The role of metacognition and its indirect effect through Cognitive Attentional Syndrome on fear of cancer recurrence trajectories: a longitudinal study

Running head: Metacognition and Cognitive Attentional Syndrome in Fear of cancer recurrence trajectories

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Abstract

Objective: This longitudinal study mapped distinct trajectories of Fear of cancer recurrence (FCR) over 12 months among patients with breast (BC) or colorectal (CRC) cancer, and examined if metacognition, indirectly via attentional bias, intrusive thoughts and avoidance **(**hallmarks of cognitive attentional syndrome; CAS) predicted FCR trajectory membership.

Methods: 270 BC (n=163) or CRC (n=107) patients were assessed at 8-weeks, 3-months, 6-months, and 12-months post-surgery on a measure of FCR (FCRI-SF). Metacognition (MCQ-30), Intrusive and Avoidant Thoughts (CIES-R) and Attentional bias (dot-probe tasks) were assessed at baseline. Latent growth mixture modelling identified FCR trajectories. Fully-adjusted Multinomial Logistic Regression identified whether direct and indirect effects of metacognition through CAS determined FCR trajectory membership.

Results: Three distinct FCR trajectories were identified, namely, Low-stable (62.4%), High-stable (29.2%) and Recovery (8.3%). Negative beliefs about worry, Cognitive confidence, and age predicted FCR trajectories (χ^2 (6) = 38.31, p<0.001). Compared with Low-stable group, Recovery FCR patients held greater Negative beliefs about worry (OR=1.13, p=0.035) and High-stable FCR patients reported poorer Cognitive confidence (OR=1.12, p=0.004). The effect of Negative beliefs about worry was partially mediated by avoidance (β=0.06, 95% CIs 0.03-0.12) and fully mediated by intrusive thoughts (β=0.14, 95% CIs 0.08-0.20). Attentional bias did not predict FCR trajectories.

Conclusions: While most patients experienced low level of FCR, 3 in 10 persistently worried about cancer returning over the first 12-months post-surgery. Modifying metacognitive knowledge to interrupt maladaptive cognitive processing including intrusion and avoidance may be an effective therapeutic intervention for patients at risk of persistent FCR.

(word 248)

Introduction

Fear of cancer recurrence (FCR) is defined as "fear, worry, or concern relating to the possibility that cancer will come back or progress" [1], with high FCR associated with impaired quality of life.[1] Studies show that 7-49% of cancer patients report elevated FCR from early post-diagnosis/treatment onwards [1], but thereafter conflicting reports show no change [1], intial increases [2] or declines [3] in FCR, before stablizing after several months.[1] The broad FCR prevalence estimates and mixed findings in longitudinal studies may reflect individaul response differences or methodological effects. One longitudinal study using group-based trajectory analysis has examined FCR trajectory patterns.[4] Manne et al. identified three distinct FCR trajectories in a sample of ovarian cancer survivors, most with stage III disease, over 6 months post-diagnosis.[4] Most (49.1%) experienced persistently high FCR, 25.6% reported low-stable FCR, and the remainder showed progressive declines. Advanced disease stage explains the large proportion reporting persistent high FCR levels. Whether the trajectories described by Manne et al. generalize to other cancer populations is unknown.

FCR research clarifying underlying mechanisms has identified the Self-Regulatory Executive Function (S-REF) theoretical model [5] implicates metacognition in FCR. Metacognition, refers to individual beliefs or knowledge regarding one's own cognitive processes.[6] The S-REF model postulates that certain metacognitive beliefs about the value of worry (e.g. worrying is dangerous) may underlie a particular pattern of information processing, known as cognitive attentional syndromes (CAS). CAS features perseverative negative thinking, threat monitoring (attentional bias toward threat-related information), and maladaptive coping strategies (e.g. avoidance or thought suppression). Positive beliefs about worry (e.g. worrying helps prepare for cancer recurrence) may reinforce ruminative worry as an emotional coping strategy, leading to FCR. Similarly, negative beliefs about worry (e.g. worrying causes cancer to spread) may promote counterproductive thought and/or emotional suppression, promoting intrusive and catastrophic thoughts [7], and attentional bias towards threat-related information, exacerbating and maintaining FCR. We propose that if positive and negative metacognitive beliefs activate CAS, this can exacerbate FCR.

