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Review article

The relationship between cancer patient's fear of recurrence and chemotherapy: A systematic review and meta-analysis

Yuan Yang[a], Yunhong Wen[b], Carolyn Bedi[c], Gerry Humphris[c,d,*]

[a] Department of Psychiatry and Psychology, Southern Medical University Nanfang Hospital, Guangzhou, Guangdong, China
[b] Institute of Neuroscience, Newcastle University, Newcastle upon Tyne, UK
[c] Edinburgh Cancer Centre, Western General Hospital, Edinburgh, UK
[d] School of Medicine, University of St Andrews, St Andrews, UK

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ABSTRACT

Objective: The study aim was to provide an overview of the current evidence available on the link between chemotherapy (CTX) and fear of cancer recurrence (FoR).
Methods: PubMED, Medline, Embase, PsycINFO and Web of Science databases were searched to identify relevant studies. Two authors independently selected and assessed the studies regarding eligibility criteria. Meta-analysis of suitable studies was conducted, and quality rated.
Results: Forty eligible studies were included in the systematic review and twenty-nine of them were included in further meta-analysis. Meta-analysis of the available data confirmed a weak relationship between CTX and FoR (29 studies, 30,176 patients, overall $r = 0.093$, 95% CI: 0.062, 0.123, $P < 0.001$).
Conclusions: The meta-analysis demonstrates a weak but significant relationship between cancer patient's FoR and the receipt of chemotherapy. However, these results should be interpreted with caution. Further investigation is warranted to explore possible mechanisms of FoR increase in patients who receive chemotherapy. Longitudinal studies assessing the trajectory of FoR during chemotherapy are also warranted.

1. Background

Fear of cancer recurrence (FoR) is often defined as 'fear or worry that the cancer will return or progress in the same place or a different part of the body' [1,2]. However, in August 2015, a consensus on a new definition of FoR was reached by expert researchers, patient advocates, and policy makers, that is, 'fear, worry, or concern relating to the possibility that cancer will come back or progress' [3]. As one of the most common and aversive psychological phenomenon among cancer patients, FoR has received growing attention among researchers. Cancer survivors with high levels of FoR may report negative behaviour change (e.g. avoidance and excessive personal checking behaviours) [4], increased health service use [5], difficulties making plans for the future [6] and excessive psychological distress [1,7,8].

A number of studies have investigated factors that are associated with patient's FoR level. Personal characteristics such as, younger age, and being female were consistently found to be significant predictors of higher FoR [2,9,10]. However, evidence for other demographic variables has been mixed. The association between race, educational level, marital status, employment status, income and FoR was inconsistent [2,9]. With respect to clinical characteristics, time since cancer diagnosis was generally unrelated to patient's FoR level, but evidence for the association between cancer type, disease stage, treatment modality, physical comorbidity and FoR was still conflicted [2,9,10].

There have been several studies focusing on the relationship between patient's FoR and treatment modality, however the findings varied. A previous systematic review by Simard et al. [2] reported a weak to moderate association between treatment type (surgery/chemotherapy/radiotherapy) and FoR, and a recent meta-analysis confirmed a weak but significant relationship between patient's FoR and the receipt of radiation treatment [11]. However, several researchers [12–16] reported heterogeneous results that treatment type was not related to patients' FoR. Moreover, Llewellyn et al. [17] and Custers et al. [18] reported that FoR had no association with any sociodemographic or treatment/clinical variables. Even though many studies have investigated the link between cancer patient's FoR and the receipt of chemotherapy (CTX), they failed to demonstrate conclusive findings. However, as one of the major types of cancer treatment, studies found that patients with CTX are at higher risk of getting psychological problems, such as depression [19] and symptom distress [9]. In addition, study showed that adverse effects caused by CTX can contribute to greater FoR [20].

* Corresponding author at: School of Medicine, Medical and Biological Sciences Building, University of St Andrews, North Haugh, St Andrews, Fife, KY16 9TF, UK.
E-mail address: gmh4@st-andrews.ac.uk (G. Humphris).

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To date, no study focused solely on the possible association between FoR and CTX. Therefore, in this study, we aim to conduct a systematic review and meta-analysis of CTX-FoR-related quantitative studies to explore the relationship between them. We hope by systematically summarizing current evidence, an indication of association between CTX and FoR may be provided. Knowledge of factors associated with FoR may help to better understand the nature of this fear that is of substantial importance for further intervention development. Findings from this study may also help health professionals to identify cancer patients that are at risk for greater FoR.

2. Method

2.1. Literature search

The study was conducted according to the PRISMA guidelines for a systematic review and meta-analysis [21]. Five databases, namely, PubMED, Ovid Medline (1946 to Nov, 2016), Ovid Embase (1974 to Nov, 2016), PsycINFO (1806 to Nov, 2016) and Web of Science were searched. The key search terms were: chemo or chemotherapy, cancer or carcinoma or neoplasm, fear or worry or concern, and recurrence or progression or relapse or return. The search was performed by two authors (YY and YW) using the OR and AND functions. The reference lists of identified review articles, as well as all included studies, were also screened manually for any additional relevant studies. No restrictions were placed on publication date. Search strategy samples are outlined in Supplementary Table 1.

