors are inextricably linked to social factors, social support plays an important role in quality of life and health outcomes after breast cancer diagnosis and treatment (Thompson et al., 2017). Previous studies have found a positive effect of social support on ameliorating FCR, and in Niu et al.'s (2019) study of 342 breast cancer patients, social support was found to be an independent predictor of FCR; Hong et al.'s (2020) study also highlighted that successful psychological adjustment of cancer patients receiving chemotherapy may be facilitated by improved social support. The mechanism of action by which social support affects FCR is unclear. Nevertheless, according to Mishel's (1988,1990) uncertainty in illness theory, among the antecedents of IU formation, social support, as an important component of structure providers, influences the patient's understanding of disease-related stimuli and plays a crucial role in the eventual generation of IU. Therefore, we hypothesized that social support may be mediating the impact on FCR through improvements in IU for cancer survivors.

In summary, based on the literature reviewed previously, two hypotheses were proposed: H1, social support is negatively correlated with FCR; H2, IU mediates the effect of social support on FCR. The hypothesized model is illustrated in **Figure 1**.

MATERIALS AND METHODS

Study Design and Participants

This was a descriptive cross-sectional study, which follows the STROBE guidelines. A convenience sample was recruited from a general hospital in Shenyang, China, between February and September 2021. Inclusion criteria were as follows: (1) survivors with a clinicopathological histological or cytological diagnosis breast cancer; (2) age $\geq$ 18 years; (3) good reading and communication skills in Chinese; (4) and volunteer for this study. We excluded patients who were diagnosed with other complications and those who were unable to complete the questionnaire due to psychological or cognitive impairment. Depending on the requirements of the structural equation model (SEM), a sample size of between 200 and 400 being appropriate (Hair et al., 1998). We distributed the survey questionnaire to 245 potential participants, ten survivors declined to participate due to

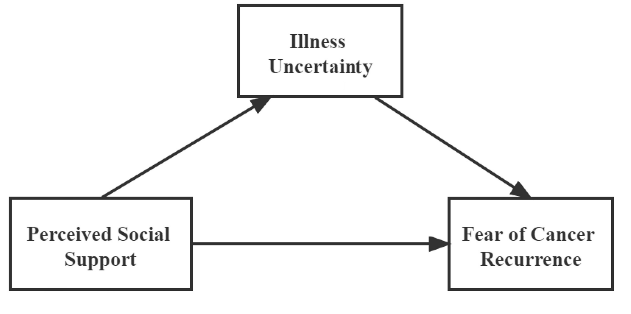

FIGURE 1 | The hypothesized model.

health issues or lack of interest, and four survivors were absent when the survey was conducted. Therefore, the final sample comprised 231 participants with an 94.3% overall response rate. The sample size met the requirements for SEM analysis.

Procedure

The present study uses a Chinese version of the questionnaire to collect information about participants. The questionnaire consisted of four main self-report sections: Sociodemographic Characteristics, Perceived Social Support Scale (PSSS), Mishel Uncertainty in Illness Scale (MUIS), and a shorter form of the Fear of Cancer Recurrence Inventory (FCRI-SF). The assessors used a uniform instruction guide to brief the participants on the purpose and significance of the study and assisted the participants who had difficulty reading the questionnaire. The assessors collected the completed questionnaire on the spot, and asked the participants to fill in any missing options. All participants were given a small gift as compensation for completing the questionnaire.

Ethics Approval

Ethical approval for this study was obtained from the Ethics Committee of Shengjing Hospital of China Medical University. In accordance with the Declaration of Helsinki, participants were informed of the purpose and procedures of the study before it began. They had the right to leave the study at any time and were not required to answer any questions. All participants were given written informed consent, which indicated that they fully understood the study procedures.

Measures

Sociodemographic Characteristics

A self-designed questionnaire was used to collect sociodemographic characteristics of patients including age, education, marital status, primary caregivers, cancer stages, and with or without breast cancer recurrence.

Perceived Social Support Scale

The social support was assessed using the Chinese version PSSS, which was developed by Zimet (Blumenthal et al., 1987) and modified by Jiang (Huang et al., 1996). It consists of 12 items, including three dimensions, namely, family support, friend support, and other support, each containing four items. Each item was scored on seven-point Likert scales (ranging from 1 to 7). The higher the score, the higher the level of social support as perceived by the individual. A total score between 12 and 36 is considered low support, 37–60 is moderate support, and 61–84 is high support. The Cronbach's α for the total scale was 0.88 (Huang et al., 1996). Cronbach's α in the current sample was 0.92.

Mishel Uncertainty in Illness Scale

The IU was assessed using the Chinese version MUIS, which was developed by Mishel (1997) and modified by Xu and Huang (1996). It consists of 25 items and includes two dimensions: ambiguity (15 items) and complexity (10 items). These items were scored on five-point Likert scales, ranging from strongly disagree to strongly agree. The scale scores range from 25 to 125 and can be divided into three levels, low level 25–58, medium level 59–91, and high level 92–125. Higher scores indicate higher levels of uncertainty about the patient's illness. The content validity index (CVI) was 0.92 and Cronbach's α was 0.87 (Xu and Huang, 1996). In the current sample, Cronbach's α was 0.86.

Fear of Cancer Recurrence Inventory-Shorter Form

The FCR was assessed using the Chinese version FCRI-SF, which was developed by Simard and Savard (2015) and modified by Su et al. (2018). It consists of nine items, which were scored on five-point Likert scales (ranging from 0 to 4). Cancer patients with a score greater than 13 may have FCR. The Cronbach's α was 0.90. Cronbach's α in the current sample was 0.79.

Statistical Analysis

Descriptive statistics were used to describe the sociodemographic characteristics of the participants and the main study variables (PSS, IU, and FCR). In addition, tests for normality and homogeneity of variance were performed. One-way ANOVAs and *t*-tests were used to determine the relationship between participant characteristics and the three variables, and Pearson correlations were used to test for unadjusted associations between variables. These data above were statistically analyzed using IBM SPSS Statistics 26.0 (IBM Corporation, United States). The hypothetical model was tested using SEM with IBM SPSS AMOS version 26.0 (IBM Corporation, United States). The maximum-likelihood estimation of the entire system in a hypothesized model, and enables the assessment of variables with the data (Jöreskog and Sörbom, 1982). Finally, bootstrap tests were used to measure the direct, indirect and total effects of the model (Hayes, 2009). Statistical significance was set at 0.05.

RESULTS

Sociodemographic and Psychosocial Characteristics

A total of 231 females with breast cancer participated in this study. The descriptive statistics for all study variables are shown in **Table 1**. The mean age of breast cancer patients was 52 years (standard deviation [SD] = 11), with a range of 31–82 years. The majority were married (80.5%), junior high school or less (36.4%), spouse of the patients (42.0%), breast cancer stage II (53.7%), no recurrence (83.1%), moderate social support (55.4%) and IU (78.8%), and FCR scores more than 13 (67.5%). The mean scores for PSSS, MUIS and FCRI-SF were 58.83 (SD = 10.94), 66.26 (SD = 10.95), and 14.19 (SD = 5.31).

Social Support, Illness Uncertainty, and Fear of Cancer Recurrence, According to Sample Characteristics

As shown in **Table 2**, survivors aged ≤ 35 years reported significantly higher FCRI-SF scores than those aged 36–59 years and ≥ 60 years ($F = 7.308$, $P < 0.01$). Regarding primary caregivers, survivors whose care was provided by an attendant reported lower PSSS scores and higher MUIS and FCRI-SF scores

TABLE 1 | Sociodemographic and psychosocial characteristics (n = 231).

	n	%	M	SD	Range
Age			52	11	31–82
Marital status					
Married	186	80.5			
Other	45	19.5			
Education					
Junior high school or less	84	36.4			
High school	74	32.0			
Bachelor and above	73	31.6			
Primary caregivers					
Spouse	97	42.0			
Parents	11	4.8			
Children	68	29.4			
Relatives and friends	36	15.6			
Attendant	19	8.2			
Cancer stages					
I	34	14.7			
II	124	53.7			
III	55	23.8			
IV	18	7.8			
Recurrence					
Yes	39	16.9			
No	192	83.1			
PSSS Total			58.83	10.94	35–84
Family support			20.61	4.27	10–28
Friend support			18.76	4.12	11–28
Other support			19.46	3.96	11–28
Low	2	0.9			
Moderate	128	55.4			
High	101	43.7			
MUIS Total			66.26	10.95	25–100
Ambiguity			40.77	7.53	15–73
Complexity			25.49	5.24	10–37
Low	48	20.8			
Moderate	182	78.8			
High	1	0.4			
FCRI-SF Total			14.19	5.31	3–32
≥13	156	67.5			
<13	75	32.5			

M, mean; SD, standard deviation; PSSS, Perceived Social Support Scale; MUIS, Mishel Uncertainty in Illness Scale; FCRI-SF, Fear of Cancer Recurrence Inventory-Shorter Form.

TABLE 2 | Social support, IU, and FCR, according to sociodemographic characteristics (n = 231).

Outcomes	PSSS	MUIS	FCRI-SF
Age			
≤35	59.45 ± 11.48	66.14 ± 14.78	17.86 ± 7.95[a]
36–59	58.11 ± 11.16	66.46 ± 9.69	13.45 ± 4.73
≥60	60.27 ± 10.21	65.86 ± 12.27	14.63 ± 4.95
F	0.897	0.068	7.308
P	0.409	0.935	0.001**
Education			
Junior high school or less	61.07 ± 8.69	64.93 ± 11.31	13.63 ± 5.33
High school	57.62 ± 12.44	65.91 ± 10.23	13.68 ± 4.49
Bachelor and above	57.47 ± 11.35	68.16 ± 11.10	15.36 ± 5.90
F	2.827	1.777	2.611
P	0.061	0.170	0.076
Marital status			
Married	58.95 ± 11.33	65.84 ± 11.19	14.08 ± 5.28
Other	58.31 ± 9.22	68.02 ± 9.77	14.64 ± 5.48
t	0.352	−1.202	−0.639
P	0.725	0.231	0.524
Primary caregivers			
Spouse	60.33 ± 11.57	65.66 ± 9.64	13.19 ± 5.55
Parents	61.27 ± 9.79	62.09 ± 14.41	14.27 ± 4.43
Children	60.22 ± 9.23	64.84 ± 12.73	14.35 ± 4.74
Relatives and friends	56.31 ± 11.16	68.28 ± 10.17	15.00 ± 5.09
Attendant	49.53 ± 8.64[b]	73.05 ± 6.16[a]	17.16 ± 5.86[a]
F	5.127	2.995	2.654
P	0.001**	0.020*	0.034*
Cancer stages			
I	61.12 ± 9.57	67.62 ± 12.96	13.12 ± 5.04
II	57.17 ± 11.72	67.51 ± 9.49	14.47 ± 5.27
III	60.65 ± 9.21	63.31 ± 12.05	13.60 ± 5.15
IV	60.33 ± 11.56	64.17 ± 11.62	16.11 ± 6.22
F	2.102	2.303	1.601
P	0.101	0.078	0.190
Recurrence			
Yes	57.41 ± 11.27	69.23 ± 10.08	16.62 ± 6.21
No	59.11 ± 10.88	65.66 ± 11.04	13.70 ± 4.98
t	-0.887	1.867	3.191
P	0.376	0.063	0.002**

$*P < 0.05$, $**P < 0.01$. [a]Post-hoc tests showed the score of this group was higher than the scores of the other groups. [b]Post-hoc tests showed the score of this group was lower than the scores of the other groups. IU, Illness Uncertainty; FCR, Fear of Cancer Recurrence; PSSS, Perceived Social Support Scale; MUIS, Mishel Uncertainty in Illness Scale; FCRI-SF, Fear of Cancer Recurrence Inventory-Shorter Form.

than compared with those whose care was provided by spouse, parents, children, relatives, and friends ($F = 5.127$, $P < 0.01$; $F = 2.995$, $P < 0.05$; $F = 2.654$, $P < 0.05$). Survivors with recurrent breast cancer reported higher FCRI-SF scores than those without recurrence ($t = 3.191$, $P < 0.01$).

The Correlations Between Social Support, Illness Uncertainty, and Fear of Cancer Recurrence

Pearson's correlation analysis (**Table 3**) showed that FCR (i.e., FCRI-SF total scores) were significantly and negatively correlated with social support (i.e., PSSS total and dimensions scores) ($r = -0.31$ to -0.38, $P < 0.01$). FCR were significantly and positively correlated with IU (i.e., MUIS total and dimensions scores) ($r = 0.40$ to 0.54, $P < 0.01$). Furthermore, social support was significantly and negatively associated with IU ($r = -0.21$ to -0.51, $P < 0.01$).

Common Method Variance

As with all self-reported data, there is the potential for common method variance (CMV) leading from multiple sources (Podsakoff et al., 2003). As a result, we performed a Harmon one-factor test was conducted on the 46 items in our hypothetical

TABLE 3 | Correlations (*r*) between social support, IU, and FCR (*n* = 231).

	1	2	3	4	5	6	7	8
1. PSSS Total	1							
2. Family Support	0.90**	1						
3. Friend Support	0.84**	0.59**	1					
4. Other Support	0.92**	0.79**	0.66**	1				
5. MUIS Total	−0.40**	−0.39**	−0.29**	−0.37**	1			
6. Ambiguity	−0.24**	−0.21**	−0.21**	−0.21**	0.90**	1		
7. Complexity	−0.48**	−0.51**	−0.29**	−0.46**	0.79**	0.45**	1	
8. FCRI-SF Total	−0.38**	−0.36**	−0.31**	−0.34**	0.54**	0.50**	0.40**	1

***P < 0.01. IU, Illness Uncertainty; FCR, Fear of Cancer Recurrence; PSSS, Perceived Social Support Scale; MUIS, Mishel Uncertainty in Illness Scale; FCRI-SF, Fear of Cancer Recurrence Inventory- Shorter Form.*

model (Podsakoff and Organ, 1986). According to Jukka (2009), the first factor tends to explain over half of the variance, indicating the presence of CMV. The results showed that 12 factors are present and the most covariance explained by one factor is 24.00 percent, indicating that CMV is not a likely contaminant of our results.

Test of the Model

We use a causal step strategy to investigate the first mediation condition with respect to hypothesis 1 (Baron and Kenny, 1986). As shown in **Table 3**, the correlation coefficients indicated that social support was significantly and negatively associated with FCR ($r = -0.38$, $P < 0.01$). Additionally, the results of the direct effect of social support on FCR (standardized direct effect = –0.38, $P < 0.001$, see **Figure 2**) was statistically significant. Hypotheses 1 was thus supported.

To test hypothesis 2, we measured the second condition of mediation. The correlation coefficients indicated that social support was significantly and negatively associated with IU ($r = -0.40$, $P < 0.01$), IU was significantly and positively associated with FCR ($r = 0.54$, $P < 0.01$). In addition, the results of the direct effects of social support on IU (standardized direct effect = –0.40, $P < 0.001$), and the direct effect of IU on FCR (standardized direct effect = 0.46, $P < 0.001$, see **Figure 3**), were all statistically significant. To investigate the indirect effects of the dependent variable through mediation, we conducted bias-corrected percentile bootstrapping and percentile bootstrapping with 5,000 bootstrap samples at 95% confidence interval (**Table 4**; MacKinnon, 2008). We calculated the confidence interval of the lower and upper bounds to test whether the indirect effects were significant (Wang et al., 2014). The result of the bootstrap test confirmed the existence of a significant mediating effect for IU between social support and FCR (standardized indirect effect = –0.18, $P < 0.01$). Therefore, hypothesis 2 was supported.

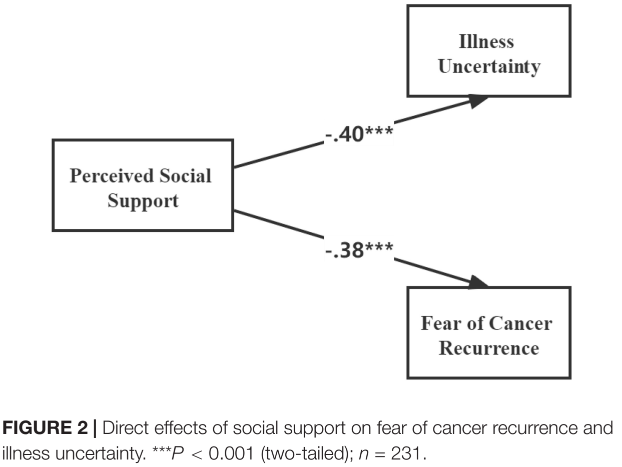

FIGURE 2 | Direct effects of social support on fear of cancer recurrence and illness uncertainty. ***$P < 0.001$ (two-tailed); $n = 231$.

DISCUSSION

The purpose of this study was to investigate the interactions between social support, IU, and FCR. The results of this study showed that there was a negative association between social support and IU and FCR, while a positive association was presented between IU and FCR. The findings further emphasize the importance of social support in promoting the development of psychological wellbeing in breast cancer survivors. Similar results have been found in previous studies (Taha et al., 2012; Hamama-Raz et al., 2021). Furthermore, to our knowledge, the present study is the first theoretically based and empirical study to examine whether IU mediates the negative relationship between social support and FCR.

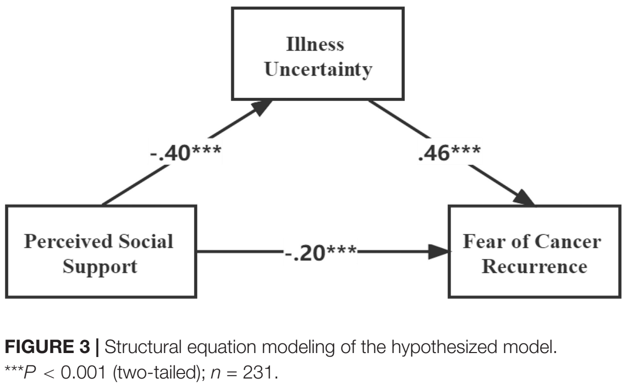

FIGURE 3 | Structural equation modeling of the hypothesized model. ***$P < 0.001$ (two-tailed); $n = 231$.

TABLE 4 | Standardized direct, indirect, and total effects of the hypothesized model.

	Point estimate	Product of coefficients		Bootstrapping				Two-tailed significance
				Bias-corrected 95% CI		Percentile 95% CI		
		SE	Z	Lower	Upper	Lower	Upper	
Direct effects								
SS → FCR	−0.200	0.057	−3.509	−0.309	−0.086	−0.311	−0.088	0.001**
Indirect effects								
SS → FCR	−0.181	0.033	−5.485	−0.255	−0.123	−0.251	−0.121	0.000***
Total effects								
SS → FCR	−0.381	0.048	−7.938	−0.473	−0.284	−0.475	−0.285	0.000***

*Estimating of 5,000 bootstrap sample, **P < 0.01, ***P < 0.001. SS, Social Support; FCR, Fear of Cancer Recurrence.*

Fear of cancer recurrence is recognized as the most common psychological problem among cancer survivors, and the FCR score of breast cancer survivors in this study was found to be 14.19 ± 5.31. According to the diagnostic threshold of FCRI-SF, 67.5% of breast cancer survivors in this study had FCR, and the occurrence of FCR is not optimistic. Although there is no consensus on the clinical cutoff value for FCR, current findings generally suggest that the incidence of FCR is gender-related and that women are more likely to develop FCR (Tauber et al., 2019; Borreani et al., 2020; Muldbücker et al., 2021). Breast cancer, as the most prevalent type of cancer in women, suggests that healthcare providers should increase screening for FCR in this group to achieve early identification, diagnosis, and intervention to avoid adverse outcomes due to FCR. The results of this study found that approximately close to 80% of breast cancer survivors had moderate to high levels of IU, suggesting that IU may be prevalent. Consistent results were also reported in a study of breast cancer survivors by Hagen et al. (2015). Breast cancer survivors may need to undergo one or more treatments including surgery, chemotherapy, radiation, endocrine therapy, and biologic therapy. Not only that, post-treatment survivors face complex rehabilitation and self-care. As a result, survivors who lack the medical background often appear overwhelmed and eventually develop IU. Finally, this study found that almost all breast cancer survivors perceived moderate to high levels of social support, which supports the previous study's conclusion (Sørensen et al., 2020). Social support can be classified according to its source as endogenous family social support and exogenous family social support. The emphasis on family is an important feature of Chinese culture, while family support is generally considered to be dominant within the social support system. The predominance of spouses and children as caregivers for the breast cancer survivors included in this study also provides some evidence of the unique position of family in the Chinese heart, and it may also be the reason for the overall high level of social support in the results.

When social support, IU and FCR were examined according to sociodemographic characteristics, the differences in partial PSSS, MUIS, and FCRI-SF were significant. The present study, survivors aged less than 35 years reported higher levels of FCR. Similarly, Lane et al. (2019) found that adolescent patients generally had higher levels of FCR than middle-aged and older patients. Younger survivors are usually at a critical stage of growth in life, with more work and family responsibilities, and may face more financial and social challenges and fear negative career and family consequences due to cancer recurrence, while older survivors have more experience and exposure, are more resilient to stress and have more positive emotional responses. As a result, younger survivors are likely to have higher FCR levels. In terms of primary caregivers, survivors who were cared for by attendant perceived lower levels of social support and higher levels of IU and FCR than survivors whose spouses, parents, children, relatives and friends provided care. This may be due to the influence of the employment relationship. Attendant only provide care for survivors and are less intimate with survivors, less emotionally invested in survivors and more concerned with their own interests than the survivors' families. However, kinship relationships are unchangeable and care from spouses, parents and children can give more support to survivors. In addition, breast cancer survivors who have experienced cancer recurrence have higher levels of FCR, which may be due to the length of time it takes to treat the cancer and the severe side effects of the treatment. The painful memory of the experience adds to the fears of cancer survivors who have experienced recurrence.

In line with our proposed hypothesis 1, this study found a negative direct effect between social support and FCR, suggesting that breast cancer survivors with higher levels of social support were less vulnerable to experiencing FCR. This result is generally consistent with the findings of a recently published evidence-based study (Zhang et al., 2021). According to the social support buffering model, social support functions as a buffer between the subjective experience of stress and illness (Cohen and Wills, 1985). Breast cancer survivors need to be constantly alert to the risk of cancer recurrence, and the prolonged state of high alertness inevitably generates severe psychological stress resulting in fear of recurrence. The timely intervention of social support can provide survivors with more problem-solving strategies and reduce the importance of the problem, thus reducing the adverse effects of stress such as anxiety, depression, and FCR. In addition to its contribution to the psychological wellbeing of cancer survivors, social support may also have a positive impact on patient survival. A Meta-analysis of 106 randomized controlled trials by Smith et al. (2021) found that psychosocial support fostered motivation to exercise and encouraged patients to complete treatment, and increased overall patient survival by 29%. Therefore, given the positive impact of social support on the physical and mental health of cancer survivors, it is necessary to implement some effective interventions to improve the level of social support for cancer survivors. However, it is worth noting that because each cancer survivor may have different personality traits, cultural environment, and nature of stressors, their needs for types of support may be different. For example, a qualitative study by Korotkin et al. (2019) found that more anxious cancer survivors were more likely to want companionship support, while younger cancer survivors were more likely to want home care support. This suggests that healthcare professionals should ideally individualize their social support interventions to meet the psychological needs of different cancer survivors in order to maximize the benefits of the intervention.

The results of the present study confirm our proposed second hypothesis that IU plays a partially mediating role in the negative effect of social support on FCR. This indicates that when breast cancer survivors are faced with a stressful disease event and inadequate social support, they first develop IU, and the stimulus of IU is perceived by cancer survivors as a threat of death that ultimately causes them to experience FCR. The results highlight the importance of IU in the development of FCR and validate the antecedent framework of Mishel's (1988) uncertainty in illness theory. Previous studies have also reported a negative association between social support and IU similar to the results of this study (Lee and Park, 2020). Cancer survivors' perceptions and interpretations of stressful disease events are often considered to be key factors in the occurrence of IU (Zhang, 2017). In contrast, social support can act as an intermediate link between stressful events and subjective appraisals (Cohen and Wills, 1985). Social support can enable cancer survivors to more accurately predict and understand their experiences, will underestimate the damaging nature of stressful scenarios, and reduce IU by improving subjective perceptions and self-coping skills and reducing evaluations of the severity of stressful illness events. It seems that the direction of social support for managing IU and FCR in cancer survivors could be in terms of increasing physician-patient communication and facilitating the exchange of disease-related information. Effective physician-patient communication has been shown to have a positive effect on reducing IU and FCR (Dawson et al., 2016). Hence, as cancer gradually becomes a chronic disease, healthcare professionals, by providing cancer survivors with disease-related information and teaching self-health management skills will help survivors to re-evaluate their disease status to a great extent, enabling them to gain motivation to accept and adhere to rehabilitation treatment, which promotes psychological adaptation to avoid IU and FCR.

Limitations

The present study has a number of limitations. First, this study was cross-sectional and although we used SEM to conduct a simultaneous testing of our proposed model in breast cancer survivors, the results still need to be treated with caution. It is suggested that future studies could address this issue by obtaining longitudinal data to strengthen the causal relationship between social support, IU, and FCR. Second, our data came from self-reports, which raises the possibility of CMV. However, as the variables examined in this study, namely, social support, IU, and FCR, reveal the psychological state of the individual, there is a sound theoretical basis for collecting these data from the survivors themselves. In addition, statistical analyses were conducted to reduce or prevent the potential impact of CMV. Finally, this study was a single-center study that used convenience sampling to recruit participants and therefore limited generalization due to potential selection bias. It is hoped that multi-center and random sample studies will emerge in the future.

CONCLUSION

This preliminary study supports the final model. Good social support can directly mitigate FCR, while illness uncertainty can play a mediation role between social support and FCR. Further studies should be conducted to explore effective interventions for social support and IU to ultimately mitigate FCR in cancer survivors.

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 Ethics Committee of Shengjing Hospital of China Medical University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JS and ZCY conceptualized the study, and contributed to final analysis and interpretation of the data. ZCY and JS undertook data collection and preliminary analysis assisted by DS. All authors developed the methodology and analytical plan, read, and approved the final manuscript.

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BRIEF RESEARCH REPORT
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Mindfulness Affects the Level of Psychological Distress in Patients With Lung Cancer *via* Illness Perception and Perceived Stress: A Cross-Sectional Survey Study

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Purpose: The aims of the study were first to investigate the association between illness perception and psychological distress and second to determine whether mindfulness affects psychological distress *via* illness perception and perceived stress in patients with lung cancer.

Methods: Among 300 patients with lung cancer who participated in this cross-sectional study, 295 patients made valid responses to distress thermometer (DT), the Five Facet Mindfulness Questionnaire (FFMQ), the Brief Illness Perception Questionnaire (B-IPQ), and the Perceived Stress Scale (PSS) between January and July 2021. The possible pathways of mindfulness affecting psychological distress were analyzed based on the structural equation modeling analysis.

Results: A total of 24.4% patients with lung cancer had DT > 4. Illness perception ($\beta = 0.17$, $p = 0.002$) and perceived stress ($\beta = 0.23$, $p < 0.001$) had a direct effect on psychological distress. Mindfulness had a direct effect on illness perception ($\beta = -0.16$, $p = 0.006$) and mindfulness indirectly influenced psychological distress ($\beta = -0.04$, $p = 0.009$) through affecting illness perception alone or simultaneously affecting both the illness perception and perceived stress in patients with lung cancer.

Conclusion: Lung cancer suffered from varying levels of psychological distress. Mindfulness may alleviate psychological distress by reducing the level of illness perception and perceived stress. We suggest developing a comprehensive factor model to clarify potential mechanisms of mindfulness on psychological distress due to the very low effect of mindfulness on psychological distress *via* illness perception and perceived stress.

Keywords: lung cancer, psychological distress, mindfulness, illness perception, perceived stress, structural equation model

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INTRODUCTION

According to the National Comprehensive Cancer Network (NCCN) guideline, psychological distress is a multifactorial and unpleasant emotional experience, involving changes in psychological, social, spiritual, and physical aspects (Riba et al., 2019). Psychological distress can be detected at any stage in patients with cancer and even remain throughout the cancer trajectory (Gao et al., 2010). Overall, studies reported a prevalence of 20–52% for psychological distress [distress thermometer (DT) > 4] among patients with cancer (Funk et al., 2016; Mehnert et al., 2018). However, compared to patients with other types of cancers, patients with lung cancer reported the highest incidence of psychological distress (Zabora et al., 2001), with a detection rate of 17.0–73.0% (Lynch et al., 2010; Chambers et al., 2015; Tian et al., 2021a). It is noted that approximately 220 million new lung cancer cases were estimated in 2020, ranking second place among all the cancers (Sung et al., 2021). Therefore, the anticipated prevalence of psychological distress among patients with lung cancer should be especially emphasized.

Psychological distress has become a major psychological problem faced by patients with cancer because it has been demonstrated to be associated with the occurrence of several adverse consequences (Riba et al., 2019). As an example, psychological distress was found to be the contributor to the interruption of anticancer treatment (Mausbach et al., 2015; Lin et al., 2017; Yee et al., 2017). Meanwhile, psychological distress has also been found to be associated with longer hospital stays (Nipp et al., 2017), poor quality of life (Chambers et al., 2015), and increased risk of mortality (Batty et al., 2017; Hamer et al., 2009). Moreover, psychological distress was evidenced to accelerate the growth of tumor cells (Zhang et al., 2020a). Therefore, to develop effective intervention protocols to address psychological distress among patients with lung cancer, it is critically important to clarify the potential mechanisms involved in the development and progress of psychological distress (Riba et al., 2019).

BACKGROUND

Mindfulness refers to an individual's focused attention on the present moment and non-judgmental awareness (Kabat-Zinn, 2003). As a protective source of negative psychological outcomes, several studies have suggested the positive effects of mindfulness among different populations (Kashiwazaki et al., 2020), even in the general population (Freudenthaler et al., 2017). At present, several meta-analyses have demonstrated that interventions involving mindfulness elements (Cillessen et al., 2019; Zhang et al., 2019; Nnate et al., 2021; Rieger et al., 2021), such as mindfulness-based cognitive therapy (MCT), mindfulness-based art intervention, and mindfulness-based stress reduction (MBSR), significantly improved the psychological wellbeing of patients with cancer. It should be noted that, moreover, our previous study consistently determined the negative association between mindfulness and psychological distress among patients with lung cancer and further clarified the influence of mindfulness on psychological distress through the mediating role of social support and perceived stigma, with a slight total effect of 0.048 (Lei et al., 2021). However, are there other potential mechanisms else in the association between mindfulness and psychological distress among patients with lung cancer to be discovered and elucidated?

Illness perception refers to an individual's reflection in both the cognitive and emotional aspects and coping styles through personal knowledge and experiences when one confronts symptoms or illness threats, which have been revealed to have an impact on health outcomes (Leventhal et al., 2016). In a prospective, longitudinal, and observational study, illness perceptions were demonstrated as a potential predictor of psychological distress in patients with non-muscle-invasive bladder cancer (Zhang et al., 2020b). Meanwhile, illness perception has been found to predict psychological distress in head and neck cancer survivors (Zhang et al., 2018), esophageal cancer survivors (Dempster et al., 2011), and breast cancer survivors (Zhang et al., 2017). However, it is not yet known whether the same association holds for patients with lung cancer. Moreover, no study has investigated the association between mindfulness and illness perception; however, mindfulness-based interventions have been found to reduce the level of negative illness perceptions in patients with rheumatoid arthritis (Dalili and Bayazi, 2019) or acute coronary syndrome (Nasiri et al., 2020). We, therefore, assume that the association between mindfulness and illness perception also holds among patients with lung cancer.

Perceived stress refers to an individual's subjective perception of stress and assessment of the ability of processing stress (Kim and Jang, 2020), which was positively related to psychological distress among patients with lung cancer in our previous study (Tian et al., 2021a). Meanwhile, perceived stress was also speculated to be associated with mindfulness because mindfulness-based intervention protocols had generally been shown to reduce stress (Lengacher et al., 2021). Interestingly, the negative association between mindfulness and perceived stress has been detected in patients with digestive tract cancer (Zhong et al., 2019). Moreover, some studies have also investigated the relationship between illness perception and perceived stress and found that individuals will experience greater levels of perceived stress if they negatively perceived their illness (Miceli et al., 2019). Unfortunately, these relationships of variables introduced above have not yet been determined in patients with lung cancer.

In the light of the above, we performed this study to examine three hypotheses as follow: (a) illness perception is positively associated with perceived stress and psychological distress, (b) mindfulness can influence psychological distress through illness perception, and (c) mindfulness has an impact on psychological distress through simultaneously influencing illness perception and perceived stress among patients with lung cancer.

METHODS

Study Design

This study was a cross-sectional descriptive survey design.

Participants

We recruited eligible patients with convenience sampling method from a tertiary hospital in Chongqing between January and July 2021 according to the inclusion criteria which was designed according to our previous studies (Tian et al., 2021a,b): adult patients were diagnosed with lung cancer based on definitive and route methods and confirmed to have ability to clearly and accurately read and write. Patients who were confirmed to have a mental disorder or received psychological treatment before eligibility evaluation or participated in those studies with similar study aims were excluded from this study.

Sample Size

In this study, we used structural equation modeling technique with maximum likelihood to examine all the paths between variables, the N:q rule with a ratio of 10/1 was, therefore, used to calculate the theoretical sample size, in which N and q indicate required cases and the number of parameters that require statistical estimates, respectively (McDonald and Ho, 2002). In this study, q was identified to be 10 and, thus, a minimum sample size of 120 was calculated under the consideration of 20% invalid questionnaires.

Study Variables

Demographic information was collected using a self-designed questionnaire and other variables, namely, psychological distress, illness perception, and perceived stress were measured using validated instruments, which have been translated into Chinese and published publicly in academic journals.

Demographic Information

In this study, we collected the following sociodemographic and clinical variables by the self-designed information collection form, namely, gender, age, educational degree, marital status, place of residence, occupational status, family history, pain, cancer metastasis, and tumor's TNM stage.

Psychological Distress

We used DT to measure psychological distress at an 11-point thermometer scale from 0 to 10 in this study and 0 and 10 indicate no distress and extreme distress, respectively (Riba et al., 2019). The reliability and validity of DT have been extensively tested across different settings (Hong et al., 2015). According to several empirical studies, an individual with a score of 4 was defined to have clinically significant psychological distress (Donovan et al., 2014; Hong et al., 2015). There was no exception in China, a score of 4 was also demonstrated as the cutoff value of defining clinically significant psychological distress in Chinese cancer populations (Hong et al., 2015).

Mindfulness

We used the Five Facet Mindfulness Questionnaire (FFMQ), which was developed by Baer and colleagues in 2006 (Baer et al., 2006), to measure the level of mindfulness at a 5-point Likert scale. In the original version, total of 39 items were effectively pooled to assess mindfulness from five facets as follows: observing, describing, acting with awareness, non-judging, and non-reacting (Baer et al., 2006). The original FFMQ has been translated into Chinese by Deng et al. (2011), with acceptable psychometric propertiesDeng et al., 2011.

Illness Perception

We used the Brief Illness Perception Questionnaire (B-IPQ), which was developed by Weinman et al. (1996), to measure emotional and cognitive representations of illness at an 8-item continuous linear scale from 0 to 10. Higher scores represent more negative illness perceptions. Broadbent et al. (2006) have shown the B-IPQ to have good test-retest reliability and predictive and discriminant validityBroadbent et al., 2006. The B-IPQ has been translated into Chinese (Xue and Lin, 0000) and has been widely used as a screening tool for assessing illness perceptions in China (Broadbent et al., 2006).

Perceived Stress

We used the 10-item Perceived Stress Scale (PSS), which was developed by Cohen et al. (1983), to measure the level of perceived stress at a 5-point Likert scale from 0 to 4. A higher score represents a greater stress level. The Cronbach's alpha was 0.84 at the instrument development stage. The Chinese version of the 10-item PSS has been found to have the Cronbach's alpha of 0.619 (Yuan and Lin, 2009).

Procedure

We strictly performed this study following the provision of the Declaration of Helsinki. The Institutional Review Board (IRB) approved our protocol and assigned an ethical identifier of CZLS2021183-A to this protocol before enrollment commenced. Before conducting the formal survey, all eligible patients were informed about objectives and the risks and benefits of the study and required to sign informed consent. Study questionnaires were independently and anonymously completed by patients. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were utilized to guide us to report all the data (von Elm et al., 2014).

Statistical Analysis

All the valid questionnaires were completely written by responders. Descriptive statistics for all the variables were calculated using Statistical Package for the Social Sciences (SPSS) version 22.0 (Chicago, IL, United States). Age, the score of psychological distress, mindfulness, social support, and perceived stigma were expressed as median with interquartile range (IQR) because all did not follow normal distribution according to the results from the Kolmogorov–Smirnov test. The Spearman's rank correlation analysis was conducted using SPSS version 22.0 to examine the relations between mindfulness, illness perception, perceived stress, and psychological distress. The mediation model was tested using AMOS version 21.0 (Chicago, IL, United States). In these analyses, we used 2,000 bootstrap resamples and focused on the bias-corrected and accelerated CI. The following indices were calculated to evaluate the fitness of the overall model: the ratio of the chi-squared (χ^2) to degrees of freedom (df), comparative fit index (CFI), goodness-of-fit index (GFI), adjusted GFI (AGFI), Tucker–Lewis index (TLI), incremental fit index (IFI), and root mean square error of approximation (RMSEA) with 90% CI. Model fit was regarded as good when a ratio of χ^2/df was equal to or less than 3. For GFI and AGFI, a value of $p < 0.90$ indicates a good model fit. Moreover, CFI of ≥ 0.90 and RMSEA of < 0.05 were also suggesting a good model fit. A $p < 0.05$ indicated significance for all the analyses.

RESULTS

Sample Characteristics

A total of 300 eligible patients with lung cancer were recruited to participate in this survey study eventually, of which 295 patients returned valid questionnaires, representing a valid response rate of 98.3%. Among these 295 patients, 72 patients were defined to have clinically significant psychological distress, with a detection rate of 24.4%. Sociodemographic and clinical variables of 295 patients are shown in **Table 1**. Most patients were men (71.2%) and did not get adequate education (67.1%) and a significant number of patients were married (97.6%). Most patients lived in urban (71.5%) and balanced medical expenditure with medical insurance (96.9%), and more than half of them suffered from cancer metastasis (64.1%). Although most patients had no family history (92.2%), a significant number of patients were at the advanced stage (81.0%) and had no or mild pain (99.0%).

Relationships of Psychological Distress, Mindfulness, Illness Perception, and Perceived Stress

Overall, the median score of psychological distress was 0 with an IQR of from 0 to 3. The score of mindfulness, illness perception, and perceived stress was 115 (109 to 119), 43 (39 to 47), and 20 (17 to 23), respectively. We designed **Table 2** to display the relationships of psychological distress, mindfulness, illness perception, and perceived stress. The results of the Spearman's rank correlation analyses suggested that all the variables were significantly correlated with one another.

Structural Equation Modeling of the Association of Psychological Distress, Mindfulness, Illness Perception, and Perceived Stress

We first constructed the relationship structure of all variables according to the results of the correlation matrix. After conducting model fit analysis, we found that the direct path from mindfulness to psychological distress or perceived stress was not statistically significant (**Figure 1A**). We therefore eliminated those two paths to good fit the structural model ($\chi^2/df = 0.867$, CFI = 0.999, GFI = 1.000, CFI = 1.000, TLI = 1.019, and RMSEA = 0.000 [0.000 to 0.111]).

As illustrated in **Figure 1A**, illness perception ($\beta = 0.18$ and $p = 0.002$) and perceived stress ($\beta = 0.23$ and $p < 0.001$) had direct positive effects on psychological distress. The direct pathways from mindfulness to illness perception ($\beta = -0.16$ and $p = 0.006$) and from illness perception to perceived stress ($\beta = 0.17$ and $p = 0.003$) were all statistically significant.

The results from the bootstrap test for the significance of all pathways are shown in **Table 3**. Results for indirect pathways indicated that the indirect pathways between illness perception and psychological distress through perceived stress were statistically significant ($B = 0.04$, 95% CI [0.02–0.07], and $p = 0.009$). Overall, the total effect of illness perception on psychological distress was 0.22 [95% CI (0.12–0.30) and $p = 0.007$]. Furthermore, mindfulness had only an indirect

TABLE 1 | Psychological distress among patients with different sample characteristics ($N = 295$).

Characteristics	Frequency (%)	Mean rank	Z/χ^2	P
Gender			−1.197	0.231[a]
Male	210 (71.2)	144.65		
Female	85 (28.8)	156.26		
Age, years			0.567	0.753[b]
18–40	4 (1.4)	164.00		
41–60	144 (48.8)	150.55		
>60	147 (49.8)	145.06		
Education			1.650	0.648[b]
Illiterate or elementary school	88 (29.8)	142.61		
Junior school	110 (37.3)	146.97		
Senior high school	57 (19.3)	149.27		
College or above	40 (13.6)	160.88		
Marital status			2.535	0.282[b]
Married	288 (97.6)	146.91		
Unmarried	1 (0.4)	199.50		
Widowed or divorced	6 (2.0)	191.67		
Residence			−0.120	0.905[a]
Urban	211 (71.5)	148.33		
Rural	84 (28.5)	147.17		
Occupation status			3.616	0.164[b]
Unemployed	112 (38.0)	145.60		
Employed	40 (13.6)	169.01		
Retired	143 (48.4)	144.00		
Medical insurance			0.502	0.478[a]
Self-paying	9 (3.1)	130.44		
Medicare	286 (96.9)	148.55		
Family history			−1.860	0.063[a]
No	272 (92.2)	150.38		
Yes	23 (7.8)	119.89		
Pain			27.307	<0.001[b]
No	190 (64.4)	131.84		
Mild	102 (34.6)	176.74		
Moderate	2 (0.7)	143.75		
Severe	1 (0.3)	295.00		
Cancer metastasis			−3.181	0.001[a]
No	106 (35.9)	166.66		
Yes	189 (64.1)	137.53		
Tumor stage			7.687	0.053[b]
I	30 (10.2)	159.30		
II	26 (8.8)	183.69		
III	38 (12.9)	141.16		
IV	201 (68.1)	142.99		

[a] *Mann–Whitney U test.*

[b] *Kruskal–Wallis H test.*

TABLE 2 | Spearman correlations for mindfulness, illness perception, perceived stress, and psychological distress.

Variable	Median (P_{25}, P_{75})	Psychological distress	Mindfulness	Illness perception	Perceived stress
Psychological distress	0 (0, 3)	1			
Mindfulness	115 (109, 119)	−0.143*	1		
Illness perception	43 (39, 47)	0.233**	−0.181**	1	
Perceived stress	20 (17, 23)	0.235**	−0.116*	0.143*	1

$^*P < 0.05$, $^{**}P < 0.01$.

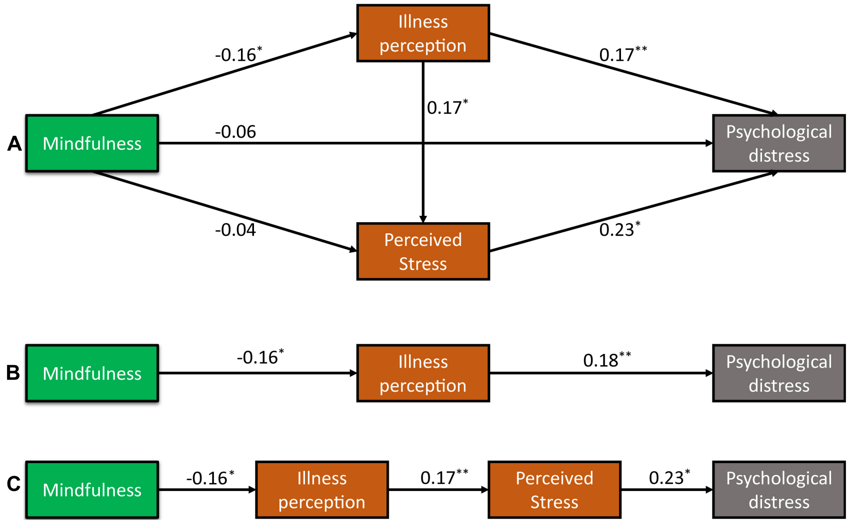

FIGURE 1 | Mechanisms of mindfulness on psychological distress among Chinese patients with lung cancer. Theoretical mechanisms of mindfulness on psychological distress according to correlation analysis **(A)**, influencing of mindfulness on psychological distress through illness perception **(B)**, and influencing of psychological distress on psychological distress through the chain mediating role of illness perception and perceived stress **(C)**. $^*P < 0.05$, $^{**}P < 0.01$.

TABLE 3 | Effect estimates of mindfulness to psychological distress through illness perception and perceived stress.

	Direct effect (95% CI)	Indirect effect (95% CI)	Total effect (95% CI)
Direct path			
Mindfulness → Illness perception	−0.16 (−0.27, −0.07)	n.a.	−0.16 (−0.27, 0.07)
Illness perception → Perceived stress	0.17 (0.08, 0.26)	n.a.	0.17 (0.08, 0.26)
Illness perception → Psychological distress	0.18 (0.09, 0.26)	n.a.	0.18 (0.09, 0.26)
Perceived stress → Psychological distress	0.23 (0.10, 0.30)	n.a.	0.23 (0.10, 0.30)
Indirect path			
Illness perception → Psychological distress	0.18 (0.09, 0.26)	0.04 (0.02, 0.07)	0.22 (0.12, 0.30)
Mindfulness → Perceived stress	n.a.	−0.03 (−0.07, −0.01)	−0.03 (−0.07, −0.01)
Mindfulness → Psychological distress	n.a.	−0.04 (−0.07, −0.02)	−0.04 (−0.07, −0.02)

CI, confidence interval; n.a., not available.

negative effect on perceived stress through illness perception, with an indirect effect of −0.03 [95% CI (−0.07 to −0.01) and $p = 0.009$]. However, mindfulness had an impact on psychological distress through influencing only illness perception (**Figure 1B**) or influencing simultaneously illness perception and perceived stress (**Figure 1C**). Specifically, the indirect effect of mindfulness on psychological distress was −0.03 through mediating effect of illness perception alone, and the indirect effect of mindfulness on psychological distress was −0.01 through the chain mediating effect of illness perception and perceived stress. Overall, the total effect of mindfulness on psychological distress was −0.04 through two indirect pathways. The results suggested that illness perception and perceived stress play a chain mediating role in the relationship between mindfulness and psychological distress among patients with lung cancer.

DISCUSSION

Psychological distress has been demonstrated to be associated with several negative clinical outcomes such as interruption of anticancer treatment, poor quality of life, and higher morbidity and mortality (Riba et al., 2019). It is imperative to clarify the potential mechanisms of the development and progress of psychological distress among patients with lung cancer to develop a more effective intervention protocol (Lei et al., 2021; Riba et al., 2019). The major aim of this study is to determine whether negative illness perception is positively related to be psychological distress and whether mindfulness may have a protective effect on psychological distress through negatively influencing illness perception and perceived stress among patients with lung cancer.

After completing this study, we found that 24.4% of patients experienced clinically significant psychological distress, which was consistent with previous findings (Tian et al., 2021a) although there also are some studies that reported a higher detection rate (Hong et al., 2015; Carlson et al., 2004). It is possible that the relatively lower detection rate of psychological distress in our study can be explained by the fact that patients experience significantly serious stigma after confirming the diagnosis of advanced lung cancer (Maguire et al., 2019), which has an impact on the tendency of patients to deliberately conceal their psychological distress. Moreover, as stated in our previous study (Lei et al., 2021), DT is not specific to patients with cancer (Hong et al., 2015) and cannot differentiate the risk of initial psychological distress from the accumulated risk of psychological distress, which may be an explanation for our findings.

Leventhal's commonsense model of illness representations proposes that individuals' illness perceptions are the major determinants of their health outcomes (Diefenbach and Leventhal, 1996). The individual will concurrently construct or elaborate both cognitive and emotional representations of their symptoms and illness to relieve the adverse impacts resulting from the symptom or an illness (Dempster et al., 2011). Some studies have revealed the association between illness perception and psychological distress among different populations (Zhang et al., 2017, 2018, 2020b). In this study, we first investigated the association between illness perception and psychological distress among patients with lung cancer and determined that illness perception was positively related to psychological distress.

As a positive psychological trait, mindfulness was found to be beneficial for improving adverse psychological outcomes through effective self-designed regulation and keeping positive emotional status (Ludwig and Kabat-Zinn, 2008). We have previously determined the direct association between mindfulness and psychological distress in patients with lung cancer; however, this specific association was not held in this study, which may be explained by the relatively mild severity of psychological distress compared with our finding (Lei et al., 2021). Moreover, we did not separately investigate the relationships of facets in mindfulness scale and psychological distress (Burger et al., 2021). Interestingly, we first determined the negative association between mindfulness and illness perception and revealed that mindfulness has an indirect impact on psychological distress through correcting negative illness perception. Illness perceptions refer to the attitudes, beliefs, and expectations of patients about symptoms or illnesses (Dalili and Bayazi, 2019), which are related to health information behavior practices and coping strategies (Katavic et al., 2016). Several studies have established that mindfulness-based interventions were associated with increased positive health perceptions and health behaviors (Roberts and Danoff-Burg, 2010), which provide theoretical support for our findings.

This study also revealed another novel finding that mindfulness indirectly influenced psychological distress among patients with lung cancer through the mediating effect of illness perception and perceived stress. As we introduced earlier, a higher negative perception of symptoms or illness represented worse psychological outcomes (Weinman et al., 1996). As one of the most common psychosocial risk factors, perceived stress has been suggested as a precursor state of adverse psychological outcomes because it has a negative impact on individual psychological adjustment (Kim and Jang, 2020). Previous studies also revealed the predictive effect of illness perception on perceived stress (Miceli et al., 2019; Sadeghi et al., 2019), which was further demonstrated in this study.

This study has some potential limitations that should be further interpreted. First, we used a convenience sample to investigate the associations between variables, which may introduce bias. Second, we calculated the theoretical sample size according to the number of variables, rather than performing an estimation based on acceptable statistical power. Third, all the patients were recruited from a single hospital in a single city and the sample size was relatively small; therefore, the generalizability of the study is questionable. Fourth, the level of mindfulness, illness perception, perceived street, and psychological distress were measured by using the self-report instruments, which may introduce subjective bias from patients. Definitively speaking, the prevalence of psychological distress and the type of scale could have some effects on the results.

CONCLUSION

This study first shows that illness perception is positively related to the perceived stress and psychological distress in patients with lung cancer and negatively related to mindfulness. This study provided some evidence for the hypothesis that mindfulness can relieve the severity of psychological distress by decreasing the level of negative illness perception alone or decreasing the level of negative illness perception and perceived stress simultaneously. Based on these findings, illness perception and perceived stress screening should be enrolled in mindfulness-based intervention strategies for patients with lung cancer. Certainly, the total effect of mindfulness on psychological distress through the two targeted pathways in this study was very low; we, therefore, suggest continuing to explore other potential mechanisms.

CLINICAL IMPLICATIONS

This study further clarified the potential mechanism of mindfulness on psychological distress through influencing illness perception and perceived stress in patients with lung cancer. From our current findings, mindfulness-based intervention protocol focusing on the correction of illness perception and reduction of perceived stress may be feasible and effective in improving psychological distress among patients with lung cancer.

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 the Institutional Review Board of Chongqing University Cancer Hospital. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LT and XT: had full access to all of the data in the study and are held responsible for the integrity of the data and accuracy of the data analysis. X-PQ, LT, XT, and MJ-H: concept and design. X-PQ, LT, XT, and L-JY: acquisition, analysis, or interpretation of data. X-PQ, XT, and MJ-H: drafting of the manuscript. XT, G-HC, and MJ-H: critical revision of the manuscript for important intellectual content. X-PQ and XT: statistical analysis. XT: obtaining funding, administrative, technical, or material support. MJ-H: supervision. All authors contributed to the article and approved the submitted version.

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Side Effects of Endocrine Therapy Are Associated With Depression and Anxiety in Breast Cancer Patients Accepting Endocrine Therapy: A Cross-Sectional Study in China

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Objective: Hormone positive breast cancer patients bear side effects of endocrine therapy and that may be related to depression and anxiety. We sought to find an association between mental health and side effects of endocrine therapy.

Methods: A total of 398 patients participated. Sociodemographic, disease profile, and side effects questionnaires were administered. We screened for depressive and anxiety disorders by using the SDS (Self-Rating Depression Scale) and SAS (Self-Rating Anxiety Scale).

Results: The prevalence of depression and anxiety in our study were 33.4% (133) and 13.3% (53), respectively. Depression was linked to education level (≤8 years, OR = 3.59, 95% CI: 2.22–5.78), night sweats (yes, OR = 1.90, 95% CI: 1.17–3.09), vaginal dryness (yes, OR = 2.22, 95% CI: 1.19–4.16), and fatigue (yes, OR = 1.94, 95% CI: 1.21–3.11); anxiety was associated with education level (≤8 years, OR = 3.13, 95% CI: 1.62–6.08), time to diagnosis (≤ 3 years, OR = 2.14, 95% CI: 1.13–4.07), osteopenia (yes, OR = 2.43, 95% CI: 1.26–4.70), loss of hair (yes, OR = 2.80, 95% CI: 1.10–7.15), and fatigue (yes, OR = 2.89, 95% CI: 1.54–5.43). A stratified analysis according to age (≤45 years and > 45 years) was performed as an exploratory. None of factor-age interactions was statistically significant.

Conclusion: Side effects of endocrine therapy were significantly associated with anxiety and depression. Side effects deserve greater emphasis and clinical interventions are needed to reduce anxiety and depression in breast cancer patients accepting ET.

Keywords: anxiety, breast cancer, depression, psycho-oncology, side effects

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INTRODUCTION

Depression and anxiety are very common among breast cancer patients, which could lead to poor adherence to the treatment, and is associated with substantial functional impairment and increased risk of mortality (Pitman et al., 2018; Shim et al., 2020). However, there is not enough attention given to the psychological conditions of the breast cancer survivors in clinical practice for several reasons, such as insufficient medical resources. Identification of patients at high risk of depression and/or anxiety is needed.

Apart from body image issues (Woertman and van den Brink, 2012), identity construction (McGannon et al., 2016), social and intimate relationships (Sebri et al., 2021), which have been confirmed relate to breast cancer patients' mood disorders by the literature, cancer patients' tumor characteristics, treatment, sociodemographic characteristics, such as marital status, educational status, and age, may affect psychologic status to a large extent (Stark et al., 2002; Osborne et al., 2003; Linden et al., 2012; Tsaras et al., 2018). However, the conclusion from previous studies have been discrepant. For example, educational status was a significant predictive factor in some studies (Tsaras et al., 2018), while it did not exhibit significant differences in other studies. In addition, the prevalence of depression and anxiety varies widely among studies (Krebber et al., 2014; Tsaras et al., 2018; Hashemi et al., 2020), indicating the prevalence varies between different individuals is large. Breast cancer patients accepting endocrine therapy (ET) is a particular population.

Endocrine therapy is a standard treatment for hormone positive (HR+) breast cancer patients (Noordhoek et al., 2021). The widespread used medicine includes tamoxifen, a selective estrogen-receptor modular (SERM), and aromatase inhibitor (AI), such as letrozole, anastrozole or exemestane. The standard treatment period lasts for 5 years. However, a recent study showed extending adjuvant ET for 10 years linked to a survival benefit for selected women (Noordhoek et al., 2021). Beyond this, some subgroup patients could benefit from ovarian function suppression (OFS) (Nagaraj and Ma, 2021; Noordhoek et al., 2021). As a strategy of breast cancer therapy, ET is associated with the side effect, especially when the intensity of the medication increases. Estrogens therapies could lead to estrogen deprivation and have widespread toxicity, involving multiple systems. The side effect of ET could impair patients' quality of life and is associated with depression and anxiety (Condorelli and Vaz-Luis, 2018).

We aimed to investigate the rate of depression/anxiety in breast cancer patients accepting ET and the relationship between side effects of ET and mood disorders, recognize the most commonly observed side effect related to depression and anxiety, and generate basic data. Therefore, this study may contribute evidence to support screening for depression/anxiety and integrating it into treatment.

MATERIALS AND METHODS

Ethical approval was obtained through the Shanxi Bethune Hospital Ethics Committee. Patients with breast cancer who had visited Shanxi Bethune Hospital between March 2012 and December 2017 were recruited. Female patients were included in the study if they met the following inclusion criteria: (1) aged 18 or older; (2) had undergone breast surgery and were undergoing adjuvant endocrine therapy; (3) could read, understand, and write in mandarin; and (4) could be connected by telephone. (1) Who was at the disease progression stage; (2) was diagnosed the pre-existing mental illness; or (3) those who did not want to participate in the study were excluded. This resulted in a final sample size of 398 patients.

A coordinator nurse recruited eligible patients and explained the study to them by phone. Once oral consent had been received from the patients, an electronic informed consent would send to them by WeChat, and the participant provided an electronic signature. Then the data was collected immediately by phone, including demographic, disease-specific information (e.g., surgery and menopausal status), side effects of ET, depression and anxiety. Depression and anxiety were evaluated by scale.

Side Effects of Endocrine Therapy

Estrogens therapies could impact the reproductive, musculoskeletal, cardiovascular, and central nervous systems. The main clinical manifestations are vaginal irritation, dryness, arthralgia, osteopenia, osteoporosis, bone fractures, hypercholesterolemia, angina, myocardial, hot flashes, night sweats, fatigue, and headache (Condorelli and Vaz-Luis, 2018). The nurse ticked the box according to the patients' answers. The detailed meaning would be explained by the nurse if necessary.

Self-Rating Depression Scale and Self-Rating Anxiety Scale

For assessment of the patient's subjective view of symptoms, we used the SDS (Self-Rating Depression Scale) (Zung, 1965) and SAS (Self-Rating Anxiety Scale) (Zung, 1971). The SDS has a split-half reliability of 0.73 (Dunstan et al., 2017) and is with an alpha coefficient of 0.68–0.81 (Knight et al., 1983; Tanaka-Matsumi and Kameoka, 1986; DeForge and Sobal, 1988). Reported correlations with other depression scales include 0.41 with the Hamilton Rating Scale (Carroll et al., 1973), 0.54 with the Depression Adjective Checklist, and 0.68 with the Beck Depression Inventory (Tanaka-Matsumi and Kameoka, 1986). The SAS has been shown to have good internal consistency with a Cronbach's alpha of 0.82 (Tanaka-Matsumi and Kameoka, 1986); fair concurrent validity, correlating significantly (0.30) with the Taylor Manifest Anxiety Scale (Zung, 1971). The SDS and SAS both contain 20 items and their designs were based on the diagnostic criteria for depression and anxiety. Subjects scored each item according to how they have felt during the past several days using a 4-point Likert scale. The raw sum score of the SDS and SAS ranges from 20 to 80 but results are usually presented as the SDS or SAS Index, which is converted by the raw score to 100 points scale. We used 50 points on the SDS and SAS index score for cutoff value (Dunstan and Scott, 2019, 2020).

Statistical Analysis

All data were analyzed through Statistical Package for Social Sciences (SPSS) V.26. Missing values were imputed using 20-fold multiple imputation. Categorical variables are reported as a proportion (%), and numerical data are reported as median and corresponding 25th and 75th percentiles (interquartile range; IQR) or range. Univariate and multivariate logistic analysis were performed for statistical analysis and the odds ratios (OR) and their 95% confidence intervals (CI) were calculated. In the multivariate regression model, the Stepwise Forward method was used. In addition, a stratified analysis was performed as an exploratory, adjunct analysis. Factor-age interactions were evaluated by logistic model including an interaction term between factors and age. All *p*-values were considered statistically significant at two-tailed $p < 0.05$.

RESULTS

Demographic and Disease-Related Characteristics

A total of 398 patients were analyzed in our study. Participants' median age was 51 years (range: 24–92 years); 29.1% (116) were 45 years or younger; a total of 35.9% (143) lived in urban area; 25.6% (102) were working; 50.8% (202) accepted education less than 8 years; 94.5% (376) were married; and 39.7% (158) participants with cessation of menses for $>$ 1 year. Most patients (312, 78.4%) without comorbidity and 44% (175) accepted breast-conserving surgery. The majority of patients conducted chemotherapy (314, 78.9%) and radiotherapy (273, 68.6%), and only 9% (36) conducted HER2-targeted therapy. Most patients were stage 1/2, accounting for 76.8% (306). At the time of the investigation, 52.0% (207) were diagnosed less than 3 years and 35.2% (140) were treated with ET less than 1 year. 61.6% (245) patients accepted AI and the others accepted tamoxifen or toremifene (153, 38.4%).

About one-third of patients suffered from depression (133, 33.4%) and one of seven suffered from anxiety (53, 13.3%). 35.7% (142) patients suffered from depression or anxiety, and 11.1% (44) patients suffered from depression and anxiety. The demographic and disease-related characteristics distribution in the depression group and anxiety group were similar to the total population. 4.3% (17) patients in our study seek help from a psychiatrist, and the rates were higher in the depression group (7, 5.3%) and anxiety group (3, 5.7%). Over a half of patients (226, 56.8%) seek help from their relatives. Patients suffering from depression (77, 57.9%) tended to seek relatives' help than patients suffering from anxiety (24, 45.3%) (**Table 1**).

Side Effects of Patients During Endocrine Therapy

Side effects of ET included night sweats (130, 32.7%), facial flushing (47, 11.8%), vaginal bleeding (10, 2.5%), vaginal dryness (54, 13.6%), sexual dysfunction (59, 14.8%), venous thrombosis (12, 3.0%), endometrial thickening (39, 9.8%), eye toxicity (6, 1.5%), hypertension (35, 8.8%), dyslipidemia (19, 4.8%), musculoskeletal symptoms (131, 32.9%), osteopenia (89, 22.4%), weight gain (99, 24.9%), loss of hair (30, 7.5%), loss of appetite (32, 8.0%), and fatigue (123, 30.9%). Most proportions of positive symptoms in the two groups were similar to the total population.