Several studies examined metacognition in FCR, support the utility of the S-REF model in cancer contexts.[8-11] For example, positive correlations between different metacognitive beliefs and FCR were reported among young breast cancer (BC) survivors.[8]

Negative beliefs about worry and need to control thoughts appear to be influential metacognitive components.[8] Similar associations between FCR and Positive and Negative beliefs about worry were also found in a sample of BC and prostate cancer survivors [9]. After controlling for potential confounders, Negative beliefs about worry was associated consistently with heightened FCR in mixed cancer samples [10], and BC and colorectal cancer (CRC) survivors.[11]

However, in the S-REF model, mediation by CAS has been tested rarely, and only in cross-sectional studies. Smith et al. reported an independent contribution of intrusive thoughts to FCR, but insignificant interaction effects with Negative beliefs about worry on FCR.[10] Although attentional bias is commonly observed in distressed cancer survivors [12-14], only two studies examined its effect on FCR.[9, 15] Custers et al found that attentional bias did not differentiate BC survivors with high and low levels of FCR using the modified Stroop task.[15] Using a computerized dot-probe task, Butow et al. reported no association between attentional bias towards threat-related words and heightened FCR.[9] However, Butow et al used short probe stimuli duration (500ms) for capturing initial automatic attentional processing [9], but this may not capture conscious attentional bias proposed by the S-REF. Conscious attentional bias in FCR remains uncertain. No study has as yet clearly demonstrated the postulated causal role of metacognition and mediating effects of CAS (including intrusive thought, avoidance, conscious attentional bias) on the relationship between metacognition and FCR.

The present study (1) longitudinally identified FCR trajectories, (2) determined if metacognitive beliefs differentiate FCR trajectories, and (3) tested if attentional bias, intrusive thoughts and avoidance mediate between metacognitive beliefs and FCR trajectories among BC and CRC survivors. Based on the S-REF model [5], we hypothesized (a) that maladaptive metacognitive beliefs predict FCR trajectories over 12 months, and (b) that effect of maladaptive metacognition on FCR trajectories is mediated by attentional bias, intrusive thought and avoidance (CAS).

Methods

Participants and design

Following Ethical approval (ref: UW 15153), Chinese cancer patients who (i) were Cantonese- or Mandarin-speakers; (ii) recently diagnosed with curable (stages 0 to III) BC or CRC; (iii) had surgery as primary treatment within the past eight weeks, were recruited at

two breast centers and two CRC surgical-oncology units in Hong Kong during their post-surgical follow-up. Exclusion criteria were: metastatic BC or CRC; language or intellectual difficulties. Following written fully-informed consent, participants completed a standardized face-to-face questionnaire-based interview immediately (baseline), and follow-up interview at 3-months, 6-months, and 12-months post-baseline (Figure 1).

Outcome variable

Fear of cancer recurrence (FCR)

The nine-item Fear of Cancer Recurrence Inventory-Short Form (FCRI-SF) assessed FCR.[16] Total scores range from 0 to 36, with higher scores indicating greater FCR. FCRI-SF scores $\geq$13 represent subclinical cases.[16] The FCRI-SF has strong internal consistency (Cronbach's $\alpha = 0.89$), convergent validity, and test-retest reliability.[17] The Chinese version also demonstrates good internal consistency across four assessment points (Cronbach's $\alpha = 0.83$-0.87).[11] FCR was assessed at 8-weeks, 3-months, 6-months, and 12-months post-surgery.

Predictors/Covariates

Metacognition

Metacognition was assessed using the 30-item Metacognitions Questionnaire-30 (MCQ-30).[19] Five 6-item subscales measure Positive beliefs about worry, Negative beliefs about worry (uncontrollability and danger), Cognitive Self-Consciousness, Cognitive Confidence, and Need to control thoughts.[18] Responses are rated on 4-point Likert scales, higher scores indicating greater maladaptive metacognitive styles. The MCQ-30 has good construct and internal consistency (Cronbach's α=0.72-0.93).[18] Its subscales, except Need to control thoughts (Cronbach's α=0.58), demonstrate good internal consistency in this study (Cronbach's α=0.83-0.87).[11]

Demographics and medical characteristics

Participants' self-reported socio-demographic (age, gender, marital status, education, occupation, and household income) data were collected at baseline interview; clinical data were extracted from medical records.