2.2. Inclusion and exclusion criteria

In order to be included in the systematic review, references had to (a) be published in a peer-reviewed journal; (b) be written in English; (c) include patients who had been treated with CTX (with/without other treatments) (d) be quantitative studies and report FoR results. Studies using similar, but not accurate key terms, such as ‘fear of dying’, ‘fear of the worst happening’, ‘fear of the future’, ‘neoadjuvant treatment’ or ‘chemoradiotherapy’ were excluded. In addition, studies were excluded if they were commentaries, reviews, dissertations, brief reports, case studies, conference abstracts, as well as qualitative studies. Studies were screened for eligibility and codetermined by two independent authors (YY and YW). Senior author GH overviewed these procedures.

2.3. Data extraction

The search identified potential eligible studies that were subsequently more extensively screened for suitability. After removing duplicate records, titles and abstracts were reviewed and unsuitable studies were excluded. Then full papers were obtained and examined, and articles that fulfilled the inclusion criteria for the review were included. For each retained study, the following basic information was noted: first author's name, year of publication, country where the study was conducted, study design, sample size, and mean age of the participants. In addition, cancer type, measure of FoR and main findings were also recorded.

2.4. Quality assessment

The quality of each included article was assessed using Standard Quality Assessment Criteria for Quantitative Studies (QualSyst Criteria) [22]. Items were scored on the specific criteria (No = 0, Partial = 1, and Yes = 2). A summary score was calculated for each paper and defined as limited (score of $^{<}0.50$), adequate (0.50–0.70), good (0.70–0.80), or strong ($^{>}0.80$). Any paper of limited quality was excluded. The process was performed by two reviewers independently (YY and YW). In situations of disagreement on the assessment of a paper, the two reviewers repeated their assessment of the study until consensus was achieved. The quality assessment table is shown in Supplementary Table 2.

2.5. Statistical analysis

Upon completion of the systematic review, the programme Comprehensive Meta-analysis was for quantitative studies was employed [23]. The effect size was calculated by applying routines to derive a correlation (r) with accompanying 95% confidence intervals (CI). The effect size was calculated by r but not Hedges' g because several of the included studies [20,24–30] had very large sample sizes ($N > 1000$), and Hedges' g was more suitable for small-sample studies [23]. The corresponding authors of articles with incomplete data were contacted to obtain the required data unavailable in the published article. Studies for which the corresponding authors could not be reached were subsequently excluded from the meta-analysis.

Statistical heterogeneity among the papers was reported using the Q statistic, a P-value < 0.10 or an I-squared value $> 50\%$ was considered as substantial heterogeneity [23]. If substantial heterogeneity was observed, the correlation would be calculated in accordance with the random-effects model, otherwise, the results would be calculated based on the fixed-effects model. The selection of the computational model was based on the understanding of the underlying distribution. Under the fixed-effect model we assumed that the true effect size was the same in all studies, while in the random-effect meta-analysis, we expected the effect size to be similar but not identical across studies. In other words, true effect sizes were assumed to be normally distributed under random-effect model [23].

Subgroup analysis based on the cancer type, year of publication, and length of scale were performed separately. The first analysis aimed to investigate the potential value of cancer type on the association between CTX and FoR. All included studies were labeled as the ‘breast group’, ‘mixed group’, and ‘other cancer group’ respectively because 17 out of 29 (59%) of the included articles focused on breast cancer patients, 8 (28%) articles focused on mixed cancer patients, and the remaining 4 (13%) studies focused on testicular (2 articles), pancreatic (1 article), and head and neck cancer (1 article). The second subgroup analysis based on the year of study was conducted to investigate the possible influence of chemotherapy on fears of cancer recurrence in the course of time. All included articles were categorized into three groups: before 2000s, 2000s, and 2010s. The third analysis based on length of scale was performed to study whether item number of the scales have an influence on the CTX-FoR association. Studies were divided into ‘single item’, ‘short’ (< 5 items) and ‘extensive’. Additionally, Rosenthal's ‘fail safe N’ procedure was adopted to estimate the number of negative studies that would be required to overturn the total aggregated result. Funnel plot and Egger's regression intercept test were also performed in order to assess publication bias.

3. Results

3.1. Characteristics of included studies

The literature search of five databases identified 3387 references. Duplicates were excluded revealing 1156 records. Examination of titles and abstracts for appropriateness left 128 articles. After retrieving full texts and further evaluation, 40 studies were identified and retained. All of them were then assessed using the QualSyst criteria, and none of them had the score of limited quality. Therefore, no study was excluded from the systematic review (quality assessment results are shown in Table 1). However, 11 studies were excluded from further meta-analysis because 10 of them failed to report specific statistic values [12–16,18,31–34], and one study considered chemotherapy as a mediator but not an independent predictor of FoR [35]. Finally, 29 articles were included in the meta-analysis. Flowchart of the search

Table 1
Quality assessment of included studies.