The most common discomforts for patients with depression or anxiety were night sweat (39.8% in the depression group and 41.5% in the anxiety group, respectively), musculoskeletal symptoms (38.3 and 45.3%, respectively), and fatigue (41.4 and 50.9%, respectively) (**Table 1**).

Univariate Analysis of Depression and Anxiety

The statistically significant factors for depression included education level (≤8 years, OR = 2.72, 95% CI: 1.76–4.21), night sweats (yes, OR = 1.62, 95% CI: 1.05–2.50), vaginal dryness (yes, OR = 2.06, 95% CI: 1.15-3.68), and fatigue (yes, OR = 2.04, 95% CI: 1.31–3.18). Significant factors for anxiety included education level (≤8 years, OR = 2.80, 95% CI: 1.48–5.27), marital status (divorced, widowed, or single, OR = 3.35, 95% CI: 1.30–8.65), chemotherapy (yes, OR = 1.97, 95% CI: 1.01–3.83), musculoskeletal symptoms (yes, OR = 1.84, 95% CI: 1.02–3.31), osteopenia (yes, OR = 2.42, 95% CI: 1.31–4.48), loss of hair (yes, OR = 2.61, 95% CI: 1.10–6.21), loss of appetite (yes, OR = 2.38, 95% CI: 1.01–5.61), and fatigue (yes, OR = 2.69, 95% CI: 1.50–4.85) (**Table 2**).

Multivariate Analysis of Depression and Anxiety

Figure 1 showed the results from multivariate analysis of depression and anxiety and their related factors. Multivariate model for depression included education level ($\leq$ 8 years vs. $>$ 8 years, OR = 3.59, 95% CI: 2.22–5.78), night sweats (yes vs. no, OR = 1.90, 95% CI: 1.17–3.09), vaginal dryness (yes vs. no, OR = 2.22, 95% CI: 1.19–4.16), and fatigue (yes vs. no, OR = 1.94, 95% CI: 1.21–3.11). Multivariate model for anxiety included education level ($\leq$ 8 years vs. $>$ 8 years, OR = 3.13, 95% CI: 1.62–6.08), time to diagnosis ($\leq$ 3 years vs. $>$ 3 years, OR = 2.14, 95% CI: 1.13–4.07), osteopenia (yes vs. no, OR = 2.43, 95% CI: 1.26–4.70), loss of hair (yes vs. no, OR = 2.80, 95% CI: 1.10–7.15), and fatigue (yes vs. no, OR = 2.89, 95% CI: 1.54–5.43).

Patients were stratified according to age ($\leq$ 45 years and $>$ 45 years) and a stratified analysis was performed as an exploratory. None of factor-age interactions was statistically significant.

DISCUSSION

Breast cancer patients in remission from cancer after therapy (surgery, chemotherapy and radiotherapy) are defined as cancer survivors, but they remain to endure psychological distress (Pitman et al., 2018). In particular, patients treated with endocrine treatment might live with side effects of ET and vulnerable to somatic symptoms. These factors are responsible for depression and anxiety observed in breast cancer patients. In this cross-sectional study, participants frequently experienced depression symptoms (33.4%), although anxiety was less common (13.3%). These women should receive support for their psychological adjustment during endocrine treatment.

The depression rate in the present study was in agreement with a previous similar South Africa study (36.6%) (Kagee et al., 2018). However, the prevalence in our study was significantly lower than a study conducted in Iran which reported the prevalence of depression among cancer patients to be 95.9% (Shakeri et al., 2016), the explanation for such

TABLE 1 | Demographic, disease-related characteristics, and side effects in total populations and depression/anxiety groups.

	Total	Depression	Anxiety
N	398 (100.0%)	133 (33.4%)	53 (13.3%)
Age at follow-up (median, range)	51 (24–92)	50 (26–88)	51 (29–92)
≤45 years	116 (29.1%)	43 (32.3%)	12 (22.6%)
>45 years	282 (70.9%)	90 (67.7%)	41 (77.4%)
Place of residence			
Urban	143 (35.9%)	50 (37.6%)	16 (30.2%)
Rural	255 (64.1%)	83 (62.4%)	37 (69.8%)
Employment status			
Working	102 (25.6%)	34 (25.6%)	10 (18.9%)
Retired	60 (15.1%)	19 (14.3%)	8 (15.1%)
Not working	236 (59.3%)	80 (60.2%)	35 (66.0%)
Education level			
≤8 years	202 (50.8%)	89 (66.9%)	38 (71.7%)
>8 years	196 (49.2%)	44 (33.1%)	15 (28.3%)
Marital status			
Divorced, widowed, single	22 (5.5%)	9 (6.8%)	7 (13.2%)
Married	376 (94.5%)	124 (93.2%)	46 (86.8%)
Menstrual status			
Cessation of menses for ≤ 1 year	240 (60.3%)	85 (63.9%)	35 (66.0%)
Cessation of menses for > 1 year	158 (39.7%)	48 (36.1%)	18 (34.0%)
Comorbidity			
Yes	86 (21.6%)	31 (23.3%)	12 (22.6%)
No	312 (78.4%)	102 (76.7%)	41 (77.4%)
Surgery			
BCS[†]	175 (44.0%)	61 (45.9%)	25 (47.2%)
Mastectomy	223 (56.0%)	72 (54.1%)	28 (52.8%)
Chemotherapy	314 (78.9%)	105 (78.9%)	36 (67.9%)
HER2-targeted therapy	36 (9.0%)	13 (9.8%)	3 (5.7%)
Radiotherapy	273 (68.6%)	99 (74.4%)	40 (75.5%)
TNM stage			
0	10 (2.5%)	6 (4.5%)	1 (1.9%)
1	116 (29.1%)	41 (30.8%)	19 (35.8%)
2	190 (47.7%)	66 (49.6%)	25 (47.2%)
3/4	82 (20.6%)	20 (15.0%)	8 (15.1%)
Time to diagnosis (median, IQR[‡])	34.6 (20.7–52.5)	31.5 (18.1–52.9)	26.5 (14.2–55.4)
≤36 m	207 (52.0%)	74 (55.6%)	33 (62.3%)
>36 m	191 (48.0%)	59(44.4%)	20 (37.7%)
ET[§] duration (median, IQR)	24.0 (12.0–36.0)	20.0 (9.3–42.0)	18.0 (9.0–48.5)
≤12 m	140 (35.2%)	50 (37.6%)	20 (37.7%)
>12 m	258 (64.8%)	83 (62.4%)	33 (62.3%)
ET medicine			
Tamoxifen/toremifene	153 (38.4%)	53 (39.8%)	25 (47.2%)
AI[¶]	245 (61.6%)	80 (60.2%)	28 (52.8%)
Side effects			
Night sweats	130 (32.7%)	53 (39.8%)	22 (41.5%)
Facial flushing	47 (11.8%)	18 (13.5%)	6 (11.3%)
Vaginal bleeding	10 (2.5%)	2 (1.5%)	2 (3.8%)
Vaginal dryness	54 (13.6%)	26 (19.5%)	9 (17.0%)
Sexual dysfunction	59 (14.8%)	26 (19.5%)	10 (18.9%)
Venous thrombosis	12 (3.0%)	5 (3.8%)	2 (3.8%)
Endometrial thickening	39 (9.8%)	18 (13.5%)	3 (5.7%)
Eye toxicity	6 (1.5%)	3 (2.3%)	1 (1.9%)
Hypertension	35 (8.8%)	16 (12.0%)	5 (9.4%)
Dyslipidemia	19 (4.8%)	8 (6.0%)	2 (3.8%)

(Continued)

TABLE 1 | (Continued)

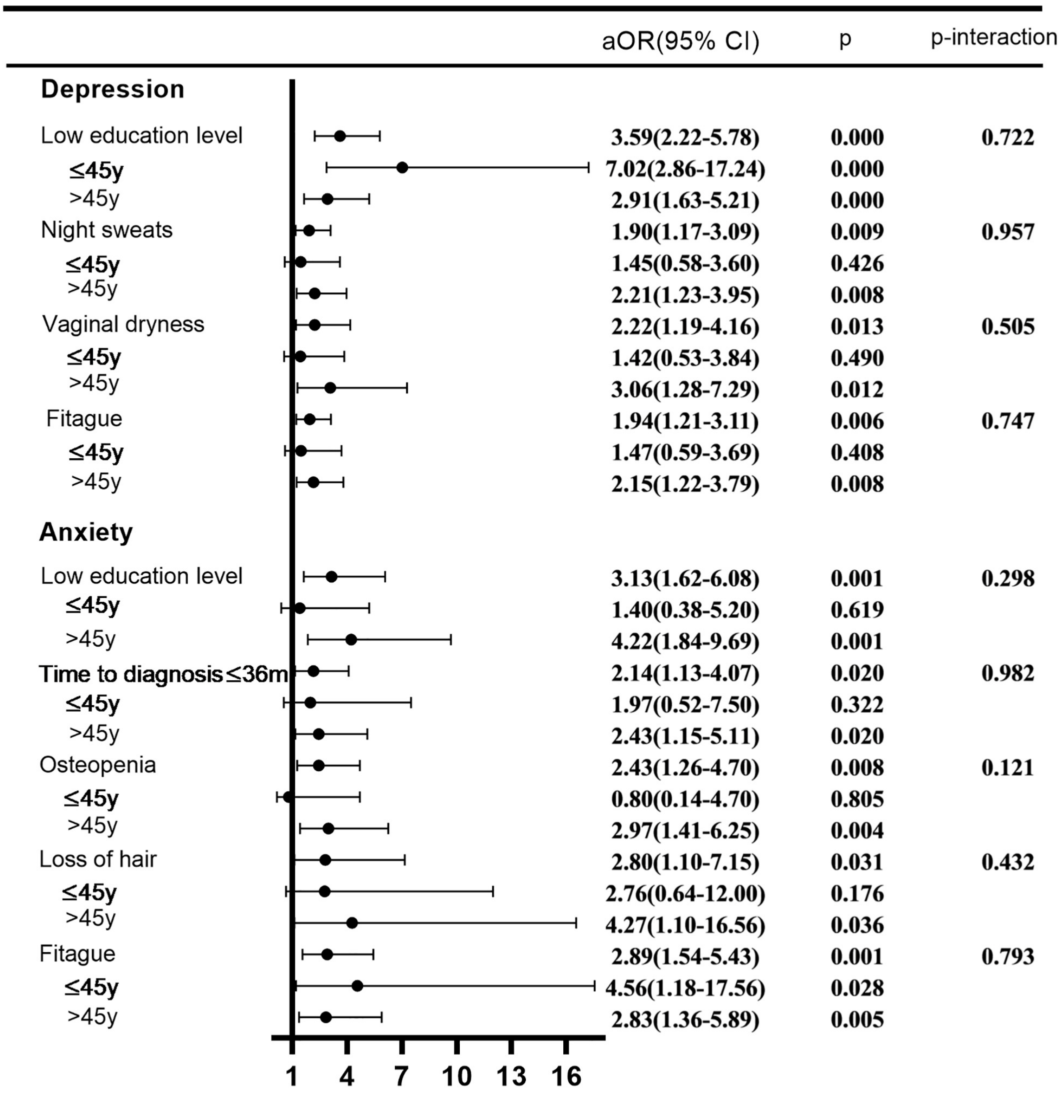
	Total	Depression	Anxiety
Musculoskeletal symptoms	131 (32.9%)	51 (38.3%)	24 (45.3%)
Osteopenia	89 (22.4%)	37 (27.8%)	20 (37.7%)
Weight gain	99 (24.9%)	39 (29.3%)	14 (26.4%)
Loss of hair	30 (7.5%)	12 (9.0%)	8 (15.1%)
Loss of appetite	32 (8.0%)	15 (11.3%)	8 (15.1%)
Fatigue	123 (30.9%)	55 (41.4%)	27 (50.9%)
Seek care from a psychiatrist	17 (4.3%)	7 (5.3%)	3 (5.7%)
Seek care from relatives	226 (56.8%)	77 (57.9%)	24 (45.3%)
Pharmacotherapy	37 (9.3%)	16 (12.0%)	7 (13.2%)

†*Breast-conserving surgery;* ‡*interquartile range;* §*endocrine therapy;* ¶*aromatase inhibitor.*

TABLE 2 | Univariate analysis of depression and anxiety.

	Depression		Anxiety	
	cOR	**95% CI**	**cOR**	**95% CI**
Age (years, vs. >45)	1.26	0.80–1.98	0.68	0.34–1.34
Place of residence (vs. rural)	1.04	0.67–1.62	0.69	0.37–1.32
Employment Status (vs. not working)				
Working	1.00	0.61–1.64	0.66	0.31–1.39
Retired	0.91	0.49–1.70	0.78	0.32–1.86
Education level (years, vs. >8)	2.72*	1.76–4.21	2.80*	1.48–5.27
Marital status (vs. married)	1.41	0.59–3.38	3.35*	1.30–8.65
Menstrual status (vs. > 1 year)	0.91	0.59–1.40	0.89	0.49–1.63
Comorbidity (vs. no)	0.94	0.57–1.55	1.10	0.52–2.30
Surgery (vs. mastectomy)	1.12	0.73–1.70	1.16	0.65–2.08
Chemotherapy (vs. yes)	1.12	0.69–2.00	1.97*	1.01–3.83
HER2-targeted therapy (vs. yes)	0.96	0.41–2.23	2.25	0.56–9.03
Radiotherapy (vs. yes)	0.84	0.53–1.31	0.67	0.33–1.37
Stage (stage 2/3/4 vs. stage 0/1)	1.18	0.74–1.88	1.30	0.71–2.41
Time to diagnosis (vs. 36 m)	1.24	0.81–1.88	1.61	0.89–2.92
ET† duration (vs. >12 m)	1.17	0.76–1.81	1.12	0.62–2.04
ET medicine (vs. AI‡)	1.09	0.71–1.67	1.51	0.84–2.70
Side effects				
Night sweats (vs. no)	1.62*	1.05–2.50	1.56	0.86–2.82
Facial flushing (vs. no)	1.27	0.68–2.39	0.95	0.38–2.35
Vaginal bleeding (vs. no)	0.49	0.10–2.34	1.65	0.34–8.00
Vaginal dryness (vs. no)	2.06*	1.15–3.68	1.36	0.62–2.98
Sexual dysfunction (vs. no)	1.71	0.97–3.00	1.41	0.66–2.98
Venous thrombosis (vs. no)	1.44	0.45–4.63	1.31	0.28–6.17
Endometrial thickening (vs. no)	1.82	0.93–3.55	0.52	0.15–1.74
Eye toxicity (vs. no)	2.02	0.40–10.12	1.31	0.15–11.42
Hypertension (vs. no)	1.77	0.88–3.57	1.09	0.41–2.96
Dyslipidemia (vs. no)	1.48	0.58–3.77	0.76	0.17–3.37
Musculoskeletal symptoms (vs. no)	1.44	0.93–2.23	1.84*	1.02–3.31
Osteopenia (vs. no)	1.58	0.97–2.57	2.42*	1.31–4.48
Weight gain (vs. no)	1.42	0.89–2.27	1.10	0.57–2.12
Loss of hair (vs. no)	1.36	0.64–2.92	2.61*	1.10–6.21
Loss of appetite (vs. no)	1.85	0.90–3.84	2.38*	1.01–5.61
Fatigue (vs. no)	2.04*	1.31–3.18	2.69*	1.50–4.85

†*Endocrine therapy;* ‡*aromatase inhibitor. *indicated a significant difference between the results of different groups.*



	aOR(95% CI)	p	p-interaction
Depression			
Low education level	3.59(2.22-5.78)	0.000	0.722
≤45y	7.02(2.86-17.24)	0.000	
>45y	2.91(1.63-5.21)	0.000	
Night sweats	1.90(1.17-3.09)	0.009	0.957
≤45y	1.45(0.58-3.60)	0.426	
>45y	2.21(1.23-3.95)	0.008	
Vaginal dryness	2.22(1.19-4.16)	0.013	0.505
≤45y	1.42(0.53-3.84)	0.490	
>45y	3.06(1.28-7.29)	0.012	
Fitague	1.94(1.21-3.11)	0.006	0.747
≤45y	1.47(0.59-3.69)	0.408	
>45y	2.15(1.22-3.79)	0.008	
Anxiety			
Low education level	3.13(1.62-6.08)	0.001	0.298
≤45y	1.40(0.38-5.20)	0.619	
>45y	4.22(1.84-9.69)	0.001	
Time to diagnosis≤36m	2.14(1.13-4.07)	0.020	0.982
≤45y	1.97(0.52-7.50)	0.322	
>45y	2.43(1.15-5.11)	0.020	
Osteopenia	2.43(1.26-4.70)	0.008	0.121
≤45y	0.80(0.14-4.70)	0.805	
>45y	2.97(1.41-6.25)	0.004	
Loss of hair	2.80(1.10-7.15)	0.031	0.432
≤45y	2.76(0.64-12.00)	0.176	
>45y	4.27(1.10-16.56)	0.036	
Fitague	2.89(1.54-5.43)	0.001	0.793
≤45y	4.56(1.18-17.56)	0.028	
>45y	2.83(1.36-5.89)	0.005	

FIGURE 1 | Multivariate analysis of depression and anxiety.

a big difference could be the different living environments and medical conditions. High prevalence of depression was also reported from Turkey (46%) (Bener et al., 2017), Mexico (43%) (Pérez-Fortis et al., 2017), Qatar (47.2%) (Bener et al., 2017), and Nigeria (40.3%) (Popoola and Adewuya, 2012). Notably, depression prevalence in our study was higher than studies conducted in Ethiopia (25%) (Wondimagegnehu et al., 2019), Malaysia (22.0%) (Hassan et al., 2015), Levent (24.7%) (Akel et al., 2017), and Morocco (26.9%) (Berhili et al., 2017). The various depression prevalence rates reflect the differences in different demographic groups. Different tools used in studies, including Beck Depression Inventory (BDI) tool, Hospital Anxiety and Depression (HADs) tool, Center for Epidemiologic Studies Depression Scale (CESD) and Mini International Neuropsychiatric Interview (MINI), might also have contributed to this disparity.

Thoughts about death and recurrence of illness often disrupt patients' focus, decision making, and sleep, showing different levels of anxiety. In a recent meta-analysis on breast cancer patients, the prevalence of anxiety among breast cancer patients was 41.9% (CI: 95%: 30.7–53.2%) (Hashemi et al., 2020). In the present study, the prevalence of anxiety in breast cancer patients accepting ET was 13.3%. Differences in the tools used to measure anxiety may lead to a wide range of anxiety prevalence among breast cancer patients (Hashemi et al., 2020). Although there are several tools for measuring anxiety, such as the Hospital Anxiety and Depression Scale (HADS), socioeconomic development index countries (SDI), the State-Trait Anxiety Inventory Questionnaire (STAI), they are lack specificity to specific clinical symptoms of breast cancer patients (Trask et al., 2000). Another reason could be the different study populations. Stage of the disease, the amount of family support, the patient's economic level, their cultural context, level of education, residential status, other chronic medical illnesses, a history of psychiatric disorders, and perceived functioning limitations and demographic characteristics impact the level of anxiety in breast cancer patients (Stark et al., 2002; Pitman et al., 2018).

In totally, the different prevalence rates of anxiety and depression in different studies are due to the following reasons: (1) using different measurement tools, (2) the differences in the disease, socioeconomic and demographic factors. The prevalence of mental disorders among breast cancer patients was relatively high, which will have an adverse impact on patient's adherence to treatment, quality of life and overall survival. This phenomenon should trigger our attention.

A significantly related factor to depression and anxiety was education level. Our finding reinforces the conclusion from the existing literature (Tsaras et al., 2018) and supports the conjecture that education can be a predictive factor in the occurrence of depression and anxiety among breast cancer patients dealing with the disease. This finding can be explained by the fact that women with higher educational levels can have better access to information regarding their health condition and they can fully understand the treatment plan and prognosis.

We found fatigue was strongly associated with mental disorders, which was consistent with the found of Lueboonthavatchai (2007). Cancer survivors have reported more frequent fatigue than their counterparts without a history of cancer (Bower et al., 2000). In cancer patients, fatigue constitutes a very distressing symptom that characteristically does not relieve with sleep (Fabi et al., 2020). A previous study showed fatigue might be more common among breast cancer survivors than among other cancer survivors and play an important role in survival (Matias et al., 2019). However, it is well known to be underdiagnosed and undertreated by clinic workers (Bower, 2014). Prior research found fatigue is mainly associated with anxiety, depression, distress, and sleep (Berger et al., 2012; Jones et al., 2016). In addition, endocrine therapy is a well-known trigger to fatigue (Franzoi et al., 2021). Fatigue is usually diagnosed by diagnosis tools, such as Fatigue Symptom Inventory (FSI), Cancer Fatigue Scale (CFS), and Fatigue Questionnaire (FQ). However, the difference in the use of diagnostic tools, and/or diagnostic criteria could lead to various prevalence rates (Krebber et al., 2014). Except for fatigue, we also found that other side effects of ET were related to depression and anxiety. However, further studies are warranted to verify our results.

It is noteworthy that patients have not received adequate attention from themselves. Only half of patients suffering from depression or anxiety seek help from their relatives and less than 6% of patients seek help from a psychiatrist. The *status quo* demands immediate attention from clinical workers.

Study Limitations

This study had some limitations. First, it was a cross-sectional investigation, which could not reflect the factors associated with depression and anxiety in each period. Second, data were collected via telephone interviews, so the patience of the interviewee may affect the reliability. Third, side effects of ET included physical and psychological symptoms, some of which resemble the symptom of anxiety and depression. Fourth, economic status was lacking, which was meaningful factor in some previous studies. In addition, as already mentioned, body image issues, identity construction, social and intimate relationships are potential factors, but these factors were not incorporated in the present study, which may cause some bias. Finally, fatigue in our study was subjective patient-reported sensation rather than tool diagnosed, so the actual incidence might be overestimated. However, this study is meaningful because it provided useful guidance for clinical workers by identifying factors related to anxiety and depression in breast cancer patients accepting ET.

CONCLUSION

Our study results confirmed that side effects of ET were significantly associated with anxiety and depression. Based on our results, more emphasis should be paid on minimizing the drugs side effects and clinical interventions are needed to reduce anxiety and depression in breast cancer patients accepting ET.

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 the Shanxi Bethune Hospital Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JG, RZ, and HL: conceptualization. JG: project administration. RZ: methodology and formal analysis. HL: data curation. JG and RZ: manuscript preparation. All authors approved the final manuscript.

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Emotional Self-Care: Exploring the Influencing Factors Among Individuals With Cancer

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Cancer is a leading source of distress and fatality worldwide. Cancer-related aberrant cell proliferation causes excruciating pain and impairment. To cope with pain and manage symptoms and illness, pharmaceutical and non-pharmacological options are available. Self-care behaviors are recognized as a key source in symptom management and improving quality adherence to treatment among the current non-pharmacological strategies. The intervention measures to improve self-care were hardly impacted because of the narrow focus on physical self-care. Bringing in emotional self-care and addressing the individual's emotional health can enhance the effectiveness of interventions on a holistic level. Hence, this study has attempted to explore the factors that influence emotional self-care among individuals with cancer. Following an exploratory research design, the data were collected from 15 participants (4 men and 11 women) using purposive sampling and semi-structured interviews. Through thematic analysis, eight major themes were identified: physiological factors, social factors, family factors, psychological factors, individual factors, socioeconomic factors, cultural factors, and spiritual factors. The findings explained the emotional self-care among patients with cancer and how different identified factors influence their emotional self-care practices.

Keywords: cancer, emotional self-care behaviors, factors influencing emotional self-care, wellbeing, qualitative study

INTRODUCTION

In today's world, non-communicable diseases (NCDs) and psychiatric illnesses are the most wellacknowledged health hazards. It impacts individuals and systems across the globe, especially making the developing nations vulnerable to these threats that are uncontrollable (World Health Organisation, 2018). NCDs are growing as the largest cause of death and disease across the globe (World Health Organisation, 2007), and the associated pain and disability that is inflicted on an individual, are also an increasing cause of poverty and distress in individuals (Allen and Feigl, 2017). Cancer is the fourth most prevalent non-communicable disease, with the highest rates of morbidity and mortality (World Health Organisation, 2014). In India, cancer is the second-leading cause of mortality in urban regions and the fourth-leading cause of death in rural areas (Smith and Mallath, 2019; Mathur et al., 2020).

Cancer can strike a person for a variety of reasons, including epidemiological shifts (He et al., 2020), psychosocial impacts (Shahab et al., 2018), and environmental and genetic factors (Al Ajmi et al., 2020; Oluwasanu and Olopade, 2020). The European Code Against Cancer (ECAC) has identified several cancer risk factors, including alcohol consumption, being an active or passive smoker, being overweight or obese, physical inactivity, poor dietary habits, increased ultraviolet radiation exposure, and human papillomavirus (HPV) infection (World Health Organisation, 2007; Shahab et al., 2018; Coates et al., 2020). Treatment modalities for cancer have evolved from extremely invasive to minimally invasive (Gotoda and Hatta, 2017). However, the after-effects and modifications made to the patients' bodies create agony and misery, resulting in their inability (Nipp et al., 2017; Granek et al., 2018; Carlson et al., 2019). As a result, the most effective method for reducing such discomfort and assisting patients in managing their symptoms is to engage in self-care.

Multiple physiological and psychological changes can be brought in individuals diagnosed with cancer when they follow a strict self-management technique (Whitaker et al., 2015). Self-care habits are thought to have more positive elements since they improve people's wellbeing, ability to move around, and help to keep healthcare coverage effective (Riegel et al., 2019). World Health Organization has devised several implementation tools to prevent non-communicable diseases, where they define "self-care as the ability that an individual or a group has, to promote health, prevent disease, maintain health, and cope with illness and disability with or without the support of a healthcare provider." Prior shreds of evidence have found self-care itself as an important non-pharmacological aspect that helps to manage many chronic illnesses, including cancer (Rico et al., 2017).

Self-care for an individual can be done in many ways and dimensions, including physical self-care, emotional self-care, or even spiritual self-care practices (Goudarzian et al., 2017a). Physical self-care is the process in which the individual personally takes care of oneself and optimizes physical function and keeps safe from all unhealthy activities. Zimmermann et al. (2018) reported that physical self-care methods can effectively control somatic symptoms and pain management, as well as a variety of psychosocial problems experienced by patients with cancer. Emotional self-care instills in the individual a belief that they can manage their symptoms (Qian and Yuan, 2012). Emotional self-care can be explained as maintaining a positive and compassionate view of the self, negotiating external and internal demands, identifying, accepting, and expressing a range of emotions (Dorociak, 2015). Among individuals diagnosed with cancer, emotional self-care can be an effective mechanism that supports them to preserve their self-confidence in overcoming the disease (Mesurado et al., 2018). Kawasaki et al. (2011) and Nasri et al. (2020) identified that emotional self-care helps the individual to rationalize their emotions and thoughts related to their diagnosis as well as help them to be prepared for the treatment, its side effects, and also to manage all their negative emotionality. With the help of emotional self-care, the individual acquires a transition from the state of fear to a state where they strive to accept the new condition and make new strategies to overcome the situation (López et al., 2021). By answering the question of why an individual succumbs to the practice of emotional self-care behaviors, there can be multiple reasons which includes their physical conditions and treatment processes, psychological makeup and mental states, influence from societies and families, socioeconomic conditions, etc. (Goudarzian et al., 2017b). Adaptation to new situations and the ability to cope with side effects and treatment-related changes can all be achieved with good emotional self-care (Bressi and Vaden, 2017).

According to the research, a greater emphasis is placed on understanding the various elements that influence physical self-care. Self-care has different dimensions, and integration of all those dimensions gives proper management of the symptoms and helps to improve the conditions and swelling of the patients (Goudarzian et al., 2017b; Wallace et al., 2020). Nasri et al. (2020) pointed out that there is a lack of theoretical understanding of emotional self-care among patient, and due to this, various self-care and self-management intervention that was conducted did not show the expected results (Mikolasek et al., 2018; Stoerkel et al., 2018). Johnson et al. (2018) reported that there was a significant increase in the quantity of self-care patients engaged during the first phase of the trial, but that these behaviors did not remain the same following the intervention. Further, they reported that interventions were ineffective because people oppose the emotional part and place a high priority on physical self-care. It is critical to maintain adequate control over emotional health, as this influences the impact of an individual's health behavior (Haghshenas, 2017; Arslan, 2018). Hence, this focuses on the different factors that influence emotional self-care, considering the significance of improving the overall wellbeing of patients with cancer.

METHODS

Participants and Recruitment

The explorative design was used to conduct the study. The individuals diagnosed with cancer and undergoing treatments such as surgery, chemotherapy, radiation therapy, or other major medical management techniques were recruited using purposive sampling. Out of the 46 participants approached, 15 participants (4 men and 11 women) willingly gave their consent to be the part of the study. The major reason reported to decline in the participation was their ill-health condition. The sociodemographic characteristics of the participants are included in **Table 1**. The study focused on participants who had access to quality treatment methods. Therefore, data were collected from patients who were taking treatment in Tata Memorial Hospital, Mumbai. This hospital has been considered as one of the top hospitals in India where patients from different states come for treatment. The interview schedule was developed with an extensive review of literature; finally, a set of 17 questions were formulated and were verified by three experts, such as psycho-oncologist, oncologist, and researcher working in the area of psycho-oncology and health psychology. According to the suggestions and feedback, necessary modifications have

TABLE 1 | Sociodemographic characteristics of the participants.

Variable	*n* (15)	%
Age		
20–35	6	40%
36–40	3	20%
41–55	2	14%
56–60	3	20%
61–75	1	6%
Gender		
Male	4	27%
Female	11	73%
Educational qualification		
Schooling	2	14%
Under graduation	7	47%
Postgraduation	6	40%
Residence		
Urban	14	94%
Rural	1	6%

been made and face validity of the interview schedule has been established.

Data Collection Procedure

Prior to the data collection, hospitals have been approached to obtain permission to collect the data. As this study was conducted during the pandemic period, many of the hospitals did not give consent to conduct the study. So, social media platform has been used as a source to get the details of the patients with cancer. Initially, researcher identified a specific health group through Facebook, which includes healthcare professionals, cancer survivors, and patients with cancer working and taking treatment in the Tata Memorial Hospital, Mumbai. The main purpose of this self-help group is to share their experiences and support and psycho-educate each other. Later, the researcher introduced herself to a doctor of that group who is known, then, the doctor added the researcher to that group, and the researcher introduced herself and explained the purpose of the study and requested for the voluntary participation. After getting the contact details of the participants from the group, participants were approached individually. As this study was conducted during the pandemic period, many patients were not comfortable to participate in the study through a face-to-face interview. Therefore, the telephonic method was chosen to conduct the interviews. Before conducting the interview, their convenient time to participate in the interview was confirmed. During the process of interview, a good rapport and trust were established between the interviewer and respondent, and the purpose of the study was explained. It was made sure that the interview process was sufficiently long for the subjects to express themselves in detail. The researcher used a semi-structured interview schedule, and the same interview schedule was used to ask the questions to all the participants and tried to receive the apt responses related to the study objective. They were asked to clarify whether there is an ambiguity in the question been asked. The conversation was recorded with prior permission from the participants. The questions that were asked to the participants are as follows: "*What do you think emotional self-care can be? Can you elaborate on it?" or "Can you explain your opinion about the factors that influence your self-care practices by several negative feelings like fear, anxiety, depression, and feeling of uncertainty?."* Some participants were encouraged to speak with the help of several questions, such as "Can you clarify a little more" or "Will it be possible for you to explain it with examples." Further, after the completion of each interview, the recordings were transcribed by the first author and it has been cross-verified by other authors. The necessary suggestions were received from experts and made an effort to enhance the skills of analysis, and all the responses were recorded. After the data were analyzed by the first author, it was reviewed by the other authors.

Data Processing and Analysis

Interviews that were conducted were transcribed. In this study, Braun and Clarke (2006) concept of qualitative thematic analysis is used for data analysis. In the process of transcription, the recordings were listened to multiple times to ensure the familiarity of the information shared and underwent multiple amounts of scrutiny to ensure the information. Through the verbatims, primary-level codes were identified. During this process, the more frequently used codes which are close to the point of exploration of the objectives of this study were given more weightage. Further, different codes obtained from the data set were sorted into potential themes, different subthemes, and main themes. For each subtheme that was identified, categories and subcategories were very identified, to give much clarity to the findings. The identified theme and subtheme were reviewed to represent the data; later, the themes were named and defined, so they ideally summed up the essence of the data and addressed the research question directly. Based on these conclusions, the report was generated (**Figure 1**).

Ethical Consideration

Informed consent was taken, and the study details were provided to participants before the interview. Participation was voluntary, and no remuneration was provided for the participants. The participants were briefed about confidentiality and their rights to withdraw from the study at any time during the study. Permission to record the telephonic interview and the confidentiality of the voice clip recorded were assured. At the end of the interview, debriefing of the information collected and the purpose of the study were mentioned to all the participants. The permission to conduct the study was obtained by the Department of Psychology, Central University of Karnataka.

RESULTS

From the information collected and analyzed through thematic analysis, eight major themes emerged (**Tables 2**, **3**). These are (1) physical factors, (2) social factors, (3) family factors, (4) psychological factors, (5) individual factors, (6) socioeconomic factors, (7) cultural factors, and (8) spiritual factors.

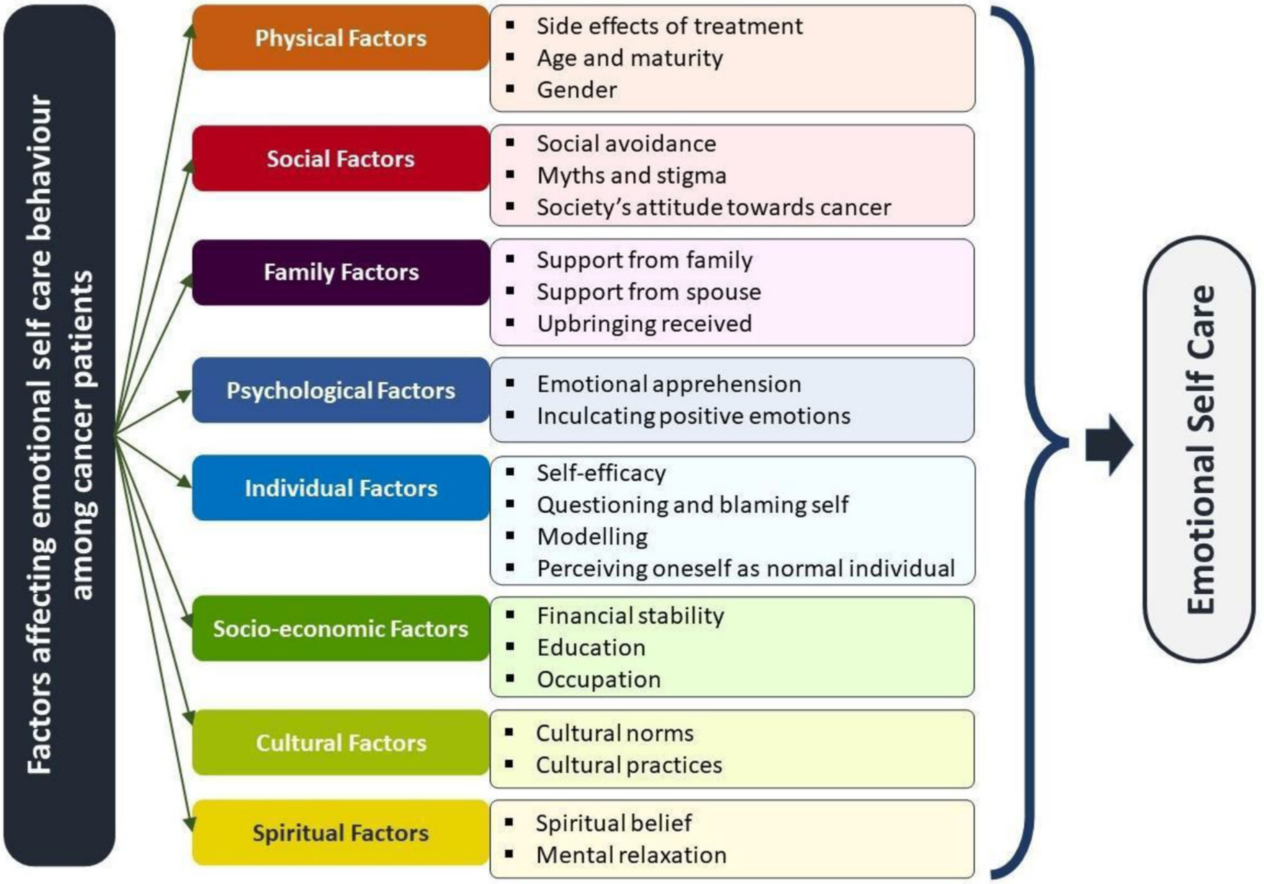

FIGURE 1 | Explored factors that influence emotional self-care among cancer patients.

Theme 1: Physical Factors

From the responses, one of the influential factors was the individual's physical abilities. Body and mind are connected entities; any disturbances in the physical makeup of the individual will show a change on an emotional level. The three subthemes that are identified include (1) side effects of treatment, (2) age and maturity, and (3) gender**.**

Side Effects of Treatment

When the body is exposed to high levels of radiation and other chemicals, there are several short- and long-term consequences. Some of the participants reported side effects, such as hair loss, skin patches and rashes, extreme mouth ulcers, lack of saliva, cessation of a body part, like the breast, and so on. This was found to have a negative impact on the practices of emotional self-care. For example,

> *……. went to get treated, he said (doctor) that you won't be getting saliva for your whole life. So on that day, I was very depressed; if I don't get saliva, the food pipe doesn't open, and if the food pipe does not open, I won't be able to eat food, then why am I living?…. (PARTICIPANT 5, AK)*

Age and Maturity

When it comes to emotional self-care, participants agreed that the individual's age and the maturity that comes with age play important roles. As they get older, their emotional experience grows, and they feel mature enough to care for themselves. Such life experiences, as they accumulate over time, will impact emotional self-care practices. For instance, the participants responded like,

> *… So, if you are mature enough; you have to take care of yourself. If you are a child then you will have to see it…. (PARTICIPANT 2, RH)*

The "aging" process also determines their ability to tolerate pain and provides a perspective of maturity that influences an individual's ability to deal with a problem. For example, participant SIL reported that,

> *… Age also influences because as you become more mature, even if you get a little bit of trouble, you will have the ability to bear it. (PARTICIPANT 7, SIL)*

TABLE 2 | Themes, subthemes, and categories identified, their codes and *n*%.

Themes	Subtheme	*n*%
Physical factor	Side effects of treatment	57%
	Age and Maturity	40%
	Gender	23%
Social factors	Social avoidance	30%
	Myths and stigma	17%
	Society's attitude toward cancer	53%
Family factor	Support from family	31%
	Support from spouse	23%
	Upbringing received	12%
Psychological factors	Emotional apprehension	47%
	Inculcating Positive emotions	50%
Individual factors	Self-efficacy	49%
	Questioning and blaming self	30%
	Modeling	28%
	Perceiving oneself as Normal individual	45%
Socio economic factors	Financial stability	46%
	Education	41%
	Occupation	37%
Cultural factor	Cultural norms	41%
	Cultural practices	22%
Spiritual factors	Spiritual belief	21%
	Mental Relaxation	16%

TABLE 3 | Themes and subthemes identified.

Objective	Theme	Subtheme
Factors influencing emotional self-care	Physical factor	Side effects of treatment
		Age and maturity
		Gender
	Social factors	Social avoidance
		Myths and stigma
		Society's attitude toward cancer
	Family factor	Support from family
		Support from spouse
		Upbringing received
	Psychological factors	Emotional apprehension
		Inculcating positive emotions
	Individual factors	Self-efficacy
		Questioning and blaming self
		Modeling
		Perceiving oneself as normal individual
	Socio economic factors	Financial stability
		Education
		Occupation
	Cultural factor	Cultural norms
		Cultural practices
	Spiritual factors	Spiritual belief
		Mental relaxation

The maturity that an individual gains through aging results in a positive change.

Gender

The gender with which a person identifies also demonstrates an influence on emotional self-care practices, as reported by the participants. Being recognized as a woman or man, which is a part of their self-identity, is seen to influence the patients regarding their outlook on pain and management of the conditions. For example, participant DS identifies,

> *Women have a unique ability, they have a lot of feminine and motherly instinct in them that would eventually help them face much more... like something very usual, but the men find it quite difficult to face it.... (PARTICIPANT 10, DS)*

Theme 2: Social Factors

Participants have stated that the attitude of society is very crucial to them. This theme was developed by analyzing participants' responses to the perceived presence and absence of social support received by the individual. Participants opined that society and family have an impact on their disease condition and self-care practices. The subthemes that are identified include (1) social avoidance, (2) myths and stigma, and (3) society's attitude toward cancer.

Social Avoidance

Participants reported that identifying and avoiding negative people and the environment helps them to stay away from the judgment of society, and irrelevant and incorrect information.

> *....People generally give examples of others in their journey of cancer and how all they deal with and fought over it. In my opinion, it's better to cut off and avoid such people. It's always better to keep relationships that you are confident about rather than having so many people who make you feel uncomfortable.... (PARTICIPANT 15, AM)*

Patients who avoided people who were influencing them in a negative way had a positive influence and were seen to engage in more positive emotional self-care behaviors.

Myths and Stigma

There are many myths and stigma associated with cancer due to the lack of awareness about the disease, which has a negative impact on emotional self-care behaviors. The majority of participants responded that this disease is considered as the person's Karma. The society views cancer as a natural death penalty for bad deeds, such as enjoying and living a life that the patient used to live. For example,

> *People connect it with karma, 'I did a lot of bad things in my previous life', and that's why I have it, they say 'I used to spend and*

> *waste a lot of money going to pubs', and 'this is happening to me because I used to enjoy my life'......(PARTICIPANT 10, DS)*

Some participants also explained that people consider that cancer is transmitted through touch; hence, they do not use the utensils used by them nor come near their house premises. In such cases, the families also experience a lot of stress and dilemmas. As reported by participant BK,

> *People also face untouchability during the treatment. I know some people who have complained that no people are touching them because they have cancer......*
> *(PARTICIPANT 6, BK)*

Society's Attitude Toward Cancer

Concerning myths and stigma, which are having a negative impact, participants also responded that when the people around them and the situation they are in foster support and hope, the patient feels external support and is motivated to engage in self-care behaviors. For example, participant RH reports,

> *I used to stay in a building where we have a long term relationship with each other, when I meet them, that person will always tell me that I will pray for you to get well soon and all, so those kinds of words create hope, receiving support is essential when you undergo treatment......(PARTICIPANT 2, RH)*

However, when a patient is neglected by society and social support, it creates a hostile environment and emotions, causing them to exacerbate their condition. For example, participant SW reported,

> *So, it is you who choose the circle and with whom you want to live. Near my house I have neighbors who are very negative. They won't come and visit me because they feel that if they come and see me, they will also become a patient.......(PARTICIPANT 1, SW)*

Hence, the way society understands and approaches the patient also plays an integral role in the patient's life.

Theme 3: Family Factor

Participants identified the importance of understanding the role of the family and the importance of each member, including the patient himself. As the family is a system that connects the individual to society, the responses and the support that the patient needs from the family to make a difference are also identified to be very important. A total of three subthemes are identified likewise to understand the family influences, which are, (1) support from family, (2) support from a spouse, and (3) upbringing received.

Support From Family

Participants responded that family support is an essential factor that helps the patient to focus on more of their issues. The strength that the family gives in terms of support and companionship helps the individual to face all the negative social influences. This support was seen to positively influence emotional self-care. As a source of support alongside the patient, the participants reported that they benefit individuals emotionally and feel the strength to fight cancer. For example, participant KM reports,

> *My family is very important. So, when I can see so much love and support from my family, I feel that you need to go back and get better soon for them and that motivates me......(PARTICIPANT 9, KM)*

Support From Spouse

Participants reported that the support from their spouse also influences their emotional self-care practices. When such support is received from the spouse, it influences the patient more positively. Participants reported that if the partner can understand and support the patient throughout the treatment, it helps them with their emotional self-care practices.

> *....my husband is like my friend, he is very deep, he knows that I'll win. He always encourages me to fight....(PARTICIPANT 14, BJ)*

Upbringing Received

The way their parents raised the individuals, helps to deal with their situation and stress. Parenting impacts the emergence of emotional self-care practices, which they follow even before the diagnosis.

> *For example, a similar view was shared by Participant AM and SIL,*
> *.... the way I was brought up also influenced me. The personal things that we get from our home and our background also may influence us....(PARTICIPANT 7, SIL)*

Theme 4: Psychological Factors

This subtheme refers to the various psychological factors that influence the client's constructive participation in emotional self-care behaviors, and these factors can affect the patient both positively and negatively in such practices. There are majorly 2 categories in this subtheme, which are (1) emotional apprehension and (2) inculcating positive emotions.

Emotional Apprehension

Another factor that was identified to influence emotional self-care practices is the different emotional apprehensions that the patient faces. Their apprehension may be related to various feelings of fear, stress, and ambiguity about the future. A number of four categories were identified which include (1) fear of relapse, (2) negative emotions, (3) stress, and (4) uncertainty of the treatment.

Fear of Relapse

Participants reported that even when they are in remission, there is a chance that the disease will reappear in various forms or types. This fear instills anxiety in participants, affecting their emotional self-care practices and having a negative impact on their emotional self-care. For example, participant RH responded,

> *..... Many people fear the relapse of cancer. Again, this will lead to stress, anxiety, fearfulness, and again you will not be able to manage your emotions right....(PARTICIPANT 2, RH)*

Uncertainty of Treatment

As participants highlighted, cancer treatment is both painful and expensive. Even after high intensities of radiation exposure, there is no assurance that the treatment will be completely effective for the patient. As a result, there is always some doubts in the participants' minds about whether their treatment will work or not.

> *Even though we are getting the treatment, we are not sure whether our treatment will work or not, we are not emotionally healthy. So, if the treatment somehow doesn't work as it should, there will be an increasing impact on the emotional part because I myself experienced that.... (PARTICIPANT 3, NK)*

Negative Emotions

The patients experience a variety of negative emotions. This includes a range of worries and concerns about the health conditions, their future, their present psychological status, and physical support system. When they engage in such negative emotions and thoughts, their level of acceptance is called into question, and the intensity of these negative moods begins to rise, for example,

> *One thing is definitely depression because it is like a chain reaction you think about one thing, it leads to another, and it goes on, so what one needs to do is, we need to snap out of that negative emotion once and look into the positive side even in your negative situations.... (PARTICIPANT 10, DS)*

Stress

As a patient, they will be subjected to various stressors. In this condition, most of the participants have reported encountering more distress than eustress; hence, this also gives a lot of negative emotional reactions to the occurrence of that. Majorly identified stressors were the physical changes they had to undergo due to the treatment and financial instabilities.

> *Stressors are everywhere, and stress will influence your self-care when you allow it to influence you, if you deal with your stress you can handle it properly. Because stress comes when you don't handle your problems, and you make it a big issue, stress comes there.... (PARTICIPANT 1, SW)*

Inculcating Positive Emotions

Participants identified that being open to incorporating more positive emotions into their lives will aid them in their emotional self-care, allowing them to deal with their conditions in a constructive manner. In this subtheme, three categories are identified which are (1) emotional stability, (2) optimism, and (3) sense of gratitude.

Emotional Stability

Even though there are several negative and positive situations and conditions that the individual experiences, the ability to face all emotions and bring stability and confidence was identified as emotional strength. For example, participant DS responded

> *.... If you are positive and emotionally stable, I think that would be enough. If you are emotionally in a good place, your emotional self-care also will be better. You become more positive about it.... (PARTICIPANT 10, SW)*

Being emotionally stable also aids in understanding and respecting one's own and other people's emotions. This has made a significant difference in the patient's emotional self-care practices and has positively impacted emotional self-care. Participants also reported that emotional stability is one of the keys helping them to manage their conditions on one's own

> *.... So, if you are emotionally stable, you start understanding your emotions as well as others emotions, and also you'll understand why the other person is doing it.... (PARTICIPANT 12, KJ)*

Optimism

The participants identified that it is important that one must seek a positive attitude and have hope that they will be able to overcome the condition, and along with that, they also have to spread positivity to others as well. This helps them to positively influence others. Being so, the emotional self-care one takes also helps them to stand out, and through seeking a more positive outlook of the condition, their emotional self-care will be quite intact.

> *.... I think positiveness is the most important thing. If I am suffering with the current procedure, I think I'll go for other procedures. It's okay. We have to. That is the most important thing in health care.... (PARTICIPANT 14, BJ)*

Sense of Gratitude

Participants reported that having a sense of gratitude for being able to receive treatment, adequate help and support is an important part of understanding and respecting. Even the smallest gesture of support that the patient receives makes them feel in a positive way. For example, participant SW responded that

> *.... a gratitude book is with me, a paper or a diary I keep every time with me. Whatever good happens to me, I write, thank god for this, thank god for this, thank god for this, whatever small thing it was..... So, that makes me positive... when I am in distress or depressed, I read that and I get happy.... (PARTICIPANT 1, SW)*

Participants also perceive cancer as an opportunity to reflect and consider it as a signal to begin caring for oneself. Through this experience, patients try to see life from a different perspective and enjoy each moment of their life to its fullest. For example, participant SD reported,

> *To be frank, this thing helped me change my perspective a lot. I would say that my attitude has changed after it happened to me.. it changed me as a person and made me a better person.. (PARTICIPANT 4, SD)*

Theme 5: Individual Factors

One of the important factors that have been observed to influence is the individual's internal self. While taking care of oneself emotionally, both external and internal factors are influenced. Based on the internal makeup of the individual, they perceive a situation, act, and deal accordingly. Four categories were identified, which include (1) self-efficacy, (2) questioning and blaming self, (3) modeling, and (4) perceiving oneself as normal individual.

Self-Efficacy

Self-efficacy, or believing that one can overcome the disease, is an important factor that will help them endure harsh treatment which also increases their chances of survival. For example,

> *Without belief in yourself or without will power, we can't work. So, this is the way we are dealing with our emotions or any type of problem or situation, our own beliefs are very important for all the problems. . . . (PARTICIPANT 6, BK)*

Participants reported that having a strong belief in oneself creates confidence in themselves, which helps them to be emotionally strong. The patients understand that this is one phase of life, which adds to their acceptance of the situation and the disease.

> *.... Emotional self-care practices happen when you believe in yourself, you need to have confidence that everything is going to be alright.... Belief in self is very important. . . . (PARTICIPANT 9, KM)*

Questioning and Blaming Self

Participants reported that after receiving the diagnosis report, they begin to question why everything is happening to them, develop a negative attitude toward their life, and begin blaming themselves for being sick. For example, participant DS responded,

> *I had phases and times where I really used to question myself how long it will take to get my hair back, whether life will still be the same, but then I pushed myself and made sure that I will not be in the loop of those negative thoughts. . . . (PARTICIPANT 10, DS)*

Modeling

Modeling is how a patient learns and is motivated to engage in proper health care by observing others. When they meet individuals who are improving both mentally and physically through active engagement in self-care behaviors, the participants report that they will begin to follow suit, which will have a positive impact on the patient's emotional self-care behaviors.

> *If I see someone doing good, doing proper activities for his or her own self-care and indulging in some or other activities and it brings a positive effect on his or her life then, it would influence me to do that, and I would definitely follow it as well. . . . (PARTICIPANT 1, SW)*

Participants also reported that modeling also gives a patient another way to understand perceive the condition.

> *. . . when we try to see a person from a different perspective, we look at the world according to our perspective. . . So when we step out we look at it in a different way. . . . (PARTICIPANT 10, DS)*

Perceiving Oneself as a Normal Individual

Some patients reported that even after understanding and knowing the diagnosis, the patient perceives themselves as a normal person and does not give much thought to being ill which helps them to stay more positive and also helps them to identify themselves as being a part of society.

> *If something like that happens you have to stop thinking about it and keep yourself completely engaged. Should not be like sitting in a corner saying that I am having this disease and I am not able to do anything and my life is at an end, I don't have anything to do. You should avoid such kinds of thoughts... . . . (PARTICIPANT 8, TN)*

Theme 6: Socioeconomic Factors

As a social being, several factors, such as level of education, residence, and financial income, play a role in appropriately managing the condition. According to participants, these factors can also affect their outlook on how well they can emotionally manage themselves and take good emotional care of themselves. This theme particularly identifies such influences that are made by the individual's external characteristics. Three major sub-themes are identified which are (1) financial stability, (2) education, and (3) occupation.

Financial Stability

Participants have identified that having financial stability is an essential part when it comes to the treatment part of cancer. The available treatment options are prohibitively expensive. Once the individual feels secured in terms of the financial aspect, participants reported that they need not keep worrying or preoccupied with the future treatment and hence will be able to follow emotional self-care, for example,

> *A financially wellsettled person might have better emotional self-care and there are too many people to support, so that person will be in better emotional self-care, so that will also have an impact... . . . (PARTICIPANT 2, RH)*

Education

According to the participants, education provides wisdom and knowledge of the world from a different and more mature perspective. With good education, individuals become well aware of the various treatments available. Some participants identified that they were able to take care of themselves as a result of education, and this has an impact on their emotional self-care practices.

> *I feel that through my education I was probably able to understand myself. . . probably understand my emotion and probably how to control my emotions and how to deal with it......... (PARTICIPANT 11, DS)*

Education gives an individual a power of confidence and self-acceptance, which will help them in accepting their condition and also helps in dealing with them.

Occupation

The occupation and its specific nature also influenced emotional self-care practices. The respect that the society gives an individual with a job will help them to gain self-confidence. Further, the financial stability that the job provides was reported to have influenced their self-care practices.

> *Because I have a job we need not have a setback for aversion to going inside and speaking to someone. This is all an experience for us. My job was actually very positive for me. It has given me a lot of confidence to look......... (PARTICIPANT 8, TN)*

Theme 7: Cultural Factor

Through this study, another factor that was found to influence emotional self-care practices was cultural influences. There are a lot of indigenous cultural practices that a person is supposed to follow, which correspond to different sets of laws and regulations of the religion they follow or the ethnic group they are part of. Participants have identified that cultural factors make a difference in their levels of engagement in emotional self-care practices. Two subthemes were identified which are (1) cultural norms and (2) cultural practices.

Cultural Norms

The specific set of rules and regulations of the ethic group or community that a person adheres to are cultural norms. This ranges from normal appearances to various dietary habits and lifestyle choices. These norms are sometimes aimed at patients as well, which has a negative impact on their emotional self-care practices. When an individual identifies themselves within a specific community, they follow and abide by its norms, not though but to an extent.

> *Being rigid with rules and regulations affect you in a negative way because when you are emotionally weak, people around you and your family need to be flexible with what they follow, like they should think if you are able to follow it at that time or not, but being rigid in those rules and regulation is the negative part during those hard times.... (PARTICIPANT 11, DY)*

Cultural Practices

Unserviceable cultural practices by our forefathers have very less priority and importance in the current scenario. Following such cultures even now would bring in more anger and negative feelings, and hence effective management of emotional self-care becomes difficult with different physical conditions. This kind of practice also stigmatizes women, and more restrictions are imposed on them. This also brings in negative influences, such as guilt and shame. For example, participant SW pointed out,

> *In a Brahmin family, if you are on your periods and even if it is in the late midnight also, you need to take a proper bath and need to shampoo your hair, which I don't like ok... the reason is that I am not healthy and my body is weak so how can I just force myself for a tradition or a bad practice of my forefathers to wash my hair in the middle of the night in winters and get ill and have a number of medicines which is going to make my body weak. I don't follow that custom.... (PARTICIPANT 1, SW)*

Theme 8: Spiritual Factors

Spirituality is one of the factors seen to have an influence on the individual's emotional self-care practices. While understanding the influence of spirituality, even though the participants come from a specific religious background, they responded that following a specific religion and beliefs does not create any difference in emotional self-care. Rather, it is an individual's belief in the God entity and being one with God which led them to seek more positivity and improve their emotional self-care practices in a positive way. Two subthemes were identified under this theme, which are (1) mental relaxation and (2) spiritual beliefs.

Spiritual Belief

Along with the mental peace and calmness that they have, participants reported the belief that they have in their superior, which helps them to have a sense of hope and support and feel that God will be protecting them in such a vulnerable time. This belief instills hope and confidence in them, which helps them to see the disease condition more positively which in the long run, will help them in engaging in emotional self-care.

> *it is my conviction that he (God) will help me... (PARTICIPANT 7, SIL)*

Mental Relaxation

Participants reported feeling calm and relaxed after engaging in meditative practices, such as chanting mantras or being in the presence of the supreme. This relaxation provides them with mental peace, which aids them in having better control over their emotions. For example, participant AM reported that,

> *..... We have a lot of Mantras and those are very powerful mantras. When you chant those mantras, you will definitely get positivity .... (PARTICIPANT 15 AM)*

DISCUSSION

Cancer treatment necessitates both an understanding of its symptomatology and the provision of specific medical treatments for better management. In addition to the medical treatment procedures, research evidence has also found several psychosocial interventions that are effective to face the challenges that a patient encounters during the treatment process and afterward (Park et al., 2019). The primary goal of this study was to better understand the various factors that influence cancer patients' emotional self-care behavior. Wang et al. (2019) explained that though the individual desires to have an optimistic view of their life several factors promote and hamper them from engaging in this behavior. The factor identified from this study which adds on to the existing knowledge is discussed here.

Physical Factors

According to participants, treatment side effects could have a significant impact on their ability to adhere to emotional self-care routines. The intense pain and treatment's impact on the patient's body result in permanent changes and traumatic memory. Experiencing such profound effects makes it difficult for them to change their emotional self-care habit, and the majority of patients believe that this will have a negative impact on their emotional health. Niedzwiedz et al. (2019) pointed out that there can be a potential impact on patients' mental health when there are long-term mitigating effects owing to treatment load and uncertainty in numerous strata of their lives.

It has also been found that age and the maturity of individuals also count in their emotional experiences. In accordance with this study findings, patients who are aged found it easier and more prudent enough to take care of their own emotional health. Evidence indicates that age stands the moderating factor in terms of dealing effectively with their psychological distress (Zhang et al., 2020). The majority of participants reported that as they grew older and gained more experience, they gained a better understanding of the situation and were able to care for themselves emotionally and physically.

Gender was another factor found in the study that influenced the extent of which the individual engages in emotional self-care behaviors. In the study, most participants reported that, compared to men, women were better able to deal with their emotions and take care of their emotional health. Research indicates that there are significant gender differences that exist in understanding several conditions, such as depression and anxiety among patients with cancer (Pham et al., 2019). In terms of the pain tolerance and management of their conditions, it was seen that the female population were more tolerant compared to male population (Hinz et al., 2019).

Social Factors

Society plays the vital role in improving and rehabilitating patients with cancer during and after treatment. There is a collectivist cultural trend in India that diminishes the role of society in an individual's life (Oyibo, 2021). The attitude of society toward such disorders and how they deal with such situations have a significant impact. According to the participants, the social avoidance and neglect that individuals face from society had a negative impact on their emotional self-care behavior. Because of a lack of understanding and awareness, society frequently views cancer as a communicable disease and avoids patients in social situations. This is a societal attitude that has a negative impact on the patient's emotional wellbeing and frequently leads to disorders, such as depression and anxiety (Pan et al., 2019). In pointing out the lack of awareness and information about cancer and relating this concept to Indian culture, the community predicts a large interconnection, which they link to Karma. In Indian tradition, terrible life experiences and meta-beliefs are generally attributed to the belief in Karma. Mishappenings are linked to God's will and fate in Indian literature (Dalal, 2020).

Family Factors

The individual's immediate society is his or her family. All of the significant units in this group have a significant impact on the individual in terms of enhancing and engaging in emotional self-care behaviors. Participants in the study reported that the support and companionship they receive from their family is very important in terms of their emotional wellbeing. When an individual is placed in a non-suppurative setting, coping with the situation becomes challenging, compromising the individual's emotional wellbeing (Curigliano et al., 2020). According to the researchers, family members' perceptions of support have a critical role in coping with various negative emotions during the treatment and diagnosis process (Nuraini et al., 2018).

Another significant factor identified in the study was the spouse's support. Their corresponding spouse's companionship and support were found to significantly impact their emotional self-care routines. To overcome the challenges that they faced, spouses were considered as a supportive and inspiring unit within themselves. Evidence demonstrates that emotional support provided by their spouse aids the individual in overcoming a variety of emotional and psychological issues (Lee et al., 2018).

Individuals' interactions with emotional self-care were influenced by their upbringing and the environment in which they were raised since childhood. The environment in which they were frequently exposed aided them in adequately dealing with a variety of problems, and it was thought that improving their emotional health would be much easier. Parenting practices and the environment in which they grew up contribute to shape their attitudes and impressions of a variety of conditions that are viewed as bad. Having the mindset to overcome adversity is developed in an individual due to such experience and practice (Anthony et al., 2019).

Psychological Factors

The individual's psychological makeup was also observed to have an impact on their engagement in emotional self-care actions. The psychological characteristics indicated by the participants had an impact on their emotional self-care participation, both positively and negatively. This study discovered the negative impact that many emotional apprehensions can have on people's participation in self-care routines. Cancer treatment is frequently ambiguous in terms of its impact and course after therapy. Even if the treatment appears to be effective, the individual is often plagued by a fear of recurrence.

When people live in constant fear, it affects their emotional state, which can lead to intrusive thoughts that prevent them from engaging in emotional self-care routines (Cupit-Link et al., 2018). Previous research shows that the diagnosis of cancer and the treatment process also have a comorbidity with certain conditions, such as depression and anxieties. There are many external and internal factors that can cause negative emotions, and having too many of them can have a negative impact on an individual's emotional self-care practices (Kennifer et al., 2009).