Physical symptom distress

Physical symptom distress, a strong correlate of FCR[1], was assessed using the 12-item physical symptom distress subscale from the Memorial Symptom Assessment Scale Short-Form (MSAS-SF).[19] Participants indicated any listed symptoms experienced in the past seven days, and scored associated distress on 5-point Likert scales.[19] Mean item scores range from 0 to 4 , with higher scores indicating greater physical symptom distress.[19] The Chinese version of the MSAS-SF shows good internal consistency (Cronbach's α 0.84-0.91).[19]

Mediating variables (indicative of CAS)

Attentional bias

Two modified dot-probe tasks [20] using Chinese ideograms as target stimuli were implemented to measure attentional bias at baseline (Supplementary Figures 4-5). The paradigm was presented on a 15.6-inch laptop using E-Prime. For each task, participants were seated approximately 50 cm from the laptop.

Avoidance and intrusive thoughts

The 22-item Chinese Impact of Events Scale-revised (CIES-R) comprised three subscales: avoidance, intrusive thoughts and hyperarousal symptoms measured using 5-point Likert scales.[21, 22] Higher mean scores on each subscale indicate greater avoidance/intrusiveness/arousal. The CIES-R subscales have good internal consistency (Cronbach's α 0.83-0.89) and good validity.[21]

Apart from FCR, other measures were assessed once only at baseline.

Data analysis

Standard descriptive analyses assessed sample characteristics. FCR trajectories over 12-months follow-up were identified using latent growth mixture modelling (LGMM) [23], (Mplus Version 8.2). A robust full information maximum likelihood (FIML) estimations procedure, assuming data missing at random, was applied for missing data.[24] As such, patients dying during the study were excluded from analyses. To generate reliable estimates of missing data, participants missing >2 assessment points were also excluded.[25]

Three steps were involved in LGMM analyses.[26] Firstly, a univariate single-class growth model without covariates was obtained. Next, to determine the optimal number of trajectories, a series of unconditional growth mixture models were tested. Model indices

(Bayesian (BIC), sample-sized adjusted Bayesian (SSBIC), Aikaike information criteria (AIC), entropy values, the Lo-Mendell-Rubin likelihood test (LRT) and the bootstrap likelihood ratio test (BLRT)) were assessed and compared across models. Models in which growth parameters and associated covariances were both constrained to be equivalent across classes, and in which these constraints were relaxed were examined. Lower values for the BIC, AIC, SSBIC, higher entropy values, and significant p-values ($p<0.05$) for both the LRT and the BLRT indicate better model fit. Additionally, sample proportions for each class must exceed 1%. Finally, a conditional growth mixture model was developed by including covariates of class-membership. To avoid too many covariates limiting model convergence, only the study covariates (MCQ scores and bias indices) were included in this step.

Univariate analyses examined associations of FCR trajectories with each demographic and clinical variable. Only associations exceeding $p<0.05$ significance were included in subsequent analyses.[27]

Mediation was tested using Baron and Kenny's 4-step approach.[28] A fully adjusted multinomial logistic model first regressed FCR trajectory on metacognition (Model 1). Next, avoidance, intrusive thoughts and attentional bias (the proposed mediators) were independently regressed on metacognition (Model 2). Model 3 then regressed FCR trajectory on each of the proposed mediators. Finally, FCR trajectory was regressed on metacognition and the proposed mediators (Model 4). Given significant associations were shown in Model 1 to Model 3, a post-hoc path analysis was applied using INDIRECT macro within SPSS to test the significance of the indirect pathway, that is metacognition affects FCR trajectory by influencing the CAS.[29, 30]

Results

Overall, 63% (293/463) of eligible patients gave informed consent. Attrition rates for the follow-up assessments were within 14% (Figure 1). During the study patients who died, were diagnosed with metastatic disease, unknown cancer stage, or missed >2 follow-up assessments were excluded from analyses. Final sample comprised 270 patients, 163 (60.4%) BC and 107 (39.6%) CRC (Table 1). Socio-demographics did not differentiate between patients included and those excluded from analyses. More excluded patients had started chemotherapy at baseline (4.3% vs 0.4%, $\chi^2 = 4.95$, $p=0.026$).

FCR trajectories

Unconditional model

The best fitting unconditional models had intercept and slope variances constrained to be equivalent across classes. AIC, BIC and SSBIC decreased progressively in models of up to three classes (Supplementary Table 3) beyond which there was no significant improvement in model fit.[26] These results indicated the three-class model was optimal.