Study	Item 1 Question Describe	Item 2 Study Design	Item 3 Method of subject	Item 4 Subject characteristics	Item 5–7 Intervention/ blinding	Item 8 Outcome/ measure	Item 9 Sample size	Item 10 Analytic methods	Item 11 Estimate of variance	Item 12 Confounding control	Item 13 Result Report	Item 14 Conclusion	Quality
Simard	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Philips	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Deimling[1]	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Deimling[2]	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Koch	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Deimling[3]	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Boehmer	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
McGinty	2	2	2	2	N/A	2	2	2	2	2	2	2	Strong
Mellon	2	2	2	2	N/A	2	2	2	2	2	1	2	Strong
Savard	2	2	2	2	N/A	2	2	2	1	2	2	2	Strong
Van de Wal	2	2	2	2	N/A	2	2	2	2	1	2	2	Strong
Crespi	2	2	2	2	N/A	2	2	2	2	0	2	2	Strong
Fisher	2	2	2	2	N/A	1	2	2	1	2	2	2	Strong
Lebel	2	2	1	2	N/A	2	2	2	2	2	2	1	Strong
Janz[1]	2	2	2	2	N/A	2	2	2	1	1	2	2	Strong
Costanzo	2	2	2	2	N/A	2	1	2	2	1	2	2	Strong
Vickberg	2	2	2	2	N/A	2	2	2	2	0	2	2	Strong
Langeveld	2	2	2	2	N/A	2	2	2	2	1	1	2	Strong
Hartl	2	2	2	2	N/A	2	2	2	2	0	2	2	Strong
Park	2	2	2	1	N/A	2	2	2	2	1	2	2	Strong
Mehnert	2	2	2	2	N/A	2	2	2	2	0	2	1	Strong
Pedersen	2	2	2	2	N/A	1	2	2	1	1	2	2	Strong
Liu	2	2	2	2	N/A	2	2	2	1	0	2	2	Strong
Shay	2	2	2	2	N/A	1	2	2	2	1	1	2	Strong
Skaali	2	2	2	2	N/A	1	2	2	2	0	2	2	Strong
Petzel	2	2	1	2	N/A	2	2	2	2	0	2	2	Strong
Melchior	2	2	2	2	N/A	2	1	2	2	2	1	1	Strong
Stanton	2	2	2	1	N/A	2	1	2	2	2	1	2	Strong
Aghdam	2	2	2	2	N/A	1	2	2	2	1	2	1	Strong
Janz[2]	2	2	2	2	N/A	1	2	2	1	1	1	2	Strong
Tewari	2	2	2	1	N/A	1	2	2	0	2	2	2	Strong
Carver	2	2	2	2	N/A	2	2	1	1	0	2	2	Strong
Rogers	2	2	1	2	N/A	1	2	2	2	0	2	2	Strong
Taylor	2	2	1	2	N/A	1	1	2	2	2	1	2	Strong
FreemanGibb	2	2	2	2	N/A	1	1	2	2	0	1	2	Good
Custers	2	2	1	2	N/A	2	1	2	2	0	1	2	Good
Lasry[1]	2	2	2	1	N/A	2	2	2	1	0	1	2	Good
Leake	2	2	2	2	N/A	1	2	1	0	0	1	2	Adequate
Lasry[2]	2	2	1	1	N/A	2	2	1	0	0	1	2	Adequate
Northouse	2	2	1	2	N/A	2	0	1	2	0	1	1	Adequate

Deimling[1]: Deimling et al. (2008); Deimling[2]: Deimling et al. (2006a); Deimling[3]: Deimling et al. (2006b); Janz[1]: Jan et al. (2011); Janz[2]: Jan et al. (2016); Lasry[1]: Lasry (1992); Lasry[2]: Lasry (1987).

Table 2
Characteristics of included studies.