Stress is one of the most common and documented factors that influence emotional self-care behaviors and these unpleasant feelings. Individuals' psychological stress has been linked to the tumor's initiation and progression (Soung and Kim, 2015).

Psychological stress is a determinant that has a significant impact on their viewpoint and interactions with one another during treatment (Levkovich et al., 2018).

Psychological factors are also acknowledged as important in eliciting pleasant feelings to optimize emotional self-care practices. The positive emotions identified by the individual assisted them in maintaining an optimistic outlook and taking a positive step during the course of cancer. According to researchers, individual's optimism and emotional stability are related to each other, if people have optimism, his or her quality of life would improve (Finck et al., 2018). Optimism has been reported to be a strong predator of depression in various studies, and it has also been demonstrated to be a helpful coping technique among patients with cancer of all countries and ethnicities (Fasano et al., 2020). Gratitude was identified as a component that aids the individual in bringing a positive attitude to their situation, and they were able to improve and engage in emotional self-care behaviors more optimistically with the virtue of gratitude (Sztachańska et al., 2019).

Individual Factors

From the identified themes, one of the factors that influenced emotional self-care practices is individual factors. Individual self-efficacy is essential when it comes to engaging in emotional self-care activities. The presence of a strong conviction and belief in one's own ability to engage in activities promotes physical and emotional wellbeing, and it acts as a triggering element in determining the amount of time and quality of emotional self-care practices that an individual engages in Chin et al. (2021). When a person is given a diagnosis, they go through a phase of struggle before accepting it. However, the individual's mind will always be preoccupied with blaming actions and questioning the fate. This has a negative and destructive impact on self-efficacy, leading to degenerative practices in terms of emotional self-care on the inside (Doble et al., 2020). The study discovered that questioning and blaming oneself was one of the most common answers presented to the participants to clarify that most of the participants had gone through and had a negative impact on their emotional self-care behavior. Emotional self-care is developed not only by the individual but also by the influence that others have on them. Modeling someone who actively engages in emotional self-care activities encourages others to engage in such health-promoting behaviors on their own, allowing them to care for themselves both physically and emotionally (Lin et al., 2019). The difference between the individual's condition before and after treatment is enormous. To assist the treatment, people must make a variety of changes to their daily routine (McGeechan et al., 2022). Even when there is a significant difference between what was and what is now, participants observed that people who consider themselves to be patients frequently lose strength and capacity and are perceived as weak. Individuals who see themselves as normal people who go about their daily lives as they always have instilled greater power and confidence in themselves to overcome their circumstances (Kohi et al., 2019).

Socioeconomic Factors

Socioeconomic factors were elicited to understand its influence on the engagement of emotional self-care practices. According to the findings, when insurance and other agencies take care of financial platforms, there is less tension and concern than when people lack financial assistance and stability. This intriguing aspect links specific predisposing ideas to poor emotional health, resulting in a reduction in the quality of emotional self-care actions that the individual engages in Carrera et al. (2018). Another factor that was identified to influence the emotional self-care behavior was education. Individuals' awareness of the importance of self-care and dealing with medical conditions, particularly understanding their conditions and how effectively they can deal with them, has significantly impacted their emotional self-care practices. Individual self-care was observed to improve and be applied more frequently when there was a presence of education and a clear idea for the individual self-care in general (Kohi et al., 2019). Connecting to an individual's financial stability and occupation is also important in emotional self-care techniques. Being in a work environment allows individuals to improve their personal and professional lives by demonstrating genuine concern and adopting a normal-life attitude. Occupation improves a person's financial situation and makes them feel strong and supported by their coworkers and their work (Murfin et al., 2020). When a person has a positive view, the amount of time working on their emotional health can increase.

Cultural Factors

As the study is conducted in India, the cultural diversity among the specific geographical areas has an influence on certain behaviors. The wide variety of cultural aspects, religious beliefs, and norms that the society follows differ accordingly. Stemming from different mythological and religious texts, there are specific norms and thoughts which are beneficial as well as detrimental in nature (Bose, 2012). Participants in the study stated that following the cultural norms and practices is difficult and infuriating when there is societal pressure to conform to certain norms and practices. These cultural norms and practices often go too far, affecting an individual's emotional self-care. Several norms and practices will not agree or go along with the idea of emotional self-care when there is a complete shift in how an individual seeks time away from society and takes care of themselves emotionally (Williams et al., 2016). This creates a negative outlook and hinders the individual's ability to engage in a variety of emotional self-care practices that actually would help them to deal with their conditions and pain.

Spiritual Factors

In terms of emotional self-care, an individual's belief in a higher power has been found to be an influencing factor and a supportive structure. The spiritual conviction gave them hope that they would be able to overcome their serious medical problem. Belief in spiritual powers, such as God, instilled a sense of optimism in patients. Prior evidence showed that an individual's faith in God had a major influence on shaping behaviors, leading them to engage in a variety of activities that assisted in improving their living situations through the developed and spiritual health locus of control (Meadows et al., 2020). Individuals' meditative practices and characteristics were also found to provide them with a sense of calmness and relaxation, allowing them to improve and engage more effectively in their emotional self-care, resulting in quality emotional wellbeing (Nuraini et al., 2018).

Limitations of the Study

One major limitation of this study is the sample chosen focusing on patients with cancer in general, with participants majorly diagnosed with breast and lung cancer. Hence, more unique information could have been gathered by focusing on specific cancer types. The study was conducted amidst the COVID-19 pandemic, therefore, the researcher had chosen the telephonic interview method, and the major limitation of this method was that it restricts the interviewer from observing nonverbal responses. As this study used a purposive sampling method, it restricts the findings from generalization. Hence, future studies can focus on understanding cancer-type-specific self-care behaviors to accumulate precise information. The lack of participation encountered during the initial data collection process is also one of the limitations of the study. Due to this, the researchers could not collect data from the large sample size.

Conclusion and Future Directions

Emotional self-care is a significant aspect that studies have identified as an important part of proper symptom management. This study identified the various factors that influence emotional self-care among Indians. In a pandemic-stricken era, being more at risk for infection and lack of proper accessibility to health care, a patient with cancer was not able to get proper health attention (Wang et al., 2021). Currently, illness management is encouraged to be done by the self; this knowledge assists health workers in developing effective cancer management techniques by improving the component of emotional self-care. When the patient engages in self-care practices, they should also be physically and emotionally at equilibrium to have symptom management. But most of the available interventions and studies have given an extreme focus to physical self-care, leaving out the emotional self-care aspects. In the future, incorporating this study findings' specific measures to understand emotional self-care behaviors and engagement can be formulated. Also, new effective interventions can be formulated by involving emotional self-care, so that effective self-management can be catered. This study findings also focus on how the caregiver and the society should be trained and made aware of these influencing factors to adopt holistic management by engaging the patient and the society to bring about a difference in the patients' lives. Incorporating this information, professionals working in this field can formulate productive plans and techniques to enhance holistic self-care practices. Services can be rendered through several self-help awareness classes for the patients along forming self-help groups among patients to enhance and incorporate self-care techniques into their treatment regime. This technique will also provide psychoeducation to society on how to respond to the treatment and diagnosis of cancer.

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 Ethical Review Board for the Protection of Human Subjects in Research, Central University of Karnataka, Kalaburagi, India. The Ethics Committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

AS has contributed to the conceptualization of the study, investigation, validation of data, and writing of the manuscript. ER has contributed to conceptualization, methods, supervision, and reviewing. RJ has contributed to conceptualization, methods, validation of data, and reviewing. MD has contributed to data analysis, reviewing, and writing of the manuscript. AG contributed in supervision and reviewing. RG has contributed to the data analysis. TJ has contributed to the preparation and editing of the manuscript. All authors contributed to the article and approved the submitted version.

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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.

APPENDIX

INTERVIEW SCHEDULE

Self-Care Awareness

1. What is your idea/viewpoint about self-care behaviors?
2. According to you can you explain what are self-care practices and self-care behavior?
3. What do you think emotional self-care can be? Can you elaborate on it?
4. Can you explain about what could be the possible difference between physical and emotional self-care according to you?

FACTORS INFLUENCING EMOTIONAL SELF-CARE

Psychological

5. How do you think that your emotional states and your emotional wellbeing influence your emotional self-care practices?
6. Can you explain about your opinion about the influences that are made in your self-care practices by several negative feelings, such as fear, anxiety, depression, and feeling of uncertainty?
7. According to you do, can you explain whether that the belief that you have in your abilities actually influences your emotional self-care practices?
8. How do you think that self-image and self-identity can influence your emotional self-care practices?
9. Do you think the level of stress that you encounter actually can bring about a influence in your emotional self-care practices?

Social and Cultural

10. Can you elaborate on your viewpoints about the influence that your society play on emotional self-care practices? Do you think the amount of social support that an individual receive plays a role in their emotional self-care practices?
11. Around you, if there is a presence of someone who engages in a proper self-care regime actually influence you in engaging in self-care practices and why?
12. Do the culture and the ethnic group you belong to, its rules and regulation, and its ethical standards actually influence your emotional self-care practices, can you elaborate why?
13. Does, the religion or the belief system that you follow have an impact on the emotional self-care practices that you follow and how do you think it happens?

Sociodemographic Variables

14. Do the age and the gender that you belong to influence your emotional self-care practices and can you explain why?
15. Can you elaborate on to what extend do think that your education and occupation play an important role in the emotional self-care practices?
16. What can be the influences of your socioeconomic states have an influence on your emotional self-care practices and can you explain why?
17. How do you think that your marital status determines your level of engagement in emotional self-care practices?
18. According to you, how do you think the type of residence that you belong to have an influence on your emotional self-care practices?

SYSTEMATIC REVIEW
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The Impact of Mindfulness-Based Stress Reduction (MBSR) on Psychological Outcomes and Quality of Life in Patients With Lung Cancer: A Meta-Analysis

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Objective: The impact of the mindfulness-based stress reduction (MBSR) program on psychological outcomes and quality of life (QoL) in lung cancer patients remains unclear. This meta-analysis aimed to evaluate the effectiveness of the MBSR program on psychological states and QoL in lung cancer patients.

Methods: Eligible studies published before November 2021 were systematically searched from PubMed, EMBASE, Cochrane Library, PsycINFO, China National Knowledge Infrastructure (CNKI), and Wanfang databases. The risk of bias in eligible studies was assessed using the Cochrane tool. Psychological variables and QoL were evaluated as outcomes. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to grade the levels of evidence. Statistical analysis was conducted using RevMan 5.4 and STATA 14.0.

Results: A total of 17 studies involving 1,680 patients were included for meta-analysis eventually. MBSR program significantly relieved cancer-related fatigue (standard mean difference [SMD], −1.26; 95% confidence interval [CI], −1.69 to −0.82; moderate evidence) and negative psychological states (SMD, −1.35; 95% CI, −1.69 to −1.02; low evidence), enhanced positive psychological states (SMD, 0.91; 95% CI, 0.56–1.27; moderate evidence), and improved quality of sleep (MD, −2.79; 95% CI, −3.03 to −2.56; high evidence). Evidence on MBSR programs' overall treatment effect for QoL revealed a trend toward statistical significance ($p = 0.06$, low evidence).

Conclusion: Based on our findings, the MBSR program shows positive effects on psychological states in lung cancer patients. This approach should be recommended as a part of the rehabilitation program for lung cancer patients.

Systematic Review Registration: https://archive.org/details/osf-registrations-mwvbq-v1, identifier: 10.17605/OSF.IO/MWVBQ.

Keywords: lung cancer, mindfulness-based stress reduction, physical and psychological wellbeing, quality of life, meta-analysis

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INTRODUCTION

According to the Global Cancer Statistics 2020, lung cancer ranked second for incidence and first for mortality among all types of cancers worldwide (Sung et al., 2021). Currently, several treatment modalities are available for lung cancer patients, such as surgery, chemotherapy, radiotherapy, immunotherapy, biotherapy, and complementary and alternative therapy (Gadgeel et al., 2012; Jurisevic and Bolevich, 2020; Yang and Luan, 2020); however, patients continue to suffer from serious psychological symptoms (Iyer et al., 2013; Morrison et al., 2017) because most treatment modalities simultaneously destroy both tumor and normal cells (Yang et al., 2020). Meanwhile, except for the adverse effects resulting from treatment modalities, cancer diagnosis also contributes to the development and progression of distressing symptoms (Iyer et al., 2014; Sung et al., 2017).

Patients with lung cancer have more symptom burdens than patients diagnosed with other types of cancer (Chan et al., 2009; Iyer et al., 2014; Morrison et al., 2017). Distressing symptoms can negatively affect the psychosocial wellbeing of patients with lung cancer (Yang et al., 2020; Lee, 2021). A recent study indicated that psychological stress accumulated tumor growth and increased the risk of radio-resistance associated with the activation of epithelial-mesenchymal transition by stress hormone-stimulated adrenergic receptors (Zhang et al., 2020). Moreover, several studies also demonstrated the association between high-level distressing symptoms and poor quality of life (QoL) (Möller and Sartipy, 2012; Park et al., 2016; Choi and Ryu, 2018). Fortunately, psychological interventions have been demonstrated to significantly improve the psychological wellbeing of patients with cancer (Galway et al., 2012; Huang et al., 2016; Cillessen et al., 2019).

Among the currently available psychological interventions, mindfulness-based stress reduction (MBSR), initially developed by Kabat-Zinn et al., 1998, has been widely applied in cancer settings (Lee et al., 2017; Cillessen et al., 2019). The standard MBSR program comprises an 8-week psycho-educational program and four meditative techniques, including sitting meditation, body scan, gentle Hatha yoga, and walking meditation (Kabat-Zinn et al., 1985, 1992, 1998). The exact mechanisms of the MBSR program in improving psychological wellbeing have not been fully clarified, although some studies revealed that it could affect cancer patients' neuroendocrine and immune regulation functions (Davidson et al., 2003; Robinson et al., 2003; Carlson et al., 2004; Hölzel et al., 2011). According to the previously published evidence (Kabat-Zinn et al., 1985; Kabat-Zinn and Santorelli, 2002; Kabat-Zinn, 2003), the practice of mindfulness can guide participants purposefully pay attention to the present moment and non-judgmentally monitor the unfolding of experiences moment by moment, and therefore, having a profound benefit *via* the mind-body connection.

Nevertheless, Garland et al. (2009) proposed a causal model helping to explain the mechanism of mindfulness, named as "Mindful Coping Model." In this model, mindfulness plays a critically important role in the positive reappraisal process (Shapiro et al., 2006). Specifically, if a threat, harm, or loss exceeds one's coping capabilities, then an individual's attention may be transferred from contents to the dynamic process of consciousness by distracting stress appraisal into the model of mindfulness and then increasing individual's attentional flexibility and broadens awareness. From the vantage point of this expanded, metacognitive awareness, one can reconstrue appraisal of the given event as positive by attributing to it a new meaning, which may arise either through a conscious process of reflection or a more automatic process based on spontaneous insight. The reappraisal of the given event then triggers positive emotions to reduce stress and influences subsequent appraisal processes. According to this model and empirical evidence, destructive effects resulting from external and internal stressors (given events) may break an individual's psychosomatic balance (one's coping capabilities) and impair an individual's health status. However, mindfulness can trigger positive emotions by imitating the positive reappraisal (psychological adjustment) to restore psychosomatic balance and improve clinical outcomes.

Currently, studies have demonstrated the effectiveness and safety of the MBSR program on psychosocial wellbeing and QoL (Lee et al., 2017; Cillessen et al., 2019; Xie et al., 2020; Xunlin et al., 2020). Some studies also initially investigated the role of the MBSR program in patients diagnosed with lung diseases, such as lung cancer (van den Hurk et al., 2015; Schellekens et al., 2017) and interstitial lung diseases (Arefnasab et al., 2013; Sgalla et al., 2015). However, the benefits of the MBSR program on psychological wellbeing and QoL of lung cancer patients remain unclear because published studies reported conflicting results. More importantly, the sample size of published studies regarding lung cancer was extremely small, significantly increasing the risk of generating false results. Therefore, we performed this meta-analysis to comprehensively evaluate the effectiveness of the MBSR program on psychological outcomes and QoL of lung cancer patients.

METHODS

Study Design

We reported all results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page et al., 2021). We registered the protocol of this meta-analysis at the Open Science Framework (OSF) (registration number: 10.17605/OSF.IO/MWVBQ) and publicly published it in an academic journal (Tian et al., 2021). This study did not need ethical approval and patients' informed consent because it was a meta-analysis of published data.

Information Sources

Two reviewers independently searched PubMed, EMBASE, Cochrane Library, PsycINFO, China National Knowledge Infrastructure (CNKI), and Wanfang database for relevant randomized controlled trials (RCTs) investigating the effectiveness of the MBSR program on psychological outcomes and QoL among patients with lung cancer. The literature search was limited from its inception until November 2021. The search strategy was constructed by using both the medical subject heading (MeSH) and text words, which were logically connected using Boolean operators. We also checked reference lists of previous systematic reviews with a similar topic and eligible studies to add additional studies. The consensus principle was imposed to resolve any disagreement between the two reviewers. Details of search strategies of English databases are shown in **Supplementary Table 1**.

Study Selection

After removing duplicate studies, two independent reviewers conducted study selection based on the title, abstract, and full-text screening. Studies were included in the meta-analysis if they met the following criteria: (a) adult patients were cytologically or histologically diagnosed with lung cancer; (b) patients in the intervention group received both the MBSR program and usual care (UC), and patients in the control group received UC program alone, which contained at least five elements, including dietary instruction, health education, rehabilitation excise, emotional counseling, and medication instruction; (c) at least one of psychological outcomes and QoL was reported, and corresponding data were suitable for statistical analysis; (d) RCTs published in full-texts; and (e) publication language was restricted into English and Chinese because an extensive range of related research is published in English and Chinese, and no translator of other languages is available in our team. Studies were excluded if they covered at least one of the following criteria: (a) the MBSR program was designed as the part of a comprehensive strategy; (b) mixed patients were enrolled but patients with lung cancer were not separately analyzed; (c) duplicate reports of same data published by the same group; and (d) conference abstract without sufficient data.

Data Extraction

Two reviewers independently extracted essential data from eligible studies using a predesigned standard information extraction sheet, including the first author's name, publication year, country, condition of patients, tumor stage, sample size, mean age, details of the MBSR program, outcomes, and measurements. We extracted the data at the end of the intervention or the last follow-up for statistical analysis. We contacted the corresponding author to obtain the essential data if necessary. The consensus principle was introduced to resolve the disagreement between the two reviewers.

Risk of Bias Assessment

Two reviewers independently assessed the risk of bias in eligible studies using the Cochrane risk of bias assessment tool from seven items (Higgins et al., 2011): random sequence generation, allocation concealment, blinding of personnel and participants, blinding of outcome assessor, incomplete outcome data, selective outcome reporting, and other bias sources. Each item was rated as "low," "unclear," or "high" risk according to the matching level between actual information and assessment criteria. The level of overall methodological quality was judged as "high" if all items were rated as "low" risk of bias, as "low" if at least one item was rated as "high" risk of bias, and "moderate" if at least one item was rated as "unclear" risk of bias, but no item was rated as "high" risk of bias. The consensus principle was introduced to resolve the disagreement between the two reviewers.

Statistical Analysis

Statistical analysis was conducted using Review Manager (RevMan) 5.4 (Cochrane Collaboration, Oxford, United Kingdom) and STATA 14.0 (StataCorp, Texas, USA). All outcomes were continuous variables in this meta-analysis. We, therefore, used mean difference (MD) or standard mean difference (SMD) with a 95% confidence interval (CI) to express all pooled results. We comprehensively evaluated statistical heterogeneity using the Chi-square test (Cochrane Q) and I^2 statistic (Higgins and Thompson, 2002; Higgins et al., 2003). Substantial statistical heterogeneity was considered if the p-value was <0.1 and I^2 was more than 50%. Nevertheless, we used the random-effects model to conduct a meta-analysis because variations across studies are inevitable in real settings. We also designed a series of subgroup analyses to investigate the influence of the MBSR program on different functional dimensions. We did not perform a publication bias test because the number of eligible studies for individual outcomes did not exceed 10 (Egger et al., 1997; Sterne and Egger, 2001; Page et al., 2018). Statistical significance was judged based on two-tail, and a p-value of <0.05 was regarded as the cutoff value of statistical significance.

Quality of Evidence Assessment

Two independent reviewers used the Grading of Recommendations Assessment, Development and Evaluation system (Guyatt et al., 2008) to rate the level of evidence as "high," "moderate," "low," or "very low." With the GRADE system, the level of RCT was initially rated as high, and 5 factors could downgrade the level, including the risk of bias, inconsistency, indirectness, imprecision, and publication bias. Certainly, some factors could also upgrade the level of evidence, such as large effects. The consensus principle was introduced to resolve the disagreement between the two reviewers.

RESULTS

Study Selection

Figure 1 shows the process of study retrieval and selection. We identified 123 records from the database. Notably, 43 duplicate records were first removed. Then, 50 studies were excluded after checking their titles and abstracts. Thirty studies were further assessed for eligibility, while 13 studies were excluded due to: (a) non-RCT design ($n = 3$), (b) lack of essential data ($n = 1$), and (c) unrelated topic ($n = 9$). Finally, 17 studies were included in this meta-analysis (Ning et al., 2017; Schellekens et al., 2017; Wang et al., 2017; Guan and Zhou, 2018; Liu, 2018; Tang et al., 2018; Chen et al., 2019; Liu J. L. et al., 2019; Liu T. et al., 2019; Tian et al., 2019; Wang, 2019; Xu et al., 2019; Ding and Chu, 2020; Feng and Gong, 2020; Wu, 2020; Xi et al., 2020; You, 2020).

Characteristics of Included Studies

All studies (Ning et al., 2017; Wang et al., 2017; Guan and Zhou, 2018; Liu, 2018; Tang et al., 2018; Chen et al., 2019; Liu J. L. et al., 2019; Liu T. et al., 2019; Tian et al., 2019; Wang, 2019; Xu et al., 2019; Ding and Chu, 2020; Feng and Gong, 2020; Wu, 2020; Xi et al., 2020; You, 2020) were conducted in China except for

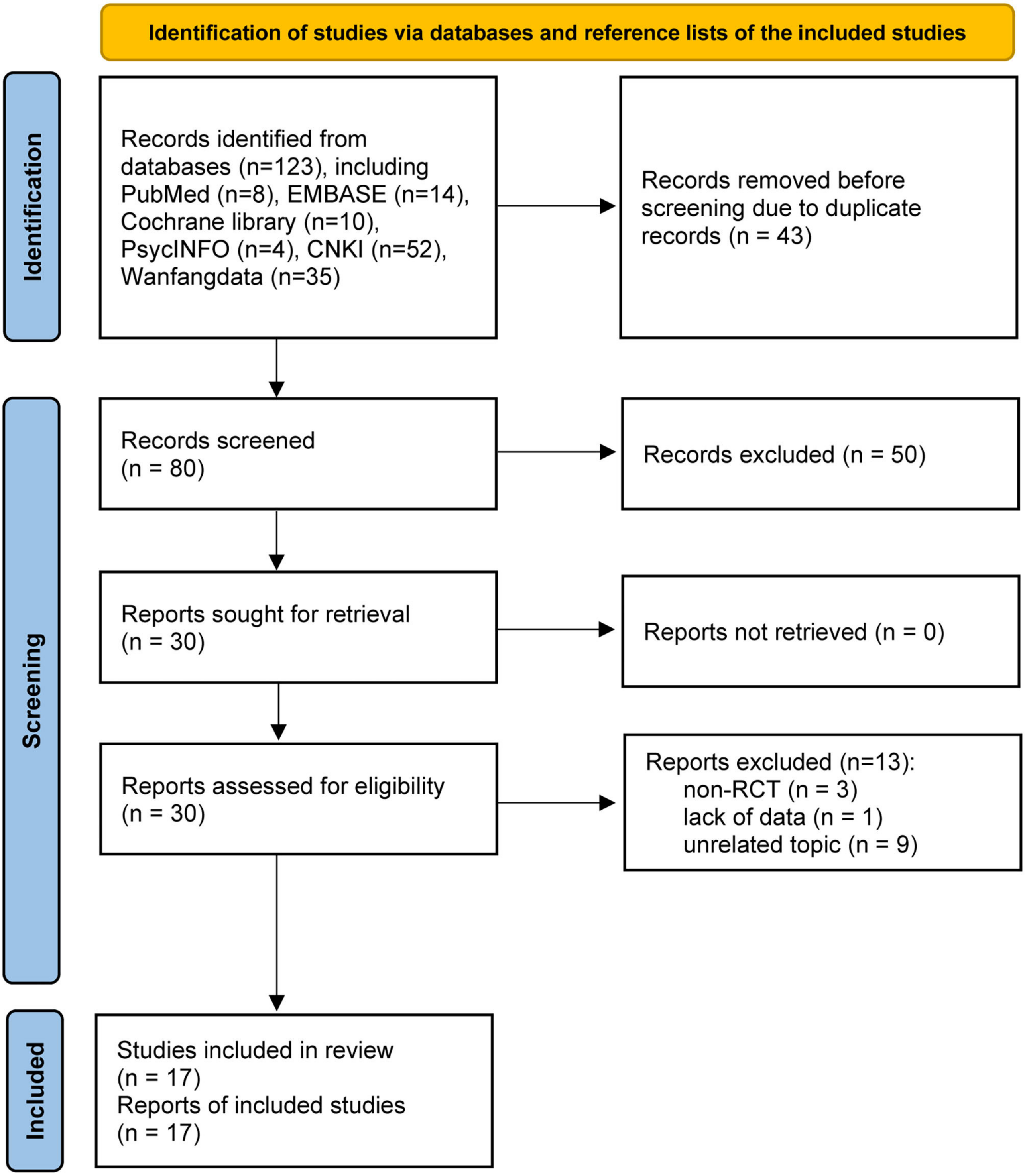


FIGURE 1 | PRISMA flowchart of study retrieval and selection process. CNKI, China National Knowledge Infrastructure.

one study, which was conducted in the Netherlands (Schellekens et al., 2017). All studies were published between 2017 and 2020. The sample size of individual study ranged from 36 to 378, with a total number of 1,680. A total of 13 studies (Ning et al., 2017; Schellekens et al., 2017; Wang et al., 2017; Guan and Zhou, 2018; Liu, 2018; Tang et al., 2018; Chen et al., 2019; Tian et al., 2019;

Xu et al., 2019; Ding and Chu, 2020; Feng and Gong, 2020; Wu, 2020; Xi et al., 2020) used standard 8-week MBSR program, but four studies used modified MBSR protocols, including 3-week program (Liu T. et al., 2019), 4-week program (Liu J. L. et al., 2019; Wang, 2019), and 6-week program (You, 2020). The remaining characteristics of eligible studies are shown in **Table 1**.

Risk of Bias

The risk of bias assessment of included studies is displayed in **Supplementary Figure 1**. Overall, more than half of the studies (52.94%) (Ning et al., 2017; Schellekens et al., 2017; Wang et al., 2017; Chen et al., 2019; Liu J. L. et al., 2019; Tian et al., 2019; Feng and Gong, 2020; Wu, 2020; You, 2020) were judged as "low" risk of bias due to the attrition bias. Generally, the majority of studies (Ning et al., 2017; Wang et al., 2017; Guan and Zhou, 2018; Liu, 2018; Tang et al., 2018; Chen et al., 2019; Liu J. L. et al., 2019; Liu T. et al., 2019; Tian et al., 2019; Wang, 2019; Xu et al., 2019; Ding and Chu, 2020; Feng and Gong, 2020; Wu, 2020; Xi et al., 2020; You, 2020) did not report details of allocation concealment and blinding of personnel, participants, and outcome assessors.

Cancer-Related Fatigue

A total of seven studies reported the overall level of cancer-related fatigue (Wang et al., 2017; Guan and Zhou, 2018; Liu, 2018; Tang et al., 2018; Chen et al., 2019; Wang, 2019; Wu, 2020); however, five (Wang et al., 2017; Liu, 2018; Tang et al., 2018; Wang, 2019; Wu, 2020) and three studies (Guan and Zhou, 2018; Chen et al., 2019) used the Revised Piper Fatigue Scale (R-PFS) and Cancer Fatigue Scale (CFS) to measure this outcome, respectively. Therefore, SMD was used to express the pooled results. Meta-analysis revealed a significant improvement in patients receiving MBSR program (514 patients; $I^2 = 80\%$; SMD, −1.26; 95% CI: −1.69 to −0.82; $p < 0.001$; **Figure 2A**), which was supported by moderate evidence (**Table 2**).

Negative Psychological Status

A total of eight studies (Ning et al., 2017; Chen et al., 2019; Liu J. L. et al., 2019; Tian et al., 2019; Xu et al., 2019; Ding and Chu, 2020; Wu, 2020; You, 2020) reported the changes of negative psychological states, including anxiety, depression, and psychological distress. It is noted that the level of anxiety was measured by using the Self-rating Anxiety Scale (SAS) and Hamilton Anxiety Scale (HAMA), and the level of depression was measured by using the Self-rating Depression Scale (SDS) and Hamilton Depression Scale (HAMD), and the level of psychological distress was measured using Distress Thermometer (DT). Therefore, SMD was selected as the measurement to express the pooled result of negative psychological states. Meta-analysis suggested that patients receiving the MBSR program had a significantly lower level of negative psychological outcomes compared with patients receiving UC alone (1,029 patients; $I^2 = 92\%$; SMD, −1.35; 95% CI, −1.69 to −1.02; $p < 0.001$; **Figure 2B**), which was only supported by low evidence (**Table 2**). It is noted that the level of anxiety (1,029 patients; $I^2 = 88\%$; SMD, −1.48; 95% CI, −1.91 to −1.05; $p < 0.001$), depression (765 patients; $I^2 = 52\%$; SMD, −0.98; 95% CI, −1.21 to −0.76; $p < 0.001$), and psychological distress (470 patients; $I^2 = 97\%$; SMD, −2.05; 95% CI, −3.64 to −0.45; $p = 0.01$) were all significantly lower in the MBSR group.

Positive Psychological Status

Among the 17 included studies, four studies reported changes in positive psychological states, including self-efficacy and mindfulness. We selected SMD to express the pooled result because self-efficacy and mindfulness were combined as an individual outcome. For self-efficacy, the "strategies used by people to promote health (SUPPH)" was used as the measurement; however, the level of mindfulness was measured by using the Mindful Attention Awareness Scale (MASS) and Five Facet Mindfulness Questionnaire (FFMQ). Meta-analysis suggested that the MBSR program significantly improved the positive psychological states (292 patients; $I^2 = 62\%$; SMD, 0.91; 95% CI, 0.56–1.27; $p < 0.001$; **Figure 3**), which was only supported by moderate evidence (**Table 2**). It is noted that the level of self-efficacy (253 patients; $I^2 = 76\%$; SMD, 0.97; 95% CI, 0.42–1.52; $p < 0.001$) and mindfulness (139 patients; $I^2 = 28\%$; SMD, 0.82; 95% CI, 0.39–1.25; $p < 0.001$) were all significantly improved in the MBSR group.

Quality of Sleep

Four studies (Xu et al., 2019; Feng and Gong, 2020; Xi et al., 2020; You, 2020) reported the quality of sleep, but the total score of the Pittsburgh sleep quality index (PSQI) was available in two studies (Xu et al., 2019; You, 2020). Meta-analysis suggested that the MBSR program significantly improved the quality of sleep compared with UC alone (546 patients; $I^2 = 0\%$; MD, −2.79; 95% CI, −3.03 to −2.56; $p < 0.001$; **Figure 4A**), which was supported by high evidence (**Table 2**). Subgroup analysis was conducted to investigate the impact of the MBSR program on different dimensions, including sleep quality, sleep duration, sleep disturbance, habitual sleep efficiency, sleep latency, use of sleeping medication, and daytime dysfunction, and pooled results revealed that the MBSR program only significantly influences sleep latency, use of sleeping medication, and daytime dysfunction (**Figure 4A**).

Quality of Life

Four studies (Schellekens et al., 2017; Liu J. L. et al., 2019; Wang, 2019; Wu, 2020) reported QoL, but only 3 (Schellekens et al., 2017; Liu J. L. et al., 2019; Wu, 2020) provided total EORTC QLQ-C30 score. Meta-analysis on MBSR programs' overall treatment effect for QoL revealed a trend toward statistical significance (241 patients; $I^2 = 97\%$; MD, 9.55; 95% CI, −0.47–19.58; $p = 0.06$; **Figure 4B**), which was only supported by low evidence (**Table 2**). However, subgroup analysis revealed that MBSR had considerable influence on all dimensions, including emotional, physical, role, social, and cognitive aspects (**Figure 4B**).

DISCUSSION

Lung cancer remains the leading type of cancer worldwide, accounting for ∼11.4% of new cancer cases and 18.0% of cancer-related deaths in 2020 (Sung et al., 2021). Patients with

TABLE 1 | Basic characteristics of the included studies ($n = 17$).

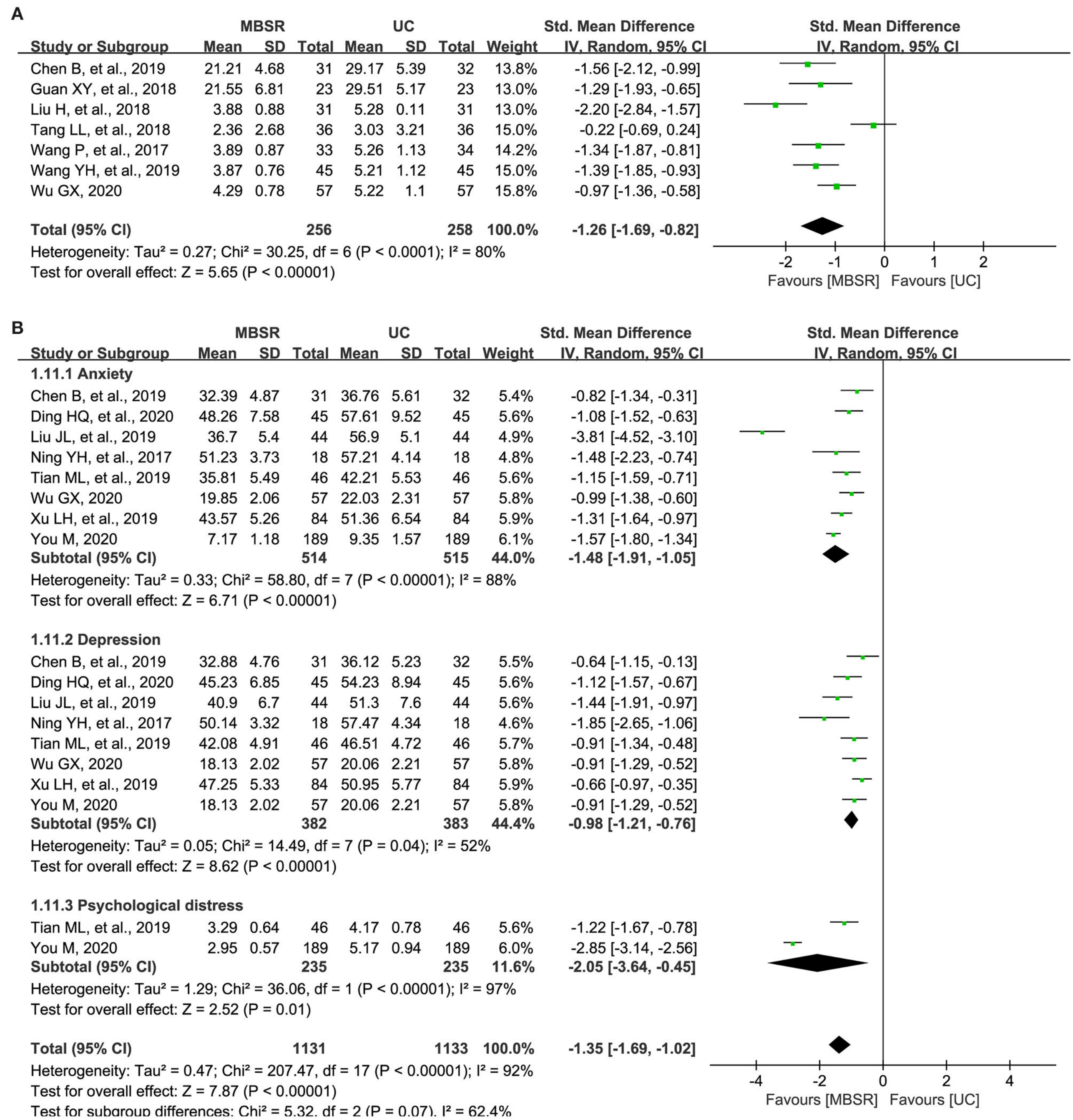
References	Country	Patients	Stage	Sample for analysis		Mean age, years		Details of MBSR	Follow-up	Outcomes	Instrument
				MBSR	**UC**	**MBSR**	**UC**				
Wang et al. (2017)	China	Lung cancer underwent surgery and chemotherapy	0, I–III	33	34	n.a.	n.a.	8-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 8 weekly group-based 2-h sessions and once-daily 30-min self-training. Patients were supervised to daily practice after discharge by a nurse using telephone or WeChat.	8 weeks	CRF	RPFS
Liu (2018)	China	Lung cancer	n.a.	31	31	62.5	62.3	8-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 8 weekly group-based 2-h sessions and once-daily self-training. Patients were supervised to daily practice after discharge by a nurse using telephone or WeChat.	8 weeks	CRF	RPFS
Wang (2019)	China	Lung cancer	0, I–III	45	45	45	56.02	4-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 10-min explanation and meditation in the first week, 10-min walking meditation in the second week, 10-min breathing meditation in the third week, and 20-min experience sharing in the fourth week. Patients were supervised to daily practice after discharge by a nurse twice weekly using telephone or WeChat.	4 weeks	CRF, QoL	RPFS, EORTC QLQ-C30
Ding and Chu (2020)	China	Lung cancer underwent chemotherapy	III, IV	45	45	55.26	53.59	8-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 8 weekly group-based 2-h sessions and once-daily self-exercise. Patients were supervised to daily train after discharge by a nurse using telephone or WeChat.	8 weeks	Anxiety, depression, CRF, self-efficacy	SAS, SDS, CFS, SUPPH
Xi et al. (2020)	China	NSCLC underwent chemotherapy	III, IV	34	34	62	62	8-week MBSR protocol training under the guidance and supervision of a nurse with qualification, consisting of 8 weekly group-based 30-min sessions. Patients were supervised to train after discharge was implemented by nurses using the telephone twice per week.	8 weeks	CRF, quality of sleep	RPFS, PSQI
Guan and Zhou (2018)	China	Lung cancer underwent chemotherapy	I–IV	23	23	54.4	51.8	8-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 6 weekly group-based 30-min sessions. Patients were supervised to daily practice after discharge by a nurse using telephone or WeChat.	8 weeks	CRF, self-efficacy	CFS, SUPPH
Xu et al. (2019)	China	Lung cancer underwent chemotherapy	II–IV	84	84	n.a.	n.a.	8-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 6 weekly 30–45-min self-practice at 9:00–10:00 a.m. and 17:00–18:00. Patients were supervised to practice MBSR for 30–45 min daily by a nurse using the telephone after discharge.	8 weeks	Anxiety, depression, quality of sleep	SAS, SDS, PSQI
Liu T. et al. (2019)	China	Lung cancer underwent chemotherapy	II, III	50	50	54.49	57.65	3-week MBSR program practice under the guidance and supervision of a qualified nurse, consisting of 3 weekly group-based 30–40-min sessions including a 15-min explanation from a trainer and 20–30 min of training. Patients were supervised to practice MBSR for 30–45 min daily by a nurse using the telephone after discharge.	12 weeks	Self-efficacy, mindfulness	SUPPH, MAAS

(Continued)

TABLE 1 | Continued

References	Country	Patients	Stage	Sample for analysis		Mean age, years		Details of MBSR	Follow-up	Outcomes	Instrument
				MBSR	**UC**	**MBSR**	**UC**				
Liu J. L. et al. (2019)	China	Lung cancer underwent chemotherapy	n.a.	44	44	56	55	4-week MBSR program under the guidance and supervision of a qualified nurse, consisting of 4 weekly group-based 2-h sessions and 30-min self-practice daily.	10 weeks	Anxiety, depression, QoL	SAS, SDS, EORTC QLQ-C30
Ning et al. (2017)	China	Lung cancer	n.a.	18	18	39.81	40.76	Standard 8-week MBSR program, which was accessed from www.iepsy.com, under the guidance and supervision of a qualified nurse.	8 weeks	Anxiety, depression	SAS, SDS
Tang et al. (2018)	China	Lung cancer underwent surgery and chemotherapy	I–III	36	36	53.22	50.55	8-week MBSR program under the guidance and supervision of a qualified nurse, consisting of 8 weekly group-based 2-h sessions including a 30-min explanation from a trainer, 30-min practice, 30-min question, and 30-min experience-sharing. Patients were supervised to practice MBSR daily by a nurse using the telephone after discharge.	8 weeks	CRF	RPFS
Tian et al. (2019)	China	Lung cancer underwent concurrent chemoradiotherapy	n.a.	46	46	53.51	54.12	8-week MBSR program, consisting of 8 weekly group-based 30–40-min sessions and self-practice daily. Patients were supervised to practice MBSR daily by a nurse using the telephone after discharge.	8 weeks	Psychological distress, anxiety, depression, the activity of daily living	DT, SAS, SDS, ADL
Wu (2020)	China	Lung cancer underwent chemotherapy	0, I–III	57	57	67.49	67.51	8-week MBSR program training under the guidance and supervision of a qualified nurse, consisting of 8 weekly group-based 30-min sessions and self-practice every day.	8 weeks	CRF, anxiety, depression, QoL	RPFS, HAMA, HAMD, EORTC QLQ-C30
You (2020)	China	Early lung cancer underwent surgery	n.a.	189	189	57.73	58.43	6-week MBSR program under the guidance and supervision of a nurse with qualification, consisting of 6 weekly group-based 2-h sessions, including 30-min explanation, 60-min self-practice, and 30-min experience-sharing.	6 weeks	Psychological distress, anxiety, depression, quality of sleep, performance status	DT, HAMA, HAMD, PSQI, KPS
Schellekens et al. (2017)	Netherlands	Lung cancer	I–IV	21	18	60.6	57	8-week MBSR program, consisting of 1 weekly 2.5-h group training, a silent day between sessions 6 and 7, and home practice assignments of about 45 min, 6 days per week.	3 months	Anxiety, depression, QoL, mindfulness	HADS, EORTC QLQ-C30, FFMQ
Chen et al. (2019)	China	NSCLC underwent chemotherapy	n.a.	31	32	57.83	59.11	8-week MBSR program under the guidance and supervision of a qualified nurse, consisting of 1 weekly 2-h group training and self-practice daily. Patients were supervised to daily practice MBSR by a nurse using the telephone after discharge.	8 weeks	CRF, anxiety, depression	CFS, SAS, SDS
Feng and Gong (2020)	China	Lung cancer underwent chemotherapy	n.a.	54	53	57.69	57.34	8-week MBSR program under the guidance and supervision of a qualified nurse, consisting of 1 weekly 2-h group practice at 9:00–10:00 a.m. or 17:00–18:00 and 30-min self-practice at home.	8 weeks	CRF, self-efficacy, quality of sleep	RPFS, SUPPH, PSQI

NSCLC, non-small-cell lung cancer; CRF, cancer-related fatigue; QoL, quality of life; R-PFS, Revised Piper Fatigue Scale; CFS, Cancer Fatigue Scale; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; HADS, Hospital Anxiety and Depression Scale; DT, distress thermometer; SUPPH, strategies used by people to promote health; MAAS, Mindful Attention Awareness Scale; ADL, Activity of Daily Living Scale; PSQI, Pittsburgh sleep quality index; EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; FFMQ, Five Facet Mindfulness Questionnaire; KPS, Karnofsky performance status; MBSR, mindfulness-based stress reduction; US, usual care; n.a., not applicable.



A

Study or Subgroup	MBSR Mean	MBSR SD	MBSR Total	UC Mean	UC SD	UC Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chen B, et al., 2019	21.21	4.68	31	29.17	5.39	32	13.8%	-1.56 [-2.12, -0.99]
Guan XY, et al., 2018	21.55	6.81	23	29.51	5.17	23	13.0%	-1.29 [-1.93, -0.65]
Liu H, et al., 2018	3.88	0.88	31	5.28	0.11	31	13.0%	-2.20 [-2.84, -1.57]
Tang LL, et al., 2018	2.36	2.68	36	3.03	3.21	36	15.0%	-0.22 [-0.69, 0.24]
Wang P, et al., 2017	3.89	0.87	33	5.26	1.13	34	14.2%	-1.34 [-1.87, -0.81]
Wang YH, et al., 2019	3.87	0.76	45	5.21	1.12	45	15.0%	-1.39 [-1.85, -0.93]
Wu GX, 2020	4.29	0.78	57	5.22	1.1	57	15.8%	-0.97 [-1.36, -0.58]
Total (95% CI)			**256**			**258**	**100.0%**	**-1.26 [-1.69, -0.82]**

Heterogeneity: Tau² = 0.27; Chi² = 30.25, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 5.65 (P < 0.00001)

B

Study or Subgroup	MBSR Mean	MBSR SD	MBSR Total	UC Mean	UC SD	UC Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.11.1 Anxiety								
Chen B, et al., 2019	32.39	4.87	31	36.76	5.61	32	5.4%	-0.82 [-1.34, -0.31]
Ding HQ, et al., 2020	48.26	7.58	45	57.61	9.52	45	5.6%	-1.08 [-1.52, -0.63]
Liu JL, et al., 2019	36.7	5.4	44	56.9	5.1	44	4.9%	-3.81 [-4.52, -3.10]
Ning YH, et al., 2017	51.23	3.73	18	57.21	4.14	18	4.8%	-1.48 [-2.23, -0.74]
Tian ML, et al., 2019	35.81	5.49	46	42.21	5.53	46	5.6%	-1.15 [-1.59, -0.71]
Wu GX, 2020	19.85	2.06	57	22.03	2.31	57	5.8%	-0.99 [-1.38, -0.60]
Xu LH, et al., 2019	43.57	5.26	84	51.36	6.54	84	5.9%	-1.31 [-1.64, -0.97]
You M, 2020	7.17	1.18	189	9.35	1.57	189	6.1%	-1.57 [-1.80, -1.34]
Subtotal (95% CI)			**514**			**515**	**44.0%**	**-1.48 [-1.91, -1.05]**
Heterogeneity: Tau² = 0.33; Chi² = 58.80, df = 7 (P < 0.00001); I² = 88%								
Test for overall effect: Z = 6.71 (P < 0.00001)								
1.11.2 Depression								
Chen B, et al., 2019	32.88	4.76	31	36.12	5.23	32	5.5%	-0.64 [-1.15, -0.13]
Ding HQ, et al., 2020	45.23	6.85	45	54.23	8.94	45	5.6%	-1.12 [-1.57, -0.67]
Liu JL, et al., 2019	40.9	6.7	44	51.3	7.6	44	5.6%	-1.44 [-1.91, -0.97]
Ning YH, et al., 2017	50.14	3.32	18	57.47	4.34	18	4.6%	-1.85 [-2.65, -1.06]
Tian ML, et al., 2019	42.08	4.91	46	46.51	4.72	46	5.7%	-0.91 [-1.34, -0.48]
Wu GX, 2020	18.13	2.02	57	20.06	2.21	57	5.8%	-0.91 [-1.29, -0.52]
Xu LH, et al., 2019	47.25	5.33	84	50.95	5.77	84	5.9%	-0.66 [-0.97, -0.35]
You M, 2020	18.13	2.02	57	20.06	2.21	57	5.8%	-0.91 [-1.29, -0.52]
Subtotal (95% CI)			**382**			**383**	**44.4%**	**-0.98 [-1.21, -0.76]**
Heterogeneity: Tau² = 0.05; Chi² = 14.49, df = 7 (P = 0.04); I² = 52%								
Test for overall effect: Z = 8.62 (P < 0.00001)								
1.11.3 Psychological distress								
Tian ML, et al., 2019	3.29	0.64	46	4.17	0.78	46	5.6%	-1.22 [-1.67, -0.78]
You M, 2020	2.95	0.57	189	5.17	0.94	189	6.0%	-2.85 [-3.14, -2.56]
Subtotal (95% CI)			**235**			**235**	**11.6%**	**-2.05 [-3.64, -0.45]**
Heterogeneity: Tau² = 1.29; Chi² = 36.06, df = 1 (P < 0.00001); I² = 97%								
Test for overall effect: Z = 2.52 (P = 0.01)								
Total (95% CI)			**1131**			**1133**	**100.0%**	**-1.35 [-1.69, -1.02]**

Heterogeneity: Tau² = 0.47; Chi² = 207.47, df = 17 (P < 0.00001); I² = 92%
Test for overall effect: Z = 7.87 (P < 0.00001)
Test for subgroup differences: Chi² = 5.32, df = 2 (P = 0.07), I² = 62.4%

FIGURE 2 | Forest plot of comparative effectiveness between mindfulness-based stress reduction (MBSR) program and UC in terms of cancer-related fatigue **(A)** and negative psychological states **(B)**. MBSR, mindfulness-based stress reduction; UC, usual care; R-PFS, Revised Piper Fatigue Scale; CFS, Cancer Fatigue Scale; SAS, Self-rating Anxiety Scale; SDS, Self-rating Depression Scale; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Scale; SD, standard deviation.

lung cancer suffer from a significant psychological symptom burden resulting from the destructive effects of anticancer treatment and cancer diagnosis (Iyer et al., 2014; Morrison et al., 2017), which greatly impair an individual's psychological wellbeing and reduce QoL (Iyer et al., 2013; Morrison et al., 2017). Psychological interventions have a positive impact on psychological outcomes among patients with cancer, and as a common type of psychological intervention, MBSR has also been extensively demonstrated to have a positive role in improving psychological outcomes among patients with cancer (van den Hurk et al., 2015; Lee et al., 2017; Xie et al., 2020). However, the role of the MBSR program in

TABLE 2 | The level of evidence based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.

Certainty assessment							**No. of patients**		**Effect**	**Certainty**	**Importance**
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**MBSR**	**UC**	**Absolute (95% CI)**		
Cancer-related fatigue											
5	Randomized trials	Serious[a]	Not serious	Not serious	Not serious	None	256	258	SMD **−1.26 lower** (−1.69 lower to −0.82 lower)	⊕⊕⊕◯ Moderate	CRITICAL
Negative psychological status											
8	Randomized trials	Serious[b]	Not serious	Not serious	Serious[c]	Strong association	514	515	SMD **−1.35 lower** (−1.69 lower to −1.02 lower)	⊕⊕◯◯ Low	IMPORTANT
Positive psychological status											
4	Randomized trials	Not serious	Not serious	Not serious	Very serious[c]	None	148	144	SMD **0.91 SD higher** (0.56 higher to 1.27 higher)	⊕⊕⊕◯ Moderate	IMPORTANT
Quality of sleep											
2	Randomized trials	Serious[b]	Not serious	Not serious	Not serious	Strong association	273	273	MD **2.79 lower** (3.03 lower to 2.56 lower)	⊕⊕⊕⊕ High	IMPORTANT
Quality of life											
3	Randomized trials	Serious[d]	Not serious	Not serious	Serious[c]	None	122	119	MD **9.55 lower** (0.47 lower to 19.58 higher)	⊕⊕◯◯ Low	IMPORTANT

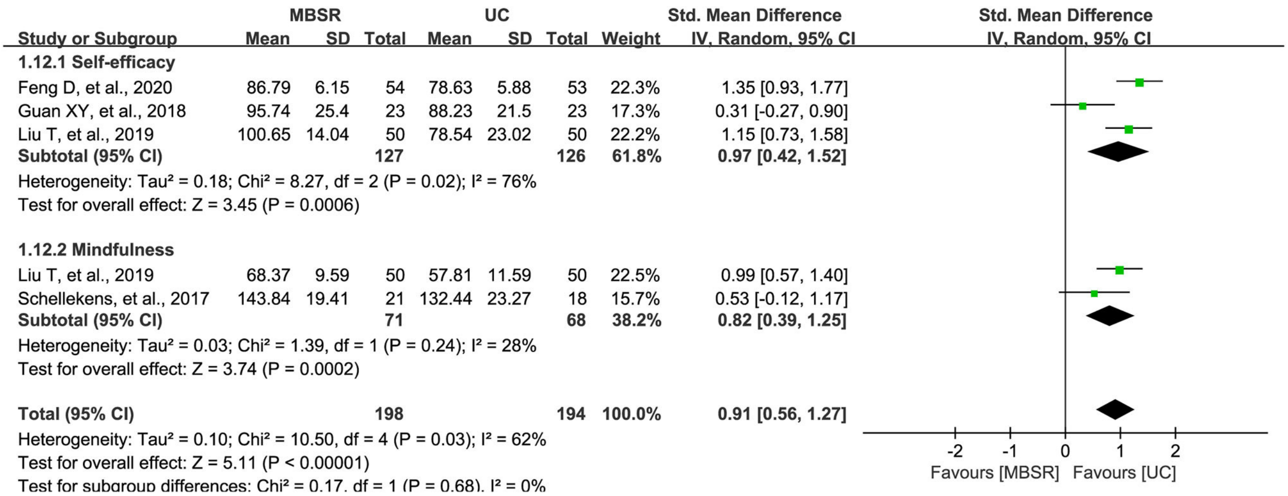
CI, confidence interval; MBSR, mindfulness-based stress reduction; MD, mean difference; US, usual care; SMD, standardized mean difference.

[a] *Two eligible studies were judged to be at high risk of bias.*

[b] *One eligible study was judged to be at high risk of bias.*

[c] *Inadequate sample size was accumulated.*

[d] *Most eligible studies were judged to be at high risk of bias.*



Study or Subgroup	MBSR Mean	MBSR SD	MBSR Total	UC Mean	UC SD	UC Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 Self-efficacy								
Feng D, et al., 2020	86.79	6.15	54	78.63	5.88	53	22.3%	1.35 [0.93, 1.77]
Guan XY, et al., 2018	95.74	25.4	23	88.23	21.5	23	17.3%	0.31 [-0.27, 0.90]
Liu T, et al., 2019	100.65	14.04	50	78.54	23.02	50	22.2%	1.15 [0.73, 1.58]
Subtotal (95% CI)			**127**			**126**	**61.8%**	**0.97 [0.42, 1.52]**
Heterogeneity: Tau² = 0.18; Chi² = 8.27, df = 2 (P = 0.02); I² = 76%								
Test for overall effect: Z = 3.45 (P = 0.0006)								
1.12.2 Mindfulness								
Liu T, et al., 2019	68.37	9.59	50	57.81	11.59	50	22.5%	0.99 [0.57, 1.40]
Schellekens, et al., 2017	143.84	19.41	21	132.44	23.27	18	15.7%	0.53 [-0.12, 1.17]
Subtotal (95% CI)			**71**			**68**	**38.2%**	**0.82 [0.39, 1.25]**
Heterogeneity: Tau² = 0.03; Chi² = 1.39, df = 1 (P = 0.24); I² = 28%								
Test for overall effect: Z = 3.74 (P = 0.0002)								
Total (95% CI)			**198**			**194**	**100.0%**	**0.91 [0.56, 1.27]**
Heterogeneity: Tau² = 0.10; Chi² = 10.50, df = 4 (P = 0.03); I² = 62%								
Test for overall effect: Z = 5.11 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								

FIGURE 3 | Forest plot of comparative effectiveness between the MBSR program and UC in terms of positive psychological status. MBSR, mindfulness-based stress reduction; UC, usual care; SUPPH, strategies used by people to promote health.

the treatment of patients with lung cancer has not yet been fully investigated.

In this meta-analysis, we obtained a comprehensive summary of studies investigating the effectiveness of the MBSR program on psychological outcomes (negative vs. positive aspects), quality of sleep, and QoL in lung cancer patients. Findings of this meta-analysis suggest that the MBSR program significantly relieves cancer-related fatigue, improves negative psychological states, including anxiety, depression, and psychological distress, enhances positive psychological states, including self-efficacy and mindfulness, and improves the quality of sleep. Unfortunately, meta-analysis does not reveal a statistical difference in QoL between the MBSR program and UC alone. However, the MBSR program tends to have a beneficial influence on QoL. Meanwhile, subgroup analysis suggests that the MBSR program significantly improved all dimensions of QoL compared with UC alone.

Till present, only one meta-analysis (Xie et al., 2020) investigated the effects of the MBSR program on cancer-related fatigue of patients with lung cancer based on subgroup analysis. In this meta-analysis, 3 eligible studies involving 185 patients with lung cancer were included to evaluate the effects of the MBSR program on cancer-related fatigue, and the result suggested that the MBSR program was significantly associated with a decreased level of cancer-related fatigue compared with UC alone (SMD, −0.95; 95% CI, −1.74 to −0.15; $p = 0.02$). Although the previous meta-analysis reported a consistent result with our meta-analysis in terms of cancer-related fatigue, our meta-analysis has more strengths than the previous meta-analysis. First and foremost, apart from cancer-related fatigue, the current meta-analysis also evaluated psychological variables, quality of sleep, and QoL. Moreover, we categorized psychological status into negative and positive aspects, which let us fully know that MBSR improves an individual's health status by simultaneously improving positive psychological states (i.e., the level of mindfulness and self-efficacy) and relieving negative psychological states (i.e., the level of anxiety, depression, and psychological distress). Second, this meta-analysis also used the GRADE system to rate the levels of evidence, which greatly facilitated clinical decision-making. Third, more eligible studies were included in our meta-analysis to greatly increase the statistical power. Although most included studies reported beneficial results to the MBSR program, the insufficient sample size greatly decreased the statistical power of the findings. Specifically, the sample size of individual studies ranged from 36 to 378, and more than 94% of eligible studies involved a sample size of <200. As stated previously, a total of 1,680 patients were accumulated to significantly increase the statistical power of this meta-analysis. Therefore, more reliable and robust results could be generated from the current meta-analysis compared with previous individual studies. Fourth, distress has been regarded as the sixth vital sign in the care of cancer persons (Stapleton et al., 2017; Fitch et al., 2018); however, the current meta-analysis found that limited studies evaluated the effect of the MBSR program on psychological distress of patients with lung cancer, which provides valuable implications for designing the future study. More importantly, this meta-analysis revealed that most studies were dedicated to evaluating the effectiveness of the MBSR program in physical and psychological wellbeing, but few studies tried to elucidate the potential mechanisms of the MBSR program in improving physical and psychological wellbeing. Therefore, future studies should be designed to clarify the possible mechanisms of the MBSR on different clinical outcomes from multiple perspectives.

Generally, the psychosomatic balance may be a moderator of psychological well-being adjustment in patients with cancer (Bărbuş et al., 2017). As a result, people may suffer from significant symptom burden, such as cancer-related fatigue

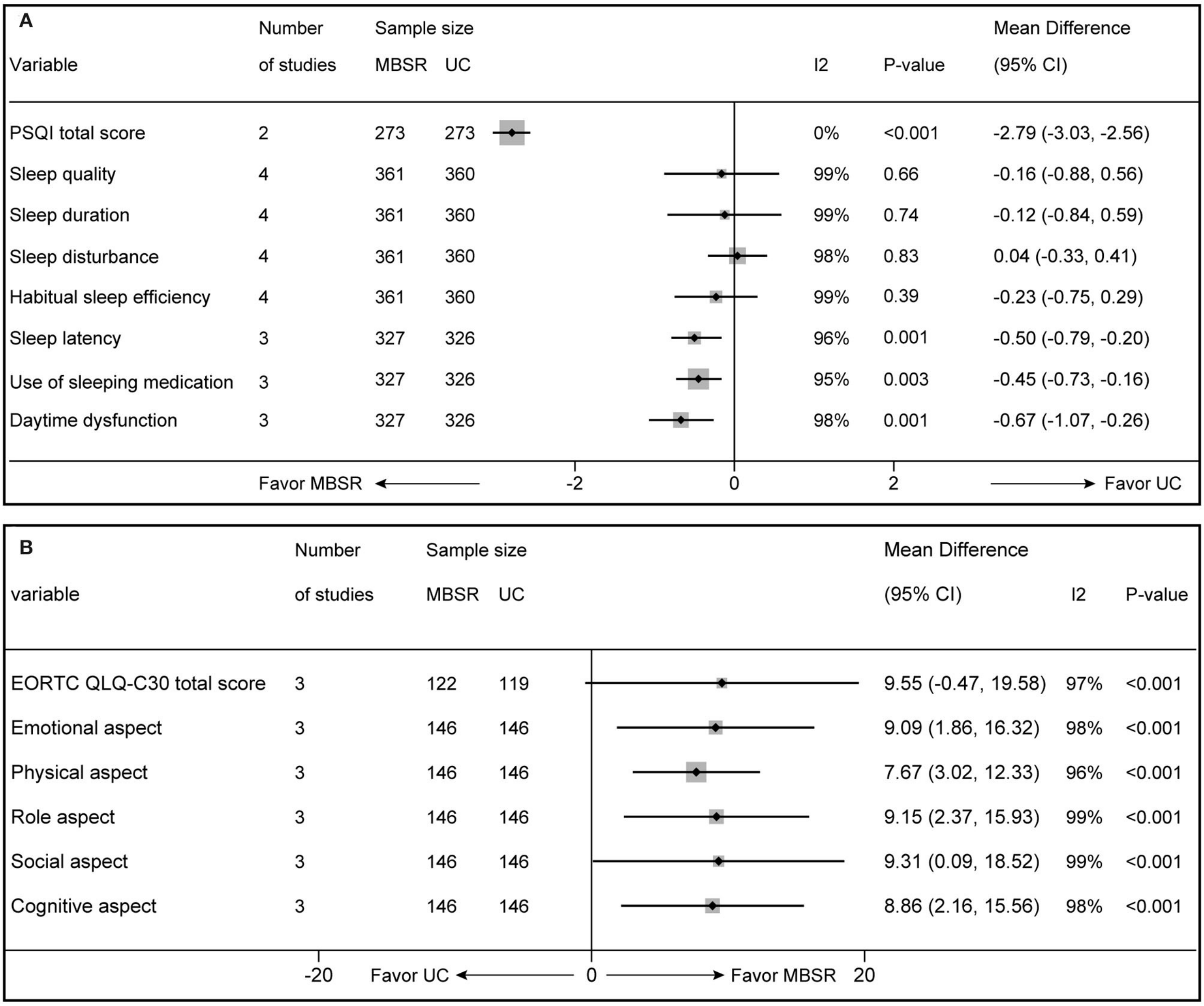


FIGURE 4 | Forest plot of comparative effectiveness between MBSR program and UC in terms of quality of sleep **(A)** and QoL **(B)**. MBSR, mindfulness-based stress reduction; UC, usual care; PSQI, Pittsburgh sleep quality index; EORTC QLQ-C30, the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire.