Conditional model

Adopting a three-class model, study covariates were included to specify a conditional model. Ten (3.7%) patients who did not complete the dot-probe tasks were excluded from the final conditional model (n= 260). Subsequent log-likelihood ratio χ^2, indicated that the conditional model fit was significantly improved ($\chi^2(34) = 289.83$, $p<0.001$). Excepting occupation status ($\chi^2(3)=20.10$, $p<0.001$) and Cognitive self-consciousness (mean=15.07, SD 4.96 in those with complete attentional bias data vs. mean=11.20, SD 2.74 for those with incomplete data, t=4.21, p=0.001), neither demographic, clinical, nor baseline variables otherwise differentiated these two groups.

Using established subclinical and clinical FCR cut-off scores of 13-21 and $\geq$22 [31], most patients (62.4%) evidenced a 'Low-stable' class featuring persistent low FCR scores (mean range 5.82-7.81) across all time points (Figure 2). A second High-Stable trajectory (29%) featured persistent sub-clinical FCR scores (mean range 15.12-17.48) over time. The remaining patients (8.3%) evidenced a 'Recovery' trajectory, featuring initially high, then declining FCR scores (baseline mean=22.05 declining to 6.58).

FCR trajectory covariates

Significant univariate associations between age, gender, cancer type, having hormonal therapy, and baseline physical symptom distress and FCR trajectories were seen (Supplementary Table 4). All covariates, except receipt of hormonal therapy which was collinear with cancer type, were included in subsequent analyses.

Model 1: Metacognition and FCR trajectory

Greater Negative beliefs about worry were more common in Recovery group patients than Low-stable group patients (OR=1.13, 95%CI 1.01-1.27, p=0.035) (Table 2, Model 1); High-stable and Low-Stable patients did not differ significantly (OR=1.08, 95%CI 0.99-1.16, p=0.055). High-stable patients less often reported Cognitive confidence (confidence in

memory capability) (OR=1.12, 95%CI 1.04-1.21, p=0.004) and were younger (OR=0.95, 95%CIs 0.92-0.98, p=0.001) than Low-stable patients. Negative beliefs about worry and Cognitive confidence were retained in the final model delineating FCR trajectory predictors.

Model 2: Metacognition and CAS

Cognitive confidence and the three CAS measures were independent. Negative beliefs about worry positively associated with Avoidance (β=0.06, 95%CI 0.04-0.08, p<0.001) and Intrusive thought (β=0.10, 95%CI 0.08-0.12, p<0.001). Subliminal (but not supraliminal) attentional bias for negatively-valenced words (priming condition) negatively correlated with Negative beliefs about worry (β=-3.86, 95% CI -7.03- -0.69, p=0.017) (Table 2, Model 2).

Model 3: CAS and FCR trajectories

Avoidance: High-stable and Recovery patients were more likely to report greater avoidance (High-stable: OR=2.36, 95%CI 1.53-4.14, p=0.003; Recovery: OR=3.54, 95%CI 1.72-7.32, p=0.001), relative to Low-stable patients (Table 2, Model 3).

Intrusive thoughts: High-stable (OR=3.12, 95%CIs 1.99-4.87, p<0.001) and Recovery (OR=3.77, 95%CIs 2.06-6.91, p<0.001) groups were more likely to report greater intrusive thoughts, relative to Low-stable group (Table 2, Model 3).

Attentional bias: Neither subliminal nor supraliminal attentional bias predicted FCR trajectories, so both were excluded from subsequent mediation analysis.

Model 4: Metacognition, avoidance, and intrusive thoughts by FCR trajectories

In Model 4 (Table 2), High-stable patients were more likely diagnosed with breast cancer (OR 2.74, 95% 1.41-5.34, p<0.05). High-stable (OR=3.12, 95%CI 1.99-4.87, p<0.001) and Recovery (OR=3.77, 95%CI 2.06-6.91, p<0.001) patients were likely to report more intrusive thoughts than Low-stable trajectory patients. Because intrusive thoughts and avoidance independently associated with both Negative beliefs about worry and FCR trajectories, we then tested if Negative beliefs about worry with FCR trajectories act through intrusive thoughts and avoidance.