First author Year, Country	Study design	Cancer type	Sample size analysed	Age Mean (SD)	FoR instruments	Reliability	Main findings
Simard [43], 2009, Canada	Cross-sectional	Mixed	$N = 600$	Breast 59.0 (0.6) Prostate 69.1 (0.5) lung 62.0 (1.5) colorectal 61.6 (1.3)	Fear of Cancer Recurrence Inventory (FCRI) 42-item	Cronbach's alpha = 0.95, test-retest $r = 0.89$	A significantly higher FCR score was found in patients who had received CTX ($r_s(599) = 0.26$, $P < 0.001$)
Janz [26], 2011, USA	Cross-sectional	Breast	$N = 1837$	56.8 (11.4)	Worry about recurrence scale (3-item, range 1–5)	Cronbach's alpha = 0.88	Women who had received chemotherapy reported higher FCR score ($P < 0.001$)
Rogers [41], 2016, UK	Cross-sectional	Head and neck	$N = 513$	65 (range 58–72)	Single Item FoR	Unknown	There was significant association between having had CTX with higher FoR ($P < 0.001$)
Philips [40], 2013, USA	Cross-sectional	Breast	$N = 202$	57 (range 33–82)	Four-item Lerman's Cancer Worry Scale	Unknown	Greater worry was associated with chemotherapy ($r = 0.09$, $P < 0.01$)
Janz [32], 2016, USA	Cross-sectional	Breast	$N = 510$	Unknown	Three-item worry scale	Cronbach's alpha = 0.87	Patients with/without chemotherapy reported similar worry (64(31.3%) vs. 64(27%)), but partners of survivors who received chemo reported greater fear
Freeman-Gibb [31], 2016, Canada	Cross-sectional	Breast	$N = 117$	44–56	Fear of Recurrence Questionnaire (22-item)	Cronbach's alpha = 0.90	Chemotherapy had no significant correlation with FCR
Skaali [29], 2009, Norway	Cross-sectional	Testicular	$N = 1336$	44.8 (10.1)	Single question of FoR	Unknown	Chemotherapy was not associated with FCR (OR = 1.13 (0.78–1.65), P = 0.51)
Koch [27], 2014, Germany	Cross-sectional	Breast	$N = 2671$	65	FoP-Q-SF	Cronbach's alpha = 0.89	Chemotherapy was not related to moderate/high FCR (OR = 1.03 (0.83–1.29))
Lasry [4], 1992, Canada	Cross-sectional	Breast	$N = 123$	Unknown	Fear of Recurrence Index	Internal reliability alpha = 0.88	Patients receiving chemotherapy expressed a greater FCR ($P < 0.02$)
Lasry [38], 1987, Canada	Cross-sectional	Breast	$N = 123$	Unknown	Fear of Recurrence Index	Internal reliability alpha = 0.88	Patients had chemotherapy displayed higher FCR ($P < 0.01$)
Hartl [54], 2003, Germany	Cross-sectional	Breast	$N = 274$	60.0 (11.6)	QLQ-C30-V2.0 questionnaire	Unknown	Chemotherapy had no significant impact on cancer patient's FCR (P = 0.55)
Mehnert [20], 2009, Germany	Cross-sectional	Breast	$N = 1083$	61.8 (9.8)	Fear of Progression questionnaire (FoP-Q-SF)	Cronbach's alpha = 0.87	Women who received chemotherapy reported higher FoP ($P < 0.001$, $\eta^2 = 0.02$)
Vickberg [44], 2003, USA	Cross-sectional	Breast	$N = 169$	59 (11.41)	Concern About Recurrence Scale (CARS)	Cronbach's alpha = 0.87	Women who have had chemo reported greater recurrence fears ($r = 0.25$, $P < 0.01$)
Deimling [47], 2006a, USA	Cross-sectional	Mixed	$N = 321$	72.3 (7.5)	Cancer-related heath worries scale (4-item)	Cronbach's alpha = 0.84	Chemotherapy was not significantly related to worry of recurrence ($r = 0.01$)
Costanzo [46], 2007, USA	Longitudinal	Breast	$N = 89$	Unknown	Concerns About Recurrence Scale (CARS)	Unknown	Chemotherapy was not associated with FCR (F = 2.66, P = 0.11)
Liu [39], 2011, USA	Longitudinal	Breast	$N = 506$	58 (10)	First four items from the Concern About Recurrence Scale (CARS)	Cronbach's alpha = 0.87	Patients who had received chemo reported greater fears 2 years after definitive surgery ($P < 0.01$)
Tewari [53], 2014, USA	Cross-sectional	Breast	$N = 392$	Unknown	Face-to-face interview (single question)	Unknown	Relationship between chemotherapy and worry about recurrence approached significance (P = 0.06)
Stanton [34], 2002, USA	Longitudinal	Breast	$N = 70$	52.63 (11.94)	6-item from 22-item fear of recurrence Questionnaire	Unknown	Chemotherapy was not significantly related to cancer patient's FoR
Northouse [51], 1981, USA	Cross-sectional	Breast	$N = 30$	Unknown	Fear of Recurrence Questionnaire (22-item)	72% of the items having correlations above 0.6	Chemotherapy was not significantly related to recurrence fear ($F = 0.01$, df = 2, 27)
Mellon [14], 2007, USA	Cross-sectional	Mixed	$N = 123$	65 (6.2)	Fear of Recurrence Questionnaire (22-item)	Reliability coefficients = 0.92	Chemotherapy was not related to patients or carers' fear of recurrence
Leake [12], 2001, Australia	Cross-sectional	Gynaecological malignancies	$N = 202$	Unknown	A single FoR question	Unknown	FCR was not related to chemotherapy
Custers [18], 2016, Netherlands	Cross-sectional	Colorectal	$N = 76$	67.3 (range 41–88)	Fear of Cancer Recurrence Inventory (FCRI) 42-item	Cronbach's alpha = 0.95, test-retest $r = 0.89$	Chi-square test showed treatment type (CTX/RT) not to be associated with FCR
Craver [37], 2006, USA	Longitudinal	Breast	$N = 163$	54.18 (10.61)	QLACS (Quality of Life in Adult Cancer Survivors Scale)	Cronbach's alpha = 0.71	Chemotherapy was related to distress about the possibility of cancer recurrence ($r = 0.21$, $P < 0.01$)
Deimling [49],	Cross-sectional	Mixed	$N = 180$	72.2	Cancer-related Health Worry Scale	Alpha reliability = 0.85	None of the treatment variables were found to be