(Besika et al., 2021) when internal (e.g., confirmation of the diagnosis of cancer) or external (e.g., anticancer treatment) stressors destructed psychosomatic balance. Then, people may suffer from a great reduction in psychological wellbeing and QoL (Zhang et al., 2019). According to the Mindful Coping Model (Garland et al., 2009), it is not surprising to the benefits of the MBSR program on psychological wellbeing, quality of sleep, and QoL. Studies have revealed that mindfulness-based interventions have a positive impact on symptom burden and psychological outcomes in patients with cancer (Rouleau et al., 2015). Specifically speaking, when patients suffer from destructive effects resulting from both external and internal stressors, the MBSR program initiates psychological adjustment to trigger positive psychological sources (positive reappraisal) (Jeffers et al., 2019), which may greatly dilute the destructive effects of stressors (Galante et al., 2021) and then restore patient's psychosomatic balance. As a result, patients' health outcomes would be significantly improved. As an example, studies have suggested that the MBSR program greatly decreased patients' symptom burden (physical wellbeing) and improved patients' psychological wellbeing and QoL (Zimmaro et al., 2020; Kim et al., 2021). Moreover, empirical studies suggested that the MBSR program also improved patients' treatment adherence and then enhanced the anticancer treatment effects, as well as improved physical status, psychological wellbeing, and QoL (Cillessen et al., 2020). According to the "Mindful Coping Model" and findings from empirical studies, we, therefore,

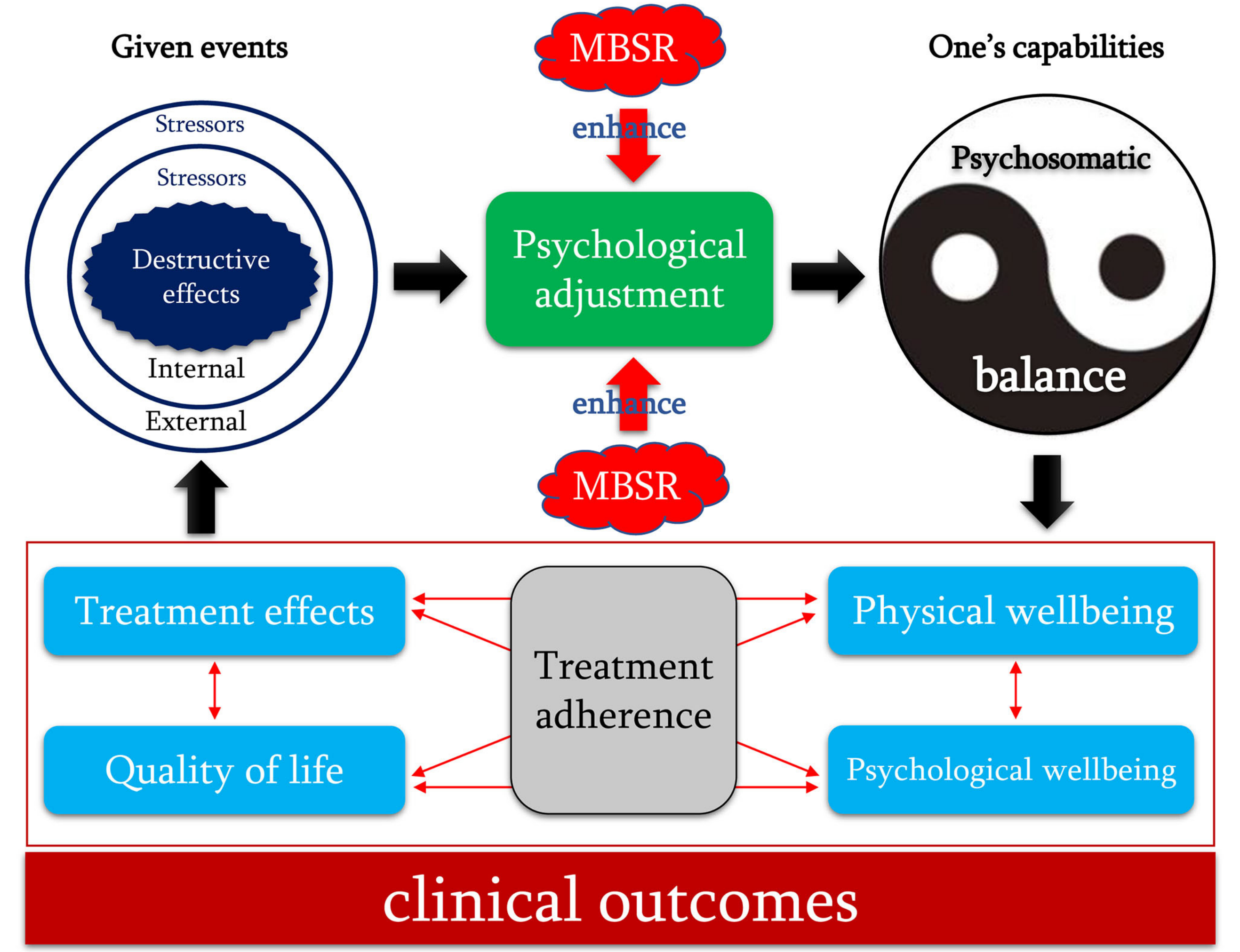


FIGURE 5 | The hypothetical causal pathway of the MSBR program for improving psychological outcomes and QoL of lung cancer patients. MBSR, mindfulness-based stress reduction; QoL, quality of life. In this hypothetical causal pathway, the black unidirectional arrow indicated the causal relationship between two elements, and the red bidirectional arrow indicated the interrelationship of two elements. Destructive effects of stressors break a patient's psychosomatic balance by initiating negative psychological adjustment and then harming clinical outcomes. In contrast, implementation of the MBSR program may enhance positive psychological adjustment by triggering positive psychological sources (e.g., self-efficacy) to gradually restore the patient's psychosomatic balance and then improve clinical outcomes.

proposed the hypothetical causal pathway that argues for the role of the MBSR program in regulating lung cancer patients' psychological wellbeing (**Figure 5**). It is noted that these potential influence pathways of the MBSR program on the adjustment in psychological status are speculated from previously published studies. Therefore, definitive mechanisms of the MBSR program from different aspects should be further clarified in patients with lung cancer because this meta-analysis has revealed the effectiveness of the MBSR program on psychological outcomes.

To our knowledge, this is the first study that investigated the effectiveness of the MBSR program on psychological outcomes, quality of sleep, and QoL in patients with lung cancer with a meta-analysis technique, and several promising findings provide a valuable reference for developing the socio-psychological rehabilitation program of patients with lung cancer. However, we must acknowledge that several limitations may impair the robustness and reliability of our findings. First, we systematically searched several electronic databases, including PubMed, EMBASE, PsycINFO, Cochrane Library, CNKI, and Wanfang, to identify relevant studies; however, some potentially eligible studies may be missed from our literature retrieval because other databases, such as Web of Science and SCOPUS, were not searched. Second, the substantial variations in the intensity, frequency, and duration of the MBSR program across eligible studies may introduce heterogeneity, which also may reduce the robustness of the pooled results. However, we utilized the random-effects model to conservatively estimate the effects of the MBSR program on psychological outcomes, quality of sleep, and QoL. Nevertheless, we still believe that it is essential to apply for a standard MBSR program in clinical practice to ensure interventional efficacy. Third, details of UC across studies were different, which also a potential source of introducing statistical heterogeneity. However, we defined five essential elements of UC protocol to ensure the similarity of various strategies, including dietary instruction, health education, rehabilitation excise, emotional counseling, and medication instruction. Fourth, the baseline status of patients with lung cancer was also different from one to another; however, subgroup analysis was not imposed due to limited data. Fifth, we could not quantitatively evaluate the impact of the MBSR program on the physical status because only one study reported this outcome. Sixth, most results of this meta-analysis were only supported by low to moderate evidence except for the quality of sleep. Therefore, attention should be specially paid to the interpretation of our findings. Seventh, we used the first version of the Cochrane risk of bias assessment tool for methodological quality assessment in this meta-analysis. However, a second version is being published, which should be cited in the future study.

CONCLUSION

The results of this meta-analysis suggest that the MBSR program is an effective psychological approach to relieve cancer-related fatigue, and negative emotional states, including anxiety and depression, psychological stress, and improving self-efficacy, mindfulness, and quality of sleep among patients with lung cancer. Therefore, it is worthy of being recommended to patients with lung cancer as part of their rehabilitation protocol. Certainly, future studies are warranted to further investigate the effects of the MBSR program on psychological distress, level of mindfulness, and QoL because these three outcomes are only supported by low evidence. Moreover, the impact of the MBSR program on the psychological states should also be investigated in future studies because it was evaluated by only one study.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

Conception and design: XT and MJ-H. Administrative support: XT, G-HC, and MJ-H. Provision of study materials or patients: XT and L-JY. Collection and assembly of data: XT, L-JY, and C-S-SL. Data analysis and interpretation: XT, L-JY, LG, CP, and G-HC. Manuscript writing and final approval of manuscript: All authors. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.901247/full#supplementary-material

Supplementary Figure 1 | Risk of bias of each eligible study. Green (+), yellow (?), and red (–) circle represents "low," "unclear," and "high" risk of bias, respectively.

Supplementary Table 1 | Search strategies of targeted English databases.

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ORIGINAL RESEARCH
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Global Research Mapping of Psycho-Oncology Between 1980 and 2021: A Bibliometric Analysis

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Background and Aim: Psycho-oncology is a cross-disciplinary and collaborative sub-specialty of oncology that focuses on the psychological, behavioral, ethical, and social aspects of cancer in clinical settings. The aim of this bibliometric study was to analyze and characterize the research productivity and trends in psycho-oncology between 1980 and 2021.

Methodology: In May 2022, the Scopus® database was searched for psycho-oncology-related publications using predetermined search keywords with specific restrictions. Lotka's law was applied to check the authors' productivity, while Bradford's law was used to assess the core journals in this field. The data was analyzed for different bibliometric indicators in the Biblioshiny package, an RStudio tool for bibliometric analysis.

Results: The initial search resulted in a total of 2,906 publications. Of which, 1,832 publications were included in the final analysis, published between 1980 and 2021. The analyzed publications were written by 7,363 authors from 74 countries and published in 490 journals. There has been a significant increase in psycho-oncology-related publications after 2010. The most productive year was 2021 (*n* = 365). The annual scientific growth rate was found to be 13.9%. The most relevant leading author in terms of publications was Luigi Grassi from the University of Ferrara, Italy (*n* = 42). Lotka's law found that the number of authors declined as the number of papers written increased. The core journals were Psycho-Oncology, Supportive Care in Cancer, and Journal of Psychosocial Oncology. The most frequently used author's keywords other than searching keywords were cancer, oncology, quality of life, depression, and anxiety. Recent psycho-oncology-related topics included mental health, COVID-19 infection in humans, people, pandemic, and tumor. The University of Sydney was the top-ranked institution. The leading country in terms of publications, citations, corresponding author country, and international collaboration was the United States of America (United States). The United States had the strongest collaboration with Australia and Canada.

Conclusion: The research hotspots include mental health conditions and interventions in cancer patients. We identified international collaboration and research expenditure to be strongly associated with psycho-oncology research productivity. Researchers' collaboration, which is visible among developed countries, should be extended to low-income countries in order to expand psycho-oncology-related research and understanding.

Keywords: psycho-oncology, bibliometric study, Scopus® database, Bradford's law, Lotka's law

INTRODUCTION

The treatment and diagnosis of cancer is the primary life stressor for patients, their families, and partners, and it is linked with psychosocial and physical difficulties that can develop at any point during the disease and continue throughout life (Zabora et al., 2001; Pitceathly and Maguire, 2003; Chambers et al., 2012). Around one-third of cancer patients in Western cultures report continuous clinically significant discomfort, such as depression and anxiety, post-traumatic stress reactions, worries of cancer recurrence, and adjustment disorders, which may exacerbate over time (Zabora et al., 2001; Stein et al., 2008). In the 1970s, psycho-oncology came into existence to decrease these psychological symptoms and provide psychosocial assistance to cancer patients, caregivers, and families. Psycho-oncology is a cross-disciplinary and collaborative sub-specialty of oncology that focuses on the psychological, behavioral, ethical, and social aspects of cancer in clinical settings. The discipline also offers research and clinical materials to health professionals (Holland, 2002, 2018). Psychosocial rehabilitation and psychotherapeutic interventions in oncology have been shown to generally benefit and reduce the severity of psychiatric symptoms and somatic symptoms (Johannsen et al., 2013; Zainal et al., 2013).

Psycho-oncology focuses on the cancer patient to improve their well-being, quality of life, and return to work

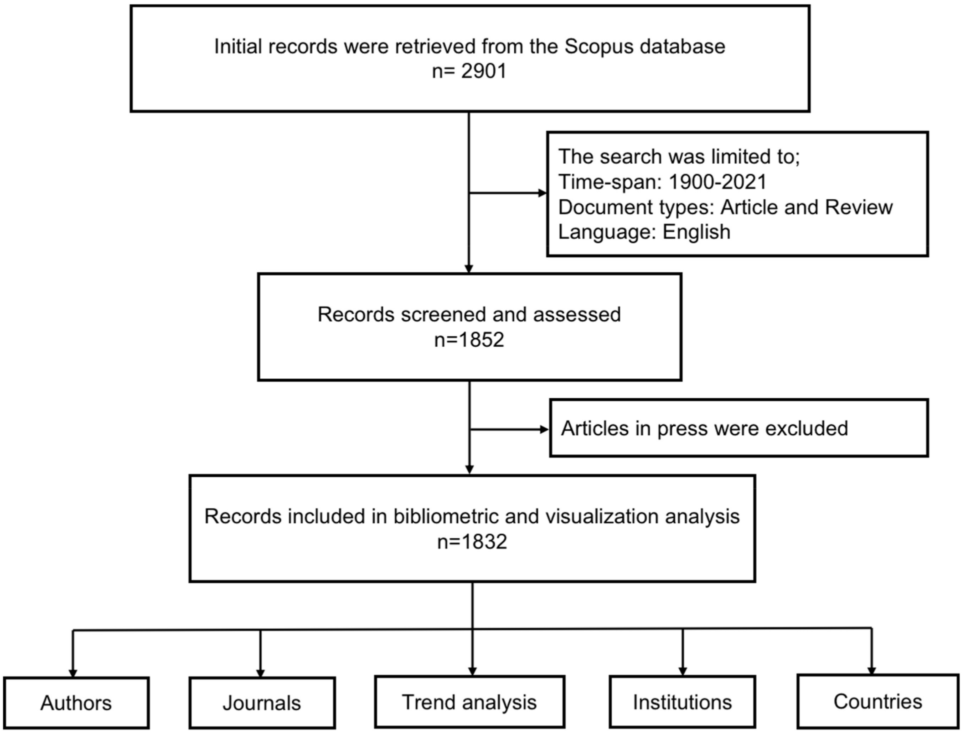

FIGURE 1 | Flow diagram of the included publications.

(Hunter et al., 2017a,b) and focuses on possible survival and illness behavior (Galway et al., 2012; Spiegel, 2012; Barrera and Spiege, 2014). The supportive-expressive group psychotherapy is one of the most empirically supported therapies for relieving cancer patients' distress (Classen et al., 2008), cognitive-existential therapy (Kissane et al., 2003), and cognitive-behavioral (Johnson et al., 2016). Some other interventions are meaning-centered psychotherapy, mindfulness stress reduction, and mindfulness (LeMay and Wilson, 2008; Piet et al., 2012; Breitbart et al., 2015; Rouleau et al., 2015; Carlson, 2016; Okuyama et al., 2017; van der Spek et al., 2017).

The bibliometric analysis of published articles provides insights into the research landscape, research gaps, and future direction of a research field (Blakeman, 2018; Tang et al., 2018; Yeung et al., 2018). In this study, we performed bibliometric analysis to examine the published scientific literature and trend analysis of psycho-oncology-related research. We also identified socio-economic factors affecting research productivity in psycho-oncology.

METHODOLOGY

Study Design and Retrieved Database

A bibliometric and visualization study was conducted. In this study, the Scopus® database (Elsevier, Amsterdam, Netherlands) was utilized. The used database was accessed through the online library portal of the University of the Philippines Manila, on 20 April 2022 (step 1-initial search), and Southeast University, Nanjing, on 28 May 2022 (step 2-updated search). The Scopus® database was selected; (a) it is the world's largest abstract and citation database for scientific literature (Guz and Rushchitsky, 2009), (b) it includes a more expanded spectrum of journals (Falagas et al., 2008).

TABLE 1 | Main information about the included documents in the final analysis.

Description	Results
Main information	
Time-span	1980–2021
Documents (records)	1,832
Journals	490
Institutions	6,382
Countries/regions	74
Average years from publication	7.7
Average citations per documents	17.7
Average citations per year per document	2.003
References	6,9946
Document types	
Article	1,511
Review	321
Document contents	
KeyWords Plus	5,467
Author's keywords	2,919
Authors	
Authors	7,363
Author appearances	10,286
Authors of single-authored documents	141
Authors of multi-authored documents	7,222
Authors collaboration	
Single-authored documents	184
Documents per author	0.249
Authors per document	4.02
Co-authors per document	5.61
Collaboration index	4.38

TABLE 2 | Annual scientific production and mean citations.

Year	Number	Mean total citations per document	Mean total citations per year	Citable years
1980	2	10.50	0.25	42
1981	2	10.50	0.26	41
1982	0	0.00	0.00	0
1983	2	8.50	0.22	39
1984	1	17.00	0.45	38
1985	3	3.67	0.10	37
1986	1	77.00	2.14	36
1987	3	69.00	1.97	35
1988	2	1.00	0.03	34
1989	4	9.75	0.30	33
1990	2	15.50	0.48	32
1991	4	36.50	1.18	31
1992	6	30.33	1.01	30
1993	10	8.00	0.28	29
1994	16	13.13	0.47	28
1995	13	31.62	1.17	27
1996	13	24.15	0.93	26
1997	10	22.50	0.90	25
1998	14	46.00	1.92	24
1999	23	37.43	1.63	23
2000	15	53.47	2.43	22
2001	14	40.71	1.94	21
2002	31	48.55	2.43	20
2003	16	54.19	2.85	19
2004	28	38.46	2.14	18
2005	25	41.68	2.45	17
2006	22	37.00	2.31	16
2007	20	56.35	3.76	15
2008	28	28.25	2.02	14
2009	34	44.82	3.45	13
2010	44	25.32	2.11	12
2011	60	22.78	2.07	11
2012	69	29.49	2.95	10
2013	78	27.26	3.03	9
2014	80	32.24	4.03	8
2015	69	26.03	3.72	7
2016	80	17.19	2.86	6
2017	104	15.44	3.09	5
2018	127	11.69	2.92	4
2019	141	9.84	3.28	3
2020	251	5.00	2.50	2
2021	365	1.84	1.84	1

TABLE 3 | Most relevant authors with at least 15 publications.

Authors	Articles	Articles Fractionalized
Grassi L	42	10.71
Butow P	31	5.77
Akechi T	29	3.88
Mehnert A	22	4.30
Nanni MG	19	2.94
Turner J	19	4.51
Okuyama T	18	2.43
Caruso R	17	2.78
Girgis A	17	3.13
Herschbach P	16	1.98
Na Na	16	16.00
Jacobsen PB	15	3.66
Wiener L	15	2.41

Used Keywords and Data Extraction

A comprehensive search of the published literature was conducted. Published literature on psycho-oncology was screened and reviewed. The search keywords were discussed and reviewed by the authors to conduct a comprehensive search operation. Thus, the following potential search keywords were selected and entered in the database: "Psycho-oncology" OR "Psycho oncology" OR "Psychiatric oncology" OR "Psychosocial oncology" in the title, abstract, and keywords category. We limited the search to documents published in English and document types (article and review). Early access documents and publications in the year 2022 were also excluded as shown in **Figure 1**. A two-step search was conducted to validate all the results and data extraction. The authors extracted the following information; publication title, year of publication, publishing language, author name, journal, document type, research area, funding source, institution, and country of origin. The data were downloaded in both comma-separated values (CSV) and BibTeX format. The journal impact factor (IF) was obtained from the Journal Citation Reports 2020, released in June 2021 by Clarivate Analytics.

Data Analysis

To analyze, characterize, and map the psycho-oncology-related research, the downloaded dataset was exported into RStudio

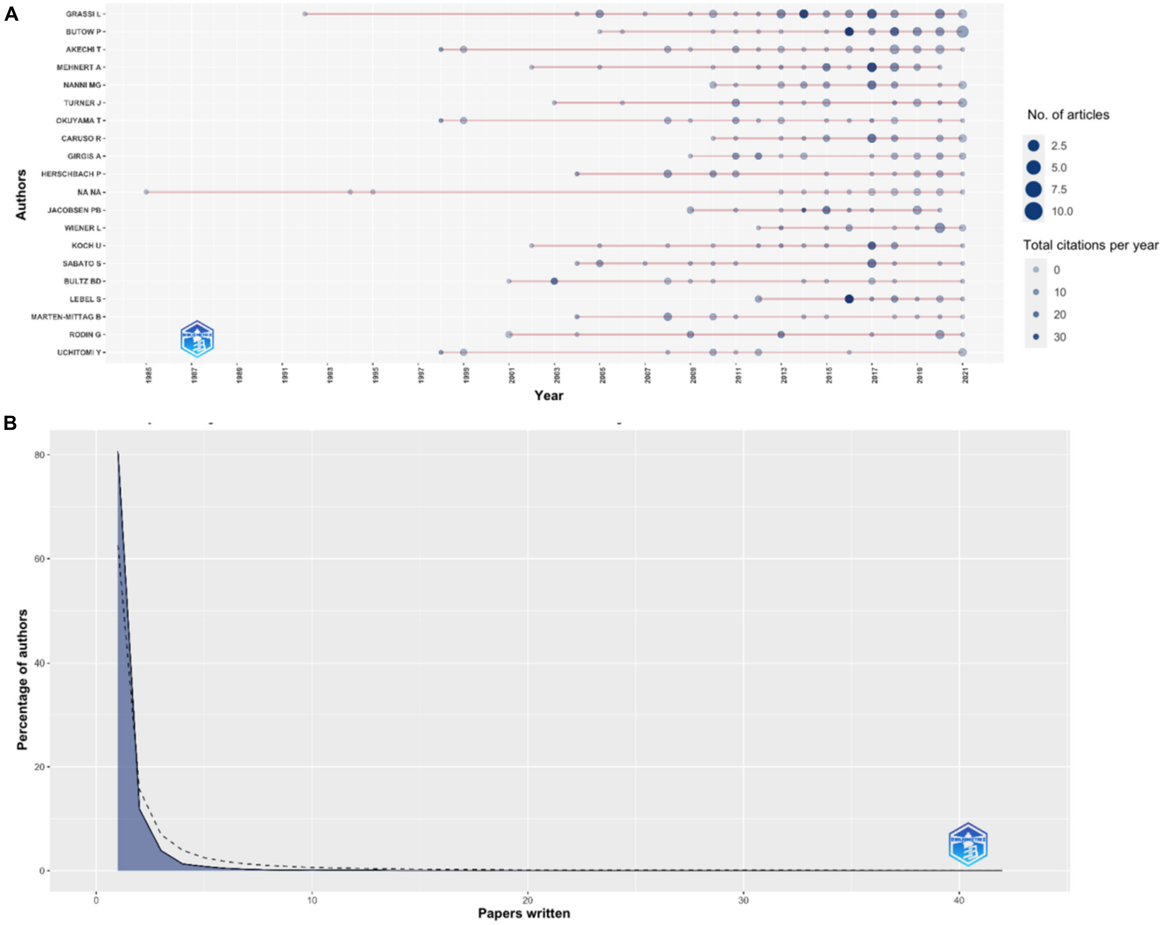

FIGURE 2 | (A) Top authors' production over time (1985–2021) in psycho-oncology research, **(B)** author productivity through Lotka's law. The blue area corresponds to the empirical or observed data, whereas the dotted line represents plotted or theoretical relationship.

TABLE 4 | Lotka's law statistics of papers written by authors in psycho-oncology research between 1980 and 2021.

Papers written	Number of authors	Proportion of authors
1	5,942	0.807
2	874	0.119
3	284	0.039
4	95	0.013
5	59	0.008
6	32	0.004
7	18	0.002
8	10	0.001
9	6	0.001
10	11	0.001
11	6	0.001
12	6	0.001
13	5	0.001
14	2	0
15	2	0
16	2	0
17	2	0
18	1	0
19	2	0
22	1	0
29	1	0
31	1	0
42	1	0

(Biblioshiny package). The key bibliometric indicators were examined that included annual scientific production, most relevant authors and journals, leading institutions, countries or regions collaboration, keywords analysis, and trend analysis of topics. However, the leading funding sources, most studied subject areas, and countries or regions that participated in psycho-oncology-related research were plotted in Microsoft Excel. The values were presented in frequency (*n*) and percentage (%).

Lotka's and Bradford's law

Furthermore, the author's productivity was examined by using Lotka's law. Lotka's law demonstrates the number of authors against the number of contributions (papers) made by each author (Lotka, 1926). Lotka's law is expressed in mathematical terms by the following formula:

$$\mathrm{A(n)} = \frac{\mathrm{A(1)}}{\mathrm{n}^2}$$

In the above equation, A (*n*) is the number of authors publishing *n* papers and A1 is the number of authors publishing a single paper.

In addition, to find out the core journals in psycho-oncology field, Bradford's law was used (Bradford, 1934). Bradford's law distributes the journals into three zones [zone 1 (core journals), zone 2, and zone 3] with a similar number of papers and an increasing number of journals.

Statistical Analysis

Spearman's rank-order correlation determined correlations between country-specific characteristics with the different bibliometric indices. The information on the population, gross domestic product (GDP), GDP per capita, research and development expenditure (%GDP), physician-to-population ratio, and researcher-to-population ratio were obtained from the World Bank. The Spearman's correlation coefficient (ρ) was considered significant if the *p*-value was less than 0.05. The statistical analysis was done using GraphPad Prism software version 7 (GraphPad Software, San Diego, CA).

Ethical Consideration

Ethical consideration was not required for the current study because no animal and human subjects were involved. All the data used in this study are available publicly.

TABLE 5 | Most relevant journals in psycho-oncology research.

Journals	Articles	IF 2020 (5-year)	Current publisher
Psycho-Oncology	466	3.894 (4.578)	Wiley111 River St, Hoboken 07030-5774, NJ
Supportive Care in Cancer	108	3.603 (3.958)	Springer, One New York Plaza, Suite 4600, New York, NY 10004, United States
Journal of Psychosocial Oncology	88	2.029 (2.111)	Routledge Journals, Taylor & Francis Ltd., 2-4 Park Square, Milton Park, Abingdon OX14 4RN, Oxon, England
Cancer	35	6.86 (7.921)	Wiley111 River St, Hoboken 07030-5774, NJ
European Journal of Cancer Care	32	2.52 (2.931)	Wiley111 River St, Hoboken 07030-5774, NJ
Palliative & Supportive Care	32	2.257 (2.541)	Cambridge Univ Press, 32 Avenue of The Americas, New York, NY 10013-2473
BMC Cancer	21	4.43 (4.372)	BMC, Campus, 4 Crinan St, London N1 9XW, England
Japanese Journal of Clinical Oncology	21	3.019 (2.847)	Oxford Univ Press, Great Clarendon St, Oxford OX2 6DP, England
Frontiers in Psychology	19	2.988 (3.618)	Frontiers Media SA, Avenue DU Tribunal Federal 34, Lausanne CH-1015, Switzerland
Journal of Pain and Symptom Management	19	3.612 (4.556)	Elsevier Science Inc., STE 800, 230 Park Ave, New York, NY 10169
Cancer Nursing	16	2.592 (2.98)	Lippincott Williams & Wilkins, Two Commerce SQ, 2001 Market St, Philadelphia, PA 19103

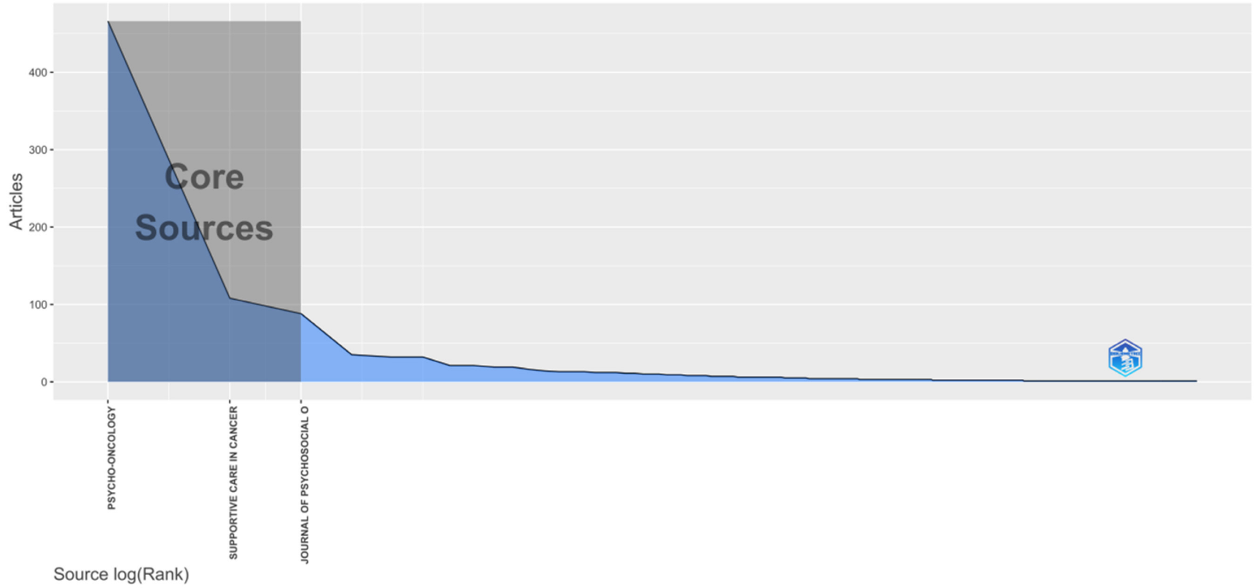

FIGURE 3 | Journals (Sources) clustering through Bradford's law.

RESULTS

The initial search retrieved 2,906 documents, of which only 1,832 documents were analyzed and characterized in the final analysis. The included documents were authored by 7,363 authors (4.02 authors per document) and published in 490 journals. In total, 1,511 (82.48%) documents were published as articles and 321 (17.52%) as reviews. As presented in **Table 1**, the authors collaboration index in psycho-oncology research was found to be 4.38.

Annual Scientific Production

The included documents were published between 1980 and 2021. There is a general increase in research output through the years, especially in the last 5 years. The most productive year in terms of publications was 2021 ($n = 365$), and 2020 ($n = 251$), as shown in **Table 2**. In addition, the mean total citations per document and per year were calculated. The documents published in 2014 received the highest number of mean total citations per year (**Table 2**). The annual scientific growth rate was found to be 13.9%.

Most Relevant Authors

As shown in **Table 1**, a total of 7,363 were involved, and appeared to be 10,286 times. In total, only 43 authors published at least 10 documents. The most relevant leading author in terms of publications was Luigi Grassi (Grassi L) from the Department of Biomedical and Specialty Surgical Sciences, Institute of Psychiatry, University of Ferrara, Ferrara, Italy with 42 publications, followed by Phyllis Butow (Butow P) from the Psycho-Oncology Co-operative Research Group, School of Psychology, The University of Sydney, Sydney, Australia ($n = 31$), and Tatsuo Akechi (Akechi T) from the Department of Psychiatry and Cognitive-Behavioral Medicine, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan ($n = 29$), as shown in **Table 3**. As shown in **Figure 2A**, Butow P published the highest number of articles in 2021 ($n = 10$). The author productivity through Lotka's law was calculated as shown in **Figure 2B**. As shown in **Figure 2B** and **Table 4**, in terms of scientific productivity (papers written) the number of authors declined as the number of papers written increased. Moreover, the paper titled "Cancer distress screening. Needs, models, and methods" published in Journal of Psychosomatic Research in 2003 was the most cited article with 279 citations (13.95 citations per year; Carlson and Bultz, 2003). This review discusses various screening instruments and screening models that could be widely adopted by psychosocial oncology programs.

Most Relevant Journals

As shown in **Table 5**, the most relevant and dominant journal in terms of publications was Psycho-Oncology ($n = 466$, 25.44%), followed by Supportive Care in Cancer ($n = 108$, 5.90%), and Journal of Psychosocial Oncology ($n = 88$, 4.80%). However, the most local cited journals were Psycho-Oncology, Journal of Clinical Oncology, and Cancer. Furthermore, the

TABLE 6 | Distribution of the journals (sources) and corresponding articles in three zones.

Zone	No. of journals	No. of articles	Percentage
1	3	662	36.14
2	59	567	30.95
3	428	603	32.91
Total	490	1,832	100

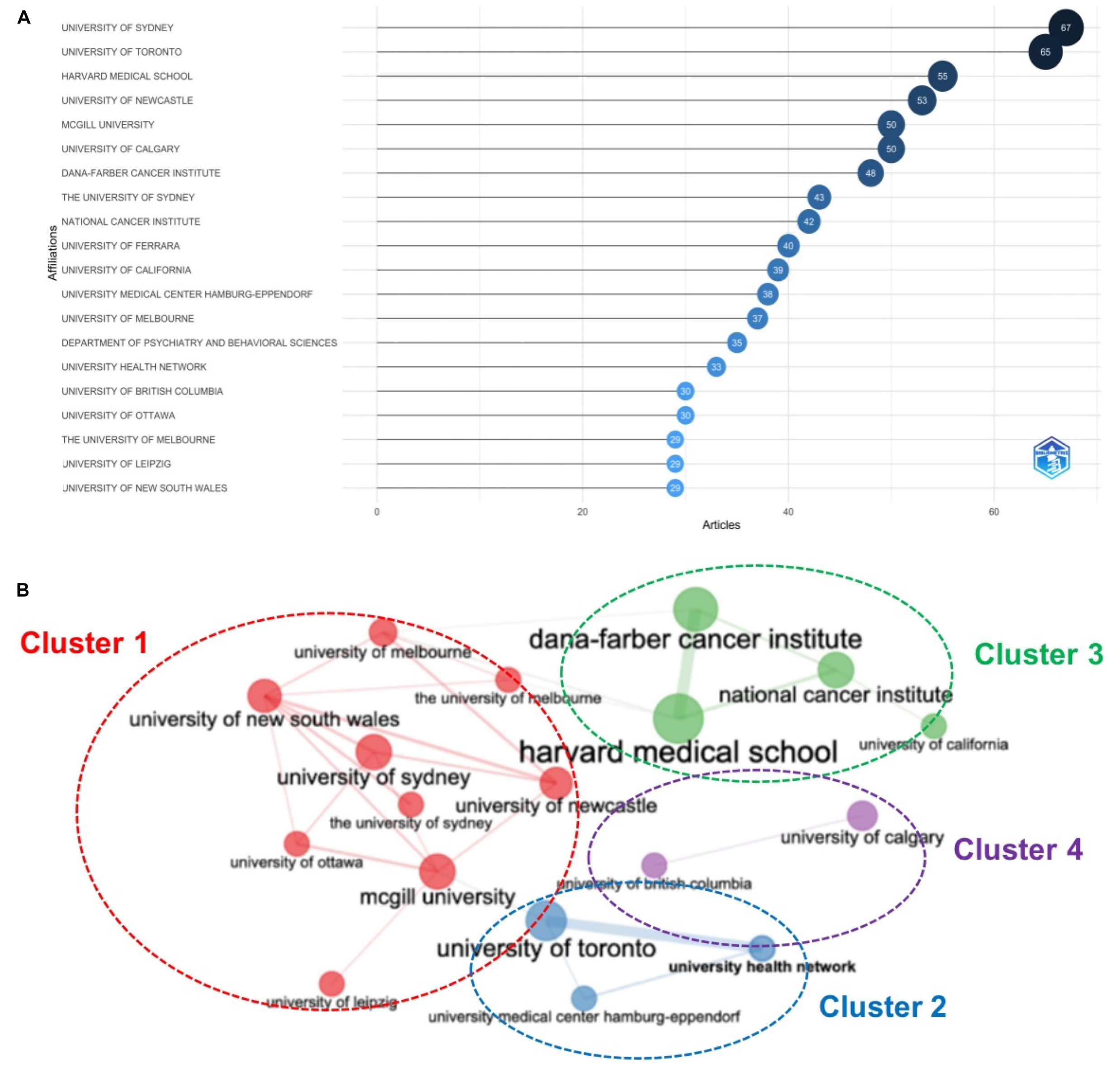

FIGURE 4 | (A) Top 20 leading institutions in psycho-oncology research between 1980 and 2021, **(B)** Institutions collaboration network.

Bradford's law was applied to assess the core journals in the field of psycho-oncology (Bradford, 1934). As shown in **Figure 3**, the core journals in the field of psycho-oncology were Psycho-Oncology, Supportive Care in Cancer, and Journal of Psychosocial Oncology. The document sources (journals) were divided in to three zones, zone 1 had 3 journals, zone 2 had 59, and zone 3 had 428, as shown in **Table 6**.

Leading Institutions

The leading institutions in psycho-oncology research were the University of Sydney ($n = 67$, 3.66%), followed by the University of Toronto ($n = 65$, 3.55%), and the Harvard Medical School ($n = 55$, 3.00%), as shown in **Figure 4A**. As presented in **Figure 4B**, the top leading institutions were plotted in to four clusters, and each color designates different cluster. The University of Toronto had the strongest collaboration with the University Health Network, while the Harvard Medical School had the highest collaboration with the DANA-Farber Cancer Institute.

Top Leading Countries or Regions in Psycho-Oncology Research

A total of 74 countries or regions participated in the included documents. As shown in **Figure 5**, the highly contributing country was the United States, followed by Australia, Germany, Canada, and the United Kingdom. As shown in **Table 7**, the

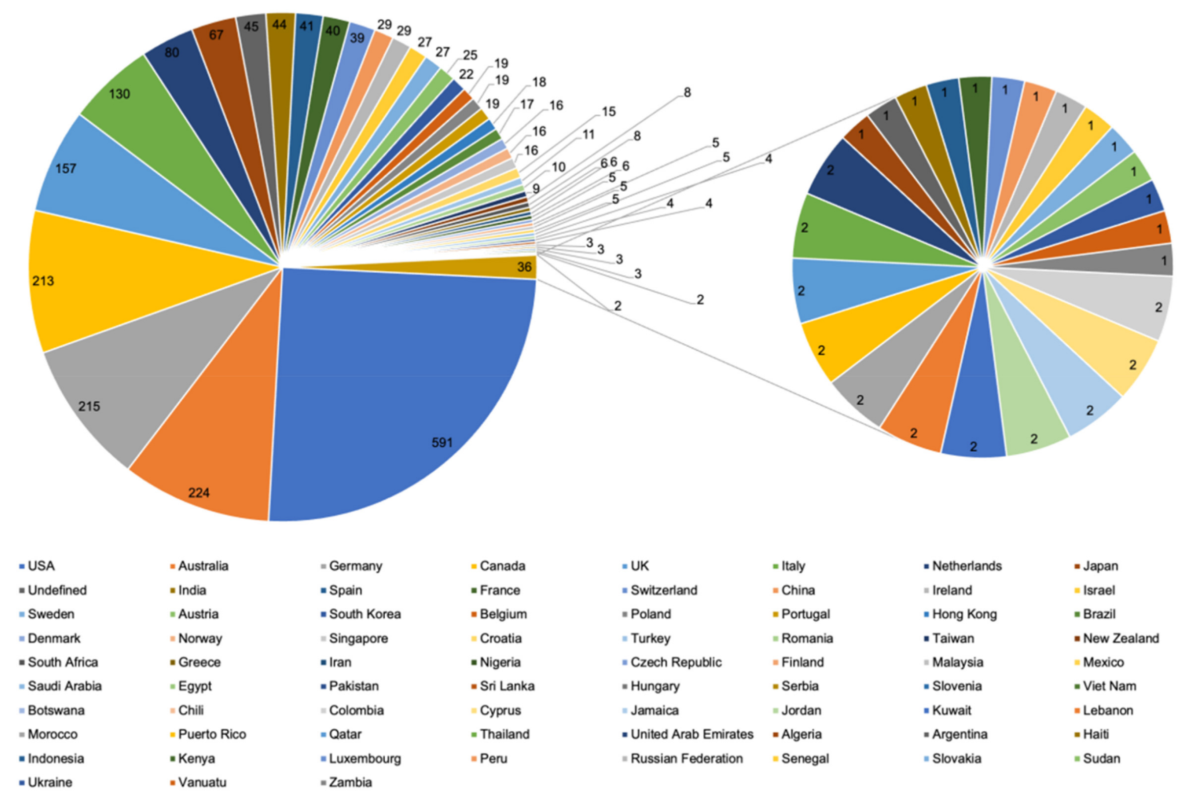

FIGURE 5 | Countries or regions participated in psycho-oncology research between 1980 and 2021.

United States was the leading country in terms of single country corresponding author's publications (*n* = 392), followed by Germany (*n* = 150), and Australia (*n* = 128), while in terms of multiple country corresponding author's publications Australia was the top ranked country (*n* = 44), followed by the United States (*n* = 37), and Italy (*n* = 36).

Countries or Regions Collaboration in Psycho-Oncology Research

As shown in **Figure 6**, the United States had the strongest collaboration with Australia in 38 publications, followed by the United States and Canada (*n* = 36), Australia and Canada (*n* = 23), the United States and Italy (*n* = 23), and Canada and the United Kingdom (*n* = 21).

Leading Funding Agencies

As shown in **Figure 7**, the leading funding agency in psycho-oncology was the National Cancer Institute (*n* = 165), followed by the National Institutes of Health (NIH; *n* = 116), and the United States Department of Health and Human Services (HHS; *n* = 153).

Most Studied Subject Areas

The subject areas that covers psycho-oncology research are mainly on Medicine (*n* = 1,651), Psychology (*n* = 818) and Biochemistry, Genetics and Molecular Biology (*n* = 232), Nursing (*n* = 181), and Social Sciences (*n* = 53), as shown in **Figure 8**.

Keywords Analysis

As shown in **Figure 9A**, the most frequently used author's keywords were plotted into six clusters. The top ten most widely used keywords were psycho-oncology, cancer, oncology, quality of life, depression, anxiety, psychosocial oncology, distress, survivorship, and breast cancer. The most appeared KeyWords Plus were female, human, adult, male, humans, middle aged, article, aged, quality of life, and neoplasms as shown in **Figure 9B**.

Trend Topics

The trend topics analysis was performed based on publication title during the last decade as shown in **Figure 10**. The recent trend topics in psycho-oncology were related to mental health, COVID-19 infection in humans, people, pandemic, and tumor. In the last 10 years, the most focused trend topic was cancer, followed by patients, and psychosocial.

Socio-Economic Factors for Psycho-Oncology Research Productivity

Lastly, we determined the socio-economic factors that may affect research productivity on psycho-oncology (**Table 8**). International collaboration showed the strongest correlation

TABLE 7 | Top 20 leading countries/regions in psycho-oncology research between 1980 and 2021 based on the corresponding author's country.

Countries/ Regions	Articles	Single country publications	Multiple country publications	Multiple country publications ratio
United States	429	392	37	0.0862
Germany	178	150	28	0.1573
Australia	172	128	44	0.2558
Canada	156	127	29	0.1859
Italy	110	74	36	0.3273
United Kingdom	86	74	12	0.1395
Japan	61	59	2	0.0328
Netherlands	49	39	10	0.2041
India	36	28	8	0.2222
China	30	24	6	0.2
France	25	20	5	0.2
Ireland	22	14	8	0.3636
Spain	22	17	5	0.2273
Switzerland	22	10	12	0.5455
Korea	20	18	2	0.1
Sweden	19	15	4	0.2105
Israel	18	15	3	0.1667
Singapore	15	10	5	0.3333
Croatia	13	12	1	0.0769
Poland	13	13	0	0

TABLE 8 | Correlation analysis between country or region-specific characteristics and bibliometric indices of psycho-oncology research.

Variables	Bibliometric Index	Spearman *R*	*P*-value
GDP	Total publications	0.730	<0.001
	H-index	0.692	<0.001
	Total citations	0.633	<0.001
GDP per capita	Total publications	0.591	<0.001
	H-index	0.581	<0.001
	Total citations	0.590	<0.001
Research and development expenditure (% of GDP)	Total publications	0.690	<0.001
	H-index	0.691	<0.001
	Total citations	0.709	<0.001
Researchers in R&D (per million people)	Total publications	0.572	<0.001
	H-index	0.593	<0.001
	Total citations	0.598	<0.001
Physicians per 1,000 population	Total publications	0.466	<0.001
	H-index	0.450	<0.001
	Total citations	0.453	<0.001
International collaboration	Total publications	0.920	<0.001
	H-index	0.901	<0.001
	Total citations	0.873	<0.001

with the bibliometric indices (total publications: $r = 0.920$, $p < 0.001$; citations: $r = 0.873$, $p < 0.001$; h-index = 0.901, $p < 0.001$). Research and development expenditure (total publications: $r = 0.690$, $p < 0.001$; citations: $r = 0.709$, $p < 0.001$; h-index = 0.691, $p < 0.001$) and GDP (total publications: $r = 0.730$, $p < 0.001$; citations: $r = 0.633$, $p < 0.001$; h-index = 0.692, $p < 0.001$) also showed a significant positive correlation. Moreover, GDP per capita, researcher per million people, and physicians per population also exhibited a positive relationship. In addition, specific characteristics of the country or region involved in psycho-oncology research is presented in **Supplementary Table 1**.

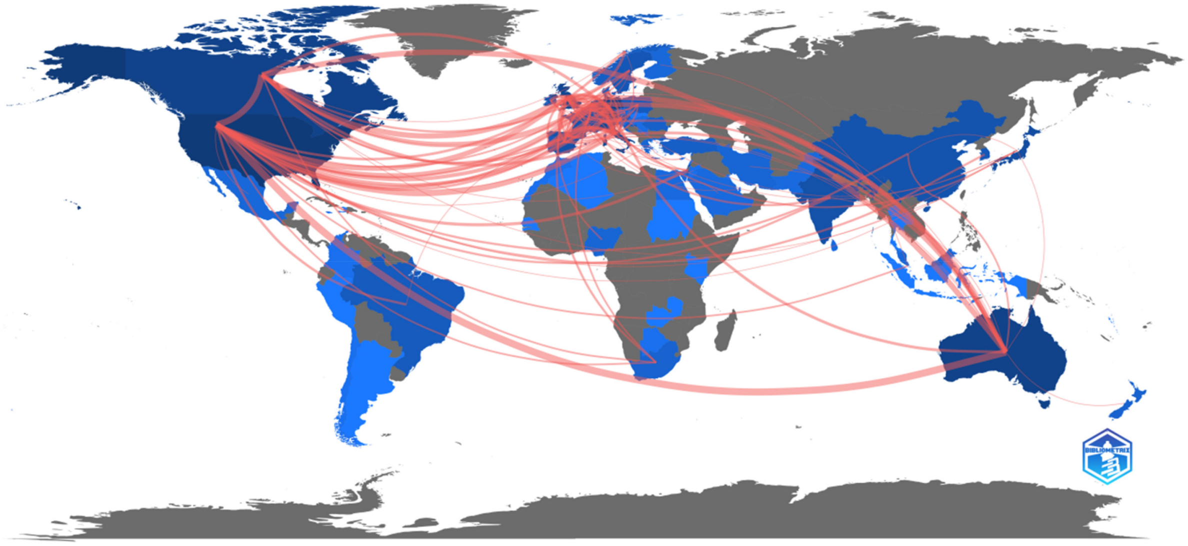

FIGURE 6 | Collaboration world map of countries or regions involved in psycho-oncology research between 1980 and 2021.

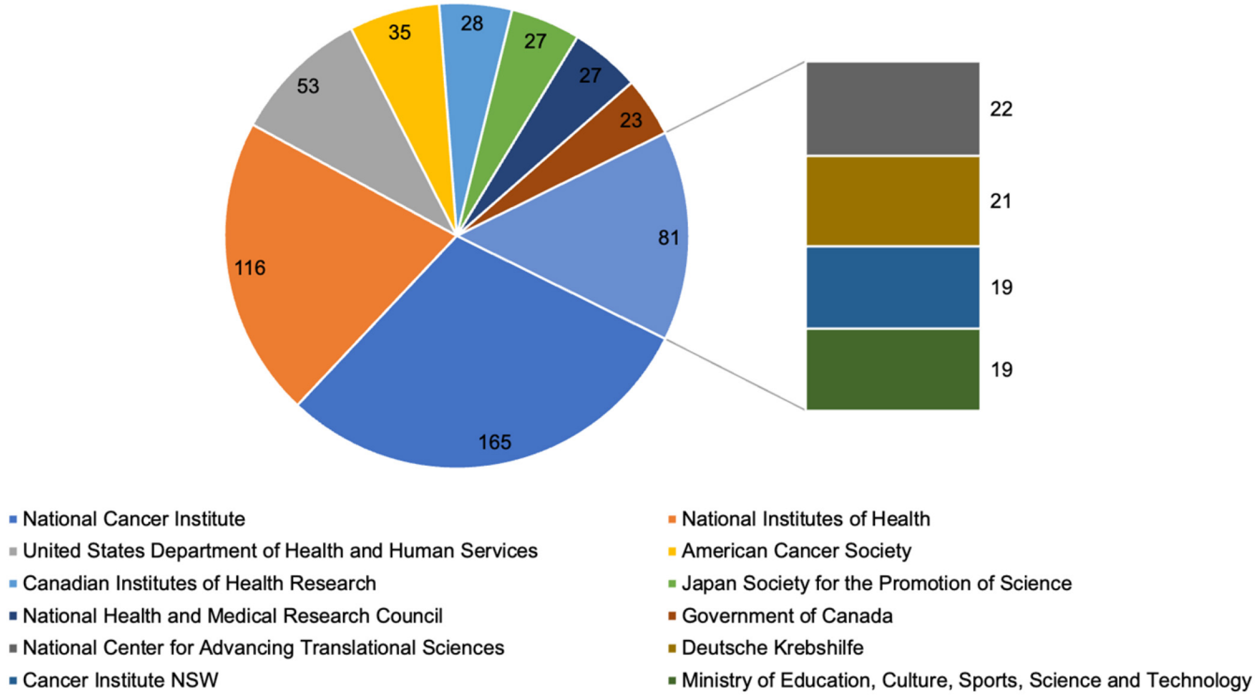

FIGURE 7 | Leading funding agencies in psycho-oncology research between 1980 and 2021 with at least 15 funded studies.

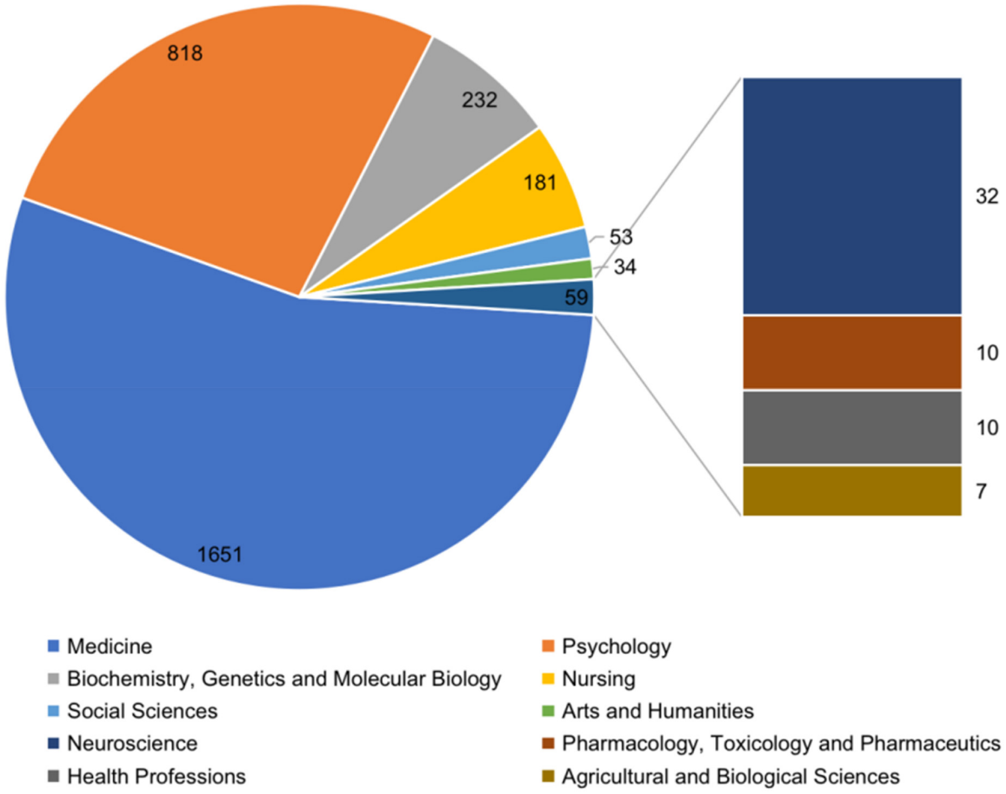

FIGURE 8 | Most studied subject areas in psycho-oncology between 1980 and 2021.

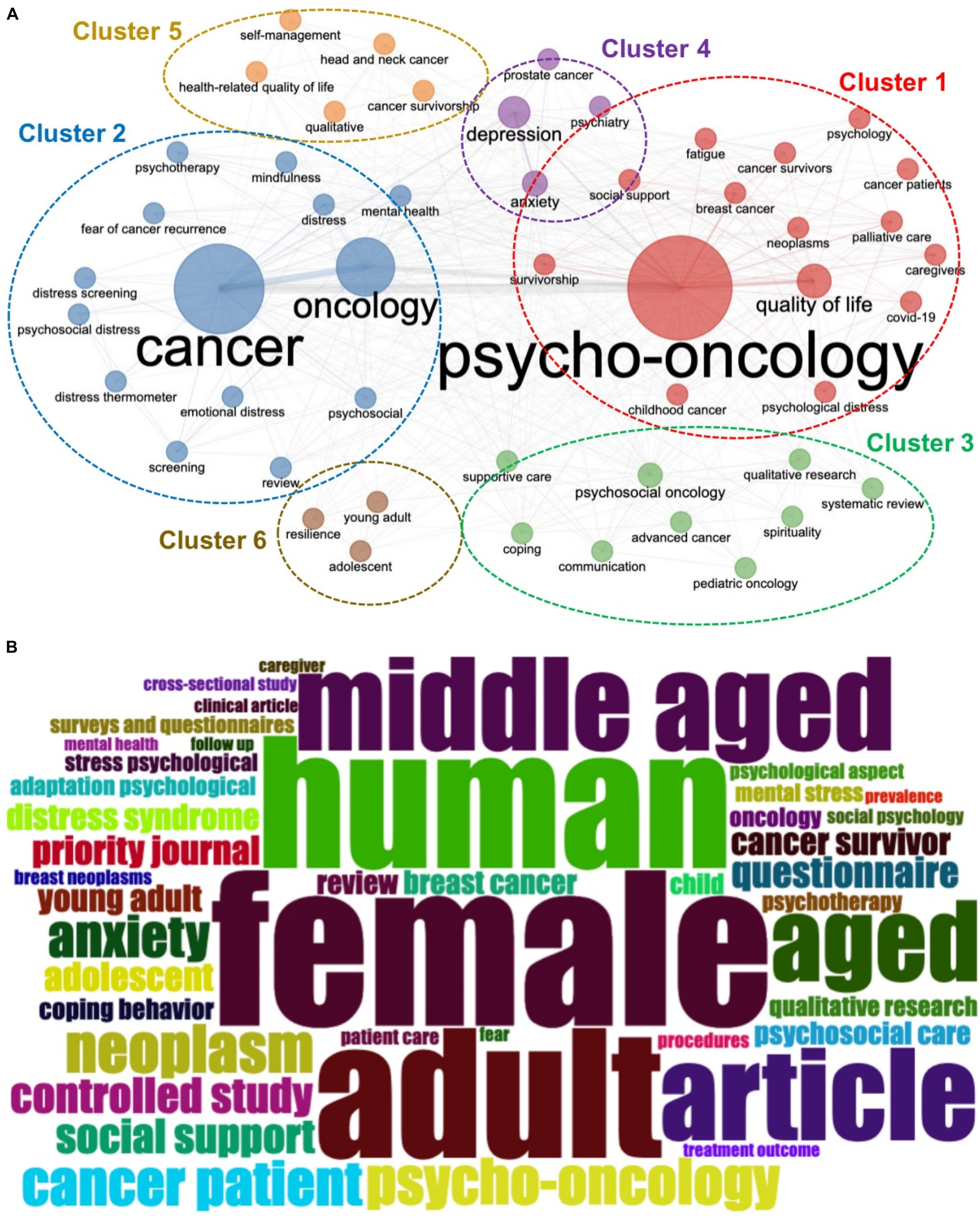

FIGURE 9 | (A) Frequently used author's keywords, **(B)** KeyWords Plus WordCloud map.

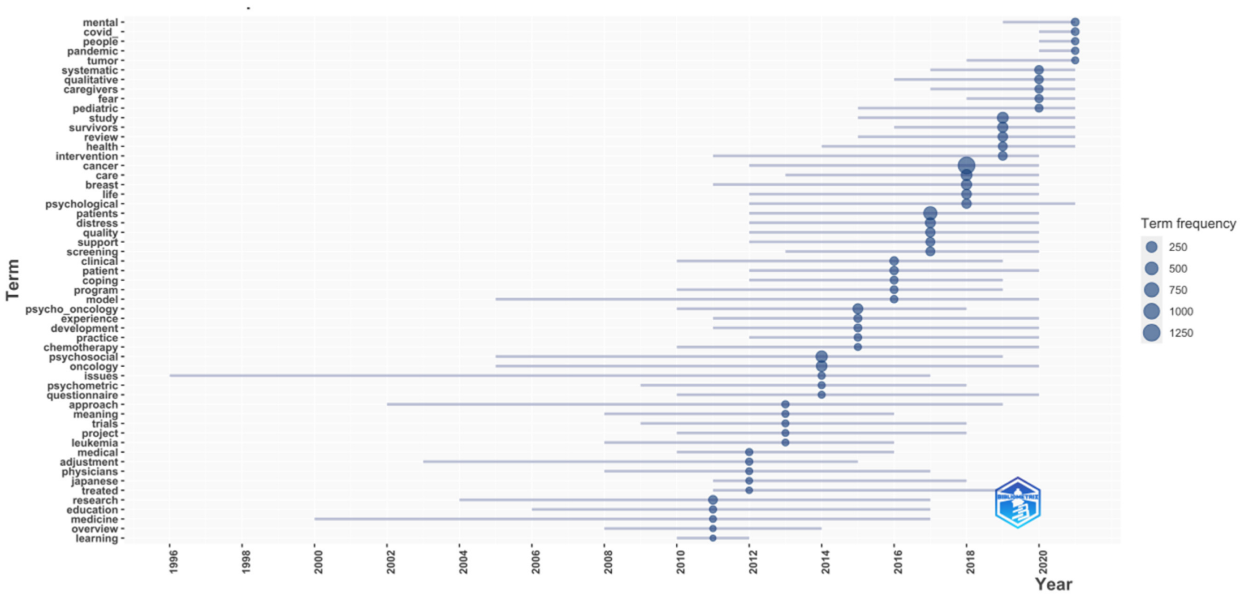

FIGURE 10 | Trend topics in psycho-oncology in the last 10 years (2011–2021).

DISCUSSION

Focused bibliometric studies are critical for providing key bibliometric indices such as most prolific authors and journals, top-ranked institutions and countries, scientific production over time and present the trend analysis of research in a particular field or research area (Donthu et al., 2021).

Although some previously published studies used a bibliometric approach to examine psycho-oncology-related specific domains (Fox et al., 2021). However, to the best of our knowledge, there is a lack of a comprehensive bibliometric analysis of psycho-oncology-related publications indexed in the Scopus® database from inception up to 31 December 2021. Thus, this study allowed us to acquire information about the developments and research trends in psycho-oncology over the last four decades.

Generally, an increase in research productivity in psycho-oncology over the years was observed. In total, 1.20% of the publications were published between 1980 and 1990, 6.77% between 1991 and 2000, 14.30% between 2001 and 2010, and 77.73% between 2011 and 2021. Overall, less than 23% of the included publications were published between 1980 and 2010. However, the overall annual scientific growth rate was found to be 13.09%. The above statistics show that, in recent times, much more research was conducted in psycho-oncology which reflects the importance and improvement of psycho-oncology-related therapies.