Mediation: Negative beliefs about worry was positively associated with FCR trajectories (Low-stable vs. High-stable/Recovery FCR trajectories; β =0.13, p<0.001), Avoidance (β =0.07, p<0.001), and Intrusive thoughts (β =0.11, p<0.001) (Figure 3). The putative mediators, Avoidance (β =0.98, p=0.0008) and Intrusive thoughts (β =1.24,

p<0.001) were individually positively associated with FCR trajectories. Bootstrapping procedures with 1000 iterations tested mediation effects.[29, 30] Negative beliefs about worry on FCR trajectories acting through avoidance (β=0.06, 95%CI 0.03-0.12) and intrusive thoughts (β=0.14, 95%CI 0.08-0.20) were identified, respectively. After controlling for the mediator, Avoidance, Negative beliefs about worry on FCR trajectories, retained a reduced but significant, (β=0.08, p=0.036) direct effect, suggesting that Avoidance partially mediates associations between Negative beliefs about worry and FCR trajectories. Conversely, after controlling for intrusive thoughts, the direct effect of Negative beliefs about worry became insignificant β=0.01, p=0.81, indicating full mediation by intrusive thoughts.

Discussion

Few previous studies have documented FCR trajectories. Low-stable, High-stable and Recovery FCR trajectories, were revealed. Though two-thirds of our sample(62%) showed stable low levels of FCR over the duration of the study, 29% showed persistently high FCR. Substantial sample differences explain the markedly different proportions reported here and in Manne et al.'s study.[4] Our findings suggest that among patients with curable disease, most experienced normal, realistic concern throughout treatment and recovery. These results confirm that FCR remains stable over time for most patients. Among patients with initial high FCR, few experience spontaneous FCR declines over time, and most will likely face persistently high FCR without early interventions.

We also examined if metacognition predicted FCR trajectories. Our findings, align with cross-sectional FCR studies, partially supporting the role of maladaptive metacognition triggering maladaptive emotional responses (FCR), consistent with the S-REF model.[5, 8-10] At post-surgical baseline, compared to Low-stable FCR patients, Recovery patients reported greater Negative beliefs about worry, and had clinical levels of FCR that gradually declined to normal level by 3 months post-baseline (~5-6 months post-surgery). Anecdotally, many patients worry that anxieties will facilitate cancer, illustrating how normal worry might heighten the sense of threat from their own thoughts and feelings. Negative beliefs about worry did not statistically differentiate High-stable and Low-stable FCR groups, though a larger sample may have produced a significant difference. High-stable FCR patients reported significantly poorer Cognitive confidence in memory, reflecting greater uncertainty, compared to Low-stable patients. A study of BC and prostate cancer patients found Negative beliefs about worry and Cognitive confidence prospectively predicted distress, but the former

became insignificant after adjustment for baseline distress [32]. Low confidence in memory may undermine perceived ability to confront threat [33], because uncertainty reflects unpredictability, reducing perceived control and impeding coping planning. Undermining instrumental threat control cognitions reinforces less adaptive coping strategies, predisposing to FCR.[34]

In High-stable/Recovery FCR groups, metacognition appears influential predominantly through intrusive thoughts, and less so, avoidance, consistent with the S-REF model proposition that self-regulatory processing guided by metacognition is initiated by internal intrusions from involuntary processing.[5, 35] Once normal concerns about potential recurrence become intrusive, metacognition-driven CAS are activated. Cancer patients perceiving worry as dangerous and uncontrollable, "worry control" through avoidance or thought suppression may counterproductively amplify ruminative worrying.[5, 35] However, avoidance, suppression and repetitive negative thinking are both cognitively demanding and maladaptive [36, 37], impeding adaptive cognitive processing including metacognitive belief modification [5, 35], perpetuating FCR.

Avoiding thoughts about potential recurrence may temporarily relieve FCR, however, in longer-term, it may restrict the flow of information for disconfimatory cognitive processing that is crucial to emotional adjustment, in turn facilitating the development and maintenance of FCR.[38]

Contradicting the S-REF model [5], conscious attentional bias was not directly associated with FCR levels. Attentional bias depends on degree of threat.[9] We recruited most patients at their first follow-up consultation, and awaiting pathology results, wound condition, and future treatment requirements can intensify threat. Along with uncertainty, the increased salience of threatening information may have enhanced attentional bias among the entire sample, diluting attentional bias variability between FCR trajectories.

Study limitations

Physical symptom distress was mostly assessed before the initiation of adjuvant treatment, resulting in relatively low scores, possibly minimizing variance in physical symptom burden impacts on FCR over the illness trajectory. However, overall adjuvant treatment status did not predict FCR trajectories. The older-age sample may also lead to low scores, potentially diminishing the age effect on FCR. Baseline interviews were conducted while awaiting follow-up appointments in hospital clinics, potentially elevating baseline FCR

scores. While patients diagnosed with breast cancer were likely to have High-stable FCR, females were overrepresented in our overall sample limiting our ability to disentangle the effect of gender and cancer type on FCR trajectories. A modest sample size obscured detection of low frequency trajectories. This study may be therefore unable to unfold all potential FCR trajectories. Lastly, metacognitive beliefs were only assessed at baseline. Hence, the longitudinal changes between metacognitive beliefs and FCR trajectory cannot be tested.