(continued on next page)

Table 2 *(continued)*

First author Year, Country	Study design	Cancer type	Sample size analysed	Age Mean (SD)	FoR instruments	Reliability	Main findings
2008, USA					(4-item)		significantly related to FCR (CTX, B = − 0.250, β = − 0.30)
Langeveld [33], 2004, Netherlands	Cross-sectional	Mixed	*N* = 400	24 (4.9)	Cancer-specific Concerns Scales	Cronbach's alpha = 0.80	Treatment type (CTX/RT/combination) has no significant relationship with concerns of having a relapse in young survivors
Crespi [24], 2008, USA	Cross-sectional	Breast	*N* = 1188	58.8 (10.1)	Impact of Cancer (IOC)-Worry Subscale	Cronbach's alpha = 0.89	Chemotherapy was significantly related to worry about recurrence (P < 0.001)
Deimling [48], 2006b, USA	Cross-sectional	Mixed	*N* = 321	61.9.3 (8.9)	Cancer-related Heath Worries Scale	Cronbach's alpha = 0.84	Chemotherapy was not significantly associated with FCR (B = 0.24, β = 0.03)
Melchior [13], 2013, Germany	Longitudinal	Breast	*N* = 118	54.2 (9.9)	Short form of the Fear of Progression Questionnaire (FoP-Q-SF)	Cronbach's alpha = 0.87	No predictive value of patients' treatment type (CTX/RT/hormone) on FoP was detected
Park [15], 2013, USA	Longitudinal	Mixed	*N* = 167	46.3 (6.3)	One single question	Unknown	Type of treatment (CTX/RT/Surgery) was not found related to neither cognitive nor emotional aspect of FoR
Van de Wal [30], 2016, Netherlands	Cross-sectional	Mixed	*N* = 2615	63.6 (12.9)	Health Worries Subscale of the Impact of Cancer Scale (IOC)	Cronbach's alpha = 0.83	FCR was not significantly associated with primary treatment type (CTX/surgery/RT/combination, P = 0.079)
Shay [28], 2016, USA	Cross-sectional	Mixed	*N* = 2497	55 (range 40–94)	A single question from the Quality of Life in Adult Cancer Survivors Scale	Unknown	Among older cancer survivors (age above 40 years or older at diagnosis), receipt of CTX was positively related to FoR (P < 0.01)
Boehmer [36], 2016, USA	Cross-sectional	Breast	*N* = 167	Unknown	Fear of Recurrence Questionnaire (22-item)	Cronbach's alpha = 0.93	Receipt of chemotherapy was a significant factor that increased survivors' FoR (*t* = 2.46, P = 0.0138)
Fisher [25], 2016, UK	Cross-sectional	Colorectal	*N* = 10,969	Unknown	Single-item assessment	Unknown	Having had chemotherapy was related to higher FCR in colorectal cancer patients (OR = 1.54 (1.42–1.68), P < 0.001)
McGinty [50], 2016, USA	Longitudinal	Breast	*N* = 160	61.48 (9.60)	Cancer Worry Scale (CWS) and Visual Analogue Scales (VASs)	CWS Cronbach's alpha ranged from 0.83 to 0.86	CTX was not a significant predictor of FoR (OR = 0.65 (0.16–2.27), P = 0.55)
Aghdam [45], 2014, Iran	Cross-sectional	Mixed	*N* = 129	45.23 (13.79)	Short Form of Fear of Progression Scale	Cronbach's alpha = 0.87	The relationship between CTX and FoR was nonsignificant (P = 0.073)
Taylor [16], 2012, USA	Cross-sectional	Breast	*N* = 51	64.24 (12.3)	Concerns of Recurrence Scale (CARS)	Cronbach's alpha = 0.87 to 0.93	FoR was not related to treatment type (CTX/RT/Hormone therapy)
Savard [42], 2013, Canada	Longitudinal	Mixed	*N* = 962	57.0 (9.9)	Severity Subscale of the Fear of Cancer Recurrence Inventory (FCRI-S)	Unknown	A relationship was obtained between greater FCR and CTX (F = 9.56, P = 0.002)
Lebel [35], 2013, Canada	Cross-sectional	Breast	*N* = 3239	unknown	Concerns of Recurrence Scale (CARS)	Cronbach's alpha = 0.87 to 0.93	Having had chemotherapy is a significant mediator of the relationship between age and FoR (Z = − 3.83, P < 0.001)
Petzel [52], 2012, USA	Cross-sectional	Pancreatic and Periampullary tumours	*N* = 240	67 (range 34–92)	Fear of Cancer Recurrence Inventory (FCRI)	Cronbach's alpha = 0.95	Receipt of chemotherapy was not associated with total FCR scores (P = 0.840)
Pedersen [19], 2012, Denmark	Cross-sectional	Testicular	*N* = 316	47.6 (10.9)	Single question	Unknown	Association between CTX and FoR was nonsignificant (OR = 1.13 (0.66–1.94), P = 0.646)

FoR: Fear of Recurrence; FCR: Fear of Cancer Recurrence; FoP: Fear of Progression; CTX: Chemotherapy; RT: Radiotherapy; OR: Odd Ratio;

process is presented in Supplementary Fig. 1.