Publications, journals, and books that reflect a field's body of knowledge are indicators of advancement. The most relevant and top-ranked journal in terms of publications in psycho-oncology was "Psycho-Oncology." According to the Journal Citation Reports released in 2021, "Psycho-Oncology" received a 3.894 IF and ranked Q1 (16/77 category ranking) and Q3 (136/242 category ranking) in psychology and oncology, respectively. The IF of the core journals (based on Bradford's law) ranges from 2.029 (Journal of Psychosocial Oncology) to 3.894 (Psycho-Oncology).

Psycho-Oncology was launched in 1992 and is the official journal of the "American Psychosocial Oncology Society" (APOS) and the "British Psycho-Oncology Society" (BPOS). The journal covers psychological, social, behavioral, and ethical aspects of cancer. This year the journal celebrating its 30th anniversary.

The main subject areas that published psycho-oncology research are medicine, psychology, and biochemistry, genetics, and molecular biology. Notably, subject areas include social sciences, arts and humanities, computer science, and engineering. This highlights the multidisciplinary nature of the research field. The keyword analysis revealed topics on mental health issues such as depression and anxiety. Moreover, growing research trends between 1980 and 2000 in psycho-oncology-related research were support and psychiatric nursing, clinical trials, and imipramine. However, between 2001 and 2010, the topics related to psychological aspects, adaptive behavior and therapy, and cancer were more emphasized and developed. Trend topics over the last decade (2011–2020) included neoplasm, human(s), female, age, psychology, and social support. Psycho-oncology developed as a sub-specialty of oncology contributing to cancer patients' care (Holland, 2002).

The United States is the leading country in psycho-oncology research productivity and is home to most of the top institutions and funding agencies in this field. Previously published bibliometric studies in different research fields also reported the highest contribution from the United States, such as congenital cataracts (Idriss et al., 2021), exosomes (Shi et al., 2021), fascioliasis (Ahmad et al., 2021c), hepatitis

(Ahmad et al., 2021e,f), myocardial infarction (Zhou et al., 2018), pediatric trauma (Ahmad et al., 2021b), psychosomatic (Shah et al., 2021), tuberculosis (Nafade et al., 2018), and vaccines (Zhang et al., 2019; Ahmad et al., 2021a,d).

Several factors influence the country's research productivity. Our results showed that international collaboration is strongly associated with all the bibliometric indices. This is consistent with the literature showing that cooperation and collaboration increase research productivity (Tantengco, 2021; Ornos and Tantengco, 2022). Furthermore, GDP and research expenditure are strongly correlated with bibliometric indices of psycho-oncology research. International collaboration in psycho-oncology-related research is very strong among developed countries.

Limitations

This study has several limitations. Firstly, all the data used in this study were retrieved from a single database. The use of other databases such as Google Scholar, PubMed, and Web of Science would yield more publications on psycho-oncology-related research. Secondly, the search was performed with some specific restrictions which limited the number of publications.

CONCLUSION

This study presents a bench of evidence that might have several applications for clinicians, researchers, and policymakers working in the field of psycho-oncology. A significant increase in psycho-oncology-related publications has been observed in the last 5 years. The annual scientific growth rate was found to be 13.9%. The most highly contributing and collaborative country was the United States. The top leading author and institution were Grassi L and the University of Sydney, respectively. Lotka's law found that the number of authors declined as the number of papers written increased. The overall authors collaboration index was 4.38. The top-ranked core journal was Psycho-Oncology. The research hotspots include mental health conditions and interventions in cancer patients. International collaboration and research expenditure are strongly associated with psycho-oncology research productivity. Researchers' collaboration, which is visible among developed countries, should be extended to low-income countries in order to expand psycho-oncology-related research and understanding.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/**Supplementary Material**, further inquiries can be directed to the corresponding authors.

AUTHOR CONTRIBUTIONS

TA: conceptualization and study design. TA and EO: methodology, data curation, software, and formal analysis. TA: analysis, visualization, and preparation of the first draft. TA, EO, SA, RA-W, IM, SS, BA-O, MB, and KT: data assessment and validation, manuscript writing, review, and editing. TA: project administration and supervision. All authors read and approved the current version for publication.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.947669/full#supplementary-material

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Hypnosis and cognitive behavioral therapy with online sessions to reduce fatigue in patients undergoing chemotherapy for a metastatic colorectal cancer: Rational and study protocol for a feasibility study

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Background: In metastatic colorectal cancer (CRCm), fatigue is pervasive, reduces quality of life, and is negatively associated with survival. Its course is explained in part by psychosocial variables such as emotional distress, coping strategies, or perceived control. Thus, to reduce fatigue, psychosocial interventions appear to be relevant. In some cancers, Cognitive Behavioral Therapies (CBT) reduce fatigue. Hypnosis is also used as a complementary therapy to reduce the side effects of cancer. While CBT requires specific training often reserved for psychologists, hypnosis has the advantage of being increasingly practiced by caregivers and is therefore less expensive (Montgomery et al., 2007). On the other hand, CBT and hypnosis remain understudied in the CRC, do not focus on the symptom of fatigue and in Europe such programs have never been evaluated.

Objectives: Implementing an intervention in a healthcare setting is complex (e.g., economic and practical aspects) and recruiting participants can be challenging. The primary objective will therefore be to study the feasibility of two standardized interventions (hypnosis and CBT) that aim to reduce fatigue in patients with CRCm treated in a French cancer center.

Methods and design: A prospective, single-center, randomized interventional feasibility study, using mixed methods (both quantitative and qualitative). A total of 60 patients will be allocated to each intervention group [Hypnosis ($n = 30$) and CBT ($n = 30$)]. Participants will be randomized into two parallel groups (ratio 1:1). Both programs will consist of 6 weekly sessions focusing on the CRF management over a period of 6 weeks. Trained therapists will conduct the program combining 3 face-to-face sessions and 3 online sessions. The feasibility and experience of interventions will be evaluated by the outcome variables, including the adhesion rate, the reasons for acceptability, relevance or non-adherence, the satisfaction, the fatigue evolution (with ecological momentary assessments), and the quality of life. All questionnaires will be self-assessment using an online application from the cancer center.

Discussion: Results will highlight the barriers/facilitators to the implementation of the program and the relevance of the program to the patients, and will be used to generate hypotheses for a randomized control trial.

Clinical trial registration: ClinicalTrials.gov Identifier: NCT04999306; https://clinicaltrials.gov/ct2/show/NCT04999306.

KEYWORDS

fatigue, cancer, intervention, hypnosis, cognitive behavioral therapy, protocol, feasibility

Introduction

In cancer patients, fatigue appears to be one of the most frequent and persistent symptoms (NCCN National Comprehensive Cancer Network, 2017). Cancer-related fatigue (CRF) has been defined as a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer and/or cancer treatment that is not proportional to recent activity and interferes with usual functioning (NCCN National Comprehensive Cancer Network, 2017). Patients consider it severe and intense (Stone et al., 2000). Fatigue can have important psychosocial consequences such as reduced daily activities, and decreased quality of life (Lawrence et al., 2004; Forlenza et al., 2005).

Patients with metastatic colorectal cancer (CCRm) may follow several chemotherapy cycles. They follow months or even years of treatments, leading to many side effects (Wagland et al., 2015) and involving a decrease in Quality of Life (QoL) and functional status (Mayrbaeurl et al., 2016). In patients with colorectal cancer, fatigue ranks first among chemotherapy-related adverse events, with 75% of patients presenting a grade 3-4 with physical and psychological consequences (Mitry et al., 2010; Mota et al., 2012; Vardy et al., 2014). Then, metastatic progression and the increasing number of treatments are also aggravating factors (Peria et al., 2012), with a study reporting that 16% of patients in a clinical trial have fatigue graded at ¾, which corresponds to a very intense fatigue (Miyamoto et al., 2016).

CRF is not only a consequence of the disease or the treatments. Indeed, some authors have made recommendations for psycho-oncology researchers to study the role of personality in developing or coping with CRC cancer and the associated QoL (Sales et al., 2014). To better understand the psychological factors associated with fatigue in CRCm patients, a recent study highlighted distinct trajectories of fatigue in this specific population during the course of chemotherapy (Baussard et al., 2022). That study was theoretically based on the Transactional, Integrative and Multifactorial (TIM) model (Bruchon-Schweitzer and Boujut, 2014) which suggests that health issues are explained by sociodemographic, medical and dispositional variables (such as personality) and by contextual variables (such as resources, e.g., coping strategies, perceived control, etc.). As shown in Figure 1A, Baussard (2018) have applied this model to the specific CRF and its evolution during the treatment. Results suggest that in CRCm patients undergoing chemotherapy, four distinct fatigue profiles were identified. The probability of belonging to each of these trajectories is explained by variables considered by the TIM model: tired patients are those reporting more emotional distress, little perceived control or inadequate coping strategies

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Abbreviations: CAM, Complementary and Alternative Medicines; CRCm, colorectal cancer metastatic; CBT, Cognitive and Behavioral Therapy; CRF, Cancer-Related Fatigue; CSQ, Consumer Satisfaction Questionnaire; EBPP, Evidence-Based Practice in Psychology; INCa, French National Cancer Institute; MFI, Multidimensional Fatigue Inventory; NCCN, National and Comprehensive Cancer Network; QLQC, Quality of Life Questionnaire in Cancer; QoL, Quality of Life; SEQ, Session Evaluation Questionnaire; VAS, Visual Analog Scale; WHO, World Health Organization.

(Baussard et al., 2022). These results corroborate the literature underlying the relationship between emotional distress and fatigue (Blesch et al., 1991; Mols et al., 2012; Yennurajalingam et al., 2016), even in CRC patients (Mota et al., 2012; Tung et al., 2016). To our knowledge, it remains, however, the only study that have investigated psychological resource variables (such as coping, perceived control, etc.), suggesting that fatigue may be a consequence of a psychological maladjustment and imply that psychosocial interventions may be proposed to patients.

To address fatigue in cancer patients, the NCCN National Comprehensive Cancer Network (2017) highlights several types of interventions such as physical activity and psychosocial interventions. In 2008, Kangas et al. conducted a meta-analysis using data from 57 studies of non-medication therapies in cancer. The results indicated that the most effective strategies were physical activity and psychosocial interventions such as Cognitive and Behavioral Therapies (CBT), with no major difference in effectiveness between these two types of intervention (Kangas et al., 2008; Mustian et al., 2017). CRC patients reported barriers to physical activity programs, including age, pain, or respiratory and cardiovascular comorbidities (Fisher et al., 2016). Thus, we believe that psychosocial interventions have value and another meta-analysis in breast cancer patients reported that, like exercise programs, CBT, relaxation, counseling and hypnosis are beneficial in improving fatigue among patients with breast cancer (Duijts et al., 2011).

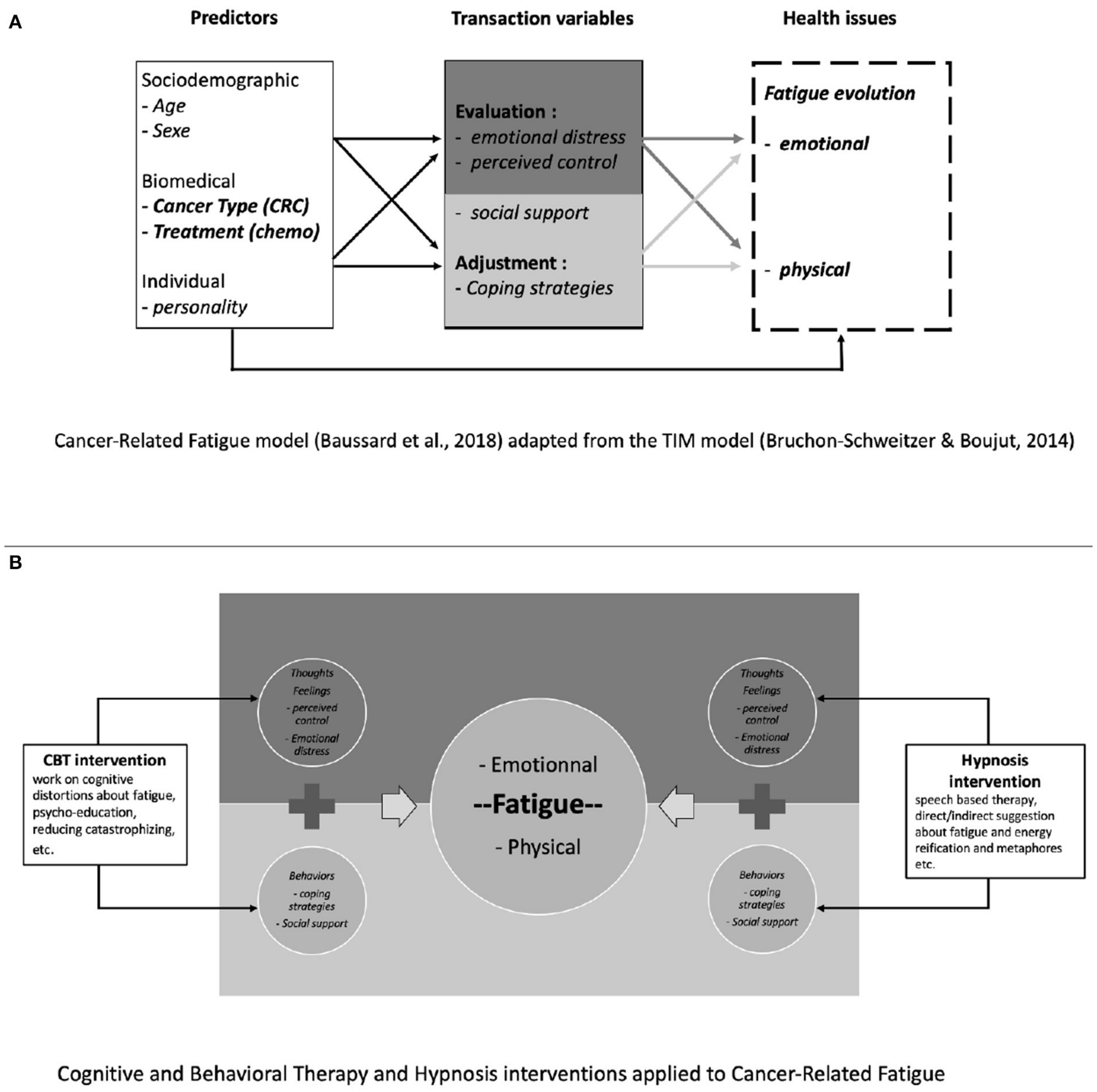
CBT for cancer patients includes therapeutic strategies focused on stress management (e.g., related to the announcement, surgery, treatment), problem solving to better cope with difficult situations, or cognitive restructuring (e.g., modification of dysfunctional cognitions associated with cancer) (Page et al., 2006; Berger et al., 2009; Chaloult et al., 2010; Cousson-Gélie et al., 2011). As shown in Figure 1B, CBT could be applied directly to CRF, by working on the thoughts and cognitive distortions associated with the symptom of fatigue. It aims to reduce emotional distress and encourage the development of a sense of control. Müller et al. (2021) found that increased self-efficacy and decreased fatigue catastrophizing, focusing on symptoms, perceived problems with activity and depressive symptoms mediate the reduction of fatigue brought by CBT. Finally, many studies have shown the effectiveness of CBT on fatigue in cancer patients (Page et al., 2006; Berger et al., 2009; Morin et al., 2009; Heckler et al., 2016) but never in patients undergoing chemotherapy for a metastatic CRCm.

In addition, the French Academy of Medicine suggest the interest of medical hypnosis in the management of the side effects of chemotherapy, such as nausea, vomiting or CRF (Bontoux et al., 2013). Hypnosis is defined as "a state of consciousness involving focused attention and reduced peripheral awareness characterized by an enhanced capacity for response to suggestion" (Elkins et al., 2015). Studies in breast cancer patients show a positive effect of hypnosis combined with CBT on symptoms of distress and physical fatigue (Cramer et al., 2015; Roe et al., 2016). A recent literature review found that only six studies investigated the effectiveness of hypnosis (not combined with another therapy) on cancer symptoms and CRF (Baussard et al., 2020). Results indicate that four studies reported effectiveness of hypnosis: two studies when the session is conducted by a therapist (Montgomery et al., 2007; Jensen et al., 2012), with effect sizes (*d*) equal to 0.80 and 2.05 respectively, and two studies reported significant efficacy of auto-hypnosis (listening audio-tape) (Bragard et al., 2017; Gregoire et al., 2017). However, these four studies remain in the minority and have limitations in generalizing the results. First, the samples are too small with $n = 8$ in the study by Jensen et al. (2012) and $n = 68$ for the studies by Bragard et al. (2017) and Gregoire et al. (2017). Second, all of these studies focused on women with breast cancer, which is a specific population. The study of Montgomery et al. (2007), a two-arm RCT with $n = 100$ for the hypnosis intervention seems more robust but assessed post-surgery fatigue, which again is very specific. Thus, this review of the international literature concludes that there is a lack of studies on the effectiveness of hypnosis for CRF (Baussard et al., 2020).

As shown in Figure 1B, as well as CBT, hypnosis could be used to manage CRF, by suggesting ways to regain energy or rest, or by working on a "safe place" to enhance relaxation, etc. The aim is to modify the patient's representations and to help her/him to tame this symptom. In addition, hypnosis has the advantage of being increasingly practiced among professional caregivers in hospitals (Montgomery et al., 2007; Gueguen et al., 2015), and also accepted by the patients (Bragard et al., 2017) which facilitates its implementation.

Thus, the relative efficacy of hypnosis and CBT on CRF has been described in oncology, but very few of these interventions have been conducted specifically on CRCm patients. The difficulties in implementing such programs in the care pathway underlines the importance of conducting this type of study. To our knowledge, there is no study proposing CBT or hypnosis in patients with CRC to reduce CRF. Since the implementation of two psychosocial intervention programs in a health care center is complex, and there is a need to develop standardized interventions for a specific population (CRCm patients), it was decided to first conduct a feasibility study. van Lankveld et al. (2018) suggest that feasibility studies should assess interest and willingness of patients to receive professional psychosocial care. To go further, evidence-based practice, defined as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients" (Trinder, 2008) has become an important feature of health care systems and health care policy.

Furthermore, several studies and meta-analyses underline a better effectiveness of face-to-face sessions (Montgomery et al., 2002; Schnur et al., 2008; Askay et al., 2009), and individual sessions rather than group sessions (Cousson-Gélie



Cancer-Related Fatigue model (Baussard et al., 2018) adapted from the TIM model (Bruchon-Schweitzer & Boujut, 2014)

Cognitive and Behavioral Therapy and Hypnosis interventions applied to Cancer-Related Fatigue

FIGURE 1
(A,B) From theory to practice–psychosocial interventions (CBT and hypnosis) applied to the determinants of cancer-related fatigue.

et al., 2011). We therefore propose individual face-to-face sessions. Beside, the programs in this study are intended to respect the chemotherapy pathway of CRC patients (i.e., a treatment every 2 weeks). This approach seems to be essential to allow a good implementation within the hospital, and not to induce an additional fatigue in patients by imposing them an additional travel.

This will also allow us to gather precise indicators (barriers/facilitators) regarding the implementation of psychosocial interventions in cancer centers, in order to meet the expectations of an increasingly personalized medicine, insisting on the essential place of support care.

Objectives

The main objective will be to assess the feasibility of two standardized interventions for fatigue reduction in patients with CCRm. One of the two interventions will propose a dedicated CBT and the other an hypnosis intervention. It seems essential to assess the proportion of volunteers to participate in these interventions as well as the acceptability of the programs, the method of data collection and the barriers/facilitators to the implementation of these two interventions. Therefore, several secondary objectives are planned:

1. To assess acceptance to participate in the study and reasons for refusal;
2. To identify the reasons for non-adherence to the program;
3. To highlight the barriers/facilitators to the implementation of the protocol;
4. To evaluate the relevance of the program (adapt to the patients' needs);
5. To assess fatigue (pre- and post-intervention) and its evolution;
6. To describe the QoL at baseline and after the intervention.

Although this is a feasibility study, patients participating in either program will benefit from a possible improvement in their fatigue status. There are no risks to report.

Method and analysis

Design

This is a prospective, single-center, randomized interventional feasibility study. This feasibility study proposes the implementation of two intervention programs (CBT and Hypnosis) to reduce CRF. Thus, patients included in the study will be randomized into two parallel groups (ratio 1:1). Procedure is detailed below. This research will use mixed methods (both quantitative and qualitative analyses) and data triangulation. Indeed, to increase the ecological validity of the study it is necessary to cross different types of data, analyses and/or participants (Salkind, 2010). In this study, combining a quantitative approach to program satisfaction with a qualitative approach to program experience allows us to answer complex research questions while taking advantage of the benefits and minimizing the limitations of qualitative or quantitative studies alone.

Population

Recruitment

Patients will be included in a French regional anticancer center. We plan to include 60 patients who will be allocated to each intervention group [i.e., Hypnosis ($n = 30$) and CBT ($n = 30$)]. The sample size will not be based on a power analysis but on the estimated recruitment capacity in the cancer institute.[1] A recruitment of 30 patients per intervention group would allow us to estimate in each group a proportion of at least 80% of patients adhering to each intervention, with their 95% confidence intervals, of amplitude 0.28 (Machin et al., 2009).

Eligibility

Inclusion criteria will be as follows:

1) Age $\geq$ 18 years
2) WHO performance status $\leq$ 2
3) Progressive colorectal adenocarcinoma after first line metastatic chemotherapy
4) Able to understand and read French
5) Visual Analog Scale for fatigue $\geq$ 4: based on our previous work on metastatic CRC patients where 48% complained of moderate fatigue throughout treatment, and since our variable of interest is fatigue, we decided to include patients already fatigued (4/10 on VAS).
6) Patients starting a second or third line of metastatic chemotherapy
7) Patients who signed the informed consent
8) Patients subscribed to a French Social Security system

The criteria for non-inclusion will be as follows:

1) Patients who do not have a telephone or devices that allow remote monitoring of sessions at home
2) Presence of brain metastases
3) Chronic pain evolving for more than 3 months and on morphine
4) Patients who used to and/or have a regular and habitual practice in meditation, or in relaxation techniques such as yoga, hypnosis or sophrology
5) Medical (neurological, psychiatric, etc.) or psychological conditions that do not allow participation in the protocol (filling out the questionnaires and the booklet, as well as following the sessions)
6) Deaf patient without hearing aids
7) Patient under guardianship or legal protection

Description of the programs

Both programs consist of 6 weekly sessions, each lasting ~1 h (shorter in the hypnosis arm), of CRF management over a period of 6 weeks. They focus on CRF and its psychosocial determinants (see Table 2):

- Session 1: Patient Education about CRF
- Session 2: Work on perceived control

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[1] The recruitment capacity and duration of the inclusions (12–18 months) are not only based on the recruitment capacity of the oncology department, but also take into account a practical aspect: the follow-up, which is the psychotherapists' capacity. Indeed, only 2 psychologists at the Center are trained in CBT and agreed to participate in the study, indicating that they will be able to follow up 2 patients per week each (i.e., 4 patients included every 6 weeks).

- Session 3: Work on emotional regulation
- Session 4: Work on social support during illness
- Session 5: Working on coping strategies
- Session 6: Review of previous exercises/sessions, synthesis

CBT

In order to standardize the program, the content of the CBT intervention was inspired by previous studies (Gielissen et al., 2006, 2007; Poort et al., 2017) and based on previous results focusing the psychosocial determinants of fatigue in metastatic CRCm patients (Baussard et al., 2022). In Gielissen et al. (2006) study, the rationale of the intervention was based on the model of precipitating and perpetuating factors, where each session focused on fatigue perpetuating factors such as coping with the experience of cancer, fear of disease recurrence, dysfunctional cognitions concerning fatigue or negative social interactions. Inspired by these studies, each session of the CBT program will focus on fatigue determinants (Table 2).

Hypnosis

Hypnosis, as a speech-based therapy, is difficult to standardize. One way to standardize the protocol is to distribute audio-scripts to patients to listen to at home independently (Bragard et al., 2017; Gregoire et al., 2017). However, this way has two main limitations. First, each patient has her/his own vocabulary, that makes uncertain the standardized and general speech-based efficacy. Then, the benefit from the session as if a therapist were present, compared with the benefit from a session with a therapist, may differs (as there is no way to ensure the state of hypnosis or the duration of the session, for example). The (Jensen and Patterson, 2006; Jensen et al., 2008, 2012) 's hypnosis included sessions based on a written script that each clinician read to the patients, although minor wording changes were allowed to facilitate verbal flow. In 2013, Montgomery et al. (2013) gave advices for setting up a standardized hypnosis program to facilitate its evaluation: introducing of the session; inducting; working on metaphors or making specific suggestions and then instructing for self-hypnosis or anchoring. Moreover, Grégoire et al. (2022) published a study protocol where hypnosis was proposed in a face-to-face and in a standardized way. Taken as a whole, these works encourage the creation of a specific program with exercises specifically designed to work on a problem-related fatigue as it is the case in the CBT intervention. Description of hypnosis sessions and associated fatigue variables are presented in Table 1.

1. The proportion of patients giving consent to participate in the study compared with the number of patients approached for the study, and the reasons for refusal to participate;
2. The qualitative reasons reported by the patients for non-adherence to the program (for patients dropping out of the program);
3. The qualitative barriers/facilitators reported by the patients to the program implementation;
4. (a) The score of the Consumer Satisfaction Questionnaire (CSQ-8) – (Kapp et al., 2014). This scale allows the quality-of-care assessment and will evaluate the acceptance and relevance of the programs.

(b) The score on the Session Evaluation Questionnaire (SEQ in order to assess the weekly satisfaction about the sessions. It takes 5 minutes and consists of 22 items. Each item represents two bipolar adjectives on which the patient ranks at the end of a therapeutic consultation. For the purposes of this study, we will consider only the first factor, the 11 items on the feeling of the session (pleasant interview, powerful, superficial, etc.) (Stiles, 1980).

5. (a) The scores on the Multidimensional Fatigue Inventory (MFI-10) - (Baussard et al., 2018). This 10-items short scale is validated in cancer patients and assess physical, emotional and cognitive fatigue.

(b) The scores on the VAS fatigue (Baussard et al., 2017). This VAS is adapted on the phone application (≪ Mon Essai Patient ≫) for the study needs, while respecting its original form. Patients are asked to indicate, with a cursor going from 0 to 10, their state of fatigue, whether physical (I lack energy) or psychological (I feel weariness).

6. The scores on the Quality of Life (QLQ-C30 – EORTC) - (Aaronson et al., 1993). The QLQ-C30 incorporates nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social); three symptom scales (fatigue, pain, and nausea and vomiting); and a global health and quality-of-life scale. The EORTC QLQ-C30 was extensively validated in European languages, including French;

Measures

In this feasibility study, the primary endpoint is the proportion of patients who have adhered to the proposed intervention program (both CBT and hypnosis programs include 6 sessions). A patient will be considered adherent if she/he participated in at least 4 of the 6 proposed intervention sessions. Adherence is defined in the same way in each intervention group. The choice to consider adherence to the programs at 4 out of 6 sessions is a commonly accepted practice in non-medication intervention studies (Brebach et al., 2016). Thus, patients participating in the study will have to receive at least 4 sessions (addressing key issues related to fatigue) in order to consider the program beneficial (hypnosis or CBT).

There are secondary quantitative and qualitative endpoints:

TABLE 1 Description[1] of the sessions for both programs.

	Hypnosis	**CBT**
Session’s themes		
Each session ends with a debriefing and Questions/Answers		
Fatigue education	Program presentation Fatigue education Short hypnosis session: “Safe place” induction Questions/Answers	Program presentation Fatigue education Introduction to CBT Questions/Answers
Perceived control	Induction with sensory data collection (fatigue as a deep feeling of tiredness) Miracle question and search for exception based on Solution-focused therapy	Discussion about patient’s representations of fatigue and cancer Exercise on causal attributions (internal, external and hazard) To think about action to implement to regain control over fatigue
Emotional regulation	Induction on breathing Safe place and work on emotion observations and rating Anchoring the feeling of wellbeing	To identify feelings and associated thoughts To list problematic situations To notice dysfunctional thoughts and searching for alternative thoughts
Social support	Questioning about relatives support and induction on today fatigue sensation Rossi’s mirroring hands to identify people who are social resources	Presentation of social support and its dimensions To identify people resources for each type of support To learn how communicate needs and assertiveness
Coping strategies	Induction with body scan to focus on a specific site where fatigue is intense (e.g., shoulders or legs) Work on metaphors and reifying the symptom	Presentation of coping strategies To think about patient’s behaviors and coping efficacy (Cunji’s circle) To consider alternative behaviors
Synthesis	Feedback on the program and on the exercises that need to be repeated To see with the patient where he/she stands	Feedback on the program and on the exercises that need to be repeated To see with the patient where he/she stands

For the content of the programs (CBT and Hypnosis), each therapist will follow a guide where each session is described (how to introduce the session, exercises during the session, at-home practices, etc.). These built guides are the property of the authors and can be provided on an argued request of interested parties (replications, systematic review).
Each session from 2 to 6. Begins with a debriefing on the previous session (feedback on home exercises for CBT; feedback on experience if self-hypnosis for Hypnosis).

Semi-directed interviews

Qualitative interviews are planned to assess the relevance of the programs. The interviews will be semi-structured to obtain as much information as possible. A first general question will ask about their general opinion of the program. Then, they will be asked to talk about their reasons for agreeing to participate in the program, as well as information about the implementation. Patients will answer whether the program seemed suitable or not and finally, whether they would recommend it to others. Each question is as broad as possible, and then participants will be prompted if more detail is needed. Patients who would like to end their participation in the program prematurely will also be invited to participate in these interviews, as the reasons for non-adherence are among the evaluation criteria. It is difficult to estimate the time, some patients will speak little, others elaborate more. For open-ended questions, we estimate a minimum of 20 min and a maximum of 1 h.

Repeated measures

Our protocol involves an ecological momentary assessment (EMA) of fatigue, ideally at the same time of day. This daily measurement of fatigue is planned from T0 to T1, i.e., 7 weeks (49 assessments). Daily fatigue assessment takes 2 min with the VAS, one for each item (Baussard et al., 2017).

Weekly satisfaction about the sessions takes 5 min and will be assessed by The Session Evaluation Questionnaire (SEQ). Each 22 item represents two bipolar adjectives on which the patient ranks at the end of a therapeutic consultation. For the purposes of this study, we will consider only the first factor: 11 items on the feeling of the session (pleasant interview, powerful, superficial, etc.) (Stiles, 1980).

Procedure

Three time points will be considered: T0 corresponds to the patient’ inclusion in the study (patient agreement and completion of the study questionnaires), T1 corresponds to the end of the intervention after 6-weeks of intervention (semi-directive interviews on the acceptability of the program and completion of the questionnaires), and T2 corresponds to a follow-up visit 3 months after the intervention (questionnaires).

During the medical consultation with the oncologist, eligible patients will be identified. After oncologist approval, only inclusion/non-inclusion criteria (including fatigue VAS) will be retrieved by the investigator. If eligible, a patient will receive the

TABLE 2 Measurements used in the study.

Measures	Screening	T0	6 weeks interventions	T1	T2
Inclusion/non-inclusion criteria	X				
Information letter and consent		X^{a}			
Sociodemographics and medical variables		X		X^{b}	
EPICES score		X^{c}			
Fatigue and Quality of Life:					
6. VAS fatigue (physical/emotional)	X	X	X^{c} Daily assessment		X^{c}
7. MFI-20		X^{c}		X^{c}	X^{c}
8. QLQ-C30		X^{c}		X^{c}	X^{c}
Feasibility					
9. SEQ			X^{c} Weekly assessment		
10. ISQ-8				X^{c}	
11. Qualitative interviews				X^{c}	

[a] Information letter and consent are delivered at screening and retrieved if inclusion at T0; [b] if progression, relapse or change of treatment; [c] E-health application; MFI-20, Multidimensional Fatigue Inventory; QLQ-C30, Quality of Life Questionnaire – Cancer; Score EPICES, precariousness and social inequalities in health; SEQ, session evaluation questionnaire; CSQ-8, satisfaction questionnaire about interventions.

information letter and consent, and will be asked to return it for cure of chemotherapy N°1 (T0).

The investigator will collect the sociodemographic (including the Score EPICES) and the medical variables. She/he will also present a web application (smartphone or tablet), available on AppStore or PlayStore ("*Mon Essai Patient*") from the company Exolis. Patients who are not comfortable with these tools have the option of having a paper format. This application allows to collect every data from the questionnaires, encourages the daily or weekly assessment and limits missing data because patients will receive a notification when a questionnaire must be completed. Then a clinical research associate will give the different self-questionnaires to the patient, responding her/his questions if necessary. As shown Table 2, the patient will fill out, during ~30 min, the MFI-20, theQLQ-C30, and the VAS fatigue.

Randomization procedure. If the patient meets all the inclusion criteria and return the consent at T0, Biometrics Unit will proceed with the randomization and return the assigned treatment arm to the investigator. This form should also be completed and submitted for patients who meet the inclusion criteria but do not agree to participate in the study. A specific section of the form will be dedicated to them in order to register these patients (this will allow to answer the first secondary objective; i.e., the acceptance of participation in the study). The randomization procedure using the random block method will allocate the Hypnosis or CBT treatments with a 1:1 ratio and will be stratified according to two factors with two modalities: the number of lines of chemotherapy (2nd or 3rd line) and the management by the support care platform in the hospital (yes, no). Regarding stratification, the number of lines of treatment may have an impact on the primary endpoint (increase in fatigue) since it implies a non-response to treatment, a progression of the disease, and possibly a deterioration in the patient's condition. Secondly, the patients received at the Center may be offered support care as part of their standard care (*e.g.,* nutritional follow-up), and this may also have an impact on the primary endpoint (*e.g.,* reduction in fatigue). Therefore, these two factors will be considered as a stratification factor.

As shown in flow-chart (Figure 2), an included patient will be assigned to one of two intervention programs. Either hypnosis with 6 standardized sessions (1/week) of ~30–45 min or CBT with 6 standardized sessions (1/week) of about 1 h. In order to respect the chemotherapy pathway of CRCm patients, one session will be done face-to-face on the day of the treatment, and the following session will be offered remotely by telephone or videoconference (at a distance) when the patient is at home during the week without chemotherapy. For the three remote sessions of the intervention, patients can choose between telephone or videoconference therapy. If patients choose video, the sessions will be conducted using a secure tele-health platform called *Starleaf* (https://starleaf.com/about-us/). This company was Founded in 2008 in Cambridge and provides secure meetings, messaging and calling to enterprises worldwide. Thus, the first session of a program will take place face to face, during treatment cure N°2 (i.e. after a respected delay after the proposal to participate in the protocol), the third and the fifth respectively during chemotherapy N°3 and N°4 in hospital. The second, fourth and sixth sessions will take place remotely. Three therapists (one for the hypnosis and two for the CBT program) will implement the interventions and all patients will receive an

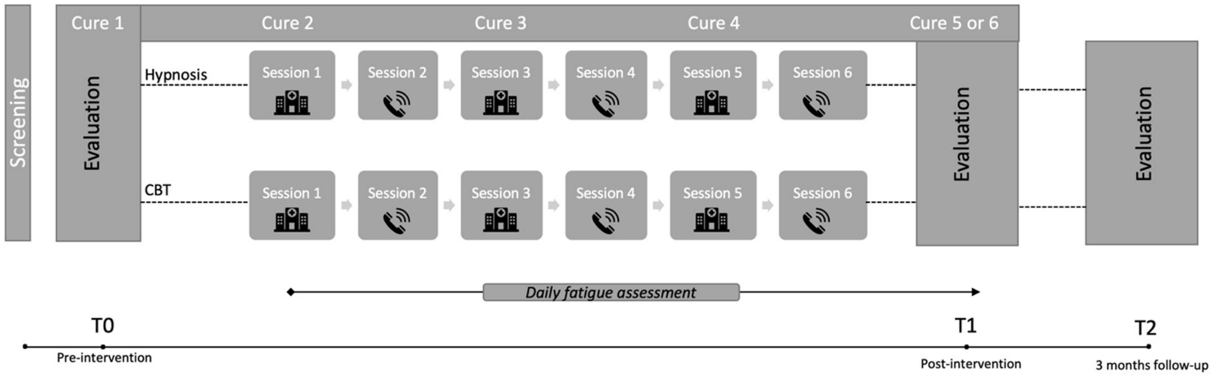

FIGURE 2
Study design with two-arms randomization (hypnosis and CBT), 6 sessions each. Flexibility in terms of sessions is foreseen, i.e., a patient may have a session shifted by 1 or 2 weeks depending on its WHO performance status and/or the therapist's availability. This takes into account the toxicities, need to always have the same practitioner for the 6 sessions, and the reality of the field (absences, vacations, etc.).

individual notebook with explanations of the program, fatigue education, and blank pages to take notes after each session. The mail of the clinical research assistant will also be presented here if any questions arise between two sessions.

At T1, after the interventions, patients will be asked to complete again the QLQ-C30, MFI, EVA fatigue and the ISQ-8 (see Table 2). They also will be interviewed by a trained psychologist about their acceptation of the program with semi-directed interviews. The interviews will be semi-structured to obtain as much information as possible. A first general question will ask about their general opinion of the program. Then, they will be asked to talk about their reasons for agreeing to participate in the program, as well as information about the implementation. Patients will answer whether the program seemed suitable or not and finally, whether they would recommend it to others. Each question will be as broad as possible, and then participants will be prompted if more detail is needed. Patients who would like to end their participation in the program prematurely will also be invited to participate in these interviews, as the reasons for non-adherence are among the evaluation criteria.

At the end, regardless of the inclusion arm, patients will receive one intervention over a period of 6 weeks and will be re-interviewed 3 months after the procedure (T2) on their level of fatigue and quality of life, representing 5 months involvement in total.

Statistical considerations

The primary outcome will be analyzed in each intervention group. The proportions of patients who adhered to each intervention program (Hypnosis and CBT) will be presented with their two-sided 95% confidence intervals (95% CI), as the proportion of patients giving consent to participate in the study among the eligible patients at the screening who were offered the study. All statistical analyses of the secondary criteria will be done by group. Categorical variables will be described by the number of observations (N) and the frequency (%). Missing categories will be counted. Quantitative variables will be described by the number of observations (N), mean, standard deviation, median, minimum, and maximum. In case of missing data no imputation method will be used.

For the comparison of qualitative variables, a chi-square test or a Fisher's exact test will be used if the theoretical number of observations is <5. For the comparison of quantitative variables, a Student's *t*-test or a Kruskal-Wallis test will be used. For comparisons between two time points a Wilcoxon test for paired samples will be used. The correlation between the VAS values for fatigue and the scores on the MFI-10 questionnaire will be studied using Pearson's correlation coefficient or Spearman's correlation coefficient. The evolution of VAS fatigue values over the course of treatment will be modeled using linear mixed models to account for the repeated nature of the measurements. The analysis of the QLQC-38 questionnaire will be performed according to the EORTC guidelines.

All statistical tests will be two-sided and the significance level is set at 5% (i.e., $p < 0.05$). Statistical analyses will be performed with STATA v16 software and a statistical report will be provided according to the current model.

Program satisfaction will be assessed on the basis of the CSQ-8 score, SEQ evaluation of each session and put into perspective with the individual semi-structured interviews analyzed with QDA Miner. This is a mixed methods and qualitative data analysis software developed by Provalis Research. The program was designed to assist researchers in managing, coding and analyzing qualitative data. QDA Miner was first released in 2004 and the latest version 6 was released in September, 2020.

Discussion

We conduct this study with a view to evidence-based practice. It is an approach that limits clinical uncertainty, based on a tripartite evaluation taking into account the patient's point of view, the clinical experience and scientific evidence (Rycroft-Malone et al., 2004). Evidence-based practice in psychology (EBPP) promotes effective psychological practice by, among other things, applying empirically supported interventions (APA Presidential Task Force on Evidence-Based Practice, 2006).

In order to better understand the needs of patients and to know the possibilities of implementing such programs in a cancer center we decided to conduct a feasibility study. As we know, there is no such studies for managing fatigue in CRCm patients, except for Teo et al. (2020) who published a feasibility study on the implementation of CBT in patients with advanced CRC. Although the focus was not on fatigue, it does provide some insight into the acceptability of a psychosocial intervention in this population. They successfully recruited the intended sample (mean age 61 years; 62% men). Most patients (88%) completed all sessions and participants reported high rates of satisfaction (97%) and helpfulness (96%) of the intervention, which remains encouraging for our study. Patients use Complementary and Alternative Medicine (CAM) more often to increase the body's ability to fight the cancer or to improve physical wellbeing (Molassiotis et al., 2005; Lawsin et al., 2007; Wong et al., 2021). Studies investigating CAM show that CCR patients are increasingly turning to this type of medicine, but hypnosis is still not well-known (Molassiotis et al., 2005; Lawsin et al., 2007; Wong et al., 2021). It therefore seems interesting to understand the acceptability of CBT or hypnosis.

Several authors agree that longitudinal studies and Randomized-Controlled Trials should be set up to overcome limitations about methodology and standardization (Sood et al., 2007; Barsevick et al., 2013; Carlson et al., 2017). This pilot study, with two standardized interventions (including a hypnosis program) will encourage us to conduct a 3-arms RCT (CBT, hypnosis and control) to evaluate the efficacy of such therapies, and to answer the question of which therapy will benefit to the most vulnerable patients.

Many arguments allow to provide hypothesis about the results. First, there are distinct profiles of CRF in CRCm patients undergoing chemotherapy (Baussard et al., 2022): intense fatigue (6.51%), moderate fatigue (48.52%), no fatigue (33%), and increasing fatigue (11.83%). Secondly, CBT are costly in terms of time and investment, require specific training (psychologist) and seems difficult to implement in the care pathway or to offer them to all patients. Thirdly, hypnosis has the advantage of being more easily implemented in the treatment process because the nursing staff (nurses, caregivers, etc.) can be trained in it. Therefore, we would expect that those with severe fatigue (6%) would require more comprehensive treatment (CBT), whereas those with moderate fatigue (48%) would benefit from hypnosis alone. We aim to understand what is easiest to implement and most relevant to patients.

There are some others inherent limitations to the study that may negatively influence the rate of adherence to the program. The emotional burden of patients diagnosed with CRCm is very high, and the patients will have lot of information to integrate. In addition, the use of the e-health application is subject to technical hazards, in addition to the weariness it can create. While access to e-health is increasing worldwide, a gap remains between those who use between those who use these digital tools and those who do not use them (Wynn et al., 2020). Finally, an assessment of the costs for implementation of the programs on a routine basis should be planned.

Implementing these two programs will allow us to understand which management is the most effective and for which profiles of fatigued patients. This study could then inform us about the number of patients who need full and more expensive treatment (CBT), and ultimately allow institutions to respond to the demands of an increasingly personalized care and underlines the importance of evaluating the relevance of supportive care.

Ethics statement

The studies involving human participants/the COLOFIGHT protocol were reviewed and approved by the Ile de France II French Ethical Committee (January 2022) and registered on ID-RCB n° 2021-A01031-40. The patients/participants will provide their written informed consent to participate in the study.

Author contributions

LB and FC-G conceptualized the initial version of the project. LB, EC, SL, and LM developed the project methodology and built the CBT program. LB, MF, and LM constructed the hypnosis program. CJ and MJ helped with the implementation in the clinical research department. MJ with the statistical considerations of the project. EG and LC will conduct the CBT sessions, and MF the hypnosis sessions. All authors contributed to the design of the study presented here.

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analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

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.

Publisher's note

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Social isolation in adults with cancer: An evolutionary concept analysis

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Background: In extant literature, the concept of social isolation has been explored primarily in the context of older adults. However, people with cancer may also experience social isolation, and there is a need for increased clarity regarding this phenomenon in this population.

Objective: To conceptualize social isolation in adult cancer care.

Methods: PubMed, Web of Science, PsycINFO, CINAHL, China National Knowledge Infrastructure, Wanfang Data, and the Chinese Biomedical Literature Database were systematically searched using the key terms "cancer," "social isolation," "social alienation," and "social exclusion" for studies (from the earliest date available to June 2022). The main disciplines involved were psychology, nursing, medicine, and public health. Rodgers' evolutionary concept analysis was employed to clarify the antecedents, attributes, and consequences of social isolation in adults with cancer.

Results: A total of 60 eligible articles were reviewed entirely and the main findings were categorized into antecedents, attributes, and consequences. The antecedents of social isolation were classified into six categories: cancer-related physiological changes, cognitive beliefs, psychological wellbeing, unsatisfactory social supports or relationships, restrictions associated with receiving treatments, and social-level barriers. Attributes were characterized according to behavior or social avoidance and negative affective experiences, while consequences were attributed to low therapeutic compliance, poor health conditions and mental health problems, and low quality of life. White's heuristic model is a potential theoretical context applicable to social isolation in adults with cancer.

Conclusion: This concept analysis provides a basis for developing multidimensional assessment tools and measures to alleviate social isolation in adults with cancer, a complex and varied phenomenon. However, while this review contributes to the current knowledge on social isolation in people with cancer, studies should further investigate the relationships among attributes associated with social isolation.

KEYWORDS

social isolation, cancer, psychological nursing, psychosocial behavior, concept analysis

Introduction

Globally, over 19 million individuals are diagnosed with cancer annually (Sung et al., 2021). Cancer diagnosis and treatment can cause severe adversity, resulting in varying psychological distress levels (Sender et al., 2020). However, with advances in healthcare, survival rates are also higher, and there is now increased advocacy to enhance the quality of survivorship care. Consequently, treatment goals include improving patients' quality of life, symptom management, and psychosocial effects (Bray et al., 2018; Nekhlyudov et al., 2019). Despite this, limited attention has been paid to severe psychosocial issues, among which social isolation is one.

The term "social isolation" was introduced in Berkman and Syme's (1979) seminal study. Initially, it referred to individuals who lacked social networks or had limited social supports. Thereafter, it was developed concurrently across multiple disciplines including public health, medicine, and nursing (Nicholson, 2009). In public health literature, the definition of social isolation evolved from "… irreversible loss of social bonds" (Berkman, 1983) to "lack of attachments within a person's social network" (LaVeist et al., 1997). In the context of nursing, the subjective feeling of the unmet needs for social connections or supports and experiences of loneliness have been emphasized (Lien-Gieschen, 1993; Biordi, 1998; Ackley and Ladwig, 2004), while medicine views it as an objective indicator of social contact (Havens et al., 2004). The final definition of this concept incorporates both subjective and objective measures. Specifically, social isolation is characterized by minimal contact with other people and limited involvement in community affairs (Iredell et al., 2004).

The aforementioned definitions of social isolation have generally been developed with reference to older adults. Thus, an oncology-specific multidimensional definition of social isolation is yet to be clarified. The experience of social isolation and its associated attributes may differ among various age groups and by health conditions. Furthermore, social isolation is a phenomenon associated with severe health consequences and has been expanded to cancer. Specifically, in the context of oncology, social isolation has been analyzed primarily in patients with breast, prostate, head and neck, and lung cancers (Ettridge et al., 2018; Ashi et al., 2020; Dornan et al., 2021; Kudjawu and Agyeman-Yeboah, 2021).

Several studies underscore the impact of social isolation. Research indicates that social isolation is linked with the increased risk of tumor recurrence and mortality among patients with breast cancer (Kroenke et al., 2017). Friedler et al. (2015) summarized several studies on the pathophysiological mechanisms of social isolation, revealing that it affects the immune system, autonomic nervous system, and neuroendocrine axis. Moreover, long-term social isolation may increase the risk of mental illness (Yuan et al., 2020), reduce patient compliance with treatment, and increase cancer care costs (de Souza et al., 2017). Despite a lack of in-depth explorations, there is increasing evidence to suggest that social isolation could impact health in adults with cancer. This may be attributed to the different implications of social isolation between adults with cancer and older adults. The concept of social isolation in adults with cancer remains unclear. Therefore, this study aimed to clarify the meaning of social isolation in adults with cancer and examine its antecedents, attributes, and consequences by conducting a concept analysis.

Materials and methods

Identifying a concept

Rodgers' concept analysis method is an inductive process (Rodgers, 2000). In Rodgers' view, concepts evolve and are shaped by the context in which they are used. Therefore, they are constantly developed and redefined. There have been studies on social isolation across various fields. Furthermore, the meaning of the associated terms has been established over the years. Thus, we applied Rodgers' evolutionary concept analysis method and reviewed the literature on social isolation focusing on people with cancer to understand social isolation in the cancer context (Table 1; Rodgers, 2000).

Sources of data

We conducted systematic electronic searches (from the earliest date available to June 2022) of PubMed, Web of Science, PsycINFO, CINAHL, China National Knowledge Infrastructure, Wanfang Data, and the Chinese Biomedical Literature Database using combinations of the terms "cancer," "social isolation," "social alienation," and "social exclusion" in the abstract or title. The inclusion criteria were articles that were published in English or Chinese; had undergone peer review (excluding dissertations, theses, or comments); and underscored social isolation in people with cancer, specifically concepts, antecedents, attributes, and consequences. Searches were conducted without any time and discipline constraints to ensure the identification of as many relevant articles as possible and to provide an overview of the concept's use over time. The exclusion criteria were published

TABLE 1 Steps for Rodgers' evolutionary concept analysis.

Step	Description
1	Identify a concept and its surrogate terms.
2	Determine and select a suitable data collection scope.
3	Data collection:
a.	Concept attributes;
b.	Contextual basis including temporal, sociocultural, and interdisciplinary variables.
4	Data analysis.
5	If necessary, provide examples supporting the concept.
6	Identify hypotheses and applications for the concept's future development.

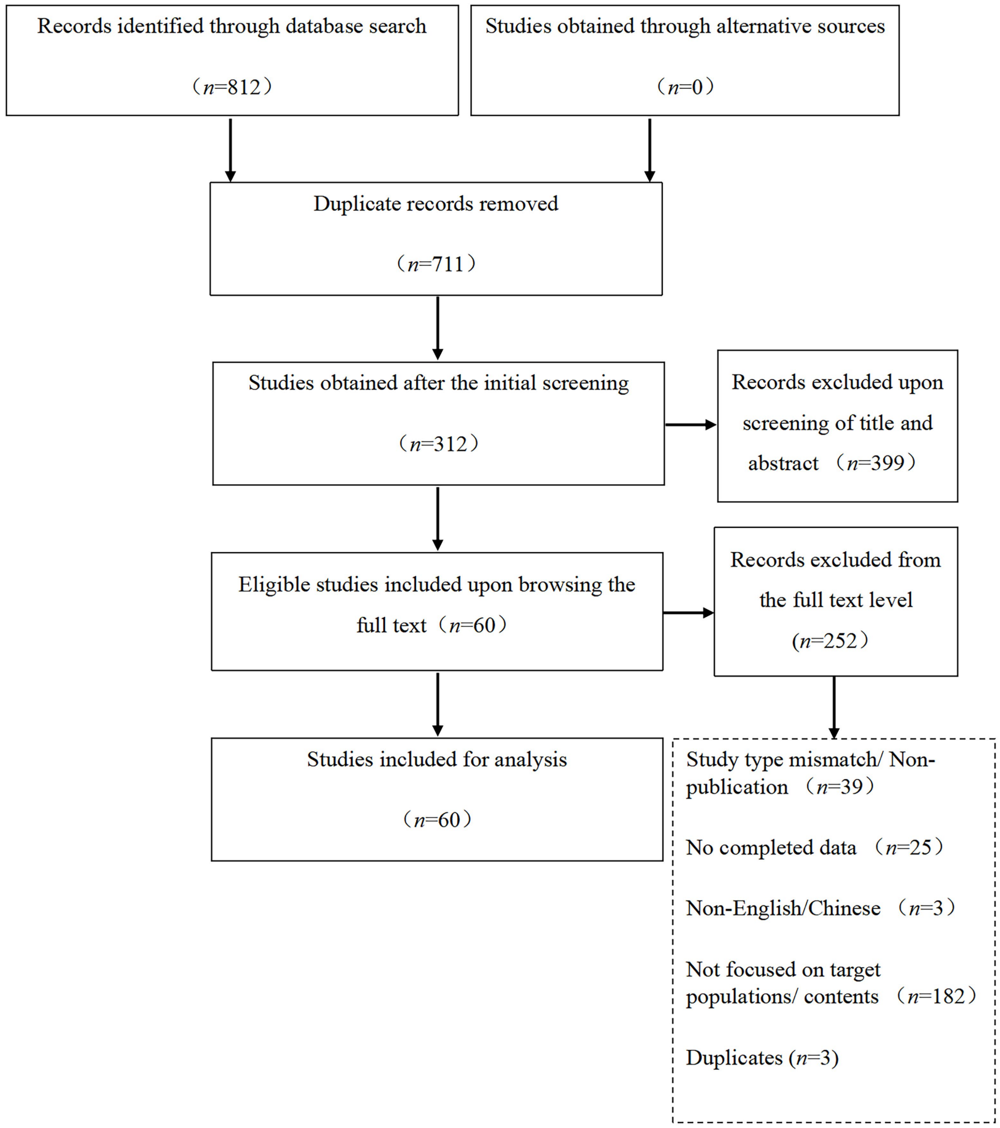

FIGURE 1
Flow chart of the study screening process. The studies obtained from each database are as follows: PubMed (*n*=16), Web of Science (*n*=5), PsycINFO (*n*=22), CINAHL (*n*=12), China National Knowledge Infrastructure (*n*=3), Wanfang Data (*n*=2), and the Chinese Biomedical Literature Database (*n*=0).

abstracts of studies that did not contain specific information on social isolation and studies conducted on non-cancer populations.

The original search resulted in 711 articles after deleting duplicates using the NoteExpress 3.5.0.9054 software (Figure 1). Upon performing further screening based on the exclusion criteria by reading the titles and abstracts of the articles, a sample size of 312 was obtained. There was no consensus on the criteria for evaluation of the data sources included in the concept analysis; only articles that mentioned social isolation in people with cancer were included. Duplicate studies that were not recognized by the software were manually deleted. Studies with insufficient information regarding the characteristics of social isolation in people with cancer, making attribute identification difficult, were also removed. This resulted in the removal of 252 of the 312 studies. Rodgers (2000) recommends that the total number of references per discipline included in a study should be approximately 20% of the total. This was not feasible in the current study. To gain a deeper insight into social isolation, the remaining 60 selected studies were included in this concept analysis. Finally, the disciplines involved were psychology ($n = 12$), nursing ($n = 24$), medicine ($n = 19$), public health ($n = 3$), medical informatics ($n = 1$), and epidemiology ($n = 1$).

Data collection and management

Based on Rodgers' method, the articles were studied for the identification of surrogate terms and related concepts.

Furthermore, they were reviewed for systematic data collection and management in terms of attributes, antecedents, and consequences of the concept. The aforementioned information was extracted and tabulated. Among the 60 articles reviewed, an explicit definition of social isolation was rare. Thus, not all articles were extracted for their attributes of the concept. The data sources were reviewed by two of the researchers and checked by a third (Zhu et al., 2018). The matrix was developed by YL and MW.

Data analysis

The included articles were coded according to antecedents, attributes, consequences, surrogate terms, contextual basis, and theoretical and practical definitions. The coding was conducted using the standard procedure of thematic analysis underscored in Rodgers' evolutionary method (Rodgers, 2000). Independently, two reviewers partially completed the work before discussing it with a third to reach a cohesive and comprehensive consensus to minimize bias as much as possible. Finally, the review team developed the conceptual definition of social isolation in people with cancer (Zhu et al., 2018).

Results

Study characteristics

The studies included in this analysis were published between 1980 and 2022; 55 were in English and five were in Chinese. Most employed cross-sectional and qualitative research designs. Patients with various types of cancer such as those affecting the lung, breast, head and neck, and prostate were included. The sample sizes ranged from three to 25,382. Only some studies included all the definitions, antecedents, attributes, and consequences of social isolation.

Surrogate terms and related concepts

Multiple terms have been used interchangeably with social isolation. For example, social alienation has been used in place of social isolation (Yang et al., 2021). While the term "social exclusion" is distinct from "social isolation," it has been used to describe social isolation in some studies (Dahill et al., 2020). There are two main concepts—alienation and loneliness—that need to be differentiated from social isolation. According to Seeman (1959), alienation encompasses powerlessness, isolation, normlessness, self-estrangement, and meaninglessness. Thus, isolation is only one psychological state of alienation. Some researchers use "loneliness" to express "social isolation." However, we did not use "loneliness" as a surrogate term in our search; using "social isolation" and "loneliness" interchangeably can be confusing, as we found loneliness to be an attribute of social isolation (Raque-Bogdan, 2019; Raque-Bogdan et al., 2019).

Social isolation definitions used in different cancer populations

Definitions of social isolation in adults with cancer have been presented in several studies with varying emphasis. Reduced social networks and loneliness are the most prevalent aspects of these definitions. Changing social health contexts, as influenced by factors such as coronavirus disease 2019 (COVID-19), have led to a spate of studies related to social isolation (Table 2).

Attributes

A concept is defined by distinct meanings, referred to as attributes. Attributes comprise a set of characteristics that can be used to categorize similar situations related to a certain concept (Rodgers, 2000). During the analysis, two attributes underscored by succinct generalizations of social isolation in people with cancer emerged. These attributes recurred in the description of social isolation in data sources, and included behaviors and states of social avoidance as well as negative affective experiences. Studies supporting each attribute are shown in Table 3. Notably, there is a significant difference between external social isolation and perceived or internal social isolation. However, some patients experiencing the former (i.e., behaviors and states of social isolation) may not experience negative affective experiences. It is imprudent to classify all the behaviors and states of social avoidance simply as social isolation and ignore emotional isolation.

Behaviors and states of social avoidance

States of social avoidance

States of social avoidance include limitations regarding social networks, which are determined by the frequency of social contact, activity, communication, size, and diversity (Liu B et al., 2021; Liu Y et al., 2021; Takemura et al., 2021). Discontinuing work after cancer diagnosis or treatment and relinquishing social roles are common for patients, and exacerbate feelings of isolation (De Blasi et al., 2018). To some extent, the choices of discontinuing work or relinquishing social roles belong to the social avoidance behavior attribute.

Social avoidance behaviors

Some cancer survivors choose to self-isolate (Ettridge et al., 2018; He et al., 2021). They are often reluctant to communicate with others, specifically concerning details of their illness. Social avoidance behaviors are more common among patients with prostate and rectal cancer (Ettridge et al., 2018; Zhu et al., 2019; He et al., 2021). Social isolation can be a passive choice induced by the inability to socialize like before due to medical conditions,

TABLE 2 Samples of social isolation definitions applied in studies included in the analysis.

Author (year)	Definitions of social isolation used in the article
Kirtane et al. (2022)	Physical and emotional social isolation is experienced during special circumstances (COVID-19).
Takemura et al. (2021)	A social relationship shortfall can be quantified by social network size, diversity, or frequency of contacts.
Liu B et al. (2021) and Liu Y et al. (2021)	People are isolated from interpersonal interaction and relationships. It is considered social isolation if people have limited social contact or communication and limited participation in social activities or meetings with friends.
Kudjawu and Agyeman-Yeboah (2021)	Social isolation refers to avoidance behaviors and feelings of isolation while dealing with breast cancer.
Liu B et al. (2021) and Liu Y et al. (2021)	Social isolation refers to an individual's unsatisfied social desire and failure to interact well with the outside world, accompanied by negative emotions such as loneliness and helplessness and negative behaviors such as apathy and rejection.
Morreale et al. (2020)	Feelings of being avoided, excluded, detached, disconnected, or not being known to others.
Yuan et al. (2020)	In traditional sociological terminology, social isolation entails a sense of anomie, which includes feelings of loneliness, inequality with others, and uselessness.
Wang et al. (2020)	Social isolation refers to the phenomenon that an individual is automatically isolated from other people and society when they are treated negatively by the world during social interaction, resulting in negative emotions such as loneliness and helplessness, and showing negative behaviors such as avoidance and rejection.
Zhu et al. (2019)	Social isolation refers to people believing that their relationships are insufficient to meet the quality and quantity of their social needs.
Raque-Bogdan et al. (2019)	The term "survivor loneliness" is used to represent the social isolation that may occur after cancer treatment. On an intrapersonal level, survivors described feeling alone as a result of acting inauthentically in relationships, feeling out of control of their bodies after the treatment, and feeling alone in their experience.
van Roij et al. (2019)	Social isolation refers to an abnormal life with an abnormal social network.
Carduff et al. (2018)	Inability to socialize or maintain existing relationships or develop new ones.
Parton et al. (2017)	According to some women, social isolation refers to being in a life stage that is not consistent with the life stages of their peers.
Biagioli et al. (2017)	Protective isolation is used to keep patients away from infections that may negatively affect them.
Hinzey et al. (2016)	A person's level of perceived social isolation (colloquially, loneliness) can be measured objectively based on criteria such as the size of their social network and number/frequency of interactions with others, or subjectively based on how isolated they perceive themselves to be.
Jeong et al. (2016)	Social interactions provide a means of measuring social isolation objectively.
Kroenke et al. (2013)	Small social networks are considered social isolation.
Fu et al. (2013)	Intentionally avoiding social or public appearances or contact. The five components that make up a social network are a spouse or intimate partner, the number of first-degree female relatives (living mother, number of biological daughters, number of full sisters), friendship relationships, religious or social ties, and community involvement.
Lee et al. (2011)	Social isolation, which refers to rejecting human contact, is practiced by patients as a way of protecting themselves.
Bennett et al. (2006)	Social isolation refers to physical and emotional isolation. It may have also been a means of protecting the self, friends, and family members. It is the result of attempting to appear "normal" and concealing one's true emotions, along with avoidance behaviors.
Hagedoorn and Molleman (2006)	Social isolation is the result of other people avoiding cancer survivors, and the survivors isolate themselves from their families and friends because of concerns about appearances and reactions.
Høybye et al. (2005)	It isolates them from loved ones and from the social world they once enjoyed.

surgery, and treatment effects. Notably, some cancer survivors conceal their identities and emotions (including hiding cancer-related information and feelings of loneliness) to protect themselves or their loved ones. This paradoxical behavior, aiming to eliminate negative emotions such as loneliness while hiding critical health-related facts from medical staff, patients, and their loved ones, requires increased prioritization (Raque-Bogdan, 2019).