Clinical implications

While most Chinese cancer patients were resilient to FCR during 12 months following treatment onset, 3-in-10 demonstrated persistently subclinical FCR, increasing vulnerability to long-term psychosocial maladjustment.[39] The S-REF model [5, 35] appears to have some predictive validity, particularly regarding the centrality of intrusive thought in enhancing and maintaining FCR, but attentional bias was not directly implicated. Furthermore, the subset of affected patients holding greater Negative belief about worry had more intrusive thoughts increasing their likelihood of using avoidant coping. Such disengagement coping can impair adaptation, thereby maintaining FCR. Early therapeutic interventions modifying metacognitive knowledge and interrupting maladaptive information processing including intrusion and avoidance [40], may benefit such patients in the initial diagnostic stage.

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Reference:

1. Simard S, Thewes B, Humphris G, Dixon M, Hayden C, Mireskandari S, et al. Fear of cancer recurrence in adult cancer survivors: a systematic review of quantitative studies. J Cancer Surviv. 2013;7(3):300-22.
2. McGinty HL, Small BJ, Laronga C, Jacobsen PB. Predictors and Patterns of Fear of Cancer Recurrence in Breast Cancer Survivors. Health Psychol. 2016;35(1):1-9.
3. Dunn L, Langford D, Paul S, Berman M, Shumay D, Kober K, et al. Trajectories of fear of recurrence in women with breast cancer. Support Care Cancer. 2015;23(7):2033-43.
4. Manne SL, Myers-Virtue S, Kissane D, Ozga ML, Kashy DA, Rubin SC, et al. Group-based trajectory modeling of fear of disease recurrence among women recently diagnosed with gynecological cancers. Psycho-Oncology. 2017;26(11):1799-809.
5. Fardell JE, Thewes B, Turner J, Gilchrist J, Sharpe L, Girgis A, et al. Fear of cancer recurrence: a theoretical review and novel cognitive processing formulation. J Cancer Surviv. 2016;10(4):663-73.
6. Flavell JH. Metacognition and cognitive monitoring: A new area of cognitive–developmental inquiry. Am Psychol. 1979;34(10):906.
7. Wong W-S, Fielding R. Suppression of emotion expression mediates the effects of negative affect on pain catastrophizing: a cross-sectional analysis. Clin J pain. 2013;29(10):865-72.
8. Thewes B, Bell M, Butow P. Fear of cancer recurrence in young early-stage breast cancer survivors: the role of metacognitive style and disease-related factors. Psycho-Oncology. 2013;22(9):2059-63.
9. Butow P, Kelly S, Thewes B, Hruby G, Sharpe L, Beith J. Attentional bias and metacognitions in cancer survivors with high fear of cancer recurrence. Psycho-Oncology. 2015;24(4):416-23.
10. Smith AB, Sharpe L, Thewes B, Turner J, Gilchrist J, Fardell JE, et al. Medical, demographic and psychological correlates of fear of cancer recurrence (FCR) morbidity in breast, colorectal and melanoma cancer survivors with probable clinically significant FCR seeking psychological treatment through the ConquerFear study. Support Care Cancer. 2018;1-10.
11. Ng DWL, Kwong A, Suen D, Chan M, Or A, Ng SS, et al. Fear of cancer recurrence among Chinese cancer survivors: Prevalence and associations with metacognition and neuroticism. Psycho-Oncology. 2019;28:1243-51.
12. Glinder JG, Beckjord E, Kaiser CR, Compas BE. Psychological adjustment to breast cancer: Automatic and controlled responses to stress. Health Psychol. 2007;22(3):337-59.
13. Chan MW, Ho SM, Tedeschi RG, Leung CW. The valence of attentional bias and cancer-related rumination in posttraumatic stress and posttraumatic growth among women with breast cancer. Psycho-Oncology. 2011;20(5):544-52.
14. Lam WW, Ng D, Wong S, Lee T, Kwong A, Fielding R. The role of cognitive bias in relation to persistent distress among women diagnosed with breast cancer. Psycho-Oncology. 2018;27:983-989.
15. Custers JAE, Becker ES, Gielissen MF, Van Laarhoven HW, Rinck M, Prins JB. Selective attention and fear of cancer recurrence in breast cancer survivors. Ann Behav Med. 2015;49(1):66-73.
16. Simard S, Savard J. Fear of Cancer Recurrence Inventory: development and initial validation of a multidimensional measure of fear of cancer recurrence. Support Care Cancer. 2009;17(3):241-51.
17. Simard S, Savard J. Screening and comorbidity of clinical levels of fear of cancer recurrence. J Cancer Surviv. 2015;9(3):481-91.