The cumulative sample size including all studies was 35,200, ranged from 30 to 10,969. The mean age of patients participating in all studies varied from 24 to 72.3 years, with ten articles not reporting a median or mean age. The publication dates of the included articles ranged from 1981 to 2016 (two articles were published in the 1980s, one in the 1990s, fourteen in the 2000s, and the remaining were published since 2010). Twenty-seven studies were conducted in North America, eleven in Europe, one in Australia and one in Iran. Regarding the FoR instruments, self-reported questionnaires were used. The number of scale items ranged from 1 to 42 and nine studies failed to report the validity/reliability of the measurement. Main characteristics and findings of the included publications are presented in Table 2.

3.2. Systematic review

Forty studies were included in the systematic review, and conflicting evidence was found among them. Fifteen articles [4,20,24–26,28,36–44] suggested that having undergone CTX was significantly associated with higher FoR. One [35] reported that having had CTX is a significant mediator of the relationship between age and FoR ($Z = -3.83$, $P < 0.001$). On the contrary, twenty-four studies [6,10,12–16,18,19,29–34,45–53] suggested that cancer patient's FoR was not related to CTX, and one study [50], though reported non-significant results, indicated that patients who had received CTX were less likely to experience high FoR (OR = 0.65, CI: 0.16–2.27).

3.3. Meta-analysis

The meta-analysis statistics derived from the 29 articles consisted of the following: P-value (fifteen articles [4,20,24,28,30,38,39,41,42,45,46,51–54]), correlation coefficients (five articles [37,40,43,44,47]), odds ratios (five article [19,25,27,29,50]), B value (two article, [48,49]), t value (one article, [36]) and means and SDs (one article, [26]). Heterogeneity test showed that the Q-value of this study was 68.890, the P-value was < 0.1, and the I-squared value was > 50% (P-value = 0.000; I-squared = 59.356), hence, substantial heterogeneity was found and a random-effect model was used. By using random-effect weights, the summary estimate of the correlation was 0.093 with a 95% confidence interval (CI) of 0.062 to 0.123. The *Z*-value was 5.959, and the P-value was < 0.001 (two tailed).

Further subgroup analysis indicated that cancer type, year of publication and length of scales were all linked to the degree of association. All subgroups showed a statistically significant and positive correlation ($P < 0.001$). In the first analysis, the correlation value of 'breast cancer group' ($r = 0.110$, CI: 0.073, 0.146) was higher than 'mixed cancer group' ($r = 0.083$, CI: 0036, 0.129) and 'other cancer group' ($r = 0.068$, CI: 0.000–0.135), however the difference was not significant (Fig. 1). The second subgroup analysis based on publication year revealed that the correlation value of 'before 2000s' ($r = 0.196$, CI: 0.066, 0.319) was higher than '2000s' ($r = 0.107$, CI: 0.066, 0.148) and '2010s' ($r = 0.079$, CI: 0.048, 0.111), however, the difference was nonsignificant, either. The result was also confirmed by 'Regression of year on Fisher's Z' analysis, which showed a nonsignificant but reducing trend of the influence of chemo on recurrence fears (slope = −0.002, $P = 0.115$). Regarding the third analysis about scale length, 'extensive' group ($r = 0.108$, CI: 0.070, 0.146) showed greater CTX-FoR association than 'short' ($r = 0.076$, CI: 0.023–0.129) and 'single item' group ($r = 0.085$, CI: 0.034, 0.136). Results of subgroup analysis are shown in Table 3. Regression plot is outlined in Supplementary Fig. 2.

The fail-safe-N-value, which calculates the number of missing studies that would bring the P-value to less than the alpha of 1.96 was found to equal 983. This value exceeded Rosenthal's recommended tolerance value of 5n + 10 (where n is the number of effect sizes) [23], which suggested that our data were resistant to potential publication bias. In the examination of the funnel plot, 29 studies were noticeably distributed symmetrically (funnel plot is showed in Supplementary Fig. 3). Egger's regression intercept test also showed no statistically significant P-value (intercept = 0.176, SE = 0.502, $T = 0.351$, and $P = 0.729$). Thus, in all, we assume that no apparent publication bias was found in this review.

4. Discussion

This is the first review and meta-analysis to focus specifically on the association between CTX and FoR, and the overall results showed a weak but statistically significant correlation between them. Fifteen studies included in the analysis demonstrated a positive association of CTX receipt with higher FoR levels. Previous research has shown that modalities such as radiotherapy are also positively associated with FoR [11].