Negative affective experiences

Loneliness has been reported as a negative effect among patients for several reasons. Cancer survivors experience distress, as they cannot speak about their illness with anyone except their intimate partners and medical specialists (Ettridge et al., 2018; Zhu et al., 2019).

Furthermore, low self-esteem, generally linked to self-discrimination, has been identified as a negative affective experience. Some patients may experience negative self-perception or self-denial due to cancer-related physiological changes, and thus avoid contact with people around them (Blinderman and Cherny, 2005; Ettridge et al., 2018). Behaviors and states of social avoidance and negative affective experiences are closely related. Another manifestation of low self-esteem is the fear of being humiliated in front of others (Johansson et al., 2005).

Feelings of social exclusion are common negative experiences resulting from the incapability to perform family or work roles owing to illness and result in survivors feeling excluded from society (Rhoten et al., 2013; Simonelli and Otto, 2017; De Blasi et al., 2018; Puigpinós-Riera et al., 2018). For some women and young adults, the feeling of being in a life stage that is not consistent with peers is also an attribute of social isolation (Parton et al., 2017; De Blasi et al., 2018; Iannarino, 2018).

Antecedents

Antecedents are events or phenomena that precede the concept (Rodgers, 2000). Six antecedents of social isolation were identified in adults with cancer. These included cancer-related physiological changes, cognitive beliefs, psychological wellbeing, unsatisfactory social supports or relationships, restrictions on receiving treatments, and social-level barriers.

Cancer-related physiological changes

Physiological change is the most common antecedent of social isolation among cancer survivors. Cancer survivors may experience physical and functional impairments caused by their illness and treatment, thus resulting in limited social integration (Noyes et al., 1990; Sandén and Hydén, 2002; Johansson et al., 2005; Lund-Nielsen et al., 2005; Bennett et al., 2006; Simonelli and Otto, 2017; De Blasi et al., 2018; Abdollahimohammad et al., 2019; Borgi et al., 2020; Stolley et al., 2020; Yuan et al., 2020; He et al., 2021; Kudjawu and Agyeman-Yeboah, 2021; Tsui and Huang, 2021). For instance, the complications associated with head and neck cancer, such as disfigurement, dysphagia, and speech impairment, can impair social functioning among survivors, exacerbating social isolation (Rogers et al., 2016; Moore et al., 2018; Kirtane et al., 2022). For gastrointestinal cancer survivors, gastrointestinal-specific morbidities such as ostomy leakage and incontinence deter them from an active social life (Martopullo et al., 2020; He et al., 2021). Other cancers (e.g., prostate, breast, and gynecological cancer) can impact survivors' sexual life, as they may consider it an embarrassing topic to raise with friends and partners. These individuals need support, such as from peer groups, to express their challenges and share experiences (Sandén and Hydén, 2002; Power and Hegarty, 2010; Campo et al., 2017; Ettridge et al., 2018; Iannarino, 2018). Thus, as their physical health deteriorates, cancer survivors become weaker, more dependent, and socially isolated, resulting in their inability to socialize as well as maintain and form relationships (Schapmire et al., 2012; Carduff et al., 2018).

Cognitive beliefs

Cognitive beliefs are also an important antecedent of social isolation. These refer to a set of habitual pattern recognitions that one is used to, which is "fundamental to a person's world view" (Charles et al., 2006). According to White's heuristic cognitive behavioral model (White, 2000), false beliefs may lead to negative behavior (e.g., social avoidance). Regarding patients with rectal cancer tolerating stomas, two extreme attitudes can arise and prevent them from engaging in social activities. Stomas are sometimes treated inappropriately by patients who think their stomas are infectious and should quarantine themselves, while other times patients overprotect them, believing that they are fragile and thus should not be exposed (He et al., 2021). Recently, cognitive and psychological influencing factors such as body image, which can lead to social avoidance in people with head and neck cancer, have become research hotspots in the tumor population (Rhoten et al., 2013). While the underlying mechanism of social isolation in people with cancer is unclear, several theories can improve the understanding of the process that leads to it. The fear-avoidance model (Newell, 1999) explains cancer-related changes from a cognitive-behavioral perspective. Social avoidance behavior among cancer survivors is caused by the fear of changing appearances and functions. Fear and avoidance are conditioned reflexes maintained by learned thinking that constantly reminds individuals of their flaws. Individuals who are unable to adapt to physical deficiencies often continue to avoid society. Regarding nursing practice, social isolation can be guided by assessing the potential factors through understanding the avoidance behaviors demonstrated by patients based on this model.

Psychological wellbeing

Psychological wellbeing is integral to holistic health. Psychological discomfort serves as an antecedent of social isolation in people with cancer. It has been suggested that social isolation correlates positively with symptoms of anxiety and depression in patients with breast cancer (Liu B et al., 2021; Liu Y et al., 2021). Studies have shown that people with cancer with impaired psychological status demonstrate higher social isolation levels (Im and Chee, 2021). Furthermore, anxiety and depressive symptoms have been identified as common predictors in patients with oral cancer who exhibit increased social isolation levels due to stigma (Yuan et al., 2020). A qualitative study conducted in Ireland found that cancer survivors experience persistent symptoms of fatigue, anxiety, depression, and pain after receiving treatment, which increases their social isolation and reduces their activity levels. Notably, the first year after treatment involves managing the transition to survivorship and returning to daily life; survivors often feel isolated during this time (Boland et al., 2019).

Unsatisfactory social supports or relationships

Unsatisfactory social support is also an important antecedent of social isolation among cancer survivors. First, it may arise from not having someone with whom to discuss cancer-related matters (D'Agostino and Edelstein, 2013; Ettridge et al., 2018; Zhu et al., 2019). According to cancer survivors, their loneliness results from external avoidance and misunderstandings from others and cancer's long-lasting impact (Fu et al., 2013; Hinzey et al., 2016; Raque-Bogdan et al., 2019; Kirtane et al., 2022). Second, the need for special attention for individuals with several intersecting identities might be unnoticed. It has been underscored that having several intersecting identities (e.g., lesbianism) may perpetuate a sense of isolation among individuals after a cancer diagnosis owing to previous experiences with societal oppression or marginalization. Thus, it is imperative to analyze individuals' underlying identities and life experiences before the illness to provide tailored social supports (Raque-Bogdan, 2019). Moreover,

TABLE 3 Overview of the characteristics and attributes of social isolation defined in the studies included in the concept analysis.

Author (year)	Country	Oncology population	Discipline	Design	Sample	Attributes: behaviors and states of social avoidance	Attributes: negative affective experiences
Kirtane et al. (2022)	United States	Head and neck cancer	Medicine	Qualitative study	20	Restricted social network	Distress
Takemura et al. (2021)	Japan	Lung cancer	Medicine	Prospective cohort study	264	Limitations with social networks (size, diversity, or frequency of contacts)	Feelings of loneliness
Liu B et al. (2021) and Liu Y et al. (2021)	China	Breast cancer	Medicine	Cross-sectional study	389	Restricted social network (contact, activity, communication)	
He et al. (2021)	China	Rectal cancer	Nursing	Qualitative study	18	Avoidant behaviors (protection from identifying with any form of cancer) Concealing their real self	
Kudjawu and Agyeman-Yeboah (2021)	Ghana	Breast cancer	Medicine	Qualitative study	8	Restricted social network (contact, activity, communication)	
Liu B et al. (2021) and Liu Y et al. (2021)	China	Lung cancer	Nursing	Cross-sectional study	288	Limitations with social networks Avoidant behaviors	Feelings of loneliness Feelings of helplessness
Yuan et al. (2020)	China	Head and neck cancer	Nursing	Cross-sectional study	230		Feelings of loneliness Feelings of uselessness
Wang et al. (2020)	China	Breast cancer	Nursing	Cross-sectional study	228	Limitations with social network Avoidant behaviors	Feelings of loneliness Feeling of helplessness
Zhu et al. (2019)	United States	Prostate cancer	Medical informatics	Retrospective study	3,138	Limitations with social networks Considering relationships insufficient to meet social needs (lacking companionship)	Feelings of loneliness Feelings of social exclusion
Raque-Bogdan et al. (2019)	United States	General cancer	Psychology	Review		Concealing their real selves (including hiding cancer facts and feelings of loneliness)	Feelings of loneliness A feeling of a lack of control over one’s body
van Roij et al. (2019)	Netherlands	General cancer	Medicine	Qualitative study	18	Abnormal social network Abnormal life	
Ettridge et al. (2018)	Australia	Prostate cancer	Nursing	Qualitative study	20	Self-isolating or concealing oneself	Feelings of loneliness Low self-esteem
De Blasi et al. (2018)	France	General cancer	Medicine	Qualitative study	3	Relinquishing former social roles	Feelings of social exclusion (working environment)
Carduff et al. (2018)	United Kingdom	Bowel cancer	Nursing	Qualitative study	16	Limitations with social networks (inability to maintain old and develop new relationships)	
Iannarino (2018)	United States	General cancer	Medicine	Qualitative study	3	Limitations with social network	
Puigpinós-Riera et al. (2018)	Spain	Breast cancer	Medicine	Mixed cohort studies	2,235	Limitations with social networks (size, frequency of contacts)	Distress
Simonelli and Otto (2017)	United Kingdom	Gynecological cancer	Psychology	Book		Limitations with social networks	Low self-esteem Feelings of social exclusion (working environment)
Parton et al. (2017)	United Kingdom	Cancer in women	Psychology	Mixed-methods study	695		Feelings of being in a life stage that is not consistent with peers’ life stages
Biagioli et al. (2017)	Italy	Hematologic malignancies	Nursing	Qualitative study	9	Protective isolation	Feelings of loneliness
Hinzey et al. (2016)	United States	Breast cancer	Medicine	Review		Limitations with social networks (size, diversity, or frequency of contacts)	Feelings of loneliness

(Continued)

TABLE 3 (Continued)

Author (year)	Country	Oncology population	Discipline	Design	Sample	Attributes: behaviors and states of social avoidance	Attributes: negative affective experiences
Jeong et al. (2016)	Korea	Lung cancer	Nursing	Systemic review		Abnormal social interactions Exclusion from social support groups Lack of advocacy Response to stigmatization	Feelings of loneliness
Fu et al. (2013)	Australia	Breast cancer	Psychology	Systemic review		Not going out Avoiding contact with others	
Kroenke et al. (2013)	Oakland	Breast cancer	Epidemiology	Cohort studies	2,264	Limitations with social networks (size)	
Lee et al. (2011)	Korea	Neutropenic cancer	Nursing	Systematic review		Limitations with social networks	Concealing real emotions Feelings of powerless
Bennett et al. (2006)	United Kingdom	Breast cancer	Nursing	Qualitative study	8	Avoidant behaviors (protection from identifying with any form of cancer) Concealing their real selves	Feelings of loneliness
Hagedoorn and Molleman (2006)	Netherlands	Head and neck cancer	Public health	Cross-sectional study	76	Avoidant behaviors (both active and passive isolation)	
Blinderman and Cherny (2005)	Israel	General cancer	Psychology	Qualitative study	40	Limitations with social networks Avoiding contact with others	
Høybye et al. (2005)	Denmark	Breast cancer	Medicine	Qualitative study	39		Feelings of loneliness
Noyes et al. (1990)	United States	Solid tumors	Psychology	Cross-sectional study	438	Limitations with social networks (family, friends)	
McGeough et al. (1980)	United States	Lung cancer	Nursing	Cross-sectional study	22	Limitations with social networks (withdrawal from family and friends)	Feelings of loneliness

individuals who live alone and do not have family or friends nearby may be more likely to experience social isolation (Fu et al., 2013; Ettridge et al., 2018; Leung et al., 2021). Some cancer survivors have reported that support from physicians and family members declines upon receiving treatment. This often leaves them feeling powerless and isolated because they still require care and support (Power and Hegarty, 2010; Kirtane et al., 2022).

Restrictions associated with receiving treatments

Patients with neutropenic cancer are sometimes placed in protective isolation at the hospital, enhancing their sense of security during treatment. Patients often practice self-isolation by refusing to interact with people, both emotionally and physically, to protect both themselves and others. Specifically, these patients often feel powerless (Lee et al., 2011). Similarly, several patients with head and neck cancer required isolation for radiochemotherapy during the COVID-19 pandemic, which exacerbated social isolation (Kirtane et al., 2022).

Social-level barriers

Research has indicated that the public health events associated with COVID-19 social distancing measures imposed more loneliness and social isolation, which are both stress-inducing factors (Miaskowski et al., 2020; Kirtane et al., 2022). Several lung cancer survivors reported that they were excluded from social activities. Consequently, experiences of exclusion increased their reluctance to engage with society (Liu et al., 2016). In Syria, cancer is not sufficiently understood and accepted by the public, and people with cancer often fear that chemotherapy will prevent them from marrying owing to effects that may impact their social functioning (Nizamli et al., 2011).

Consequences

Consequences refer to the results of corresponding events or phenomena (Rodgers, 2000). The literature suggests that social isolation is generally accompanied by three consequences, namely, low therapeutic compliance, poor health conditions and mental health status, and low quality of life.

The first consequence of social isolation is low therapeutic compliance. Healthcare professionals often emphasize treatment compliance to patients. However, perceived social isolation among patients with cancer negatively impacts their treatment compliance (de Souza et al., 2017; Iannarino, 2018; Martopullo et al., 2020; Stolley et al., 2020). The second consequence is poor health conditions and mental health status. A systematic review has indicated that social isolation and loneliness can increase mortality rates, regardless of their link to underlying medical conditions (Kroenke et al., 2013; Holt-Lunstad et al., 2015; Zhu et al., 2019). Furthermore, a high symptom burden is associated with loneliness and social isolation (Adams et al., 2018). Social isolation also has effects, as low emotional support and social isolation are clear risk factors for increased anxiety and depression (Puigpinós-Riera et al., 2018; Alcaraz et al., 2020). Furthermore, social isolation in people with cancer is a significant issue that could aggravate depressive symptoms and increase tumor activity owing to the decreased expression of brain-derived neurotrophic factors (Borgi et al., 2020). Moreover, it can potentially contribute to the development of breast cancer through hormonal, angiogenic, and inflammatory markers and mediators (Hinzey et al., 2016). Low or impaired quality of life is a major consequence of social isolation, and health-related quality of life may be negatively affected by social isolation (Simonelli and Otto, 2017; Iannarino, 2018; Dahill et al., 2020; Martopullo et al., 2020; Dornan et al., 2021; Leung et al., 2021; Takemura et al., 2021).

Conceptual definition

Based on the attributes, antecedents, and consequences identified in this analysis, we propose the following definition of social isolation in people with cancer:

> Social isolation in adults with cancer refers to individuals demonstrating behaviors and states of social avoidance (e.g., avoiding contact with others and concealing one's emotions) and experiencing specific negative affective experiences (e.g., feelings of loneliness). Social isolation can result from cancer-related physiological changes, cognitive beliefs, psychological well-being, unsatisfactory social supports or relationships, restrictions associated with receiving treatments, and social-level barriers. Social isolation can result in low therapeutic compliance, poor health conditions, mental health problems, and low quality of life.

Figure 2 illustrates the negative antecedents, attributes, and consequences associated with social isolation in people with cancer.

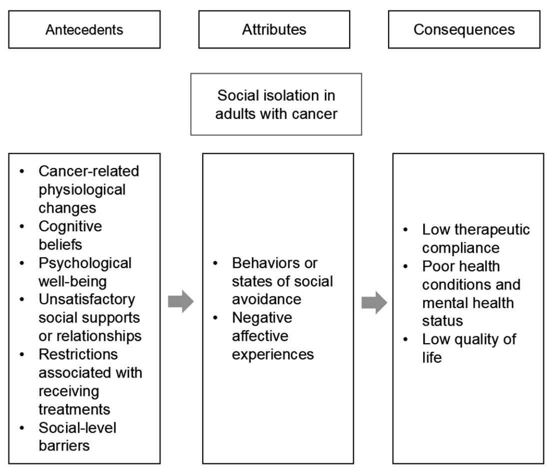

FIGURE 2
Model of social isolation concept in adults with cancer.

Discussion

Significance of findings

Clear and precise conceptual systems play a significant role in the development of nursing knowledge (Tofthagen and Fagerstrom, 2010). Based on current knowledge, this is the first study to conceptualize social isolation in adults with cancer. Previous studies have only provided an in-depth analysis of issues related to social isolation in older adults (Nicholson, 2009). Furthermore, studies have underscored the effects of social isolation at the physiological level (Friedler et al., 2015). However, limited studies in this regard focus on people with cancer, who are also affected severely by social isolation. This may be why social isolation in people with cancer has not been explained adequately using the social isolation concepts from other populations. Therefore, it is necessary to clarify this concept in the cancer population. This concept analysis has established a set of attributes to define social isolation in adults living with cancer. Using standardized language developed using the concept analysis procedure, nurses and physicians can assess social isolation among cancer survivors and differentiate it from that among older adults and non-cancer survivors. It is crucial to recognize that social isolation in cancer survivors is a multidimensional experience influenced by several factors, particularly cancer-related physiological changes.

Interpreting the results

In this analysis, the attributes of social isolation were classified into two categories, namely, behaviors and states of social avoidance and negative affective experiences. Insufficient social networks and feelings of loneliness were the most frequent characteristics of social isolation among the two categories. Table 3 indicates that only some of the included studies covered both categories. This may be owing to the varying cancer populations present in the included studies. Hence, the focus on social isolation in this analysis also differed.

No consensus was reached on the definition of social isolation in cancer populations. Compared to the behaviors and states of social avoidance, the negative affective experience attributes were more challenging to identify. Studies indicate that the latter attribute, which includes perceived social isolation and feelings of loneliness, is more harmful to mental health than the former (Liu B et al., 2021; Liu Y et al., 2021). Several patients were not aware that they were socially isolated despite having restricted social networks (Blinderman and Cherny, 2005; Tomaka et al., 2006). However, individuals can still feel lonely even if they are well-supported socially (Tomaka et al., 2006). Thus, it can be suggested that subjective or perceived social isolation warrants increased priority. During follow-up, nurses and physicians should pay close attention to the patient's psychological changes and identify social isolation early.

Identifying implications

White's heuristic model stipulates that individuals will reshape their ideal self-image when their appearance and/or physical function are damaged (White, 2000). However, excessive expectations regarding their external image can lead to persistent and unpleasant emotions as well as social avoidance behaviors. Thus, people living with cancer may rebuild their ideal self-image after perceiving changes in appearance and physical function. However, owing to stigma, among other reasons, they could demonstrate compensatory behaviors to avoid social activities.

Notably, White's heuristic model suggests that social isolation could result from incorrect self-perception, such as negative self-evaluation and unrealistic expectations. Furthermore, this model can enable nurses and physicians to analyze the internal influencing factors of social isolation among patients. Moreover, it suggests that nurses and physicians ought to predictably guide the establishment of improved self-cognition while providing psychological care to patients with cancer. It is imperative to address negative self-assessments among patients as soon as they exhibit social isolation behavior. Social isolation is a multidimensional experience, and its antecedents may comprise the aforementioned attributes; thus, future studies must provide an in-depth examination of the relationships among these attributes.

Identifying the attributes of social isolation in adults with cancer has profound implications. Along with the common attributes (i.e., limitations in social networks and feelings of loneliness), living an abnormal life and concealing individual emotions have been identified as characteristics of behaviors and states of social avoidance. The findings from this analysis illustrate the unique aspect of social isolation associated with cancer. Upon our review (Miaskowski et al., 2020; Morreale et al., 2020; Takemura et al., 2021), we also found that the measurement tools used to assess social isolation vary across studies. This confirms a lack of consensus on the concept of social isolation regarding cancer populations. Furthermore, it suggests that future research ought to explore and implement social isolation assessment tools that can perform standardized scoring to facilitate nursing assessment, as well as increase the comparability of this indicator in the cancer population. In future research, antecedent social health factors such as COVID-19 could enhance the complexity associated with the concept of social isolation. Thus, researchers should consider the issue more comprehensively.

Limitations

Several limitations and biases have been identified in this analysis, including the interpretations of the results and the possibility of an incomplete search of sources. Despite following the guidance of the inductive process underscored in Rodgers' evolutionary method (Rodgers, 2000), this analysis might contain bias. In an attempt to mitigate this, the process of data extraction was performed independently by two reviewers, and a third reviewer was consulted in case of a disagreement. While a systematic search was conducted, it is unlikely that it was comprehensive. Moreover, this concept analysis only included literature published in English and Chinese, as there is a more extensive volume of articles in these two languages.

Conclusion

The findings from this concept analysis contribute to the understanding and clarity of social isolation regarding adults with cancer. This analysis could be applied to developing cancer-specific assessment tools and measures that can facilitate early recognition of the requirements underlying psychosocial support and establish a conceptual foundation to mitigate social isolation regarding clinical practice and research. Subjective, perceived social isolation is of specific concern. Further studies are required to examine the relationships among attributes. Moreover, research mitigating social isolation is needed to assist people living with cancer to improve ways of adapting to adversity throughout their experience.

Author contributions

YL: conceptualization, methodology–data collection, methodology–data analysis, writing–original draft preparation, and writing–reviewing and editing. GH: resources and revision. MW: methodology–data collection and methodology–data analysis. LH: writing–review and editing and supervision. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Short-term effect of internet-delivered mindfulness-based stress reduction on mental health, self-efficacy, and body image among women with breast cancer during the COVID-19 pandemic

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Background and aim: During the COVID-19 pandemic, an Internet-Mindfulness-Based Stress Reduction (iMBSR) program was delivered and may be better than an in-person approach. Our study evaluated the effects of iMBSR intervention on mental health, self-efficacy, and body image in women with breast cancer in Taiwan.

Materials and methods: Sixty-seven women with breast cancer were allocated to a 6-week iMBSR ($n=41$) program or a waitlist control group ($n=26$), without heterogeneity between group characteristics. Patients from both groups were measured at baseline and postintervention using three scales: Depression, Anxiety, and Stress Scale (DASS-21), General self-efficacy scale, and Body Image Scale. Descriptive dataset analysis, paired t-test, and Student's t-test were used to evaluate the data.

Results: Although iMBSR did not significantly improve depression and stress between groups, iMBSR could improve anxiety (Δmean: −2.0 vs. −0.4, $p=0.041$) with medium effect sizes. Significant benefits were found for body image (Δmean: −3.6 vs. 0.9, $p=0.003$) and self-efficacy (Δmean: 4.2 vs. 1.5, $p=0.004$), with large effect sizes (Cohen's $d=0.73$).

Conclusion: Our preliminary study supports iMBSR as a program that can improve mental health, body image, and self-efficacy in women with breast cancer. During the COVID-19 pandemic, medical professionals can use Internet-based clinical health education.

KEYWORDS

internet-delivered therapy, internet-delivered MBSR, breast cancer, mental health, self-efficacy, body image

Introduction

A 2019 cancer registry report indicated that breast cancer had the second highest mortality rate in Taiwan and the highest incidence among cancers in women and increased by ~4.49% per year (Taiwan, Ministry of Health and Welfare, 2019).

Adverse effects of breast cancer treatment, such as cognitive impairments (Brown et al., 2021), alopecia and body scarring, and the removal of the breast, ovaries, or uterus, negatively affect gender role socialization and body image disturbance (Boquiren et al., 2013, 2016). Body image disturbance has been linked to depression, anxiety (Szymanski and Henning, 2007), sexual function (Chang et al., 2019), self-esteem, and quality of life (Richard et al., 2019). Consequently, interventions focus on reducing female body dissatisfaction are a critical topic of research (Wade et al., 2009).

Based on Bandura's theory, self-efficacy refers to the ability of an individual to control their motivation, behavior, and how they face obstacles. The theory essentially attributes an individual's belief in efficacy to their chance of achieving success in a particular situation (Bandura et al., 1999). Therefore, coping self-efficacy is a key determinant of a person's ability to successfully manage stressful situations and emotions (Chesney et al., 2006). Low coping self-efficacy is associated with stress, depression, anxiety, and feelings of helplessness, whereas higher levels promote active and effective engagement in regulating emotional distress (Zulkosky, 2009). Self-efficacy is the belief that individuals can demonstrate positive attitudes toward healthy behaviors and directly affect their health-promoting behaviors (Stuifbergen et al., 2000).

Studies have highlighted that mindfulness-based interventions have a wide range of benefits, including decreased perceived stress, anxiety, depression, and fatigue (Price-Blackshear et al., 2020), improvements in sexual functioning (Bober et al., 2020), and increased self-efficacy in stress perception (Caldwell et al., 2010). Mindfulness interventions derived from ancient Buddhist and Hatha Yoga traditions are becoming increasingly popular in the Western world. The "way of being," or to be aware in each moment, is the core of mindfulness and is achieved by "paying attention in a particular way: on purpose, in the present moment, and nonjudgmentally" (Kabat-Zinn, 1990). Over the past decade, mindfulness-based stress reduction (MBSR) interventions have grown rapidly in oncology research (Chang et al., 2021).

With the outbreak of COVID-19 in December 2019 (Wang et al., 2020a) and its rapid spread worldwide, public fear and heightened psychological symptoms have become common (Brooks et al., 2020; Wang et al., 2020b). The pandemic has increased the use of information and communication technology (ICT) interventions to help patients with breast cancer connect (Compen et al., 2019). ICT interventions can help patients comply with necessary epidemic prevention regulations while reducing the distance, time, and cost issues that arise when building and maintaining social connections and exchanging social support, thereby protecting the health of vulnerable populations (McCue et al., 2010; Galiano-Castillo et al., 2016; Compen et al., 2018).

Patients with breast cancer are at higher risk of psychological stress, and the additional stress of the COVID-19 pandemic can increase their vulnerability (Kang et al., 2021). Internet-delivered MBSR (iMBSR) improved psychological health, sleep quality, and life satisfaction in college students and young working adults (Mak et al., 2017). Goetz et al. (2020) found that applying electronic-mindfulness-based interventions (eMBI) can alleviate depression and anxiety symptoms in pregnant women at high risk of hospitalization (Goetz et al., 2020). Nourian et al. (2021) conducted an online MBSR program that improved sleep disturbance among nurses in a COVID-19 intensive care unit (Nourian et al., 2021).

A study in Denmark involving women with breast cancer and older men with prostate cancer who underwent an Internet-delivered MBI (iMBI) program found that iMBIs could improve anxiety and depressive symptoms immediately after the intervention (Nissen et al., 2020). Another study compared the effects of iMBCT with face-to-face mindfulness-based cognitive therapy (MBCT) in patients with cancer, and concluded that both interventions reduced psychological distress (Compen et al., 2018).

Considerable research explores the effects of iMBSR on physical and psychological problems in patients without cancer, and using iMBCT to resolve emotional distress in patients with cancer. However, there has been little research on iMBSR's effects on self-efficacy and body image in women with breast cancer. Therefore, our study aimed to explore the effect and feasibility of iMBSR on mental health, self-efficacy, and body image in women with breast cancer during COVID-19.

Materials and methods

Participant inclusion and exclusion criteria

Both the iMBSR and waitlist control group used purposive and snowball sampling. Potential participants were recruited from

TABLE 1 Web-based collaboration (or interactive) software (or APP).

Online software	Purpose of usage
Google	
Google Forms	
	– Recruiting Participants Online form
	– Pre-test questionnaire form
	– Post-test questionnaire form
	– Records of personal practice frequency and dosage, practice impressions, and awareness experience
Jamboard	– Sign-in form for check participation rate
Microsoft Teams	– A communication platform used as a teaching tool for online mindfulness courses
LINE App	– Share our Microsoft Teams meet link
	– Communication tool for when participants could not access Microsoft Teams
	– Reminder of course time
	– A medium for verbal encouragement and used to enhance self-efficacy
	– Share personal experience of daily practice
7-ELEVEN App	– E-coupons can be stored

visiting breast surgery clinics, cancer wards, and breast cancer affiliate websites. Inclusion criteria were as follows: had been diagnosed with stage 0–IV breast cancer within the past 5 years; aged ≥20 years old; could communicate in Mandarin; received at least recent adjuvant therapy (i.e., chemotherapy, radiotherapy, or hormonal therapy); and Eastern Cooperative Oncology Group performance score ≤ 1 (Taylor et al., 1999). Exclusion criteria were as follows: a history of psychiatric diagnosis (e.g., acute psychosis) and suicide tendencies.

Procedure

Our study has several required online software to facilitate online teaching and recruiting participants (Table 1). The recruitment period was from 1st February to 1st March, 2022. The study coincided with the official declaration of the COVID-19 outbreak by the Taiwan Centers for Disease Control on 9 March, 2022, which prohibited close activities with others (Taiwan Centers for Disease Control (TCDC), 2022). Patients with cancer receiving chemotherapy can have the adverse effect of neutropenia which can increase their risk of serious infection (Crawford et al., 2004); therefore, all data would be collected online through Google Forms.

Data collection

All participants submitted written informed consent during the orientation. Variable measurement was performed at two time points, including pretest and posttest. (1) Pretest: This was completed before the program's second session. Baseline scores were based on the participants; responses to items across the scale. (2) Posttest: After the sixth week of training, participants completed a posttest within a week. Participants received a TWD 100 electronic coupon after completing the pre and postintervention questionnaires.

Internet-based MBSR intervention

The frequency and duration of our mindfulness training were six 2-h weekly group coaching sessions led by a professionally trained psychologist using online learning with Microsoft Teams. We used Jamboard, a digital interactive whiteboard developed by Google, to measure the number of patients participating online before class. Our training aimed to improve these metrics: mindful eating, body scan, breath awareness practice, mindful walking, and sharing of group experiences. The informal training in our study was conducted through home practice using mindfulness-guided cloud-based applications such as YouTube (Chang et al., 2022). Specifically, participants performed 10–15 min of home practice at least twice daily, listened for at least half an hour before sleep, and recorded their personal experiences on a Google Forms survey. Informal practice does not require a specific amount of time and can be practiced anytime and anywhere. The informal training aimed to improve overall self-awareness, communication, learning, and listening. Although formal training is more widely discussed and practiced, supplemental informal training may be more helpful for participants to adopt mindful attitudes in their lives (Table 2).

Waitlist control group

Inclusion and exclusion criteria for WCG (delay in receiving the intervention) were the same as for the iMBSR group. WCG occurred in parallel with iMBSR. The WCG had manuals for managing symptoms and oral instructions on health and hygiene education. All participants were instructed not to participate in any other stress reduction program or mind–body therapy during the study. We offered an additional iMBSR skills study program to WCG participants following our study's conclusion.

Ethics consideration

The present study involved research with human participants who were required to sign an informed consent form before

TABLE 2 The content of iMBSR.

Sessions	Contents	Mindfulness practice	Homework
1	– Introduction to the class, how to proceed, requirements and challenges – Introduce the relationship between brain function, emotion, and cognition – Introduce the “fight or flight, freeze” stress response – Internal and external interactions: the relationship between situation (stimuli), thoughts, sensations, bodily sensations, and actions – Differences between “past,” “future,” and present – Awareness and “Autopilot Mode”	– Motivation and Intention: Why am I here? – Identify concerns – Mindful Eating	– Mindful Eating – Self-awareness of worry (or other strong emotions)
2	– The negative cycle of worry – How thoughts affect mood, physical feelings – ntroduce the cognitive model (stimuli-intrinsic responses [thoughts, sensations, bodily sensations]-actions) – The mode of doing and the mode of being of the mind – “Myocardial training”: focus and awareness	– Mindful Eating – Breath awareness practice – Be aware of the negative cycle of worry	– The negative cycle of worry – Breath awareness practice – Mindful Eating
3	– See the chaotic mind, from the breath into the presence mode – Be aware of the distraction and gently bring the focus back to the breath – Be aware of the inertial reaction pattern, and the emotional cycle is wave after wave – Resist unwanted, disliked, unpleasant – Ideas are not facts – The Second Arrow Theory of Suffering (Pain and Suffering)	– Breath awareness practice (Long Version) – Awareness of inertial response patterns – Distinguish pain and suffering	– Breath awareness exercises when strong emotions arise – Awareness of inertia and shooting arrows at yourself (automatic thinking) – Mindfulness in daily life (showering, brushing teeth…)
4	– Experience the true meaning of acceptance – Story: Fear in the Heart – There are tigers in the closet – From rejection to acceptance, not into action mode – Take care of yourself – Introduce the principles of mindfulness	– Breath awareness practice (Long Version) – Three minutes breathing room – Mindful walking	– Stress awareness – Take 3 min of breathing space during strong emotions – Mindfulness in daily life (breathing into life)
5	– Introducing S.T.O.P. – Application of Breath Awareness – Mindfulness guards the mood, not following or resisting – Observe the changes of mind and body and control inexplicable emotions – Difficulties encountered in mindfulness practice	– Three minutes breathing room – Body scan	– S.T.O.P. – Stress Reaction and Response – Body scan – Daily practice: focus on talking to people – A letter to myself (reflection lessons and outlook for future mindfulness activities)
6	– Common reactions to body scans – To be aware of the relationship between change and discomfort – Explore with an open mind – Thoughts are not me, feelings are not me, just a part of me – Mindful listening – The concept of loving-kindness	– Three minutes breathing room – Metta meditation practice – Review the difficulties of the course and bless yourself	– Mindfulness practice for living

participating in the study. All procedures in our research comply with the ethical standards of the Institutional Research Council.

Mental health, self-efficacy, and body image measures

Main research tools

Depression, anxiety, and stress

The Depression, Anxiety, and Stress Scale (DASS-21) is a 21-item tool that evaluates the participant's depression, anxiety, and stress over the past week, on a Likert-style scale ranging from 0 (never) to 3 (almost always; Lovibond and Lovibond, 1995). Higher scores indicate greater anxiety, depression, or stress index and vice versa (Lovibond and Lovibond, 1995). The DASS-Depression Inventory was correlated with the Baker Depression Inventory at 0.74 and the Anxiety Inventory with the Baker Anxiety Inventory at 0.81 (Lovibond and Lovibond, 1995). Wei et al. (2008) translated the DASS-21 scale into Chinese (Wei et al., 2008), and its psychometric properties were evaluated using an Australian immigrant sample ($n = 356$) and compared with Lovibond and Lovibond's (1995) English version of the DASS ($n = 720$). Multi-group confirmatory factor analysis found that the Chinese version of the DASS-21 effectively discriminates between depression, anxiety, and stress, but less so than the English version.

The body image scale

In collaboration with the European Organization for Research and Treatment of Cancer Quality of Life Study Group, Hopwood et al. constructed a 10-item Body-Mental Imagery Scale using datasets from seven treatment trials/clinical studies in the United Kingdom on 682 patients with breast cancer. Psychological testing was conducted and the scale showed high reliability (Cronbach's alpha 0.93) and good discriminant validity ($p < 0.0001$), with sensitivity to change ($p < 0.001$; Hopwood et al., 2001). Scores are calculated by totaling items on a scale of 0 (not at all) to 3 (very), with higher scores indicating greater body image impairment and vice versa (Hopwood et al., 2001).

General self-efficacy scale

The General Self-Efficacy Scale (GSES), developed by Jerusalem and Schwarzer, is a generic tool that is widely used to measure self-efficacy in clinical and nonclinical populations (Zhang and Schwarzer, 1995; Zhang et al., 2018). Zhang et al. (2018) translated the GSES into Chinese, which consisted of 10 items, and used a 4-point Likert scale from 1 (always false) to 4 (always true). The Chinese version of the GSES (C-GSES) exhibited good internal consistency with a Cronbach's alpha of 0.926 in a unidimensional factorial model (Zhang et al., 2018).

Basic demographic questionnaire

The questionnaire was divided into two parts. First: basic personal information, including age, marital status, and economic status. Second: disease status, including time since diagnosis (years), cancer staging, and cancer treatment. The questionnaire was collected using an online Google form.

Fidelity

To maintain the fidelity of our online mindfulness program, the 6-week intervention was conducted by a qualified clinical psychologist with specialized training in psychology at the Medical Center, Departmental Cancer Center. The instructor assessed the transfer of iMBSR skills by asking questions and discussing the material with the participants, and the patients recorded their practice duration weekly. The first author (YCC) confirmed that the practice had been completed during the intervention. We also prepared a standardized process. First, we set up a LINE messenger group with a mobile app before iMBSR to remind participants of the class schedule, provide class information, and solve the participants 'problems during the course (such as being unable to login to Microsoft Teams, unable to turn on the speaker, and unable to hear sound). Second, we regularly provided support and addressed participants' needs wherever possible. Third, we used the patient groups to care for each other and share experiences (as part of the curriculum, the grouping feature of Microsoft Teams divided participants into groups for easier discussion and teamwork). Finally, if the participants completed the program, we provided an e-coupon as a reward.

Sample size

The sample size of our study was calculated based on the results of our previous study (Chang et al., 2022). We assumed that the DASS-21-anxiety subscale score would decrease from 28.54 to 17.62, in the MBSR group, whereas the score would remain unchanged in the WCG. These estimates were in line with the DASS-21 minimum clinically significant differences. With 80% power and a 5% type I error to detect a medium effect size of 0.5, the required sample size was calculated to be 40 participants. We considered a potential dropout rate of ~20%, hence we selected 48 participants.

Statistical analysis

Data analysis was performed using SPSS for Windows 22.0 (IBM, Chicago, IL, United States). The collected questionnaires were coded, and the accuracy of the data was verified repeatedly after input. Descriptive statistics were described for the baseline demographic and clinical characteristics of the patients with breast cancer. The Kolmogorov–Smirnov test (KS test) tested raw data for adherence to the assumptions of normality and equal variance and the detection of outliers before inferential statistical procedures. Self-report data between baseline and 6 weeks were compared for within-group and between-group data analyses using paired t-tests and Student's t-tests for normally distributed continuous variables, respectively. The statistical significance level was set to a two-sided $p < 0.05$ in all statistical analyses.

To explore the magnitudes of difference between groups, Cohen suggested that effect sizes be categorized into small, medium, and large treatment effects and represented by 0.2, 0.5, and 0.8, respectively (Cohen, 1988). A website was established following Lenhard and Lenhard's (2016) principle, which could be used to determine the effect size of the *t*-test results.[1]

Results

Patient characteristics

Our study had 88 eligible participants (see Figure 1 Flow diagram of study participants). The reasons for declining participation ($n = 15$) were lack of IT skills, physical discomfort, scheduling conflict, and others. We had established baseline data for 72 participants before the first session, with six dropouts in the WCG and three who changed to the Internet format. The postintervention assessment was completed by 41 and 26 participants in the MBSR and WCGs, respectively. The demographic and clinical characteristics of the patients are listed in Table 3. All participants were women and their mean age was 49.61 ± 12.03. The average breast cancer diagnosis time was ≤2 years (55.2%), and 37 patients were diagnosed with stage II cancer (55.2%). Most participants were married (46, 68.7%), and 20 were Unmarried (29.9%). The average monthly income was NTD 10,001–70,000 (62.7%), with 11 participants earning ≥ NTD 70,001 (16.4%). During the study period, the most common treatment was hormone therapy (32, 47.8%). We found no significant differences in basic characteristic data between the experimental and WCGs, except for age ($p = 0.043$).

Effects of internet-delivered MBSR

We used DASS-21 to measure participants' current psychological problems. The DASS-21 results indicated significantly improved anxiety (Δmean: −2.0 vs. −0.4, $p = 0.041$). However, depression (Δmean: −1.5 vs. −1.5, $p = 0.918$), stress (Δmean: −2.1 vs. 0.5, $p = 0.277$), and overall DASS-21 scores (Δmean: −5.56 vs. −1.38, $p = 0.243$) were not significantly decreased. Six consecutive weeks of iMBSR sessions also improved body image (Δmean: −3.6 vs. 0.9, $p = 0.003$) and self-efficacy (Δmean: 4.2 vs. 1.5, $p = 0.004$) in women with breast cancer.

Additionally, the effect size of the two groups after the intervention differed in each outcome. The negative body image had large effect sizes, anxiety had medium effect sizes, and stress had small effect sizes; however, effect sizes < $d = 0.2$ were considered as having no treatment effect for overall DASS-21 and depression scores.

Our results indicated that those who had iMBSR experienced postintervention improvements to scores in overall DASS-21 ($p = 0.019$, 95% confidence interval [CI] = 0.27, 2.76) and significant decreases in the subscale of depression ($p = 0.002$, 95% CI = 0.79, 3.21), anxiety ($p = 0.007$, 95% CI = 0.60, 3.50), and stress ($p = 0.001$, 95% CI = 2.40, 8.72). The intervention significantly improved the participants' negative body image ($p = 0.000$, 95% CI = 1.79, 5.43) and increased self-efficacy ($p = 0.009$, 95% CI = −7.22, −1.08; Table 4).

Discussion

Few studies have been conducted on related topics, and this study complements the available research on the effects of Internet-delivered iMBSR to improve depression, anxiety, stress, body image, and self-efficacy in women with breast cancer.

The COVID-19 pandemic has increased the uptake and number of Internet services and electronic products, which has helped health professionals to provide online mental health education (Liu et al., 2020). Wei et al. (2020) applied comprehensive Internet-based interventions designed to improve relaxation, self-care, and feelings of individual safety and found that the symptoms of depression and anxiety in the intervention group were significantly lower than those in the control group (Wei et al., 2020). Some studies have found evidence of Internet-based mental health intervention program benefits, particularly for depression, anxiety, and stress, which is consistent with our findings. A large sample study ($N = 1,282$) found improvements in anxiety and depression in women with breast cancer following Internet-based Mindfulness-Based Cognitive Therapy (iMBCT; Nissen et al., 2020). However, in our study, we found no significant decrease in DASS-21 total scores, depression, and stress between the two groups. Possible reasons may be the small sample size of each group and the need for a longer intervention time to assess long-term effects.

Women treated for breast cancer experience many bodily changes, including the absence or deformity of one or both breasts, hair loss from chemotherapy, skin discolorations, and weight gain or loss. In the first few months after diagnosis, a large proportion of patients with breast cancer experienced changes in body image. Approximately 74.8% of women treated for breast cancer were dissatisfied with their body image (Guedes et al., 2018). Body image is seen as a highly subjective mental representation that reflects not only one's physical appearance, body, and attractiveness but also one's perceptions of mental health, marital quality, psychological stress, and perceived functioning (Boquiren et al., 2016; Farnam et al., 2021). Research has indicated that some patients with breast cancer experience one or ≥ two negative body image problems, accounting for 17% and 33%, respectively (Fobair et al., 2006). Therefore, it is significant that our results indicated that iMBSR improved body image and alleviated psychological problems. A potential reason why Internet-based MBSR improved body image was that women with breast cancer could avoid being

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[1] https://www.psychometrica.de/effect_size.html

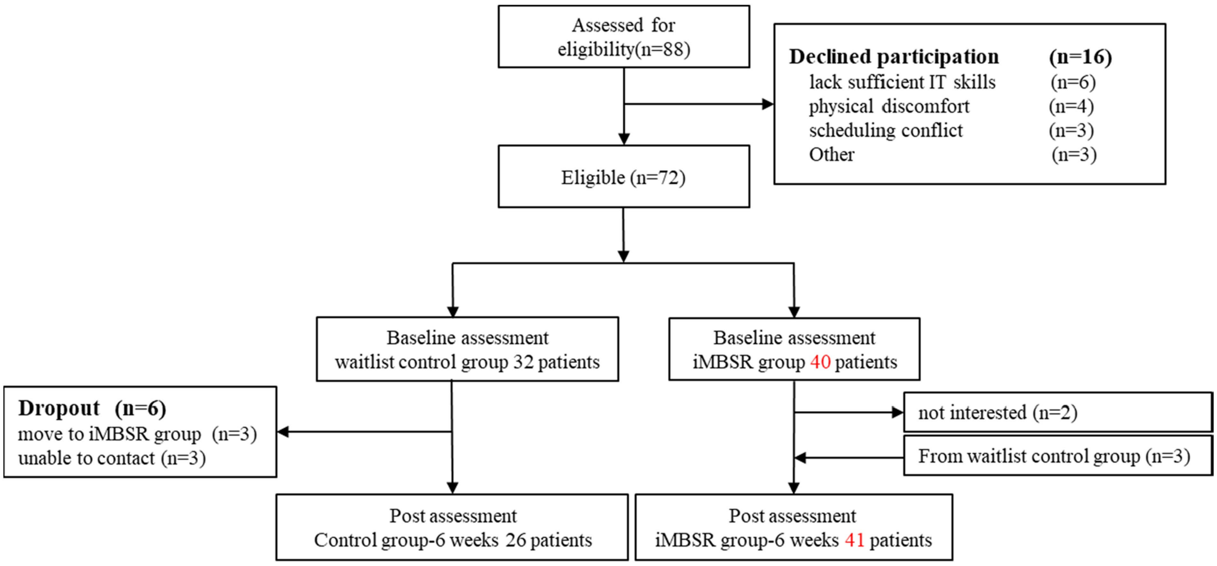

FIGURE 1
Flow diagram of study participants.

TABLE 3 The demographic and clinical characteristic of patients with breast cancer.

Characteristic	Total ($n = 67$)[a]	iMBSR ($n = 41$)[a]	WCG ($n = 26$)[a]	Value of p
Age, years (SD)	49.61 (12.03)	53.38 (13.04)	47.21 (10.83)	0.043
21–30	2 (3.0)	1 (2.4)	1 (3.8)	
31–40	17 (25.4)	14 (34.1)	3(11.5)	
41–50	25 (37.3)	15 (36.6)	10 (38.5)	
51–60	21 (31.3)	11 (26.8)	10 (38.5)	
≥61	2 (3.0)	0 (0.0)	2 (7.7)	
Time since diagnosis, years, *n* (%)				0.314
≤2	37 (55.2)	25 (61.0)	12 (46.1)	
3–5	23 (34.4)	13 (31.7)	10 (38.4)	
≥5	7 (10.4)	3 (7.3)	4 (15.4)	
Marital status, *n* (%)				0.210
Unmarried	20 (29.9)	9 (22.0)	11 (42.3)	
Married	46 (68.7)	32 (78.0)	14 (53.8)	
Divorced	1 (1.5)	0 (0.0)	1 (3.8)	
Average monthly income in TWD, *n* (%)				0.445
≤10,000	10 (14.9)	7 (17.1)	3 (11.5)	
10,001–70,000	42 (62.7)	26 (63.4)	16 (61.5)	
≥70,001	11 (16.4)	7 (17.1)	4 (15.4)	
House keeper	4 (6.0)	1 (2.4)	3 (11.5)	
Cancer staging, *n* (%)				0.102
Stage O	4 (6.0)	3 (7.3)	1 (3.8)	
Stage I	13 (19.4)	10 (24.4)	3 (11.5)	
Stage II	37 (55.2)	21 (51.2)	16 (61.5)	
Stage III	6 (9.0)	5 (12.2)	1 (3.8)	
Stage IV	7 (10.4)	2 (4.9)	5 (19.2)	
Treatment, *n* (%)				0.924
Chemotherapy	26 (38.8)	16 (39.0)	10 (38.5)	
Radiotherapy	3 (4.5)	2 (4.9)	1 (3.8)	

(Continued)

TABLE 3 (Continued)

Characteristic	Total (*n* = 67)[a]	iMBSR (*n* = 41)[a]	WCG (*n* = 26)[a]	Value of *p*
Hormone therapy	32 (47.8)	20 (48.8)	12 (46.2)	
Other	6 (9.0)	3 (7.3)	3 (11.5)	
Single or both breasts, *n* (%)				0.955
Single	62 (92.5)	38 (92.7)	24 (92.3)	
Both	5 (7.5)	3 (7.3)	2 (7.7)	

[a]Categorical variable were presented as frequencies and percentages, continuous variables were presented as mean and standard deviation. iMBSR, Internet-Based Mindfulness-Based Stress Reduction; WCG, Waitlist Control Group; SD, Standard Deviation.

TABLE 4 The effect of pre and postintervention.

Characteristic	Group	Preintervention		Postintervention		Effect of intervention				
		Mean	SD	Mean	SD	ΔMean	*t*	Value of *p*[a] (95% CI)	Value of *p*[b] (95% CI)	Effect size[c]
DASS-21	WCG	37.73	15.13	36.35	6.71	-1.38	1.18	0.243 (−2.22, 8.62)	0.132 (−0.49, 3.49)	0.07
	iMBSR	38.71	13.17	33.15	12.74	−5.56			0.019* (0.27, 2.76)	
Depression	WCG	12.19	5.66	10.69	2.13	−1.5	0.090	0.918 (−1.74, 1.91)	0.714 (−1.58, 2.28)	0.02
	iMBSR	12.12	4.28	10.61	4.33	−1.5			0.002* (0.79, 3.21)	
Anxiety	WCG	12.23	5.13	11.88	2.63	−0.4	2.283	0.041* (0.76, 3.65)	0.620 (−2.35, 1.43)	0.55
	iMBSR	12.02	4.64	10.02	4.04	−2.0			0.007* (0.60, 3.50)	
Stress	WCG	13.31	5.77	13.77	3.66	0.5	0.997	0.277 (−1.03, 3.55)	0.481 (−3.43, 1.66)	0.26
	iMBSR	14.56	5.46	12.51	5.72	−2.1			0.001** (2.40, 8.72)	
BIS	WCG	11.04	5.88	11.92	3.49	0.9	2.765	0.003* (1.22, 5.75)	0.298 (−4.52, 1.45)	0.73
	iMBSR	12.05	6.98	8.44	5.78	−3.6			0.000** (1.79, 5.43)	
GSES	WCG	10.58	5.70	12.12	4.35	1.5	−2.762	0.004* (−6.77, −1.39)	0.579 (−3.69, 6.46)	0.73
	iMBSR	12.05	6.98	16.20	6.68	4.2			0.009* (−7.22, −1.08)	

*$p \leqq 0.05$; **$p \leqq 0.001$; Δpost-test minus pre-test scores; *t* Student *t*-test; a and c The score between group; b The score within group; DASS-21 Depression Anxiety Stress Scales-21; BIS The Body Image Scale; GSES General self-efficacy scale.

stared at by others. Additionally, the Internet-based teaching method allowed the participants to practice mindfulness skills in a more comfortable place and in a relaxed manner.

Self-efficacy levels are essential in healthy behavioral change, and increases or decreases in self-efficacy can affect a person's motivation to engage in actions (Redding et al., 2000). In our study, the mindfulness-based intervention appeared to be an effective approach to developing self-efficacy and helped participants increase their training in mindful healthy behaviors, encouraging them to generate positive thoughts and motivational changes on a task-specific basis. Individuals with breast cancer who have high levels of self-efficacy in mindfulness and medical management programs may more easily deal with complex situations such as building self-confidence, self-esteem, changes in body image, and appropriate medication management. High levels of self-efficacy may also lead to higher levels of motivation because they believe they can self-manage the conditions induced by breast cancer treatment (Zulkosky, 2009). A single-blind design study recruited 81 women facing high levels of physical and psychological stress and allocated them to either a waiting list (delayed start) control group or a meditation intervention group (Goldstein et al., 2018). These findings have critical implications for developing self-efficacy in coping with cancer and alleviating life stress in these vulnerable women (Goldstein et al., 2018). These studies indicated that MBSR could improve women's self-efficacy, which was consistent with the findings of this study.

The COVID-19 pandemic meant that our intervention was Internet-based to better ensure that the study did not place women with breast cancer (and potentially with leukopenia) at risk of coronavirus infection (Kimura et al., 2021), thereby encouraging them to continue participating in the iMBSR intervention of distance learning. However, the 6-week intervention period may have been too brief to produce improvements in all areas. The most significant source of self-efficacy is constant practice because it relies on actual personal experience. Successful experiences help increase self-efficacy. Therefore, future studies can investigate the long-term effect of mindfulness skill practice on self-efficacy outcomes in breast cancer survivors. Larger samples would also strengthen the results.

Strengths and limitations

Our study has several strengths. Our investigation was during the COVID-19 pandemic, highlighting the importance of an Internet-based psychoeducational intervention. The e-delivery prevented exhaustion from long commutes and reduced infection rates, which was critical for patients with cancer and potentially compromised immune systems. Additionally, we initially expected to enroll 48 participants, but we completed the final program with 67, exceeding our expected inclusion rate. However, this study had some limitations. First, we did not measure the long-term effects of iMBSR on patients with breast cancer. Second, the average age of the participant was 49.61 ± 12.03. Some older participants struggled with the Microsoft Teams software and could not join the course, hear the sound, or operate the digital whiteboard. Therefore, the staff should have spent more time contacting individuals struggling with the software.

Conclusion

Overall, our findings indicate that we provided women with breast cancer with a convenient and cost-effective method to enhance their empowerment and confidence through mindfulness-based mental health education that taught them how to easily incorporate mindfulness techniques into their daily lives. We propose a future study investigating the acceptability and cost-effectiveness of Internet-based mindfulness interventions for people with different sociodemographic conditions.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material; further inquiries can be directed to the corresponding authors.

Ethics statement

The studies involving human participants were reviewed and approved by Research Ethics Committee, China Medical University & Hospital, Taichung, Taiwan. The patients/participants provided their written informed consent to participate in present study.

Author contributions

Y-CC: study conception and design. Y-CC, C-FC, C-KW, C-TW, L-CL, and Y-CW: data collection and critical revision of the article. Y-CC and C-KW: data analysis and interpretation and drafting of the article. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

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Development and preliminary validation of Cancer-related Psychological Flexibility Questionnaire

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The Cancer-related Psychological Flexibility Questionnaire (CPFQ) was developed and validated for assessing cancer patients' psychological flexibility, including attitudes and behavior toward cancer. In a systematic process, the CPFQ identified four factors through principal component analysis and confirmatory factor analysis: Cancer Acceptance, Cancer Avoidance, Activity Engagement, and Valued Action. The results of this study reveal that the CPFQ has a clear factor structure and good psychometric properties. The specific nature of cancer and the need for a specific measure of cancer patient psychological flexibility make this questionnaire valuable for research on psychological flexibility in cancer patients.

KEYWORDS

psychological flexibility, cancer, questionnaire, cancer acceptance, cancer avoidance, activity engagement, valued action

Introduction

Cancer is a leading cause of death and a worldwide public health issue. According to the GLOBOCAN 2020 estimates of cancer incidence and mortality worldwide in 185 countries, ~19.3 million new cancer cases and 10.0 million deaths occurred in 2020. Moreover, an estimated 28.4 million cases are expected in 2040 (Sung et al., 2021). Cancer is a chronic and life-threatening illness, and most cancer patients must undergo comprehensive anticancer treatment, including surgery, radiotherapy, and chemotherapy. Existing evidence showed that cancer patients often endure treatment-related toxicities and permanent functional impairment, which lead to multiple symptoms (Neufeld et al., 2017; Cuthbert et al., 2020; Gravier et al., 2020; Lage et al., 2020; Raphael et al., 2020). Cuthbert et al. reported that 60% and 80% of patients with a cancer diagnosis suffered from anxiety and low well-being, respectively (Cuthbert et al., 2020). Almost half of cancer survivors (43.6%) experienced a fear of relapse, and 32.1% had a severe/pathological fear of relapse in Singapore (Mahendran et al., 2021). A negative emotional state could significantly reduce the quality of life of cancer patients (Liu et al., 2021; Phoosuwan and Lundberg, 2022).

Many cancer patients adopt negative coping styles such as avoidance and pessimism when confronted with treatment-related toxicities, impaired functions, and distorted body image

(Zhang et al., 2020). They might struggle to eliminate or fight cancer-related discomfort symptoms, including pain, fatigue, nausea, vomiting, dyspnea, and edema. Some live in this self-conceptualization and think they are useless and cumbersome. They experience a diminished sense of self-worth and show avoidance and withdrawal tendencies, such as avoiding discussing disease-related issues and reducing daily activities and social interactions. Coping styles of cancer survivors plays a predictive role in psychological symptoms, psychological well-being, and quality of life. The patients with an avoidance coping style showed higher cancer distress, anxiety, depression, and lower quality of life (Cheng et al., 2019). The better we understand the mechanism that underlies cancer patients' avoidance coping style, the better we can reduce their psychological symptoms and improve their quality of life.

Psychological flexibility (PF), a new concept in clinical psychology, is defined as the ability to stay in contact with the present moment and pursue behavioral goals based on personal values and situational contexts, despite the presence of distress (Kashdan et al., 2020; Cherry et al., 2021). Psychological flexibility is a core construct of the Hexaflex model of acceptance and commitment therapy (ACT), one of the third wave of cognitive behavioral therapy (Hulbert-Williams et al., 2015). Acceptance and commitment therapy is based on Hexaflex model which is composed of six core components: acceptance, cognitive defusion, self as context, being present, values, and committed action. Acceptance and commitment therapy aims to improve the coping style and diminish the impact of adverse stressor events by deconstructing the individual experience in the context of personal values, enabling acceptance of both positive and negative responses (Hulbert-Williams et al., 2015), producing adaptive behavior change by enhancing PF (Hayes et al., 2019; Hofmann and Hayes, 2019). Many studies found that PF is associated with adaptive personality traits, including higher conscientiousness, openness to experiences, and lower negative emotionality, which may be the primary therapeutic mechanism of ACT (Hayes et al., 2006; Bryan et al., 2015). Previous studies indicated that a higher PF predicted lower anxiety, depression, and aversive emotional states in patients with breast cancer (Berrocal Montiel et al., 2016). A higher PF also resulted in a higher meaning in life in patients with thyroid cancer (Lv et al., 2021). In patients with prostate cancer, PF significantly predicted psychological distress and quality of life and moderated the relationship between the fear of recurrence and psychological distress (Sevier-Guy et al., 2021). Lucas et al. reported that PF was important for mental health and had a direct, positive effect on life satisfaction among community residents (Lucas and Moore, 2020). In conclusion, PF is a common protective factor across different contexts and populations. Therefore, quantitative assessment of PF for cancer patients can predict their psychological status and quality of life and evaluate the effect of ACT.

Psychological flexibility currently has a wide range of measurement tools. The most popular general measure of PF was AAQ-II, a version of the Acceptance and Action Questionnaire (AAQ; Cherry et al., 2021). AAQ-II has been widely used to measure PF in different contexts and populations, such as cancer patients (Lv et al., 2021) and community residents (Pyszkowska and Ronnlund, 2021). However, AAQ-II measures experiential avoidance (EA), which is an unwillingness to face unwanted experiences and acting to avoid them, and fails to capture core elements of PF (Kashdan et al., 2020). Experiential avoidance measured by AAQ-II is only a component of PF and cannot fully represent PF. In addition, there are many specific assessment tools for PF adapted from AAQ, such as the Acceptance and Action Diabetes Questionnaire (Gregg et al., 2007), the Chronic Pain Acceptance Questionnaire (CPAQ; Fish et al., 2010), and the Psychological Flexibility in Epilepsy Questionnaire (PFEQ; Burket et al., 2021), which are used to measure the PF of patients with diabetes mellitus, chronic pain, and epilepsy, respectively. However, there is no specialized assessment tool for PF in cancer patients.

Cancer is a chronic disease with long-term complex treatment and high physical and psychological burdens. Cancer is a life-threatening disease with high incidence, destruction of integrity, and high recurrence risk. Cancer patients are at risk for several comorbid psychological problems, such as anxiety, depression, and fear (Cuthbert et al., 2020; Lage et al., 2020; Raphael et al., 2020). Moreover, patients with cancer tend to confuse negative emotions and thoughts with objective facts, and immerse themselves in negative automatic thoughts, which aggravate negative emotions and form a vicious circle. Therefore, the PF of cancer patients may differ from that of patients with other non-cancer diseases owing to the characteristics of the tumor. The measure of PF in cancer patients is helpful in understanding their psychological process and coping style so that psychological interventions can be implemented to enhance PF, decrease psychosocial distress, and pursue a more meaningful and healthy life. In addition, it might reduce the specificity and sensitivity if general psychological flexibility assessment tools were used to measure PF of cancer patients. Hence, developing a self-reporting tool that specifically addresses PF in relation to cancer for both research and clinical purposes is necessary.

The present study aimed to (1) develop a tool to measure PF in cancer patients and identify its latent structure [Study 1], and (2) confirm the structure, and explore the validity of the questionnaire by using the Meaning in Life Questionnaire, the Templer's Death Anxiety Scale, and the Acceptance and Action Questionnaire II [Study 2].

Study 1: Questionnaire construction and development

Materials and methods

Participants

Participants were recruited using a convenience sampling method from a tertiary cancer hospital in Hunan Province, China. Patients were included if they: (a) were aged over 18 years old, (b) had a diagnosis of cancer and awareness of it; (c) had normal cognitive function and were able to read and write; (d) could complete the survey; and (e) were willing to participate and provide informed consent. A total of 250 questionnaires were distributed. Finally, 231 patients completed the survey, with a valid response rate of 92.4%. Of all the patients, 115 were men, aged 19–89 years, with an average age of 56.4 ± 11.3 years. Most of them were married (90%) ($n = 208$), 4.3% ($n = 10$) were single, and 5.6% ($n = 13$) were divorced or widowed. As for educational background, 27.7% ($n = 64$) completed primary school or below, 42.8% ($n = 99$) junior high school, 14.3% ($n = 33$) senior high school, and 15.2% ($n = 35$) college and above. Regarding cancer stages, 4.3% ($n = 10$) of the patients had stage I, 24.2% ($n = 56$) stage II, 39.0% ($n = 99$) stage III, 15.6% ($n = 36$) stage IV, and 16.9% ($n = 39$) were unreported.