18. Cook SA, Salmon P, Dunn G, Fisher P. Measuring metacognition in cancer: Validation of the metacognitions questionnaire 30 (MCQ-30). PLoS ONE. 2014;9(9):e107302.
19. Lam WW, Law CC, Fu YT, Wong KH, Chang VT, Fielding R. New insights in symptom assessment: the Chinese versions of the Memorial Symptom Assessment Scale Short Form (MSAS-SF) and the Condensed MSAS (CMSAS). J Pain Symptom Manage. 2008;36(6):584-95.
20. MacLeod C, Mathews A, Tata P. Attentional bias in emotional disorders. J Abnorm Psychol. 1986;95(1):15.
21. Wu KK, Chan K. The development of the Chinese version of Impact of Event Scale–Revised (CIES-R). Soc Psychiatry Psychiatr Epidemiol. 2003;38(2):94-8.
22. Horowitz M, Wilner N, Alvarez W. Impact of Event Scale: A measure of subjective stress. Psychosom Med. 1979;41(3):209-18.
23. Muthén LK, Muthén BO. Mplus User's Guide. 5 ed. Los Angeles: CA; 2007.
24. Geiser C. Data analysis with Mplus: Guilford press; 2012.
25. Curran PJ, Obeidat K, Losardo D. Twelve frequently asked questions about growth curve modeling. J Cogn Dev. 2010;11(2):121-36.
26. Jung T, Wickrama KA. An introduction to latent class growth analysis and growth mixture modeling. Soc Personal Psychol Compass. 2008;2(1):302-17.
27. Lam WW, Bonanno GA, Mancini AD, Ho S, Chan M, Hung WK, et al. Trajectories of psychological distress among Chinese women diagnosed with breast cancer. Psycho-Oncology. 2010;19(10):1044-51.
28. Baron RM, Kenny DA. The moderator–mediator variable distinction in social psychological research: Conceptual, strategic, and statistical considerations. J Pers Soc Psychol. 1986;51(6):1173.
29. Hayes AF. Introduction to Mediation, Moderation, and Conditional Process Analysis: A Regression-based Approach. New York: The Guliford Press. 2018.
30. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods. 2008;40(3):879-91.
31. Fardell JE, Jones G, Smith AB, Lebel S, Thewes B, Costa D, et al. Exploring the screening capacity of the Fear of Cancer Recurrence Inventory-Short Form for clinical levels of fear of cancer recurrence. Psycho-Oncology. 2018;27(2):492-9.
32. Cook SA, Salmon P, Dunn G, Holcombe C, Cornford P, Fisher P, et al. A prospective study of the association of metacognitive beliefs and processes with persistent emotional distress after diagnosis of cancer. Cognit Ther Res. 2015;39(1):51-60.
33. Yılmaz AE, Gençöz T, Wells A. The temporal precedence of metacognition in the development of anxiety and depression symptoms in the context of life-stress: A prospective study. J Anxiety Disord. 2011;25(3):389-96.
34. Dekker J, Braamse A, Schuurhuizen C, Beekman ATF, van Linde M, Sprangers MAG, et al. Distress in patients with cancer – on the need to distinguish between adaptive and maladaptive emotional responses. Acta Oncol. 2017;56(7):1026-9.
35. Wells A. Emotional disorders and metacognition: Innovative cognitive therapy: John Wiley & Sons; 2000.
36. Skaali T, Fosså SD, Bremnes R, Dahl O, Haaland CF, Hauge ER, et al. Fear of recurrence in long-term testicular cancer survivors. Psycho-Oncology. 2009;18(6):580-8.
37. Llewellyn CD, Weinman J, McGurk M, Humphris G. Can we predict which head and neck cancer survivors develop fears of recurrence? J Psychosom Res. 2008;65(6):525-32.
38. Wells A. Cognitive therapy of anxiety disorders: A practice manual and conceptual guide: John Wiley & Sons; 2013.