There has been a dramatic improvement in the survival of cancer patients over the last two decades. The use of combined modalities of treatment, such as surgery, chemotherapy and radiotherapy has brought great benefits to an expanding patient population. However, unsurprisingly, the achieved medical success comes at some cost in terms of patients' functioning level as well as sense of well-being, both physically and psychologically [33]. As one of the major types of cancer treatment, CTX may cause adverse effects upon normal body tissue that may manifest months or even years after treatment completion [33]. In addition to the possibility of second malignancies developing, CTX may cause side effects such as, tiredness, nausea and vomiting, loss of hair, skin and nails, endocrine dysfunction, infertility and later organ toxicities [55–57]. It has been reported that physical and cognitive impairments through side effects of cancer treatment can significantly contribute to greater fear of cancer progression (FoP) [20]. More severe fatigue and symptom burden caused by treatment has also been confirmed to be associated with higher FoR [14,40]. Therefore, it is possible that lingering fatigue and physical symptoms may serve as a reminder of the cancer or be misinterpreted as indicators of cancer returning, which leads to greater recurrence fears. Also, reports have shown that living with the effects of CTX could be stressful, frustrating and traumatic, hence, patients with CTX are at higher risk of getting psychological and emotional difficulties, such as, sleep problems, depression and anxiety [56]. A number of studies [9,19,58,59] have reported a moderate positive correlation between FoR and psychological morbidity. In particular, generalised anxiety [17], depression [19], symptom distress [9] and stress [60] has been identified as strong predictors of greater distress. Therefore, it is reasonable to conceive that CTX-related physical symptoms and psychological difficulties contribute to higher FoR.

In contrast, twenty-four studies reported nonsignificant correlation between CTX and FoR. One potential explanation is that the influence of chemotherapy on FoR may differ depending on whether the treatment is considered as signalling more serious disease or as protection against future recurrence [26]. To date, with the advance of CTX technology, more treatment-relevant information is provided to patients by health professionals, and chemotherapy is being better explained before administration [50]. Providing sufficient information assists patients to strengthen their psychosocial adjustment ability, and to cope better with the side effects. It is possible that with the improvement of patient-doctor communication and the development of technology, patients now are more likely to view CTX as a neutral routine treatment instead of a harmful and fearsome one. This could also help to explain the reason why there was a decreasing trend (although not significant) of the influence of chemotherapy on FCR in the course of time as noted from publication date.

The findings of the subgroup analysis based on cancer type, showed that the CTX by FCR association was not statistically significant across the major cancer groups, though the CTX-FoR correlation in 'breast group' was higher than the other two groups, the difference was not statistically significant. One possible reason why 'breast group' showed

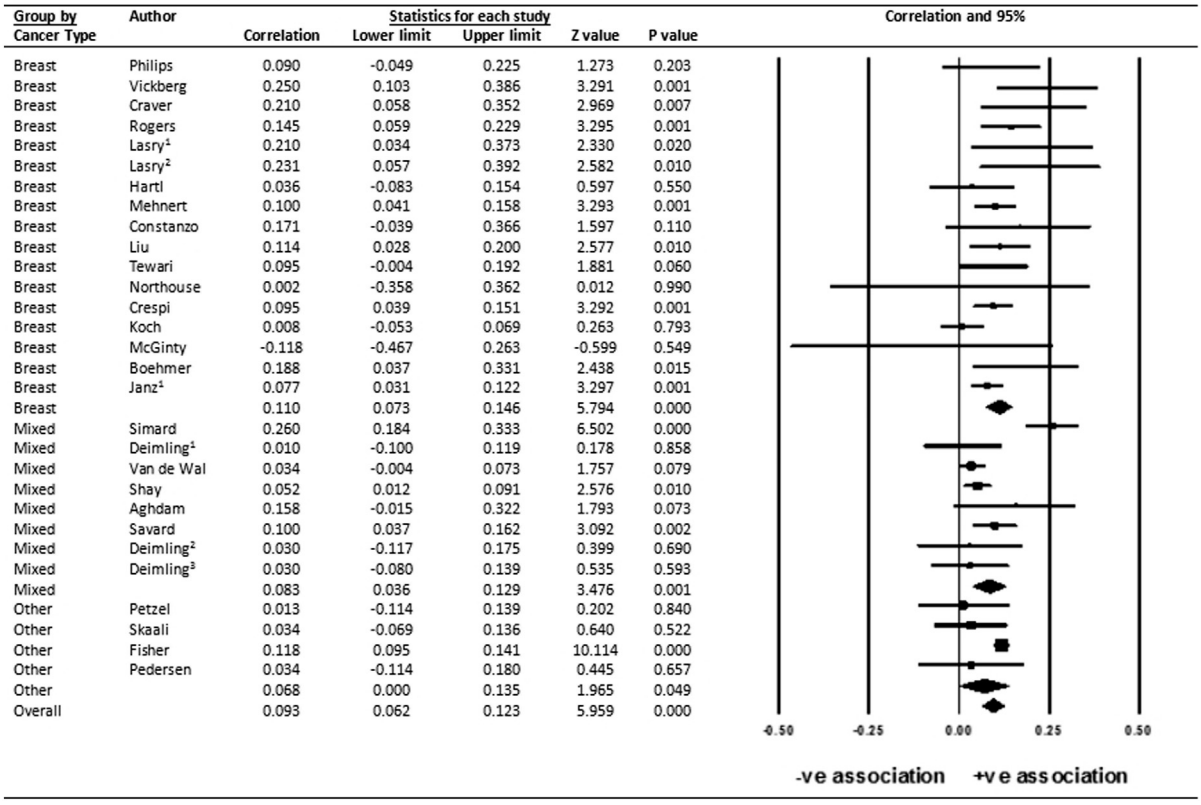

Fig. 1. Random effects meta-analysis of the correlation between CTX and FoR, and subgroup analysis by cancer type. The size of the squares indicates the weight of the study. The diamond indicates the summary correlation. CI, confidence interval. Deimling[1]: Deimling et al. (2006a); Deimling[2]: Deimling et al. (2008); Deimling[3]: Deimling et al. (2006b); Janz[1]: Jan et al. (2011); Lasry[1]: Lasry (1992); Lasry[2]: Lasry (1987).