Item generation of the pilot Cancer-related Psychological Flexibility Questionnaire

There were four steps to generate the items of the pilot Cancer-related Psychological Flexibility Questionnaire. The four steps are item generation, scoring methodology, expert consultation, and pilot test, described as follows:

Item generation

The generation of items was based mainly on the following principles. (1) It came from the analysis of the Hexaflex theoretical framework and a large number of literature reviews. According to the model, PF included two processes, which consist of six core components: mindfulness and acceptance processes (acceptance, cognitive defusion, and self as context) and commitment and behavior change processes (being present, values, and committed action). (2) It followed items of other measurement tools of psychological flexibility, such as the CPAQ (Fish et al., 2010) and the Multidimensional Psychological Flexibility Inventory (MPFI; Rolffs et al., 2018). (3) Semi-structured interviews with open-ended questions were conducted with a representative sample of cancer patients to understand their feelings and responses after a cancer diagnosis. The interview outline revised by experts was as follows: ① Please describe your experience or feeling about cancer; ② What influences or changes have tumors brought to your life, including daily life, work, social interaction, family relations, etc.?; ③ What do you do in the face of cancer?; ④What are your main concerns?; and ⑤ What are your plans for the future?. An experienced interviewer conducted one-to-one interviews in an independent and quiet room. The entire interview process was recorded. The interviewer transcribed and analyzed the interview results on the day of the interview and stopped the interview after sufficient information was gathered. Finally, 18 cancer patients were interviewed. Four themes were extracted: negative emotions (distress, shame, frustration, anxiety, and self-blame), avoidance coping (avoid disease, social isolation, workplace alienation, and meaningless life), positive coping (accept reality, cooperate with treatment, and cherish life), and future plan (adjust lifestyle, assume roles, and go with the flow).

If an item reflected one of the six core components mentioned above, it was included in the potential items pool. Following these guidelines, 32 potential items were created to reflect the construct of PF. After study group discussion, some similar items were deleted or merged, and 14 items were retained.

Scoring methodology

A 5-point Likert-type scale that ranged from "never true" to "always true" was used. Most items were reverse scored, with "never true" score as 5 points and "always true" scored as 1 point. A few items were positively scored. The total score was the sum of all items, with higher points representing better cancer-related PF.

Expert consultation

After creating the potential items pool, expert consultation was conducted by sending an email to assess the accuracy and importance of the items and proposing modification suggestions. We selected 15 psychology experts from the ACT field; however, 12 experts ended up being involved in the consultation. There were five men and seven women, with ages ranging from 30 to 55 years (with an average of 43.1 ± 8.6 years). They had been involved in psychology for at least 5 years, and most are currently active in the ACT field. Regarding academic qualifications, one was an undergraduate, and the rest had a master's or doctorate degree. Each expert evaluated the items independently.

In the first round of consultation, the experts recommended we add some items about self as context and being present, and split some items with double meanings, so that the number of items increased to 23 after this consultation. We then conducted the second round of expert consultation. After this consultation, we adjusted the items appropriately, modified the ambiguous items, adjusted the order of the items, and selected the most representative items. For example, "Even if I feel ill, I can still live a normal life" changed to "Even if I feel ill, I still try to live like before I got sick," and "I experience a lot of pain when I think about or feel certain things because of my tumor" changed to "I feel pain for suffering from a tumor." Meanwhile, according to experts' suggestions, we put together items that expressed the same concept. Finally, the initial questionnaire with 23 items was generated after two rounds of consultations.

Pilot test

The pilot test took a sample of 15 inpatients from a tertiary cancer hospital, which was used to clarify ambiguous items, and delete items that were hard to understand or with multiple meanings. No incomprehension or ambiguity were discovered. As a result, a pilot questionnaire with 23 items was left.

Procedure

Two master's students from the research team distributed the survey face-to-face between November and December 2021. Before the survey, participants were informed about the purpose of this study, the requirements for participation, potential risks/benefits, and their right to terminate participation at any time. The researchers started the survey once informed consent was obtained. The survey was conducted anonymously, and participants participated in the survey free of charge.

Data analysis

Data analysis was performed using the IBM SPSS software version 26.0 (IBM, Armonk, NY, United States). First, item-total correlations were used to test whether all items were consistent with the questionnaire. Inconsistent items were deleted based on the results. Second, the cases were divided into a high score group (the first 27%) and a low score group (the last 27%) according to the total score of the CPFQ, and then the scores of all items in the two groups were compared. Items with no significant differences indicating a lack of identification were deleted. Third, Kaiser-Meyer-Olkin and Bartlett's test of sphericity was used to test whether the data were appropriate for factor analysis. Fourth, principal component analysis (PCA) was used to explore the latent structure of the CPFQ. The criteria for dimensions and item selection were as follows (Wu, 2010): (1) eigenvalues >1; (2) factors containing three or more items; (3) items load strongly (>0.40) onto factors; and (4) items do not cross-load onto two or more factors.

Results and discussion

Based on the item analysis, the following four items were removed because the correlation coefficient (r) between the item and the total score was 0.233, 0.189, 0.254, and 0.280, respectively: Item 7: "The tumor made me realize what is important in life"; item 8: "We still live a happy life although we are in distress"; item 10: "I try not to think about the changes that cancer treatment may bring"; and item 16: "Even if I am ill, I still try to attend family, friends, or classmate gatherings." Item analysis ranked the total scores of 231 patients from low to high and assigned the first 27% as the low score group and the last 27% as the high score group. The *t*-test of two independent samples was used to detect the differences between the 23 items in the high and low score groups. The results showed no significant difference on item 7 and item 8, which further indicated that the identification of these items was low and should be deleted.

In the Kaiser-Meyer-Olkin test, an *r*-value of 0.831 indicated that the data was suitable for factor analysis. A Bartlett test of sphericity (χ^2 =2879.375, df = 171, $p < 0.001$) indicated that the analysis model was appropriate. Therefore, it was acceptable to adopt factor analysis to test the construct reliability of this scale.

Applying PCA and varimax orthogonal rotation, we set parameters and extracted four factors with eigenvalues >1 and a cumulative variance interpretation rate of 68.939%. Four factors all contained at least four items, and the loading of each item was more than 0.59 (see Figure 1). According to the content of the items, the four factors were named as cancer acceptance (six items, $M = 20.08$, $SD = 5.64$, skewness = −0.262, kurtosis = −0.376), cancer avoidance (four items, $M = 10.31$, $SD = 2.97$, skewness = −0.048, kurtosis = −0.239), activity engagement (five items, $M = 18.05$, $SD = 3.70$, skewness = −0.059, kurtosis = −0.501), and valued action (four items, $M = 16.01$, $SD = 2.63$, skewness = −0.402, kurtosis =0.824). The items of the original Chinese form are shown in Appendix.

Following a series of data analyses, Study 1 resulted in a 19-item scale with four factors. This proposed model evaluated the PF of cancer patients, and its structure was inconsistent with the existing measuring tools for PF. For example, the CPAQ-8 contains two factors, that is pain willingness and activity engagement (Fish et al., 2010). The Personalized Psychological Flexibility Index includes three dimensions (avoidance, acceptance, and harnessing; Kashdan et al., 2020). This four-factor structure of the CPFQ was based on one sample; hence study 2 was conducted to validate the factor structure in another dataset.

Study 2: Validation

To validate the four-factor structure and test the validity and reliability of the 19-item CPFQ, Study 2 collected another dataset. A CFA was conducted to test the four-factor model of PF. Furthermore, previous studies indicated a positive correlation between PF and life meaning but a negative relationship between anxiety and experiential avoidance (Lv et al., 2021). Therefore, meaning in life (assessed by the Meaning in Life Questionnaire) and death anxiety (assessed by the Templer's Death Anxiety Scale) were used to evaluate the concurrent validity of the CPFQ, and experiential avoidance (assessed by the AAQ II) was used to evaluate the convergent validity of the CPFQ.

Materials and methods

Participants

Inpatients were invited to participate in this survey from a tertiary cancer hospital in Hunan Province, China. The selection criteria of the participants were consistent with Study 1. A total of 285 questionnaires were sent to patients, and 252 patients completed the whole questionnaire, with a valid response rate of 88.4%. Of all the patients, 130 were men and were aged between 22 and 90 with an average age of 56.0 ± 11.3 years. Eighty six percent of patients (n =217) were married, 5.2% (n = 13) were single, and 8.7% (n =22) were divorced or widowed. As for educational background, 27.8% (n = 70) completed primary school or below, 40.1% (n = 101) junior high school, 17.5% (n = 44) senior high school, and 14.7% (n = 37) college and above. The cancer stages of the sample were as follows: 5.9% (n = 15) patients had stage I, 25% (n = 63) stage II, 42.5% (n = 107) stage III, 13.9% (n = 35) stage IV, and 12.7% (n =32) were not reported.

To validate the model, the subjects-to-parameters ratio could not be lower than 5:1, and the total number of subjects needed to be over 200. The new sample (n = 252) in Study 2 reached a 5.7:1 subjects-to-parameters ratio, which was appropriate for testing a model with 44 parameters, consisting of 19 factor loadings, 19 error variances, and six factor correlations.

Procedure and measures

The survey was distributed face-to-face by three master's students from the research team between January and March 2022. Before the survey, participants were informed about the purpose of this study, the requirements of participation, potential risks/benefits, and their right to terminate participation at any time. The researchers started the survey once informed consent was obtained. In order to evaluate concurrent validity and convergent validity, patients were required to complete the Meaning in Life Questionnaire, the Templer's Death Anxiety Scale, and the AAQ II.

Meaning in life questionnaire

Meaning in life (MIL) was measured by the Meaning in Life Questionnaire (MLQ; Steger et al., 2006). The questionnaire contained the following two subscales: (1) The presence of meaning (MLQ-P), which assessed the extent to which meaning is experienced in a respondent's life using statements such as "I understand my life's meaning," and (2) search for meaning (MLQ-S), which assessed a respondent's desire to find and understand MIL using statements such as "I am searching for meaning in my life." The original questionnaire had 10 items (five items for each of the two subscales) scored using a 7-point Likert scale ranging from one point (absolutely untrue) to seven points (absolutely true). Higher scores on the MLQ suggested that respondents were more likely to perceive and find MIL. Chinese scholars had previously translated and modified the questionnaire. The Chinese version, with five items for the MLQ-P and four items for the MLQ-S, was reported to have satisfactory reliability and validity (Liu and Gan, 2010). Finally, the MLQ was used to analyze the concurrent validity of the CPFQ.

Templer's death anxiety scale

The Templer's Death Anxiety Scale (T-DAS; Templer, 1970) assessed death anxiety and was used to analyze the concurrent validity of the CPFQ. The scale consisted of 15 items with dichotomous

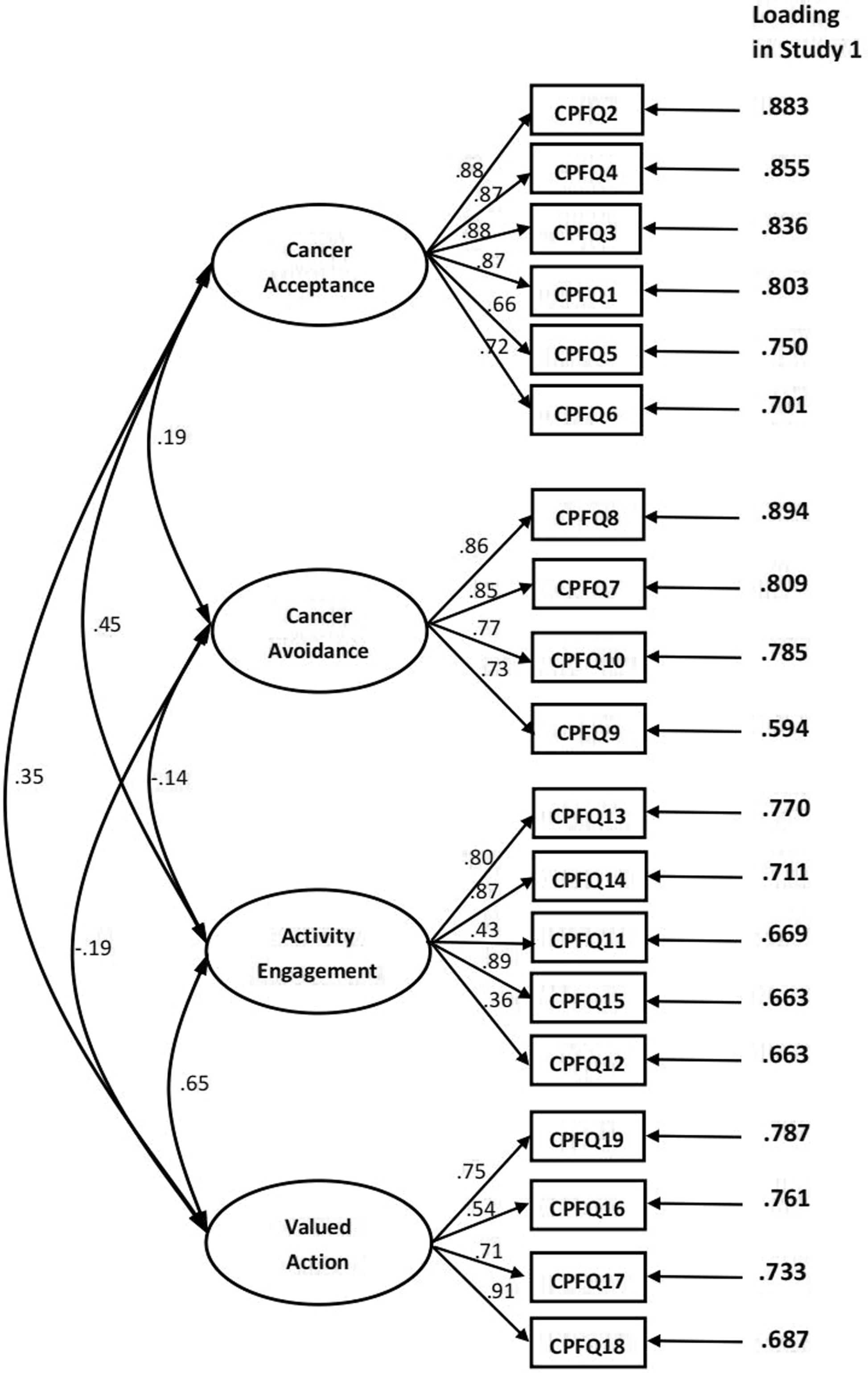

FIGURE 1
Confirmatory factor analysis in Study 2, and rotated(promax) factor loading in Study 1 with principal component analysis.

responses (true/false). Nine items were forward scored, and six were reverse scored, and higher scores indicated greater death anxiety. This scale was reported to have test–retest reliability of 0.83 and reasonable internal consistency of 0.76. This scale had been translated into multiple languages and used in several countries. The Chinese version of T-DAS contained four factors. These were labeled (1) Stress and pain, (2) Emotion, (3) Cognitive, and (4) Awareness of Time Passing. The translated measure demonstrated good reliability and validity with an estimated internal consistency of Cronbach's $\alpha = 0.71$ (Yang et al., 2012).

Acceptance and action questionnaire II

The Acceptance and Action Questionnaire II (AAQ-II; Bond et al., 2011) was a general measure of experiential avoidance and was used to analyze convergent validity with CPFQ. AAQ-II was developed by Bond et al. in 2011, a unidimensional scale with seven items based on the seven points Likert scale, ranging from one (never true) to seven (always true). The total score was summed over the seven items, with higher scores representing greater experiential avoidance and lower PF. AAQ-II had good test–retest reliability and good internal consistency ($\alpha = 0.88$). The Chinese version of AAQ-II was modified by Cao et al. in 2013 (Cao et al., 2013), which had established a good content validity index, and acceptable internal consistency with Cronbach's $\alpha = 0.88$.

Data analysis

Data analysis was performed using Amos version 23.0, SPSS version 26.0, and M*plus* version 8.3. The construct validity was identified by the confirmatory factor analysis (CFA), and the criteria for indexes that were used to assess the goodness of fit of the model as follows: $1 < \chi^2/df < 3$, comparative fit index (CFI) > 0.90, goodness-of-fit index (GFI) > 0.90, and root-mean-square error of approximation (RMSEA) < 0.08 (Wu, 2010). The equivalence of the model across gender was examined by invariance testing, and the criterion for indices that were used to evaluate the adequacy of the fit of the model as follows: ΔCFI was <0.01, ΔRMSEA was <0.015 (Cheung and Rensvold, 2002).

Descriptive statistical analysis was used to examine the mean, standard variation, skewness, and kurtosis of the four factors. In order to assess the concurrent validity of the questionnaire, Pearson's r between CPFQ, MIL, and T-DAF was calculated. In order to assess the convergent validity of the questionnaire, Pearson's r between CPFQ and AAQ-II was calculated. Internal consistency of the CPFQ was examined using Cronbach's alpha coefficient. Finally, split-half reliability R was evaluated by the correlation coefficient r between the odd and even items $\left(R = 2r/1 + r\right)$.

Results and discussion

Construct validity analysis

To obtain the construct validity of the four-factor structure developed from Study 1, CFA with the maximum likelihood method was conducted by Amos 23.0. The results showed a good fit to the data of Study 2, $\chi^2 = 297.572$, $\chi^2/df = 2.343$, $p < 0.001$, CFI = 0.948, GFI = 0.900, RMSEA = 0.073, 90% CI = 0.062–0.084. Configural or factorial invariance analysis was conducted by M*plus* 8.3 across gender group to determine whether the factor structure of the CPFQ was the same for both men and women. The results revealed the model fit the data reasonably well, with ΔCFI <0.01, and ΔRMSEA <0.015 (Table 1). Therefore, formal and measurement invariance across gender was evidenced for the CPFQ.

The standardized coefficients of each path are shown in Figure 1. Descriptive analysis revealed that the distributions were relatively normal for the overall CPFQ ($M = 63.75$, SD = 10.65, skewness = 0.112, kurtosis = −0.016) and its four factors: cancer acceptance ($M = 19.80$, SD = 5.73, skewness = −0.320, kurtosis = −0.187), cancer avoidance ($M = 10.15$, SD = 3.31, skewness = 0.290, kurtosis = 0.110), activity engagement ($M = 17.70$, SD = 3.67, skewness = 0.029, kurtosis = −0.430), and valued action ($M = 16.10$, SD = 2.63, skewness = −0.352, kurtosis = 0.656).

Concurrent and convergent validity analysis

Pearson's correlational analysis was conducted to explore the association between the CPFQ and other measures. The overall CPFQ was significantly positively associated with the presence of meaning ($r = 0.519$), search for meaning ($r = 0.257$), and MIL ($r = 0.456$), and negatively associated with death anxiety ($rs = -0.449$ to -0.591), and experiential avoidance ($r = -0.704$), which provided evidence that the overall CPFQ was measuring the essence of psychological flexibility and could estimate mental and behavioral health of cancer patients. Table 2 shows that most correlation coefficients were significant, ranging from −0.159 to.747, except for Cancer Avoidance. Cancer Avoidance was weakly correlated with AAQ-II ($r = -0.175$, $p < 0.01$) and not correlated with other measures.

Reliability analysis

The Cronbach's α coefficient of the whole CPFQ was 0.885, and the Cronbach's α coefficient for Cancer Acceptance, Cancer Avoidance, Activity Engagement, and Valued Action was 0.927, 0.874, 0.823, and 0.849, respectively, which indicated that the items were internally consistent. The odd and even items were summed and the correlation coefficient was statistically significant with $r = 0.898$, and split-half reliability was 0.946.

Effects of gender, age, and cancer stage on CPFQ

Table 3 shows the effects of gender, age, and cancer stage on the overall CPFQ and its four dimensions. Independent t-tests showed a significant difference in Valued Action ($t = -2.590$, $p < 0.05$) and no significant difference in the overall CPFQ and the other three dimensions between men and women. In terms of cancer stage, ANOVA displayed statistical differences in the overall CPFQ and its three dimensions ($F > 5.789$, $p < 0.005$), except for Cancer Avoidance. Table 3 shows that age was related to Activity Engagement, Valued Action, and the overall CPFQ ($F > 2.784$, $p < 0.018$).

Overall, the 19-item CPFQ with four dimensions showed a good model fit in a second Chinese sample. The results demonstrated good reliability, construct validity, concurrent validity, and convergent validity of the CPFQ. The overall CPFQ and its dimensions were positively correlated with MIL, and negatively correlated with death anxiety and experiential avoidance. However, Cancer Avoidance showed non-significant correlations with MIL and death anxiety. This outcome may be due to cancer patients' characteristics, whose attitudes toward cancer change over time. Future studies are needed to continue to validate the four-factor structure of the CPFQ in a bigger sample.

This study suggested women showed higher Valued Action. In China, most women undertake more roles and responsibilities than men, as they take care of many people. Even if they do not accept cancer, avoid cancer issues, and avoid socializing, they still do something based on their values, such as taking the doctor's advice to live longer.

It is worth noting that age was correlated with the CPFQ, especially for activity engagement and valued action. The younger the

TABLE 1 Invariance testing across gender group.

Invariance level	χ^2	df	χ^2/df	CFI	RMSEA	ΔCFI	ΔRMSEA
Configural	442.154	284	1.557	0.876	0.066		
Metric	466.107	299	1.559	0.869	0.067	−0.007	0.001
Scalar	491.209	314	1.564	0.861	0.067	−0.008	−0.001

TABLE 2 Means, standardized deviation (SD) of measures, and correlations between overall of CPFQ and its four subscales, two dimensions of MLQ, four dimensions of T-DAS, and AAQ-II.

	MLQ-P	MLQ-S	MLQ	DAS Stress and pain	T-DAS Emotion	T-DAS Cognitive	T-DAS Awareness of time passing	T-DAS	AAQ-II
Mean	24.62	19.10	43.71	2.83	2.08	1.67	1.03	7.60	25.56
SD	4.681	4.227	7.707	1.673	1.718	1.041	0.820	4.332	9.641
r with									
Cancer Acceptance	0.397**	0.084	0.287**	−0.538**	−0.513**	−0.574**	−0.465**	−0.637**	−0.747**
Cancer Avoidance	0.116	0.012	0.077	−0.067	−0.056	−0.039	−0.010	−0.059	−0.175**
Activity Engagement	0.496**	0.323**	0.478**	−0.405**	−0.291**	−0.395**	−0.409**	−0.444**	−0.561**
Valued Action	0.399**	0.392**	0.457**	−0.333**	−0.254**	−0.159*	−0.219**	−0.309**	−0.219**
Overall CPFQ	0.519**	0.257**	0.456**	−0.532**	−0.457**	−0.496**	−0.449**	−0.591**	−0.704**

**$p < 0.01$, *$p < 0.05$.

patient was, the more willing they were to participate in activities and do something worthwhile. However, in terms of the overall CPFQ, patients aged 31–50 show higher PF. The possible reason is that middle-aged patients are mentally more mature than younger patients and more responsible than older people. Therefore, considering the small sample size of some subgroups, future studies are necessary to explore this interesting phenomenon further.

Furthermore, the current study also revealed that patients with advanced cancer had lower PF than those with early cancer. It may be because early cancer is easier to treat, has a better prognosis, and is easier to recovery. Patients acquire posttraumatic growth after this life event and tend to cherish work, life, families, and friends more. It is interesting that irrespective of the cancer stage, they all had an attitude of avoiding cancer. One possible explanation for this phenomenon is that according to Chinese traditional culture, Chinese people are extremely sensitive about their illness and consider cancer a disgrace.

In this study, we recruited patients with different types of cancer, but we did not analyze the impact of cancer types on PF. Because there were many types of cancer and the sample size was not relatively small, cancer was difficult to classify by types. If the classification is very specific, the sample size of each category will be very small, and if classified by tumor region, the severity of diseases in the same category will vary greatly, e.g., head and neck cancer includes oral and thyroid cancer; however, the severity of these diseases is completely different. Although the extent of the impact of different types of cancer on PF is unknown, it clearly has an impact. Because different types of cancer have different symptoms and prognoses, symptoms and prognoses will affect PF.

General discussion

The current study describes the development and preliminary validation of the CPFQ, an instrument to measure PF in cancer patients. Initial scale development resulted in a 23-item instrument, which was reduced to 19 items based on item-scale correlations and PCA. After item analysis and PCA, a four-factor structure of the CPFQ indicated four dimensions of psychological flexibility of cancer patients: Cancer Acceptance, Cancer Avoidance, Activity Engagement, and Valued Action. The PCA revealed a four-dimension questionnaire consistent with the concept of PF (Cherry et al., 2021). Confirmatory factor analysis indicated a good model fit on the four-factor structure; in other words, the construct validity was satisfactory. Concurrent validity was expressed as correlations between CPFQ, MIL, and death anxiety (T-DAS) were moderate. Convergent validity, as these constructs were supposed to share some common features, expressed as the correlation between CPFQ and AAQ-II was acceptable. The internal consistency and split-half reliability were beyond the specified standard. The results showed that the CPFQ had a clear factor structure and good psychometric properties in Chinese samples. Therefore, the questionnaire is valuable and beneficial for research on the PF of cancer patients.

The CPFQ reflects both attitudes and behaviors toward cancer. The four dimensions of the CPFQ represented PF in terms of cancer acceptance, cancer avoidance, social contact, and behavior orientation. The ability to live a valuable life despite a cancer diagnosis is a type of PF related to cancer. Different from other life events, cancer is a life-threatening disease, and individuals' responses should be different from other stress events. Therefore, the PF of cancer patients may have its own essence and characteristics. Examining the four specific dimensions of the CPFQ, the former two dimensions mainly assessed the patients' attitudes toward cancer, and the latter two dimensions mainly measured their behavioral tendencies after a cancer diagnosis. These contents reflected not only the nature of PF, such as acceptance, cognitive fusion, being present, values, and action, but also the characteristics of cancer patients.

Differing from other measures of psychological flexibility, the CPFQ measures (1) individuals' psychological response to cancer

TABLE 3 Effects of gender, age, and cancer stage on the overall and four dimensions of CPFQ.

Variables	*n*	Cancer Acceptance	Cancer Avoidance	Activity Engagement	Valued Action	Overall CPFQ
Gender						
Male	130	19.35 (5.36)	10.26 (3.34)	17.63 (3.80)	15.69 (2.57)	62.94 (10.59)
Female	122	20.27 (6.08)	10.03 (3.30)	17.77 (3.55)	16.54 (2.63)	64.61 (10.68)
t		−1.266	0.547	−0.301	−2.590	−1.250
Value of *p*		0.207	0.585	0.764	0.010	0.212
Age (years)						
20–30	3	16.33 (7.37)	7.67 (4.04)	19.00 (5.29)	18.00 (3.46)	61.00 (12.29)
31–40	29	19.24 (6.58)	10.93 (3.47)	19.00 (3.55)	16.69 (2.58)	65.86 (12.13)
41–50	42	20.33 (6.36)	10.05 (3.87)	18.69 (4.13)	17.12 (2.87)	66.19 (11.49)
51–60	94	20.66 (4.62)	10.47 (3.58)	17.27 (3.38)	15.78 (2.52)	64.17 (9.32)
61–70	65	19.52 (6.14)	9.74 (2.51)	17.92 (3.42)	15.82 (2.49)	63.00 (10.41)
>70	19	16.68 (5.45)	9.42 (2.43)	14.68 (3.16)	15.26 (2.45)	56.05 (10.61)
F		1.963	1.231	4.590	2.784	2.894
Value of *p*		0.085	0.295	0.001	0.018	0.015
Cancer stage						
I	15	24.07 (4.27)	10.27 (3.67)	22.13 (3.11)	19.40 (1.40)	75.87 (7.92)
II	63	20.30 (4.48)	10.48 (3.64)	18.51 (2.84)	15.83 (2.57)	65.11 (9.39)
III	107	19.65 (5.56)	9.98 (2.94)	17.39 (3.67)	16.01 (2.39)	63.04 (9.80)
IV	35	17.20 (7.23)	9.80 (3.28)	16.11 (3.80)	15.57 (2.51)	58.69 (12.78)
F		5.789	0.438	12.126	10.257	10.664
Value of *p*		0.001	0.726	<0.001	<0.001	<0.001

and their attitudes toward the psychological response; (2) one's emotional and behavioral tendencies when thinking of cancer treatment; and (3) individuals' social interaction and behavior change after cancer. Compared with other questionnaires for measuring PF, the CPFQ has similarities and differences. For example, the CPAQ includes two dimensions, namely pain willingness (feeling little need to avoid or control painful experiences) and activity engagement (the degree to which one engages in life's activities regardless of pain; McCracken et al., 2004; Fish et al., 2010). The similarities are that both questionnaires measure patients' attitudes and behaviors toward diseases (cancer vs. chronic pain). The difference is that the content of CPFQ is more comprehensive, including not only psychological responses and behavioral orientation to diseases, but also avoidance reactions and valued actions to diseases.

The CPFQ contributes significantly by providing a valuable tool that measures components of psychological flexibility and verifies psychological flexibility from cancer patients' perspectives. As described in the "Materials and Methods" section, the items of the CPFQ were generated from both the literature review and the theoretical definition of psychological flexibility. We also refer to some items from other measurement instruments of psychological flexibility, such as the CPAQ (Fish et al., 2010) and MPFI (Rolffs et al., 2018). Moreover, we interviewed cancer patients about their feelings, attitudes, and behavior change after a cancer diagnosis. Hence, we support that the CPFQ is a questionnaire with a solid theoretical foundation and comprehensive content.

In summary, a new measurement instrument of PF was developed and validated in two samples. To our knowledge, this is the first cancer-specific psychological flexibility measurement that includes attitude and behavior components, which could provide a more accurate assessment of PF among cancer patients and help health care providers develop personalized and targeted interventions in the PF field. The CPFQ was a reliable and valid tool to evaluate the PF of cancer patients with a four-factor structure: Cancer Acceptance, Cancer Avoidance, Activity Engagement, and Valued Action. Moreover, this questionnaire has a good readability and a reasonable length with 19 items. We believe that the CPFQ can be used as a valuable measurement in the psychological flexibility field.

Limitations and future directions

The present study forms a preliminary version of the CPFQ. However, there are still some limitations. First, there may be sampling bias. The samples of Study 1 and Study 2 were from the same hospital, and it would be important to verify the reliability and validity of the current questionnaire among different groups. Future studies could apply this questionnaire to other groups, such as cancer patients from a general hospital, to validate our results. Second, one dimension of the questionnaire, namely Cancer Avoidance, showed unsatisfactory validity values, which needs further exploration in future research. Finally, our study did not evaluate test–retest reliability, because most inpatients had been discharged at the time of the retest, and there may exist a deviation between the online questionnaire survey and the face-to-face survey. When applying the questionnaire in the future, a small sample (such as 30) of cancer patients could be selected for the re-test reliability test.

Conclusion

The CPFQ includes four dimensions: Cancer Acceptance, Cancer Avoidance, Activity Engagement, and Values Actions, and it was proven to be a reliable and valid measure of psychological flexibility in cancer patients.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

M-jO, X-hX, and SS contributed to the original idea and concepts. HC and F-rC completed data collection and analysis. M-jO wrote the first draft. X-hX and SS revised the manuscript. All authors approved the final version of manuscript for submission.

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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.

Publisher’s note

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Appendix

Items of the original Chinese form of the Cancer-related Psychological Flexibility Questionnaire.

癌症接纳	1.因为得了肿瘤，我觉得自己是一个不幸的人
	2.我为患有肿瘤感到沮丧
	3.我为患有肿瘤感到羞愧
	4.我为患有肿瘤感到痛苦
	5.做任何事情前，我总会优先考虑到我的疾病
	6.我无法忍受疾病或治疗带来的改变
癌症回避	7.我尽量不去想肿瘤给我带来的糟糕感觉
	8.我会尽量避免可能导致疼痛等不适的因素
	9.我会尽量避免肿瘤治疗可能导致的副反应
	10.我会尽力去控制或摆脱因肿瘤带来的痛苦感觉和想法
活动参与	11.我不去面对周围的人
	12.我不去跟别人谈论我的疾病
	13.即便患病，我仍然尽量参加热爱的活动或事业
	14.即便患病，我仍然保持与自己喜欢的人来往
	15即便身体不适，我仍然尽量像患病前一样生活
基于价值的行动	16.我积极配合医生的治疗
	17.我采取了更加健康的生活方式
	18.我尽可能承担自己的角色
	19.我努力完成自己的心愿

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Psychosocial interventions reduce cortisol in breast cancer patients: systematic review and meta-analysis

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Introduction: Cancer initiation, progression and recurrence are intricate mechanisms that depend on various components: genetic, psychophysiological, or environmental. Exposure to chronic stress includes fear of recurrence that can affect biological processes that regulate immune and endocrine systems, increase cancer risk, and influence the survival rate. Previous studies show that psychological interventions might influence the level of cortisol that has been extensively used as a biomarker for measuring hypothalamic-pituitary-adrenal axis functioning and body's immunity response. This meta-analysis aimed to provide a quantitative scrutiny of the effect of certain types of psychosocial interventions on cortisol as a neuroendocrine biomarker in saliva or blood and might predict breast cancer (BC) progression.

Methods: A literature search was performed in the following databases: PubMed, The Cohrane Library, Scopus, WOS, PsychInfo, Google Scholar, Ovid Science Direct. After methodical selection of originally generated 2.021 studies, the search yielded eight articles that met inclusion criteria. All these studies explored effects of psychosocial interventions that measured cortisol in total of 366 participants with BC, stages 0-IV, in randomized control trial or quasi experimental study design setting. We applied random effects model to conduct meta-analyses on the parameters of salivary and plasma cortisol and used PRISMA Guidelines as validated methodology of investigation to report the results.

Results: Eight studies selected for meta-analysis have shown the reduction of cortisol level due to applied psychosocial intervention. The random effects model showed that interventions produced large effect sizes in reductions of cortisol in blood (Cohen's d = −1.82, 95% Confidence Interval (CI): −3.03, −0.60) and slightly less in saliva (d = −1.73, 95%CI: −2.68, −0.78) with an overall effect of d = −1.76 (95%CI: −2.46, −1.07).

Conclusion: Our study concluded that certain types of psychosocial interventions reduce cortisol (indicator of chronic stress) in patients with BC. Application of specific psychosocial support as adjuvant non-invasive therapy for affected females with BC at all phases of treatment could contribute to more cost-effective health care.

KEYWORDS

psychosocial intervention, cortisol, breast cancer, recurrence, meta analysis

Introduction

Cancer initiation, progression, recurrence, and metastasis are intricate mechanisms that depend on various components. Those components include genetic alterations, proliferation, vascularization, invasion, embolization, and evasion of apoptosis. When a tumor is established, its growth, metastatic spread, or eventual recovery, heavily depend on interactions with the microenvironment and psychological state of a patient (Armaiz-Pena et al., 2009). Despite the prevalence of cancer recurrence, research of primary psychological causes that might trigger the disease relapse are limited. Stress and fear of recurrence can also negatively affect biological processes that regulate immune and endocrine systems, influence the survival rate and the quality of life. Approximately 7% of patients develop disabling emotional condition including intrusive thoughts and misinterpretation of mild and unrelated symptoms. Patients with breast cancer (BC) have up to 30% of recurrence rate, and the timing of relapse varies considerably, influenced by classic prognostic factors (the axillary lymph node status, the tumor size, and the nuclear grade and histological grade) as well as the choice of adjuvant treatment strategies (Colleoni et al., 2016).

The new promising microbiological development proposes to suppress cancer relapse and metastasis by inhibiting cancer stem cells (Li et al., 2015). Not less important or complex research line exploring tumor development is related to the study of behavioral stress and immune or neuroendocrine biomarkers' changeability in response to stress. Psychoneuroimmunology (PNI) investigates in detail the connection between the psychological stress, its impact on neuro-immune system and cancer incidence or progression. Psychological stress and adverse life events can impact cellular immune response dysregulating homeostatic functionality on a cellular level and harm the protective functions of the immune system (Glaser and Kiecolt-Glaser, 2005). Specific signaling pathways are activated through neuroendocrine stress response resulting in promotion of tumor growth and metastasis. Neuroendocrine and immunological mediators of stress impact sympathetic nervous system and diverse interaction has been identified between malignant tissues and immune-cites (Batty et al., 2017). Oncologists now implicate psychological functioning in the prediction of cancer outcomes.

Finding a "gold standard" biomarker to measure body's response to allostatic load or experiential input (social, emotional, and physical experiences) has been proven to be challenging, given its complex etiology and highly individual manifestations. Cortisol, synthesized from cholesterol and released into the body fluids after activating hypothalamic-pituitary-adrenal (HPA) axis, is the main glucocorticoid hormone of the adrenal cortex that can be used as a peripheral indicator of hypothalamic neural activity (Dubey and Boujoukos, 2005) in the process of physiological response to endogenous and exogenous stressors. Evidence of recent research in molecular biology shows relationship between dysregulation of HPA axis, abnormal secretion of cortisol and protumorigenic pathways within breast cells (Figueira et al., 2022). When the HPA axis is chronically activated due to stress events and fears (major contributors being negative lifestyle, fast paced jobs, existential fears, negative emotional experiences, anxiety, depression), cortisol levels rise, and inflammatory responses are downregulated. As a response to biochemical stress, its secretion contributes to the suppression of the "stress axis" on mental health, where more inflammatory ligands (cytokines) are released into circulation in the vicinity of tumor cells (Levine et al., 2007; Lee et al., 2015). This proliferation of cytokines may affect disease progression by causing angiogenesis and endothelial-to-mesenchymal transition (EndMT) leading to metastasis (Morris et al., 2022).

Some molecular studies also suggest that cortisol's immunosuppressive effect may result in inability to combat tumor formation, reduced immunosurveillance of early-stage cancer, facilitating the immune escape and acquisition of further oncogenic mutations (Antonova et al., 2011; Coutinho and Chapman, 2011; Al Sorkhy et al., 2018). Additionally, cortisol has hyperglycaemic and obesogenic effects where both dysregulations lead to increased risk of malignancies (Nead et al., 2015). More specifically, stimulation of BC development by prolonged or elevated presence of cortisol during periods of stress may also partially occur as a result of augmented estrogen biosynthesis (Aromatase activity) (O'Neill et al., 1988). Thus, both clinical and molecular research reveals a positive correlation of high cortisol levels and the progression of BC, resulting in worse prognosis.

A small fraction of unbound free cortisol is demonstrated to be biologically active, coming out of the mitochondrion, whereas in general cortisol binds to cytosolic receptors. Cortisol migrates out of the cell into the extracellular space and into the bloodstream. Due to its low molecular weight and lipophilic nature, unbound cortisol enters the cells through passive diffusion, which makes it feasible to measure free cortisol in many body fluids. Several studies explored the potential of using cortisol as an indicator to assess cumulative biological risks, predict chronic stress, reduce the incidence of pre-phase of chronic illnesses (Dubey and Boujoukos, 2005; Levine et al., 2007; Lee et al., 2015).

Among its various manifestations, cortisol parameters are compounded of both serum (blood) and salivary measures. Levels of circulating cortisol reflect the activity of central and peripheral pathways that are responsive to experiential input. It has also been observed that 70% of BC patients show high levels of cortisol (De Brabander and Gerits, 1999). Plasma and salivary cortisol levels rise due to circadian influences as well as perturbations by stressors of the organism's environment that makes it possible to detect rather robust experimental effects (Levine et al., 2007; Lee et al., 2015).

Clinical studies dealing with the relationship between behavioral tendencies and the progression of a disease in patients that were already diagnosed with cancer have found that factors such as lack of social support, negative emotions and their suppression, fear of recurrence, hopelessness and denial are associated with poorer survival (Batty et al., 2017). Several systematic reviews and meta-analysis dedicated to causal relationship of stress, depression with incidence or progression of tumor have been inconclusive or showing only borderline association (De Brabander and Gerits, 1999; Petticrew et al., 1999; Antoni et al., 2006; Batty et al., 2017). Other studies have confirmed the adverse effect of this relationship on cancer incidence and survival (Duijts et al., 2003; Chida et al., 2008; Santos et al., 2009). Finally, in the study of Satin et al. (2009), depression in cancer patients has been exposed to be a predictive factor of mortality but not progression. These clinical data parallel results from animal-based studies, demonstrating that experimentally imposed stress can modulate cancer progression (Mustafa et al., 2013).

When determining the predictive power of psychosocial factors for the course of BC, additional biological factors and markers suggesting progression including tumor-free interval (TFI), site of recurrence, number of metastases, menopausal status and use of different medications should be taken into consideration (Levy et al., 1988; Carter et al., 1989; Lin et al., 2013; Mustafa et al., 2013).

BC is regarded to be one of the most appropriate cancers for studying psychosocial influences on disease progression due to its relatively variable course, high prevalence, and hormone sensitivity (Thaker and Sood, 2008).

Thus, data that would illustrate a relationship between behavioral risk factors and cancer initiation and progression have been inconclusive. To differentiate our research and bring novelty to the subject, this review and meta-analysis is aimed to consolidate existing data up to date (2022) and test the hypothesis if psychosocial interventions (and their variations that are subject of this study) can reduce neuroendocrine biomarker (cortisol) and can be considered as a plausible adjuvant therapy to attenuate chronic stress. The objective of this study is to provide a summary of the studies where primary or secondary outcome measure was cortisol in the population of females with BC in various stages of disease progression. Further, to present an overview of methodological and reporting aspects of these studies and to execute a quantitative analysis of association between the applied intervention and cortisol levels. We focused solely on BC and narrowed the scope of psychosocial interventions to be structured and methodical. We also considered other potential moderators, including characteristics of samples and trial quality by pooling relevant data from studies that met eligibility criteria. Although this review has focused on investigating Changes in the variable of cortisol under the influence of applied psychosocial intervention, neuroendocrine and immunological mechanisms that modulate cancer growth and might prevent cancer progression, metastasis or recurrence will remain outside of the scope of this review.

To our knowledge no other quantitative study devoted to this narrow scope of interventions and outcome measures has been conducted so far.

Materials and methods

We used the checklist of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Guidelines as a validated methodology of investigation (Page et al., 2021) to perform the selection procedure, study identification, synthesis methods and critical appraisal.

Search strategy

Databases of Pubmed, Medline, Web of Science, Scopus, PsychInfo, Embase, Dare, Cinahl (EBSCO), Google Scholar, Cochrane Library, OVID, Science Direct, ProQuest were systematically searched electronically and manually using appropriate controlled vocabulary terms according to Boolean operators' method specific for each database.

The search strategy consisted of the list of key words and Medical Subject Headings (MeSH) terms based on the principal concepts of our research. We applied the following terms: (1) Cognitive Behavioral Therapy, Mindfulness Based Stress Reduction, Psychosocial Therapy ("cognitive behavioral therapy" OR "psych*" OR "psychotherapy" OR "psychosocial" OR "psycho-education" OR "mindfulness*" OR "mindfulness-based"*); (2) breast cancer ("cancer*" OR "breast tumor" OR "breast carcinoma" OR "breast neoplasm" OR "mammary carcinoma"); (3) immune and neuroendocrine biomarkers ("biological markers" OR "neuroendocrine biochemical mediators" OR "immune biomarkers" OR "cortisol"). Further restrictions and search formulas were used to narrow the search that included academic publications in English from each database's inception through December 2022. We also examined bibliographical references of the articles identified through the search including relevant reviews or meta-analyses. These were further scrutinized to check whether they contained any other studies suitable for our review.

Eligibility criteria

Studies were included where the main PICOD (population, intervention, comparison, outcomes, design) concepts were defined as follows:

1. Population: women diagnosed with BC, stages 0-IV according to Tumor, Node, Metastasis (TNM) scale and post-operative tumor free stage (TFI).
2. Interventions: group or individual psychosocial interventions containing cognitive behavioral therapy, cognitive behavioral stress management, mindfulness-based intervention either in isolated form or combined with other modality, psychosocial support and therapy, psychotherapy, mindfulness-based stress reduction, existential cognitive group therapy, hypnotic guided imagery program, supportive expressive group therapy.
3. Control group of usual care or waitlisted comparison.
4. Variable of outcome measures: neuroendocrine biochemical mediator – cortisol.
5. Study design: randomized and non-randomized clinical trials, pre-post measurements. We limited the analysis to controlled or quasi experimental intervention studies.

Studies were excluded if:

1. The studied sample population was not diagnosed with BC. Studies where survivorship was the only outcome without measuring neuroendocrine biomarkers as a primary or secondary outcome.
2. Studies where intervention did not involve psychosocial support (in any of its variations that are subject of this study) in a group or individual format, and only involved exercise, tai chi, qi gong, yoga, aerobic or other modality, or where

the intervention narrowed to only verbal, written or telephone self-expression or self-help without any structured program.

3. Studies where the articles did not provide sufficient data to calculate effect sizes or where measurements of cortisol were not explicitly presented in mean and standard deviation (SD) numbers, or if studies had overlapping information.

Data extraction and synthesis

We prepared beforehand a coding manual to independently mark selected trials according to the inclusion criteria. Two authors (EC and MG-B) have extracted data according to this checklist including various categories related to the following characteristics: (1) study: first author's name, year of publication, country of the study; (2) study subjects: total number of participants, intervention and control group number of persons, mean age, gender, ethnicity, BC stage, recurrence or metastasis if occurred; (3) intervention: intervention design, random or non-random allocation, blinding of investigators, blinding of subjects, sample size, intervention and control type description, group or individual, duration and frequency of treatment, timing of intervention after resection surgery, patient involvement, post-surgery or post-treatment timing, follow up after intervention; (4) outcome variables: measuring techniques, continuous data from assessment of immune or neuroendocrine variables (primarily salivary and plasma cortisol), applied psychological variables, withdrawals, preintervention check of equality of the groups, differences found or not found in target population prior to the intervention, to be included or no in the final list. The manual was revised for discrepancies during the coding to incorporate important aspects of the located studies. We also extracted quantitative data to calculate effect sizes. After the process of selection of studies to be included in meta-analysis, a final list of variables was produced. This list covered baseline cortisol measurements (mean and SD) and end point cortisol measurements (mean and SD) for both intervention and control groups. Where there were multiple assessment time points, we chose post-intervention data collection. We also assessed methodological quality of included studies.

Risk of bias assessment

The quality of studies was performed by two authors (EC and MB) using methodology tool RoB2 of Cochrane Risk of Bias assessment (Higgins et al., 2022). The studies were labeled according to the outcome measure: salivary or serum cortisol. Assessment was executed for all five domains: (1) risk of bias arising from randomization process, (2) effect of assignment to intervention, (3) missing outcome data, (4) measurements of the outcome variables, (5) selection of the reported results and overall risk of bias. The studies were marked to have low risk, high risk of bias or to have some concerns (where the information was not available or unclear). The consensus of both evaluators was reached unanimously.

Statistical considerations

To evaluate the change in cortisol levels produced by the psychosocial intervention in each study, the mean difference in cortisol levels at baseline and at the end of the intervention and the SD of this difference were calculated. In the control group of each study the mean differences and SDs were also evaluated. To estimate the effect of each intervention on changes in cortisol levels vs. the control group, we used Cohen's d (d) and its 95% confidence interval (CI) as a measure of effect size. A $|d|$ value of 0.80 or higher was considered to represent a large effect size. These effects were considered as statistically significant if the CI did not include zero.

To assess heterogeneity across studies we examined forest plots and used Cochrane's Q test and I^2 statistics. $I^2 > 75\%$ was considered to present high degree of heterogeneity. In the cases of high heterogeneity, random effect models (DerSimonian and Laird method) were used. Potential publication bias was assessed through visual inspection of funnel plot and by Egger's and Begg's tests.

A p-curve analysis for a set of reported data was performed to observe distribution of statistically significant p-values ($p \leq 0.05$). All statistical analyses were performed with Stata version 17.0 (Stata Corp). All statistical tests were two-sided, i and p-value <0.05 was considered statistically significant.

Results

Search process

A preliminary search of eight databases identified 2.021 studies [(Pubmed/Medline ($n = 507$), Scopus ($n = 156$), WOS ($n = 33$), PsychInfo ($n = 17$), Google Scholar ($n = 696$), Cochrane ($n = 389$), Ovid ($n = 192$), Science Direct ($n = 31$)]. We have reached the search results of 417 articles through relevant filtering of each database, preliminary screening of the article titles, and identifying additional 27 records through other sources (examining references of certain narrative reviews). We also extracted any duplicates. Upon abstract screening, we removed 274 articles, thus reviewing full text of 143 articles. We further excluded 77 studies because they were not intervention studies (but narrative or systematic reviews) and only focused on 69 records presenting experimental or observational studies.

As a result, 36 articles met inclusion criteria and were selected for the preliminary qualitative analysis (that explored effects of psychosocial interventions with neuroendocrine and immune mediators as primary or secondary outcome). Other articles were excluded because they measured primarily survival or other parameters as an outcome of intervention effect which is outside of the scope of this research. We further classified these articles into three larger groups according to the immune or neuroendocrine biomarkers as an outcome: cortisol, lymphocytes, and pro-inflammatory cytokines in order not to lose the cortisol values if cortisol was not the primary or sole outcome of the study. Since the current paper is based on cortisol (both salivary and plasma), 16 reports were pre-selected into this category (Davis, 1986; Gruber et al., 1993; Schedlowski, 1994; van der Pompe et al., 1997; Cruess et al., 2000; Chan et al., 2006; Nunes et al., 2007; Witek-Janusek et al., 2008; Antoni et al., 2009; Matchim et al., 2011;

Phillips et al., 2011; Baker et al., 2012; Hsiao et al., 2012; Dodds et al., 2015; Webster et al., 2016; Lengacher et al., 2019). When published articles did not present sufficient data to calculate the effect size, we contacted authors for the required information. However, for the remaining seven articles, the authors either did not respond or were unable to provide essential data (Davis, 1986; Gruber et al., 1993; van der Pompe et al., 1997; Nunes et al., 2007; Witek-Janusek et al., 2008; Antoni et al., 2009; Webster et al., 2016; Lengacher et al., 2019), except one study of Baker et al. (2012), where we obtained additional information.

Therefore, only eight studies exhibited sufficient data to calculate effect size and additional data that included pre- and all postintervention means, SDs, and sample sizes for each treatment arm. Thus, eight unique trials (Schedlowski, 1994; Cruess et al., 2000; Chan et al., 2006; Matchim et al., 2011; Phillips et al., 2011; Baker et al., 2012; Hsiao et al., 2012; Dodds et al., 2015) that included a total of 366 participants with BC types (stages 0-IV) who had been randomly and non-randomly assigned to treatment groups were included in the meta-analysis for effect size computing and calculation of intervention vs. control data comparison. The flow chart of our search strategy according to PRISMA methodology is presented in Figure 1.

Study characteristics

All included articles aimed to compare psychophysiological effects of different psychosocial interventions vs. no intervention (control group) or waiting list group in BC patients. Four studies were executed in the US (Cruess et al., 2000; Matchim et al., 2011; Phillips et al., 2011; Dodds et al., 2015), two studies originated from Hong Kong, China (Chan et al., 2006; Hsiao et al., 2012), one from Germany (Schedlowski, 1994) and one from UK (Baker et al., 2012). A total sample ($N = 366$) of patients across all eight studies who were diagnosed with primary BC (stages 0-IV), with mean age ranging from 45.6 to 61.5 was included in our research analysis. Subjects were undergoing chemotherapy, radiation therapy and/or hormone therapy or were prior to proceeding to adjuvant therapy process. The population was rather homogeneous, no significant difference in demographic, disease and medical treatment variables were found at baseline.

Interventions were: (1) Haven integrated support program including psychological support, information, and a range of complementary therapies specifically designed to support the physical and emotional needs of patients with BC before, during and after standard medical treatment (therapy consultation, nutrition, counseling, touch therapies, herbal medicine, homeopathy, acupuncture, yoga, meditation, Qigong) (Baker et al., 2012); (2) Body Mind Spirit (BMS) integrated group therapy based on Chan's "Cancer Fighter" training manual consisting of concepts of positive psychology and forgiveness therapy, social support, purpose of meaning of life, developing equability in the mind and body, positive psychology on self-acceptance, autonomy, environmental mastery, personal growth, a sense of purpose in life (Hsiao et al., 2012); (3) Meditation-based program called Cognitively-Based Compassion Training (CBCT) consisting of meditative concentration, non-judgmental awareness of thoughts, self-compassion, stress reactivity, appreciation and gratitude, empathy and compassion practices, aspiration for happiness (Dodds et al., 2015); (4) Cognitive-Behavioral Stress Management (CBSM) consisting of stress management techniques (cognitive restructuring, coping skills training, assertiveness, anger management, and social support utilization skills) and relaxation training components (e.g., progressive muscle relaxation, meditation, abdominal breathing, and guided imagery) – same structured intervention applied in studies of Cruess (Cruess et al., 2000) and Phillips (Phillips et al., 2011); (5) Intervention aimed at improving immune functions by behavioral therapy consisting of relaxation techniques, information about the "body-network", health education, development and enhancement of stress- or illness-related coping skills (Schedlowski, 1994); (6) Mindfulness Based Stress Reduction (MBSR) consisting of guided awareness of bodily sensations, relaxation and breathing techniques, guided and mindfulness meditation practices, visualization and imagery techniques, gentle yoga (Matchim et al., 2011). For the study of Chan et al. (2006), we decided to take into consideration for meta-analysis only two intervention arms out of three due to having a structure and training manual backing the content of intervention: (7) Body-Mind-Spirit intervention (BMS) designed around four major themes related to normalization of traumatic experiences; "letting-go" of attachments; forgiveness and self-love and stabilization of long-term efforts to change through social support and commitment to help others. Further, (8) Supportive-Expressive (SE) subgroup designed around seven themes major part of which was dealing with fears and emotions and building relationships with family, friends. The third intervention [The Social Support Self-Help (SS)] of the study of Chan et al. (2006) was exempt because it did not include any structured program.

The studies measured both psychological variables and either different immune neuroendocrine parameters: lymphocytes (Schedlowski, 1994), NK Cells and PBMC Arginase (Baker et al., 2012), and cortisol or only cortisol (either salivary or plasma).

In all studies where salivary cortisol has been measured, several measurements have been made throughout the day. In the study of Hsiao et al. (2012), 6 daily measurements were performed (at wake-up time, 30 min after waking up, 45 min after waking up, at 12:00 h, at 17:00 h and at 21:00h); in the study of Chan et al. (2006), 5 measurements were taken (at wake-up time, 45 min after waking up, at 12:00 h, at 17:00 h and at 21:00 h); in the study of Baker et al. (2012), 3 measurements took place (at 8:00 h, at 14:00 h and at 20:00 h). Only in two studies 2 measurements of saliva were performed: in the study Dodds et al. (2015) (morning and afternoon) and in the study of Matchim et al. (2011) (at wake-up time and at 16:00 h).

In the studies where blood cortisol was measured (Schedlowski, 1994; Cruess et al., 2000; Phillips et al., 2011) the sample was withdrawn once per day at the same or nearly the same time: in the study of Cruess et al. (2000) blood was taken at 18:00 h, in the study of Phillips et al. (2011)- between 16:00 h and 18:30 h and in the study of Schedlowski (1994) - at 18:00 h (at baseline) and 20:00 h (post intervention).

For the studies with salivary cortisol, the log-transformed concentration, mean total level of daily (area under the curve, AUC) and the diurnal slope were examined. Cortisol (along with other parameters) was measured at baseline, after intervention and at

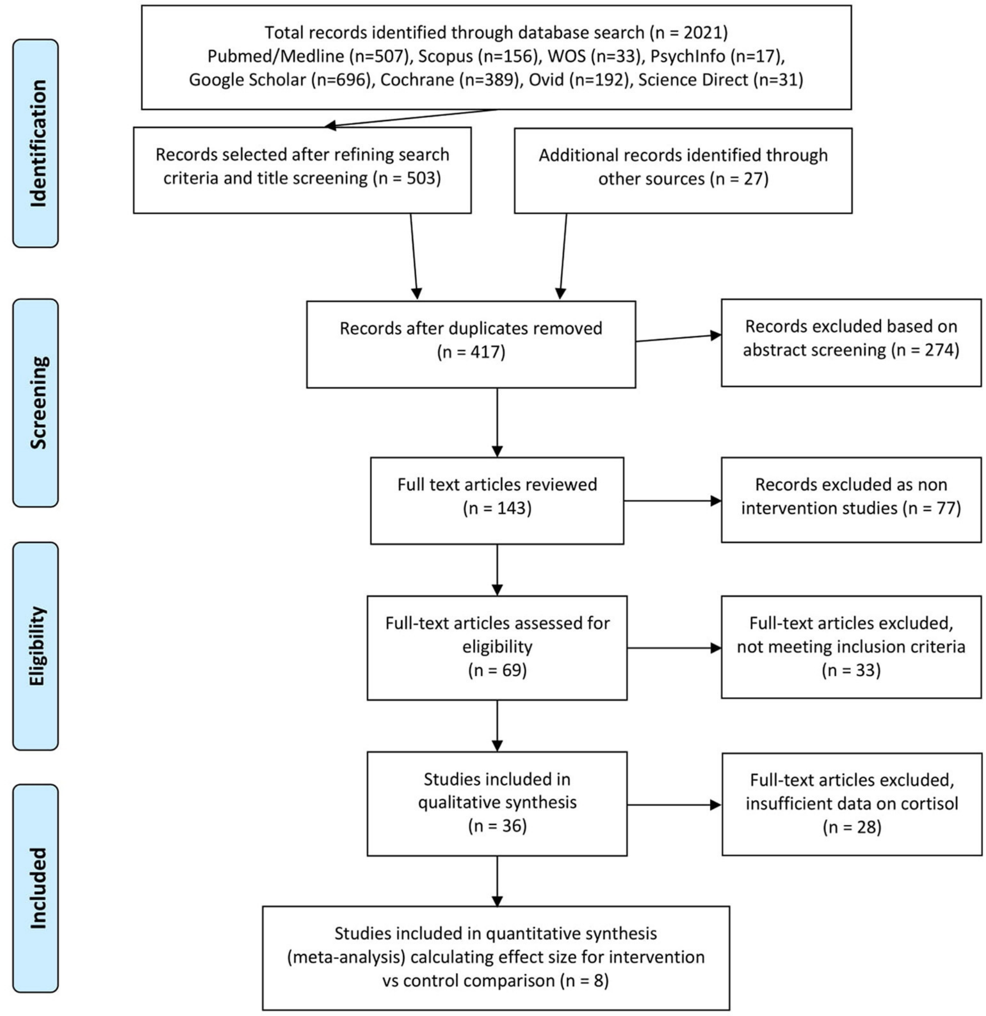


FIGURE 1
Literature selection PRISMA flow chart.

follow up period. Duration of the intervention ranged from 8 weeks to 4 months, follow up reached up to 6 months (Baker et al., 2012) and 12 months (Phillips et al., 2011). All main characteristics of the studies are summarized in Table 1.

Data quantitative synthesis of salivary and plasma cortisol

We conducted random effects meta analyses where data could be pooled for eight studies, dividing them into two subgroups: six studies for salivary cortisol including both BMS and SE intervention arms of the study of Chan et al. (2006), and the studies of Matchim et al. (2011), Baker et al. (2012), Hsiao et al. (2012), Dodds et al. (2015) into one subgroup and the three studies for plasma cortisol (Schedlowski, 1994; Cruess et al., 2000; Phillips et al., 2011) into second subgroup. The results of meta-analyses are presented in Figures 2, 3.

Across the total studies examining association of psychosocial interventions on serum cortisol (Figure 2), we have found a Cohen's $d = -1.82$ (95% CI: -3.03, -0.60) as statistically significant. The forest plot for blood cortisol showed little visual evidence of heterogeneity, even though quantitative analysis presented high heterogeneity of $I^2 = 86.28\%$, $p < 0.001$. For the studies examining association of interventions on salivary cortisol, the effect size was not significant: $d = -1.22$ (95% CI: -2.57, 0.12) and heterogeneity of these studies examining salivary cortisol was high ($I^2 = 92.67\%$, $p < 0.001$), both traceable visually and quantitively. The intervention arm (SE) of the study of Chan et al. (2006) was falling to the right of the line 0 in forest plot and the study of Dodds et al. (2015) showed a very small effect size $d = -0.08$ (95% CI: -0.86, 0.71) seen on Figure 2.

Authors of Dodds et al. (2015) explained that their intervention consisted of presential classes and "at home" practice, where the adherence to was highly warranted. In the follow up analysis of the home practice, the severity and psychological distress scales of the fear of cancer recurrence demonstrated inverse correlation. All these factors might have accounted for the waning of the effect of overall intervention.

TABLE 1 Characteristics of included studies.

Study	Design	Country	BC stage	Mean age ± SD		Sample		Intervention type		Outcome measures	Cortisol	Measurement timepoint	Time of cortisol measures	Interv, length
				Experimental group	Control group	Experimental group	Control group	Experimental group	Control group					
Baker et al. (2012)	RCT pilot	UK	0-III	52.3 ± 11.3	53.3 ± 6.4	$n = 6$	$n = 6$	Haven psychological support program including complementary therapies for BC patients	Standard medical treatment alone	Psychosocial, immune, endocrine	Salivary	Baseline, 3 m, 6 m	AM, PM	4 m
Chan et al. (2006)	RCT	Hong Kong (China)	I-III	49.52 ± 6.94 (BMS) 46.88 ± 8.79 (SE) 50.3 ± 8.40 (SS)	47.47 ± 9.81	$n = 27$ (BMS) $n = 16$ (SE) $n = 16$ (SS)	$n = 17$	BMS (body mind spirit group), SE (supportive expressive therapy group), SS (social support self-help group)	Participants were given educational materials about nutrition, diet, body care after chemo-radiotherapy, edema	Psychological, physiological	Salivary	Baseline, 4 m, 8 m	AM, PM	8 m
Cruess et al. (2000)	Randomized waitlist control trial	Florida (US)	I-III	45.65 ± 7.61	45.65 ± 7.61	$n = 24$	$n = 10$	CBSM (cognitive behavioral stress management) therapy and relaxation techniques	Waitlist Controls	Cortisol, Benefit finding, Distress	Serum	Baseline, 10w	PM	10 w
Dodds et al. (2015)	Randomized waitlist control trial	Arizona (US)	I-IV	54.7 ± 12.1	55.8 ± 9.7	$n = 12$	$n = 16$	CBCT (cognitively based compassion training)	Waitlist Controls	Behavioral, psychosocial (self-report) and cortisol	Salivary	Baseline, 8 w, 12 w	AM, PM	8 w
Hsiao et al. (2012)	RCT	Hong Kong (China)	I-III	45.8 ± 6.9	46.5 ± 10.2	$n = 26$	$n = 22$	BMS (body mind spirit group) therapy	EDU (1xeducational session on health behaviors and emotional expression)	Beck depression inventory, meaning of life questionnaire, cortisol	Salivary	Baseline, 2 m, 5 m, 8 m	PM	2 m
Phillips et al. (2011)	RCT	Florida (US)	0-III	49.69 ± 7.89	49.69 ± 7.89	$n = 63$	$n = 65$	CBSM (cognitive behavioral stress management)	One day group-based psychoeducation seminar in lecture format on stress management techniques	Stress management skills (MOC2 questionnaire), cortisol	Serum	Baseline, 6 m, 12 m	PM	10 w

(Continued)

TABLE 1 (Continued)

Study	Design	Country	BC stage	Mean age ± SD		Sample		Intervention type		Outcome measures	Cortisol	Measurement timepoint	Time of cortisol measures	Interv. length
				Experimental group	Control group	Experimental group	Control group	Experimental group	Control group					
Schedlowski (1994)	Voluntary allocation control exploratory study, pre-post	Germany	I-III	51.0	50.6	$n = 14$	$n = 10$	Relaxation techniques, "body-network", health education, guided imagery, enhancement of stress and illness related coping skills - twice a week	Controls received the same treatment two days after the second and 10th week intervention group.	Self-report coping questionnaire, lymphocytes, cortisol	Serum	Baseline, pre and post second session, pre and post 10th week	PM	10 w
Matchim et al. (2011)	Quasi experimental, pre-post control	Missouri(US)	0-II	56.87	61.47	$n = 15$	$n = 17$	MBSR (mindfulness based stress reduction) weekly teaching	No MBSR intervention	BP, heart rate. respiratory rate, mood disturbance, symptoms of stress and mindfulness state questionnaires, cortisol	Salivary	Baseline, following intervention and 1m after the program	AM, PM	8 w

In the case of SE intervention arm of Chan et al. (2006) study, the intervention had adverse effect: d = 1.43 (95% CI: 0.66, 2.20). According to the authors, the SE group was perceived by participants as helpful, but no statistically significant changes were observed neither in psychological nor in physiological outcomes (cortisol). Again, the content of the intervention was largely dealing with the fears of death and dying and changes in the body image rather than positive reaffirmations. It was the prime reason for us to consider that this intervention arm did not fit into the semantic scope of other interventions that are subject of this research. Thus, certain psychological variables related to distress caused by fear of cancer recurrence, group small sample size, not equal environment of intervention and social factors might have influenced the outcomes adversely.

At this point we decided to remove the study of Chan et al. (2006) for SE Intervention arm to re-analyze the association of psychosocial interventions on salivary cortisol. In Figure 3 we present the results of this second meta-analysis. The effect size in salivary cortisol has increased to d = −1.73 (95%CI: −2.68, −0.78), and heterogeneity have decreased both visually and quantitatively to $I^2 = 80.22\%$, $p < 0.001$.

Finally, the overall results in Figure 3 (combining psychosocial interventions that are similar yet different and combining salivary and plasma cortisol measurements), reached statistically significant very large effect size of psychosocial interventions on cortisol represented by d = −1.76 (95% CI: −2.46, −1.07) with heterogeneity analysis of $I^2 = 81.25\%$, $p < 0.01$. These results indicate the reduction of cortisol level due to applied psychosocial intervention as compared to control group or waiting list.

We have prioritized the result shown in Figure 3 as final for further discussion to confirm the hypothesis of effectiveness of psychosocial interventions for reducing chronic stress represented in cortisol measures in patients with BC, even though heterogeneity continues to be high ($I^2 = 81.25\%$, $p < 0.001$).

Publication bias and sensitivity analysis

We have tested the possibility of publication bias in the examined literature that was included in the above meta-analysis. For this purpose, we have drawn the funnel plot (Figure 4). Visual inspection of the funnel plot did not show asymmetry in the distribution of the studies, an indication that significant publication bias was unlikely. This was further confirmed by non-significant quantitative values of Egger's ($p = 0.839$) and Begg's ($p = 0.754$) tests.

Risk of bias appraisal

The summary of risk of bias analysis is presented in Figure 5. The randomization process for most of the studies was respected. Only two studies (Schedlowski, 1994; Matchim et al., 2011) did not follow the randomization protocol by offering a voluntary

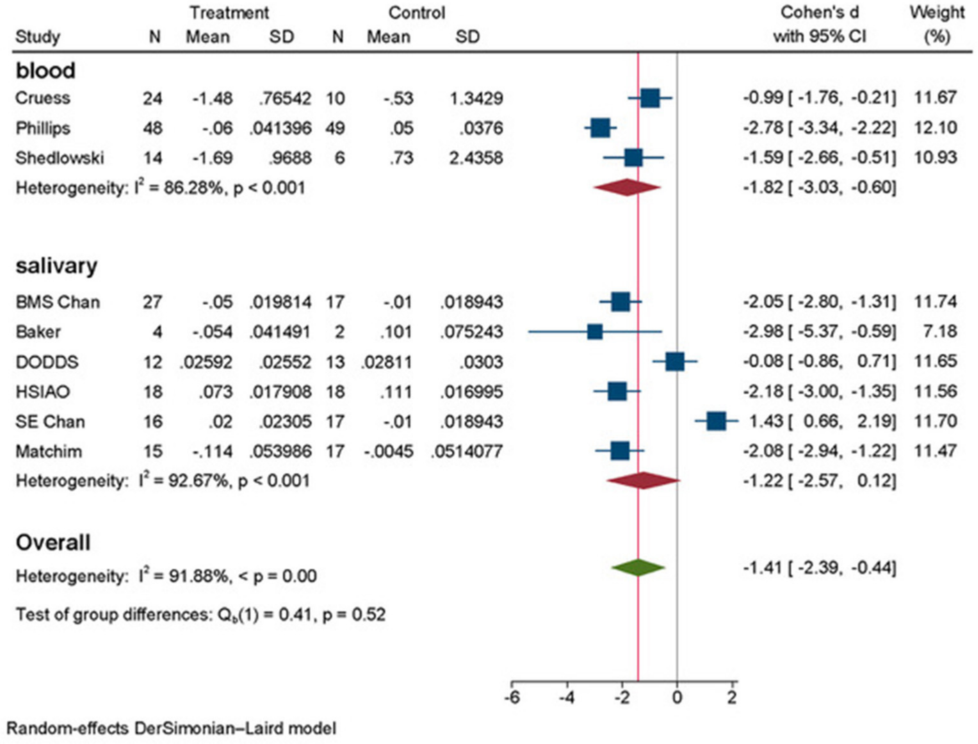


FIGURE 2
Forest plot subgroup analyses total by outcome measurements of cortisol.

participation either in intervention or control group due to ethical considerations. Otherwise, most of the studies present low risk of bias for domain 1. For the second domain, apart from the same two studies (Schedlowski, 1994; Matchim et al., 2011) where the participants were aware of the assigned intervention because of the voluntary participation, plus the study of Phillips et al. (2011) which provided no information on allocation concealment, present some concerns, whereas the rest of the studies are of low risk. For the missing outcome data domain all our studies present low risk since the outcome measures were well exhibited and the overall attrition was <20% (given rather small sample size of the studies and better traceability), except for the study of Dodds et al. (2015) where only 67% of randomized population received follow up. For domain four, most of the studies except four studies (Schedlowski, 1994; Cruess et al., 2000; Matchim et al., 2011; Hsiao et al., 2012) provided information that measurement of the outcome did not differ between groups, thus resulting in low risk. In the last domain, the quality of studies is decreasing; majority of the studies except four studies (Cruess et al., 2000; Chan et al., 2006; Hsiao et al., 2012; Dodds et al., 2015) present high risk due to reporting bias where there were multiple eligible analyses of the data. Finally, the overall risk of bias was determined to be balanced between low and high.

We have performed a p-curve analysis to improve the risk of bias assessment. We have obtained a right-skewed p-curve which is diagnostic of evidential value (Figure 6).

Discussion

The present meta-analysis aimed to test if the effect of certain types of psychosocial interventions on stress reduction can be traced by measuring cortisol in saliva or blood. We have based our research on a narrow niche of specific parameters by using cortisol as a biomarker to measure the effect size of specific psychosocial interventions (that are subject of this study) on chronic stress reduction.

Psychosocial interventions in mental health use non-pharmaceutical means to alter a person’s behaviors and relationships with society, to reduce the impact of the person’s disorder or condition and manage the causal issues better. Interventions associated with psychosocial support fall under two main umbrellas of therapy: cognitive therapy and behavioral therapy, or collectively - cognitive behavioral therapy and its sub-categories.

In our research we determined that the applied interventions within these two major arms providing non-invasive care had overall impact on the BC patients’ level of cortisol. The scope of these interventions included: Mindfulness Based Stress Reduction, Cognitive Behavioral Stress Management, Mind Body Spirit integrated therapy, cognitive restructuring, cognitive based compassion therapy, hypnotic guided imagery program, coping skills development, psychoeducation, supportive expressive therapy, behavioral modification program, spiritual and psychosocial support, various relaxation techniques, biofeedback,

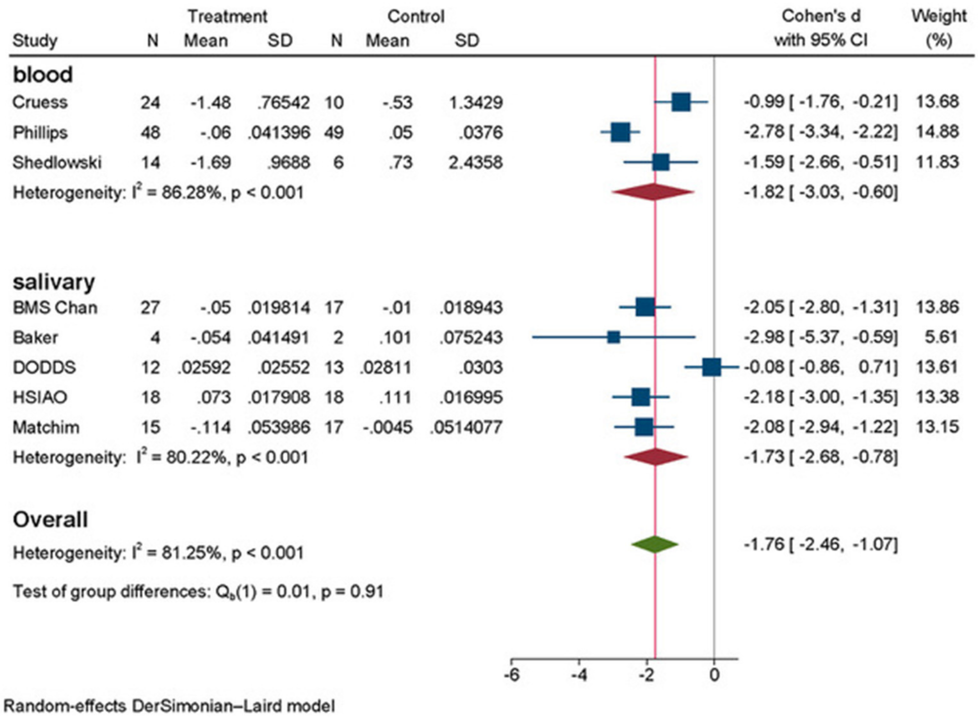


FIGURE 3
Forest plot subgroup analyses final by outcome measurements of cortisol.

complementary medical therapies involving movement in meditation modalities. All these programs emphasized positive aspects and emotionally uplifting assertions or techniques. In the studies measuring salivary cortisol (Matchim et al., 2011; Baker et al., 2012; Hsiao et al., 2012) and BMS Intervention arm of Chan et al. (2006) study the applied interventions decreased the level of cortisol in patients. In the studies of Schedlowski (1994), Cruess et al. (2000), and Phillips et al. (2011) using plasma cortisol measurements, the reduction of cortisol due to intervention was even more noticeable, thus providing stronger evidence of this relationship. These results confirmed our hypothesis that psychosocial support and mental adjustment can decrease stress marker (cortisol) in patients with BC. However, as described in Results section, interventions [study of Dodds et al. (2015) and SE intervention arm of the study of Chan et al. (2006)] that dealt partially or entirely with negativity aspects like fears of recurrence, death, dying, or accentuating distress had no effect or had adverse effect on the level of cortisol in patients with BC.

Studies of Schedlowski (1994), Cruess et al. (2000), and Matchim et al. (2011) provided information that cortisol level can be reduced rather at the intervention completion, thus showing short-term effect. Yet the study of Baker et al. (2012) registered positive results of intervention at 6 months follow up, whereas the studies of Chan et al. (2006), Phillips et al. (2011), Hsiao et al. (2012) have presented that CBSM and BMS interventions strongly predict decreased cortisol levels up to 8 or 12-months follow up respectively. The evidence that intervention is effective in applying stress reducing and relaxation habits after 6 months and plateauing afterwards suggests that there might be a need for maintenance sessions.

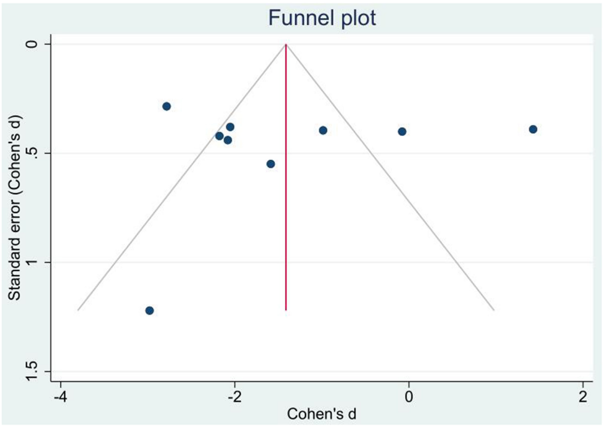
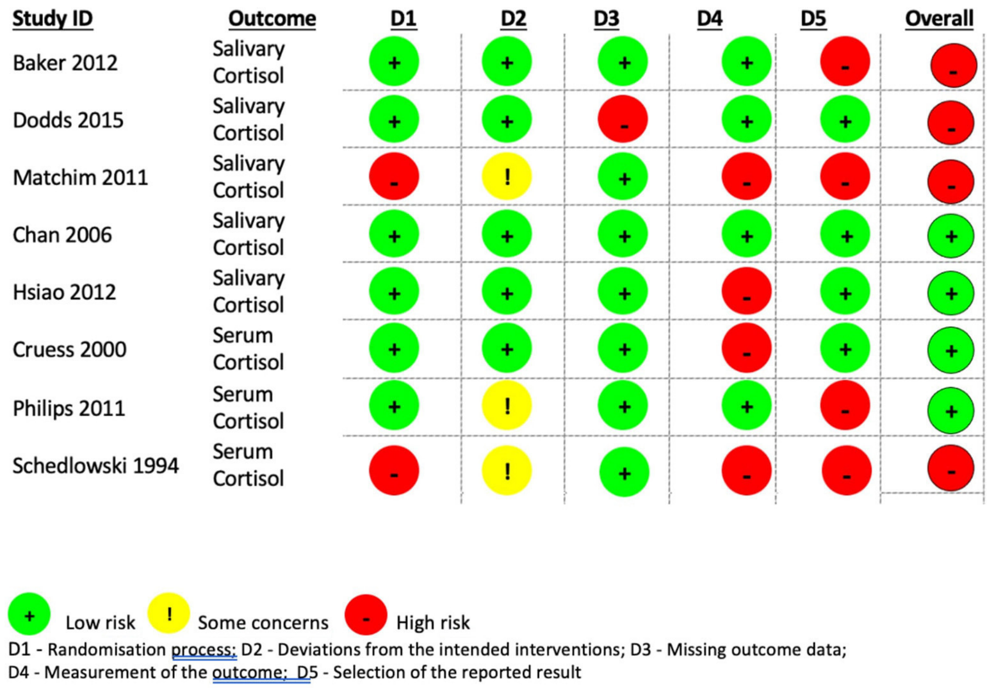


FIGURE 4
Publication bias funnel plot for standard errors and effect sizes of included studies.

According to our knowledge no other meta-analysis has dealt with this specific and comparable biomarker of cortisol for a specific target population and grouping certain types of psychosocial interventions that dealt with determined focus of positive assertion, hope, encouragement, and self-regulation techniques (as opposed to emphasizing fears). The study's limitations conclude small sample size of each study, not following



Study ID	Outcome	D1	D2	D3	D4	D5	Overall
Baker 2012	Salivary Cortisol	+	+	+	+	-	-
Dodds 2015	Salivary Cortisol	+	+	-	+	+	-
Matchim 2011	Salivary Cortisol	-	!	+	-	-	-
Chan 2006	Salivary Cortisol	+	+	+	+	+	+
Hsiao 2012	Salivary Cortisol	+	+	+	-	+	+
Cruess 2000	Serum Cortisol	+	+	+	-	+	+
Philips 2011	Serum Cortisol	+	!	+	+	-	+
Schedlowski 1994	Serum Cortisol	-	!	+	-	-	-

+ Low risk ! Some concerns - High risk
D1 - Randomisation process; D2 - Deviations from the intended interventions; D3 - Missing outcome data;
D4 - Measurement of the outcome; D5 - Selection of the reported result

FIGURE 5
Risk of bias assessment of included studies.

randomization principle in some studies, high risk of bias, some heterogeneity of the groups and quality of support in interventions. Due to small sample size, the source of heterogeneity through sensitivity analysis, meta regression and subgroup analysis was not possible to perform. This implies the necessity of further investigation in this field to be able to provide a solid base for the preventive care. Finally, to optimize patient care through understanding the relationship between the influence of glucocorticoid signaling on cancer biology to be able to implement adequate psychosocial interventions and revert the disease progression will require stronger coordinated efforts between oncologists and psychology researchers.

Our research is supported by previous similar findings that cannot be ignored falling into three main pillars of scientific evidence.

Firstly, exposure to physiological stress has been proposed to increase cancer risk and recurrence (van der Pompe et al., 1997, 2001), however combined effects of stress accompanying psychological depression and disruption of normal social life that seriously impair BC females' quality of life and wellbeing, when demonstrated, have been inconclusive. Certain personality types may enhance or degrade immune response (Oswald et al., 2006). Chronic stress has been associated with suppression of immune function and elevations in inflammatory activity, and there is evidence that the immune system may not adapt over time, while cortisol's immunosuppressive effect might be involved in cancer development, causing further oncogenic mutations (Thornton et al., 2009). Some studies have revealed that abnormal diurnal cortisol rhythms are related to poor prognoses in BC patients (Spiegel et al., 1998; Sephton et al., 2000). Thus, stress, playing a mediating role in immune modulation, might be involved in cancer development (including recurrence), while psychosocial interventions may conversely reduce stress induced suppression of immunity, hence improving cancer survival by buffering the biological effects of stress (Fife et al., 1996).

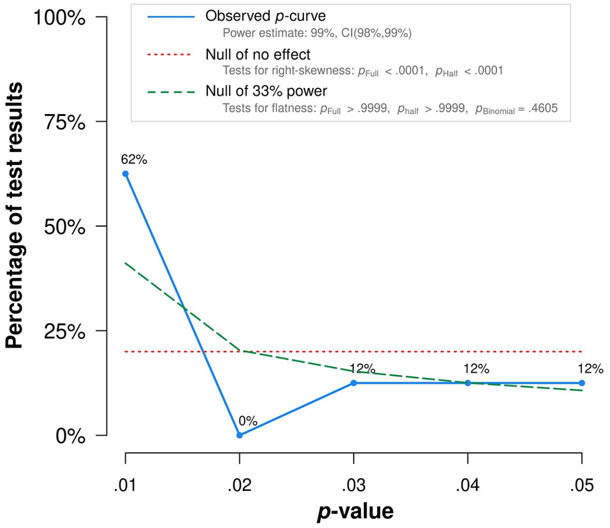


FIGURE 6
p-curve analysis.

Secondly, cortisol is included within inflammatory and immune processes, acting as an anti-inflammatory agent by causing apoptosis through the mitochondrial pathways. It has been extensively used for measuring HPA axis functioning and body's immunity, and can equally demonstrate the link of psychological stimulation, emotions, and physiological changes (both hormonal and immunological). The study of Matousek et al. (2010) indicates, that in conjunction with other biological measurements, the use of cortisol levels as a physiological marker of stress may be useful to validate even self-reported results of attributed intervention. Molecular studies demonstrate a clear overlap between intracellular stress signaling and protumorigenic pathways within breast cells but need to be integrated with other stress-BC research in order to obtain an unambiguous assessment of the potential cause-effect relationship (Antonova et al., 2011). The findings regarding specific pathways of molecular mechanisms and increased glucocorticoid signaling on the immune system and systemic metabolism related to cancer progression are described elsewhere (Volden and Conzen, 2013).

Comprehensive study of cortisol biomarker's variability due to stress modulating psychological interventions might be used as a novel prognostic factor for disease development (progression, recurrence, or recovery). Cortisol is a reliable tool to assess the adrenocortical response, yet easy and non-invasive means to perform a repeated and "non-disturbing" sampling. Salivary cortisol represents the biologically active form of the hormone, and a strong association between levels in blood and saliva has been described in animal studies. Peeters et al. (2011) indicated that total blood cortisol concentrations might account for 80% of salivary cortisol concentrations and vice versa.

A strong basal diurnal rhythm of cortisol exists: it has a tendency to surge in the morning upon waking up, increase 50–60% in the first 30–45 min after awakening, drop rapidly over the first few hours after waking, and then decline more slowly across the day to reach a low point around midnight. Therefore, it requires certain methodological prerequisites in sampling process to avoid confusion factors (circadian variations, age, gender, smoking) (Weibel, 2003). As seen in the results of this study, the temporal variability of salivary cortisol is higher than that in the plasma cortisol added to the overall diurnal tendency of fluctuation, and it is more complicated to assess the accuracy of the measurements. In our research most of the included studies followed rigorous methods in collecting salivary or plasma cortisol (using high sensitivity cortisol enzyme immunoassay or enzyme-linked immune-absorbent assay kit or intra-interassay sensitivity kit) and providing demographic overview of the participants. Also, to control cortisol circadian rhythm in the reviewed studies, several measures have been taken. In our meta-analysis, we have considered the mean cortisol value throughout the day. In this way we tried to control for diurnal changes in cortisol levels. In the studies where blood cortisol was measured, only one cortisol measurement was collected as this procedure is more invasive than the saliva sample. However, in all of them the blood was taken at the same or nearly the same time of the day. This also decreases the effect of variability in blood cortisol levels throughout the day.

Thirdly, past research in PNI has been investigating various sides of this large topic: there are some extensive narrative reviews dedicated to the subject of PNI in general (Mulder et al., 1992; Bauer, 1994; Garssen and Goodkin, 1999; Schleifer, 2007; Wahbeh et al., 2009; Subnis et al., 2014; Jassim et al., 2015; Hulett and Armer, 2016). Further, the effect of psychological and psycho-behavioral interventions on cancer in general and on BC patient's immune function (Tong et al., 2014; Zhang et al., 2016, 2019; Guarino et al., 2020). Finally, the impact of psychosocial interventions on survival time in cancer patients (Chow et al., 2004; Smedslund and Ringdal, 2004; Oh et al., 2016). Some of these published meta-analyses used specific neuroendocrine biomarkers as outcome variable and as predictors for recurrence of BC (Sephton et al., 2000; Tong et al., 2014; Zhang et al., 2016, 2019).

To understand the ambiguity of this large and complex topic, we have further examined that several previous reviews show little or no evidence that psychosocial interventions improve survival time (Jassim et al., 2015) or demonstrate only short-term improvement in survival (Chow et al., 2004). Although there is a considerable evidence of psycho-behavioral interventions' effect on immune indicators, the effect size of meta-analysis of Tong et al. (2014) is modest and the authors highlighted that intervention focus and comparable immune measures should be taken into consideration for future research. Due to heterogeneity in various studied aspects, meta-analysis in some of these reviews was not possible (Mulder et al., 1992; Hulett and Armer, 2016).

Even though the results of the reviews of Tong et al. (2014), Hulett and Armer (2016), and Zhang et al. (2016) are inconclusive, the authors suggest that interventions with mindfulness-breathing-stretching components, cognitive–behavioral therapies or relaxation training appear to offer potential improvement or stabilization of neuroendocrine-immune activity through PNI interactions in patients with cancer compared to control groups. There is growing evidence that psychosocial interventions improve the wellbeing of cancer patients, producing favorable effects on some psychological outcomes, such as anxiety, depression, and mood disturbance. Most of the studies included in the above meta-analyses suffered from small sample size and poor compliance, especially in studies involving patients with advanced disease. Although psychosocial interventions appear to be promising adaptation therapy against many of the psychophysiological impacts of cancer, according to the review of Smedslund and Ringdal (2004) they should be thoroughly defined, focus on a single diagnosis, and consider known risk factors.

If chronic psychological distress is associated with health-relevant behavioral and biological processes in cancer patients, then it is plausible that certain types of psychosocial interventions aimed to reduce distress and promote psychological adaptation could possibly influence health outcomes particularly in BC patients (McGregor and Antoni, 2009). The effect of psychological factors has been more related to cancer progression, recurrence and metastasis rather than cancer initiation (Mulder et al., 1992). The preliminary evidence of mindfulness based, or similar psychosocial supportive care, more convincingly in interventions, shows the reduction of pro-inflammatory cytokine production response in cancer patients that may strengthen coping capacity and improve BC survivorship. Relating stress biology and pro-metastatic molecular processes, clinical researchers are now looking to pioneer further development in research to mitigate adversity of cancer recurrence in part by down-regulating similar pathways (Lutgendorf et al., 2010) and link effects of chronic stress on BC progression (Sloan et al., 2010).

Even though it is still premature to conclude the effectiveness of these interventions among cancer patients, there is a call to acquire evidence of association between interventions that improve emotional wellbeing, quality of life, and objective indicators like survival /mortality/relapse/recurrence and immune responses. The evidence for efficacy of psychosocial interventions in cancer care is unequivocal, however, there is a need for an objective marker of improvement in research evaluating specific psychosocial programs standardizing content, duration, frequency, follow up and measurement methodology. Additional caveats should include analysis of the type, focus and quality of patient's support network and more personalized treatment plan. Further studies of high quality and large sample sizes are required for more solidified conclusions. We continue to explore this domain of PNI of cancer where immune reactions are more sensitive and responsive (yet measurable) to psychological influences aimed at improving overall health outcome. Results of this meta-analysis could be a promising steppingstone to grant evidence-based foundation in routine medical care.

Conclusion

Our study has concluded that certain types of psychosocial interventions reduce cortisol (indicator of chronic stress) in patients with BC. Application of specific psychosocial support as adjuvant non-invasive therapy for affected females with BC at all phases of treatment could contribute to more cost-effective health care.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding authors.

Author contributions

EM, NG-C, and RL-G contributed to conception and design of the study and wrote the first draft of the manuscript. EM-L and MA-S wrote sections of the manuscript. AM organized the database. MG-B performed the statistical analysis. All authors contributed to manuscript revision, read, and approved the submitted version.

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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.

Publisher's note

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Association of psychological distress, smoking and genetic risk with the incidence of lung cancer: a large prospective population-based cohort study

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Background: Emerging evidence suggests a potential link between psychological distress (anxiety and depression) and lung cancer risk, however, it is unclear whether other factors such as tobacco smoking and genetic susceptibility modify the association.

Methods: We included 405,892 UK Biobank participants free of cancer at baseline. Psychological distress was measured using the Patient Health Questionnaire-4 (PHQ-4). A polygenic risk score (PRS) was calculated using 18 lung cancer-associated genetic loci. Multivariable Cox regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results: During a median follow-up of 7.13 years, 1754 lung cancer cases were documented. The higher score of psychological distress was associated with an increased risk of lung cancer ($HR_{per\ 1\text{-}SD}$= 1.07, 95% CI: 1.02-1.11) after adjustment for smoking and other confounders. Mediation analysis revealed that 16.8% (95% CI: 13.0%-20.6%) of the distress-lung cancer association was mediated by smoking. Compared with never smokers with no distress, participants with heavy smoking and high distress had the highest risk of lung cancer (HR=18.57, 95% CI: 14.51-23.76). Both multiplicative and additive interactions were observed between smoking and psychological distress in lung cancer. Furthermore, the greatest relative increase in risk was observed among those with high genetic risk and high distress (HR=1.87, 95%CI: 1.50-

2.33), and there was a significant additive interaction between the PRS and psychological distress.

Conclusion: Our results indicate that psychological distress was associated with an elevated risk of incident lung cancer, and such relation was modified by tobacco smoking and genetic susceptibility.

KEYWORDS

lung cancer, psychological distress, smoking, genetic susceptibility, UK Biobank

Introduction

Lung cancer is the second most common cancer, with an estimated 2.20 million new cancer cases worldwide in 2020, and the leading cause of cancer death (1). Despite improvements being made in diagnostics and treatment strategies in recent decades, the prognosis of lung cancer remains poor, with a 5-year survival of less than 20% (2). Smoking is a well-established risk factor for lung cancer; nevertheless, it is estimated that 10%-15% of all lung cancers are attributed to factors other than tobacco (3, 4). Therefore, it is vital to identify additional modifiable and avoidable risk factors for primary prevention, as well as to identify upstream determinants of smoking.

Psychological distress is generally defined as a state of poor mental health characterized by symptoms of depression and anxiety (5). A series of studies have shown an association between psychological distress and an elevated risk of mortality (6), diabetes (7), cardiovascular disease (8), and cancer (9). Previous studies suggest potential links between psychological distress and lung cancer risk (6, 10–16); however, most of these studies were of relatively small size and reported inconsistent results. In addition, compelling evidence has shown that psychological distress is related to behavioral risk factors of lung cancer (17, 18), notably cigarette smoking. For instance, higher levels of psychological distress are associated with an individual's subsequent smoking habits (18), which further increases the risk of lung cancer. Nevertheless, it is still unclear whether smoking mediates or modifies the association between psychological distress and lung cancer risk.

Additionally, it has been also established that both genetic and behavioral factors may contribute to the development of lung cancer (19, 20). In recent years, emerging evidence has revealed that genetic factors may modify the environment-diseases relation. For example, the previous study has indicated that the association between air pollution exposure and lung cancer could be modified by genetic susceptibility (21). However, investigations on the modification effect of genetic susceptibility on the association between psychological distress and lung cancer risk are scarce. Therefore, the interaction or joint relation between genetic susceptibility and psychological distress in the development of lung cancer still deserves further exploration, which may provide greater insight into lung cancer etiology and prevention strategies.

In this study, we prospectively examined the association between psychological distress and the risk of incident lung cancer based on the UK Biobank cohort, and particularly examined the potential modifying effect of smoking and genetic susceptibility on the association. Specifically, we performed a mediation analysis to assess whether smoking mediated the distress-lung cancer association, and further assessed the joint or interaction effects of smoking and genetic susceptibility with psychological distress in lung cancer risk.

Subjects and methods

Study design and participants

The detailed study design and methods of the UK Biobank have been described elsewhere (22). Briefly, UK Biobank is a large-scale prospective population-based cohort study with over 500,000 volunteers aged 40-69 years recruited in 2006-2010. The information on social demographics, lifestyle and other health-related information was collected through touch-screen questionnaires and physical measurements. Blood samples were collected for genotyping. The UK Biobank has approval from the North West Multi-center Research Ethics Committee. All participants provided written informed consent for the study.

Among the 502,507 participants with available data, we excluded participants with prevalent cancer at recruitment (n=46,533), self-reported gender differed from genetic sex (n=318), missing data on smoking status (n=2,666) and psychological distress (n =47,098), leaving a total of 405,892 participants in the primary analysis. In addition, 394,061 individuals with available genetic information were included in the further genetic analysis. The details of the process for the construction of the analytical cohort are shown in Supplementary Figure 1.

Exposure ascertainment

Psychological distress was measured using the 4-item Patient Health Questionnaire (PHQ-4) (23), which is a brief self-report questionnaire consisting of a 2-item depression scale (PHQ-2) and a

2-item anxiety scale (GAD-2) (24). Responses to each item were either "not at all" (scored 0), "several days" (scored 1), "more than half of the days" (scored 2), or "nearly every day" (scored 3). Therefore, the total score ranges from 0 to 12, with a higher score indicating greater distress. To determine a possible dose-response relationship, participants were divided into four groups based on quartiles of the PHQ-4 score: 0, 1, 2-3, and 4-12.

Assessment of smoking and other covariates

Covariates were selected based on scientific plausibility and prior evidence (10, 25). According to the smoking status from the respondents' self-report, participants were classified into never, former, or current smokers. Pack-years smoking (PY) was calculated based on self-reported information on age at smoking initiation, the number of cigarettes smoked daily, age of smoking cessation (for former smokers) and age at recruitment (for current smokers). Subsequently, we categorized smoking levels as non-smoking (never smokers), light smoking (PY<30), and heavy smoking (PY≥30).

Other covariate data were collected at baseline using standard protocols, including socioeconomic characteristics (age at recruitment, sex, ethnic background, education, Townsend deprivation index and family history of lung cancer), and lifestyle factors (healthy diet score, BMI and physical activity). The healthy diet score was calculated based on the following diet factors: fruits: ≥3 pieces/day; vegetables: ≥ 4 tablespoons/day; fish: ≥ 2 times/week; unprocessed red meat intake ≤ 2 times/week; and processed meat intake ≤ 2 times/week (26). Missing data on covariates were coded as a missing indicator for categorical variables and with sex-specific median values for continuous variables.

Polygenic risk score calculation

Detailed information on the procedure for genotyping, imputation and quality control in the UK Biobank cohort has been previously reported (27). In the present study, we created a polygenic risk score (PRS) for lung cancer using 18 independent single nucleotide polymorphisms (SNPs) based on the largest available lung cancer genome-wide association studies (GWAS) of European descent (Supplementary Table 1) (28). The PRS was calculated using the equation: $PRS = \beta 1 \times SNP1 + \beta 2 \times SNP2 + \ldots + \beta n \times SNPn$. Individual SNP was recoded as 0, 1, or 2 according to the number of risk alleles, and the effect size (β-coefficient) for each SNP was obtained from the GWAS data. According to PRS, we classified participants into three groups of low (lowest tertile), intermediate (second tertile) and high (highest tertile) genetic risk of lung cancer.

Outcome ascertainment

In UK Biobank study, cancer cases were identified through linkage to national cancer registries in England, Wales, and Scotland. The complete follow-up date was March 31, 2016 for England and Wales, and October 31, 2015 for Scotland. We defined lung cancer outcome according to the 10th Revision of the International Classification of Diseases (ICD-10): C33 and C34. Participants were followed-up until the date of the diagnosis of lung cancer, death, loss to follow-up, or censoring date (March 31, 2017, for England; October 31, 2016, for Scotland; and February 29, 2016, for Wales), whichever came first.

Statistical analysis

Cox proportional hazards model was used to estimate the hazard ratio (HR) and corresponding 95% confidence intervals (CIs). Follow-up time was treated as the time scale. The proportional hazards assumption was tested using Schoenfeld residuals. Psychological distress was tested as a categorical variable split into quartiles and as a continuous variable (per 1-standard deviation (19) increment), respectively. The first model was adjusted for age at recruitment (continuous), sex, ethnic background (white, non-white), education (college or university degree, no degree), Townsend deprivation index (quintiles) and family history of lung cancer (no, yes). A second model further adjusted for smoking, including smoking status (never, former, current) and pack-years of smoking (continuous). In the third model, other factors include healthy diet score (continuous), BMI (kg/m2, <25, 25-29.9, ≥30), and physical activity (MET-h/week, <10, 10-50, ≥50) were added to the first model. Lastly, the fourth model contained all the covariates mentioned above. For the genetic analyses, we further adjusted for the first ten genetic principal components and the genotyping array.

Psychological distress was also significantly associated with smoking, the most important risk factor of lung cancer. Thus, psychological distress could probably influence lung cancer risk by increasing smoking amount. To further clarify the causal path of psychological distress on lung cancer risk, the causal mediation analysis was implemented within a Cox proportional hazard framework to assess mediation by pack-years of smoking on the distress-lung cancer association. With these models, we estimated the direct effect of continuous psychological distress and the indirect effect mediated through continuous pack-years. The mediation analysis was performed using the R packages of "regmedint", based on the product method proposed by Valeri and Vanderweele (29, 30). In addition, we also evaluated whether the association between psychological distress and lung cancer risk differed by smoking level or PRS by using multiplicative and additive interaction analyses. To quantify multiplicative interactions, we added an interaction term in the Cox proportional hazards regression models. In order to evaluate the interaction effect of smoking and psychological distress, we put the multiplication term of smoking and psychological distress in the model as the interaction term. In the model evaluating the interaction effect of PRS and psychological distress, we put the multiplication term of PRS and psychological distress as the interaction term. Relative excess risk due to interaction (RERI) and the attributable proportion because of the interaction (AP) was used to measure the interaction on the additive scale (31). The 95% CIs of the RERI and AP would not include 0 if there was additive interaction (32).

To assess the robustness of the results, we conducted several sensitivity analyses: (1) excluding participants who with less than two years of follow-up; (2) reclassified smoking levels based on 20 pack-years of smoking (none: never smoker, light: PY<20, and heavy: PY ≥20) (33); (3) genetic analysis only included participants of European descent. All analyses were performed using R Software (version 3.6.0), and a two-sided P-value <0.05 was considered to be statistically significant.

Results

Population characteristics

During a median of follow-up time 7.1 years (IQR 6.4-7.7 years), 1754 incident lung cancer cases were recorded. Table 1 reports the baseline characteristics of the participants according to psychological distress categories. Participants with higher levels of psychological distress were more likely to be slightly younger, female, less educated, and more deprived. In addition, they were more likely to have adverse lifestyle factors (smoking, obesity, physical inactivity and unhealthy diet).

Association between psychological distress and risk of incident lung cancer

The higher score of psychological distress was associated with an increased risk of incident lung cancer in a dose-response fashion (Table 2 and Supplementary Figure 2). In primary models, psychological distress was significantly associated with a higher risk of incident lung cancer ($HR_{per\ 1\text{-}SD}$= 1.21, 95% CI: 1.16-1.26). However, after further adjustment for smoking status and pack-years of smoking, the relationship was substantially attenuated

TABLE 1 Baseline characteristics of UK biobank participants according to psychological distress categories.

Characteristic	Quartile categories of psychological distress			
	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Participants (No.)	161087	97984	83843	62978
Age at baseline (years), mean (SD)	57.63 (7.81)	56.13 (8.11)	55.1 (8.16)	54.09 (7.94)
Female, n (%)	76741 (47.64)	54841 (55.97)	46721 (55.72)	36475 (57.92)
White ethnic background, n (%)	154278 (95.77)	94483 (96.43)	79177 (94.43)	57161 (90.76)
College or university degree, n (%)	54599 (33.89)	35415 (36.14)	29791 (35.53)	17424 (27.67)
Townsend deprivation index, mean (SD)	-1.70 (2.87)	-1.55 (2.91)	-1.24 (3.09)	-0.45 (3.42)
Family history of lung cancer, n (%)	19120 (11.87)	11758 (12.00)	10160 (12.12)	8378 (13.30)
Smoking status, n (%)				
Never smoker	91867 (57.03)	54685 (55.81)	45463 (54.22)	31667 (50.28)
Former smoker	56281 (34.94)	34311 (35.02)	29069 (34.67)	20227 (32.12)
Current smoker	12939 (8.03)	8988 (9.17)	9311 (11.11)	11084 (17.60)
Pack-years of smoking, mean (SD)	8.87 (13.86)	9.14 (14.25)	9.82 (15.00)	12.08 (17.67)
BMI (kg/m^2), mean (SD)				
Normal (<25 kg/m^2)	55409 (34.40)	32607 (33.28)	27681 (33.02)	18324 (29.10)
Overweight (25-<30 kg/m^2)	72921 (45.27)	41648 (42.50)	35035 (41.79)	24819 (39.41)
Obese (≥30 kg/m^2)	32757 (20.33)	23729 (24.22)	21127 (25.20)	19835 (31.50)
Physical activity, n (%)				
Low (<10 MET-h/week)	19667 (12.21)	15305 (15.62)	14113 (16.83)	13000 (20.64)
Moderate (10-<50 MET-h/week)	94733 (58.81)	59099 (60.31)	50025 (59.67)	36613 (58.14)
High (≥50 MET-h/week)	46687 (28.98)	23580 (24.07)	19705 (23.50)	13365 (21.22)
Healthy diet score, n (%)				
0-1	17190 (10.67)	11485 (11.72)	10810 (12.89)	9655 (15.33)
2-3	76149 (47.27)	48188 (49.18)	41689 (49.72)	32362 (51.39)
4-5	67748 (42.06)	38311 (39.10)	31344 (37.38)	20961 (33.28)

BMI, body mass index; MET, metabolic equivalent.

TABLE 2 Associations between psychological distress and the risk of lung cancer.

	No. cases/Person years	Model 1: Sociodemographic factors [a]		Model 2: Model 1 + smoking [b]		Model 3: Model 1 + other factors [c]		Model 4: All covariates [d]	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Distress categories									
Quartile 1	622/1139612	1.00 (ref)		1.00 (ref)		1.00 (ref)		1.00 (ref)	
Quartile 2	397/693101	1.20 (1.06-1.36)	4.28×10^{-3}	1.10 (0.97-1.25)	0.139	1.18 (1.04-1.34)	0.010	1.10 (0.97-1.24)	0.158
Quartile 3	368/593621	1.38 (1.21-1.57)	1.48×10^{-6}	1.19 (1.05-1.36)	7.81×10^{-3}	1.34 (1.17-1.52)	1.28×10^{-5}	1.18 (1.04-1.35)	0.011
Quartile 4	367/443704	1.85 (1.62-2.11)	8.59×10^{-20}	1.27 (1.11-1.45)	6.33×10^{-4}	1.76 (1.54-2.01)	1.19×10^{-16}	1.25 (1.09-1.43)	1.35×10^{-3}
***P* value for trend**		1.13×10^{-19}		2.06×10^{-4}		1.61×10^{-16}		4.78×10^{-4}	
Per 1 SD increment [e]		1.21 (1.16-1.26)	2.02×10^{-19}	1.07 (1.03-1.12)	1.26×10^{-3}	1.19 (1.14-1.24)	6.80×10^{-16}	1.07 (1.02-1.11)	2.95×10^{-3}

Defined: HR, hazards ratio; CI, confidence interval.

[a] Model 1: adjusted for age at recruitment, sex, ethnic background, education, Townsend deprivation index, and family history of lung cancer.

[b] Model 2: model1+ smoking status, and pack-years of smoking.

[c] Model 3: model1+ healthy diet score, BMI, and physical activity.

[d] Model 4: all covariates mentioned above.

[e] SD was the standard deviation of scores, which was 2.11.

($HR_{per\ 1\text{-}SD}$= 1.07, 95% CI: 1.03-1.12), and this association did not appreciably alter after further adjustment for other lifestyle factors ($HR_{per\ 1\text{-}SD}$= 1.07, 95% CI: 1.02-1.11) (Table 2). These results suggested that smoking might be an important mediator of the distress-lung cancer association. In the sensitivity analyses, results did not change appreciably after excluding individuals with less than two years of follow-up (Supplementary Table 2).

Similar positive associations were observed in the stratified analyses according to age at recruitment, sex, ethnic background, education, Townsend deprivation index, family history of lung cancer, smoking status, alcohol intake frequency, BMI, physical activity, healthy diet score, and histological subtypes (all $P_{heterogeneity}$>0.05) (Supplementary Table 3). Of the individual psychological distress items, depressed mood (HR=1.08, 95% CI: 1.00-1.15), and tiredness/lethargy (HR=1.10, 95% CI: 1.04-1.16) were positively associated with incident lung cancer (Supplementary Table 4).

Mediation analysis of smoking on association between psychological distress and incident lung cancer risk

The result of the mediation analysis was shown in Figure 1 and Supplementary Table 5. Mediation analysis further confirmed that the association between psychological distress and risk of lung cancer was partly mediated by smoking. Specifically, participants with higher psychological distress were associated with increased smoking (beta=0.55, 95% CI: 0.53-0.58), and there was a significant direct effect of psychological distress on lung risk (HR=1.08, 95% CI: 1.05-1.10). The indirect effect of smoking was also significant (HR=1.02, 95% CI: 1.01-1.02). These findings indicated that 16.8% (95% CI: 13.0%-20.6%) of the total effect of psychological distress on lung cancer risk was mediated by smoking.

Joint effect and interaction of smoking or PRS and psychological distress on incident lung cancer risk

We found that PRS of lung cancer was significantly associated with an increased risk of incident lung cancer ($HR_{per\ 1\text{-}SD}$= 1.20, 95% CI: 1.15-1.26), which did not change with additional adjustment for psychological distress (Supplementary Table 6 and Supplementary Figure 3). We further observed the joint association of the smoking or PRS with psychological distress on the risk of incident lung cancer in a dose-response manner (*P* trend=3.00×10^{-306} for smoking; *P* trend=2.16×10^{-14} for PRS). Compared with never smokers with no distress, those with heavy smoking and high distress had the highest risk of lung cancer (HR=18.57, 95% CI: 14.51-23.76) (Figure 2A). A similar pattern of joint effect was observed for PRS and psychological distress, the greatest relative increase of risk was observed among those with high genetic risk and high distress (HR=1.87, 95%CI: 1.50-2.33) (Figure 2B). Additionally, the positive associations between psychological distress and the risk of lung cancer were also observed in the stratified analyses according to smoking levels or PRS categories (Supplementary Table 7-8). We repeated the analyses by the reclassification of smoking levels or the inclusion of only participants with European ancestry in genetic analysis, and the results were not materially changed (Supplementary Figure 4 A, B).

Table 3 shows the results of the interaction analysis. We observed both multiplicative (*P*=2.90×10^{-8}) and additive

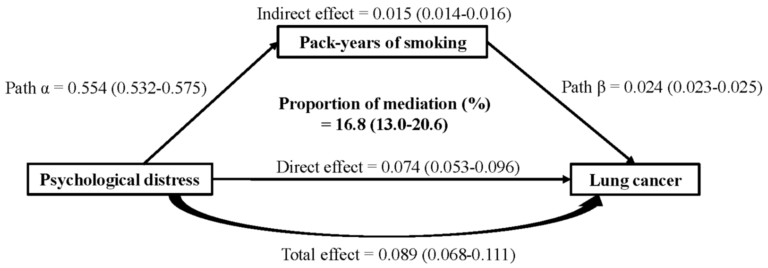


FIGURE 1
Mediating effects of smoking on the association between psychological distress and lung cancer. Coefficients and 95% confidence intervals are presented: "Path α" is the linear regression coefficient of the distress-smoking association, and "Path β" is the cox proportional hazards regression coefficient of the smoking-lung cancer association. Adjusted confounding factors were age at recruitment, sex, ethnic background, education, Townsend deprivation index, family history of lung cancer, healthy diet score, BMI, and physical activity.

interactions between smoking and psychological distress in lung cancer. Specifically, for heavy smokers with high distress, the RERI was 4.05 (95%CI: 0.83- 7.26), which suggested that there would be 4.05 relative excess risk because of the additive interaction, accounting for 22% (95%CI: 7%-36%) of lung cancer risk in participants who had both heavy smoking and high distress. Additionally, there was an additive interaction but not multiplicative (P=0.269) interaction of PRS with psychological distress. For participants with high PRS and high distress, RERI was 0.47 (95%CI: 0.05-0.89), and 25% (95%CI: 4%-46%) of the risk of lung cancer exposed to both risk factors was attributable to the additive interaction. The results remained similar after reclassifying smoking levels and excluding participants of non-European descent in genetic analyses (Supplementary Table 9).

Discussion

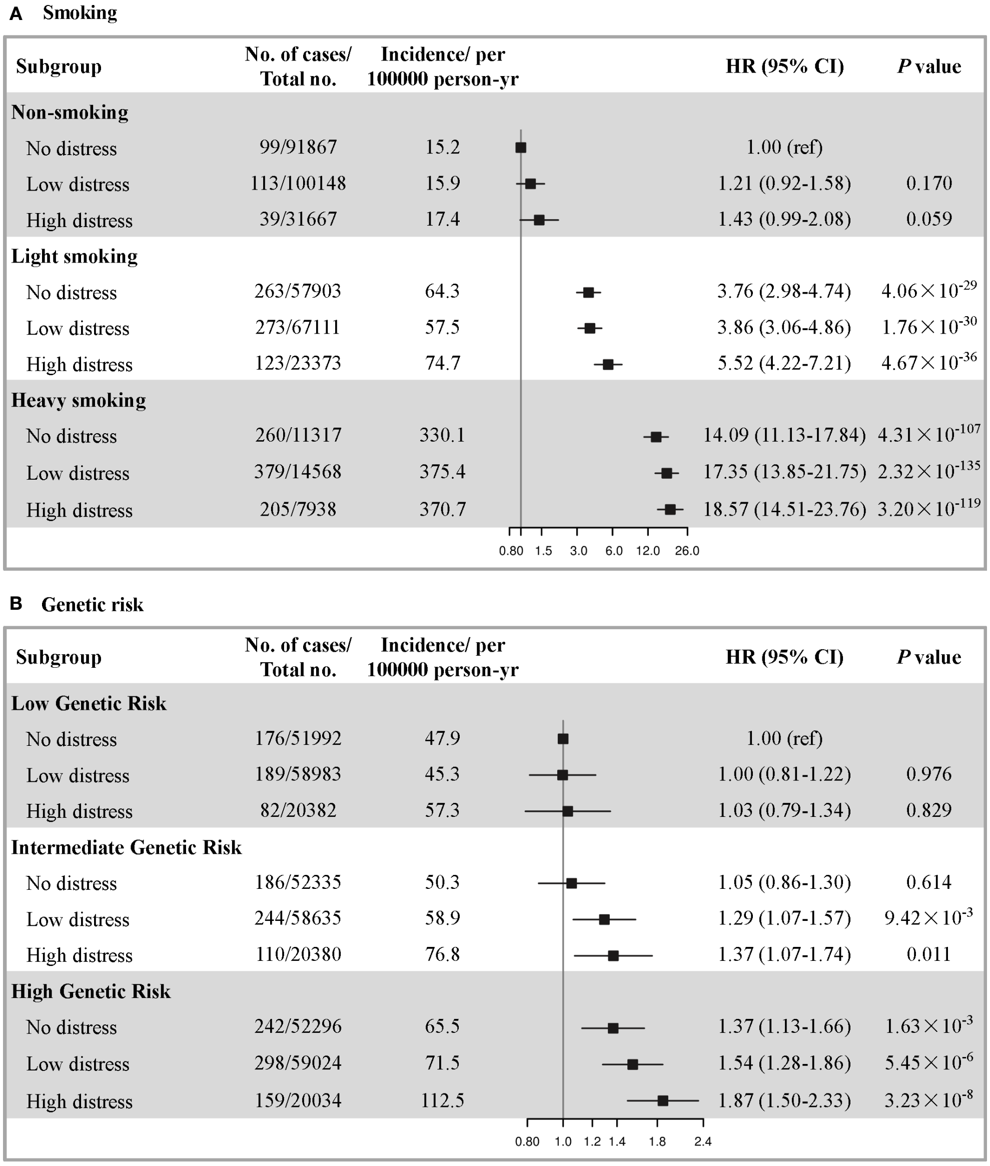
In this large prospective cohort study, we observed that psychological distress was associated with a higher risk of lung cancer, and smoking was not only a mediator but also had a multiplicative and additive interaction with psychological distress in the development of lung cancer. In addition, there was an additive interaction between PRS and psychological distress in lung cancer.

Previous studies have indicated a link between psychological distress and lung cancer risk. A recent meta-analysis of eight prospective cohort studies reported a positive association between psychological distress and risk of lung cancer, yet statistically significant heterogeneity across studies was detected (34). With a relatively large sample size and comprehensive adjustment of confounding factors, we further confirmed the association between psychological distress and incident lung cancer risk. Several underlying biological pathways may explain the relation. Psychological distress could lead to dysfunctional activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal (HPA) axis, which in turn influence endocrine and immune processes (35). The association between elevated levels of inflammatory markers (such as C-reactive protein, interleukin-1 and interleukin-6) and psychological distress have been well documented (36, 37), and these markers are linked with an increased risk of lung cancer (38, 39). Besides, psychological stress has been found to suppress the activity of DNA repair enzymes and natural killer (NK) cells function (40), which may play pivotal roles in the cancer defense process. However, the exact underlying mechanisms linking psychological distress to lung cancer still need to be elucidated by further functional research.

In addition to the above-mentioned associations, our study extends previous work in several ways. First, psychological distress could lead to alterations in behaviors, such as smoking, which may partly explain the association. So, we thoroughly investigated the potential roles of smoking on the distress-lung cancer association and found that smoking played both a mediating role and an interaction effect in the association between psychological distress and lung cancer risk. These findings were consistent with a previous study, which reported that smoking habits accounted for 38% of the association between depressive symptoms and lung cancer incidence (10). Psychological distress is a modifiable risk factor that promotes smoking initiation and interferes with smoking cessation (41, 42), hence, it should be prioritized as an upstream contributor to smoking behavior. Fortunately, recent evidences have showed that getting physical activity and keeping good sleep can relieve stress effectively (43).

Second, to the best of our knowledge, the current study is the first to examine the joint association and interaction of psychological distress and genetic susceptibility with the risk of incident lung cancer. Our findings showed that the positive association of psychological distress with the risk of lung cancer tended to be stronger in participants with higher genetic risk, as well as a significant additive interaction between genetic risk and psychological distress was observed. These results further support the opinion that the development of lung cancer is the result of the interplay between genetic and environmental risk factors, suggesting that individuals at high genetic risk of lung cancer should pay more attention to their mental health.

Several strengths of this study included the large sample size and long length of follow-up, which provides sufficient power to detect potential associations. In addition, the occurrence and development of lung cancer is a complex network, and it is difficult to precisely or effectively assess the true effect if only a



A Smoking

Subgroup	No. of cases/ Total no.	Incidence/ per 100000 person-yr	HR (95% CI)	*P* value
Non-smoking				
No distress	99/91867	15.2	1.00 (ref)	
Low distress	113/100148	15.9	1.21 (0.92-1.58)	0.170
High distress	39/31667	17.4	1.43 (0.99-2.08)	0.059
Light smoking				
No distress	263/57903	64.3	3.76 (2.98-4.74)	4.06×10^{-29}
Low distress	273/67111	57.5	3.86 (3.06-4.86)	1.76×10^{-30}
High distress	123/23373	74.7	5.52 (4.22-7.21)	4.67×10^{-36}
Heavy smoking				
No distress	260/11317	330.1	14.09 (11.13-17.84)	4.31×10^{-107}
Low distress	379/14568	375.4	17.35 (13.85-21.75)	2.32×10^{-135}
High distress	205/7938	370.7	18.57 (14.51-23.76)	3.20×10^{-119}

B Genetic risk

Subgroup	No. of cases/ Total no.	Incidence/ per 100000 person-yr	HR (95% CI)	*P* value
Low Genetic Risk				
No distress	176/51992	47.9	1.00 (ref)	
Low distress	189/58983	45.3	1.00 (0.81-1.22)	0.976
High distress	82/20382	57.3	1.03 (0.79-1.34)	0.829
Intermediate Genetic Risk				
No distress	186/52335	50.3	1.05 (0.86-1.30)	0.614
Low distress	244/58635	58.9	1.29 (1.07-1.57)	9.42×10^{-3}
High distress	110/20380	76.8	1.37 (1.07-1.74)	0.011
High Genetic Risk				
No distress	242/52296	65.5	1.37 (1.13-1.66)	1.63×10^{-3}
Low distress	298/59024	71.5	1.54 (1.28-1.86)	5.45×10^{-6}
High distress	159/20034	112.5	1.87 (1.50-2.33)	3.23×10^{-8}

FIGURE 2

The joint association of **(A)** smoking, **(B)** genetic risk and psychological distress with risk of incident lung cancer. The smoking levels were defined as none (never smoker), light (PY <30) and heavy (PY ≥30). The overall genetic risk was defined as low (lowest tertile), intermediate (second tertile) and high (highest tertile). The psychological distress was defined as none (quartile 1), low (quartiles 2-3) and high (quartile 4). For the smoking, the hazard ratios were estimated using Cox proportional-hazard models with adjustment for age at recruitment, sex, ethnic background, education, Townsend deprivation index, family history of lung cancer, healthy diet score, BMI, and physical activity. For the PRS, another adjusted for smoking status, pack-years of smoking, the first ten principal components of ancestry and genotyping batch.

single factor was considered. Therefore, we thoroughly considered the potential roles of smoking to disentangle its confounding, mediating, and modifying effects on the distress-lung cancer association. Besides, we also considered the joint and interactive effect of genetic susceptibility on the association between psychological distress and lung cancer risk. To assess the robustness of the results, we also performed a series of sensitivity analyses to assess the robustness of our findings.

Nevertheless, we also acknowledged several limitations in this study. First, psychological distress was measured only once at baseline, which was not able to take into account the changes in the distress during the follow-up. Second, as psychological distress was self-reported, measurement errors were inevitable. Third, although we controlled for a series of potential confounders, the possibility of residual confounding from unknown or unmeasured confounding factors still exists. Finally, this cohort included participants who were mostly of European descent; therefore, the generalization of the results to other populations should be interpreted with caution.

In conclusion, this large prospective cohort study demonstrated that psychological distress is associated with an elevated risk of incident lung cancer, which was modestly mediated by smoking.

TABLE 3 Interaction between smoking levels or PRS categories and psychological distress on the risk of incident lung cancer.

	Additive interaction [a]				Multiplicative interaction [a]
	Low distress [b]		High distress [b]		
	RERI (95% CI)	AP (95% CI)	RERI (95% CI)	AP (95% CI)	*P*-value
Smoking [c]					2.90×10^{-8}
Light	-0.11 (-0.83-0.61)	-0.03 (-0.21-0.16)	1.33 (0.15-2.50)	0.24 (0.06-0.42)	
Heavy	3.05 (0.55-5.56)	0.18 (0.05-0.31)	4.05 (0.83-7.26)	0.22 (0.07-0.36)	
PRS [d]					0.269
Intermediate	0.24 (-0.04-0.53)	0.18 (-0.03-0.41)	0.28 (-0.13-0.49)	0.21 (-0.06-0.48)	
High	0.18 (-0.13-0.49)	0.12 (-0.12-0.32)	0.47 (0.05-0.89)	0.25 (0.04-0.46)	

Define: RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; CI, confidence interval; PRS, polygenic risk score.

[a] For the smoking, adjusted for age at recruitment, sex, ethnic background, education, Townsend deprivation index, family history of lung cancer, healthy diet score, BMI, and physical activity. For the PRS, another adjusted for smoking status, pack-years of smoking, the first ten principal components of ancestry and genotyping batch.

[b] Defined by psychological distress: none (quartile 1), low (quartiles 2-3) and high (quartile 4).

[c] Defined by smoking levels: none (never smoker), light (PY <30) and heavy (PY ≥30); the non-smoking and no distress group was the reference categories.

[d] Defined by PRS: low (lowest tertile), intermediate (second tertile) and high (highest tertile); the low PRS and the no distress group was the reference categories.

Moreover, the interaction of smoking-distress and genetic-distress play important roles in the occurrence and development of lung cancer, which reinforce the importance of multi-factor intervention in the prevention of lung cancer. Further studies are needed to confirm our findings.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/Supplementary Material.

Ethics statement

The studies involving human participants were reviewed and approved by REC reference: 21/NW/0157. The patients/participants provided their written informed consent to participate in this study.

Author contributions

HM, WW and JZ conceived and designed the study. JZ, YW and TH conducted the statistical analysis and drafted the initial manuscript. XW, XJ, MJ, ZM, YH, and HW check the accuracy of data and results. LD, MZ and LX critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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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.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fonc.2023.1133668/full#supplementary-material

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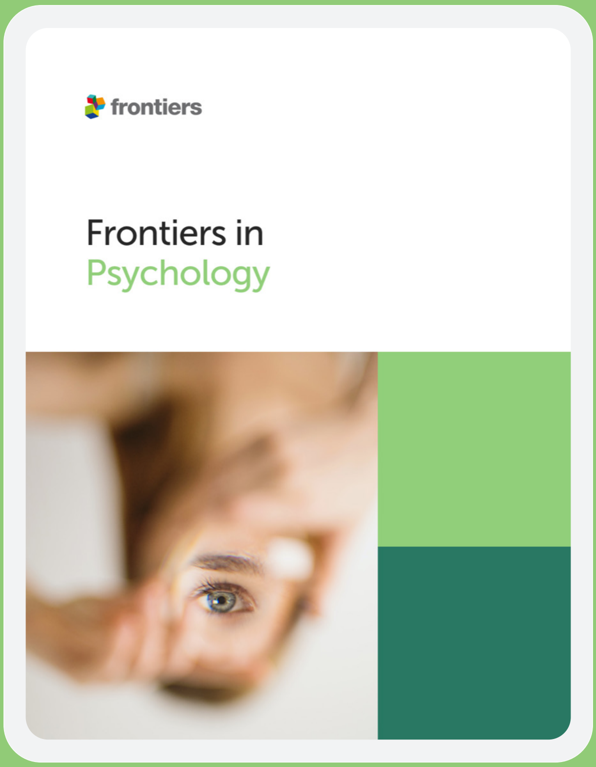
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