higher correlation value is that patients understand that unlike other disease which CTX is the only treatment, the administration of chemotherapy in breast cancer patients usually implies poorer prognosis. Also, a limitation of current FoR-related studies is that the majority have focused, specifically, on breast cancer patients [2,9]. In this review, over half of the studies recruited participants with breast cancer. Thus it is possible that the influence of breast cancer studies has somewhat generated a greater correlation value. Further careful inspection should be conducted to investigate the potential influence of cancer type on the CTX-FoR association. As the analysis based on scale length, we found no linear association between item number and the CTX-FoR association value. Correlation in 'extensive' group was higher than the other two groups, but correlation in 'single-item' group was higher than 'short' group. Thus in the review, we assume that scale length has no direct influence on CTX-FoR correlation.

One study suggested that CTX was a nonsignificant protective factor against FoR. This finding could be a manifestation of the perception that more aggressive treatment is better at ensuring no cancer recurrence or progression in the future. However, this finding should be interpreted with great caution as this was the only study which reported such results.

It was not possible to make distinctions in the studies reviewed of the interaction of CTX type (neo-adjuvant and adjuvant) and FoR as many of the studies included mixed CTX therapeutic strategies. Additional investigation where FoR levels are inspected across these treatment types would further assist our understanding of the association. A further mediating variable that has not been included, of course, is the protocol adopted in each of the specialist units of how to educate

Table 3
results of subgroup analysis.

Analysis	Effect size and 95% interval				Test of null (2-Tail)		Heterogeneity	
Groups	Number studies	Point estimate	Lower limit	Upper limit	Z value	P-value	Q-value	P-value
Group by cancer type								
Breast	17	0.110	0.073	0.146	5.794	0.000		Ref
Mixed	8	0.083	0.036	0.129	3.476	0.001	0.800	0.371
Other	4	0.068	0.000	0.135	1.965	0.049	0.785	0.375
Group by year publication								
Before 2000s	3	0.196	0.066	0.319	2.937	0.003		Ref
2000s	11	0.107	0.066	0.148	5.042	0.000	1.166	0.280
2010s	15	0.079	0.048	0.111	4.890	0.000	3.320	0.068
Group by length of scale								
Single item	6	0.085	0.034	0.136	3.276	0.001		Ref
Short	8	0.076	0.023	0.129	2.791	0.005	0.236	0.627
Extensive	15	0.108	0.070	0.146	5.581	0.000	0.487	0.458

and inform the patient and carer about the treatment itself. Such explanations that were offered to patients are likely to influence their illness and treatment representations formed during the course of the care pathways experienced by patients [61].

In all, even though we were able to include a large sample of participants, this current review has several additional limitations. First, the majority of the sample was from a white ethnic group. Therefore, our results may not generalize across other ethnic groups. Secondly, broad inclusion criteria were used in the meta-analysis, several included studies used single items or failed to report reliability details. Also, the publication dates, sample size, age of participants and item number of the scales of the included studies varied significantly, which may have an influence on our final results. In addition, timing of chemotherapy was not carefully explored in this study, it is possible that the CTX-FoR association is weaker in patients who were in post-chemo phase due to less side effects. However, we failed to analyse this factor because all included papers did not provide detailed information. Most importantly, ten studies that reported nonsignificant CTX-FoR correlation were excluded from the meta-analysis due to incomplete data. Therefore, we assume, it is likely that including these studies may result in a different overall association between CTX and FoR. Lastly, no attempt was made to search for non-English publications or unpublished articles.

5. Conclusion

This systematic review and meta-analysis indicated a weak association between patient's fear of cancer recurrence and the receipt of chemotherapy. The result should be interpreted with caution due to great variability between studies. The role of chemotherapy side effects should be specifically investigated, and further longitudinal studies should be conducted to assess the trajectory of FoR during chemotherapy, and the nonsignificant but decreasing trend of the influence of CTX on FoR. The moderators of the association between CTX and FoR should also be studied closely as they are helpful to identify patients in need. Psychological interventions focused on psychoeducation, coping skill building, and meaning finding should be designed and tested during CTX as they may likely alleviate FoR development by patients. Of special significance we argue is the underlying beliefs that patients tend to generate from their contact with their cancer team over the course of their often protracted and complex treatments. Hence we propose that illness representations that patients hold become an important focus for psychological intervention development.

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Ethics

Ethics not required. This article does not contain any studies with human participants or animals performed by any of the authors.

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Appendix A. Supplementary data

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