39. Koch L, Jansen L, Brenner H, Arndt V. Fear of recurrence and disease progression in long-term (≥ 5 years) cancer survivors—a systematic review of quantitative studies. Psycho-Oncology. 2013;22(1):1-11.
40. Butow P, Turner J, Gilchrist J, Sharpe L, Smith AB, Fardell JE, et al. Randomized trial of ConquerFear: a novel, theoretically based psychosocial intervention for fear of cancer recurrence. J Clin Oncol. 2017;35(36):4066-77.

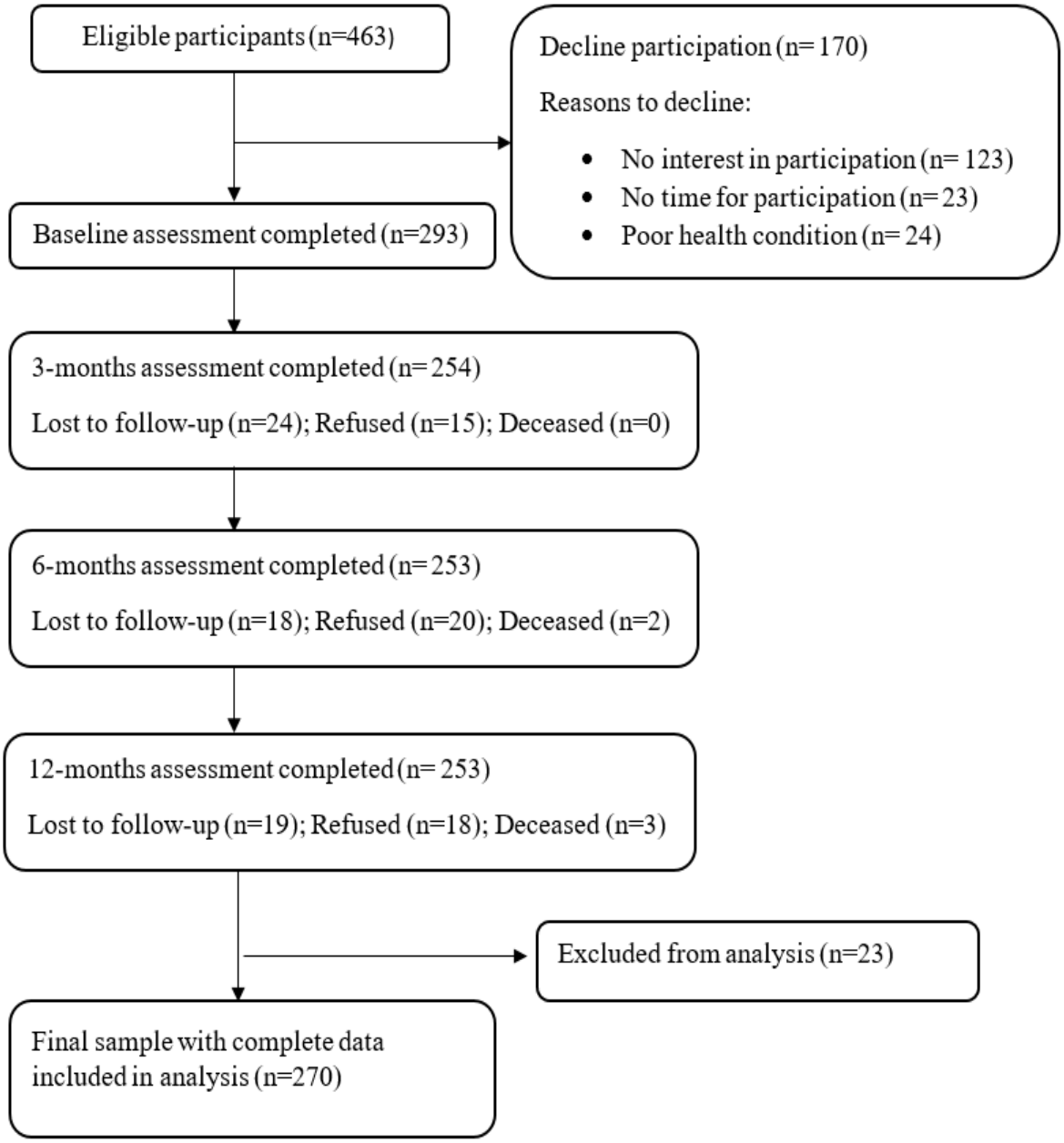


Figure 1. Sampling structure and attrition.

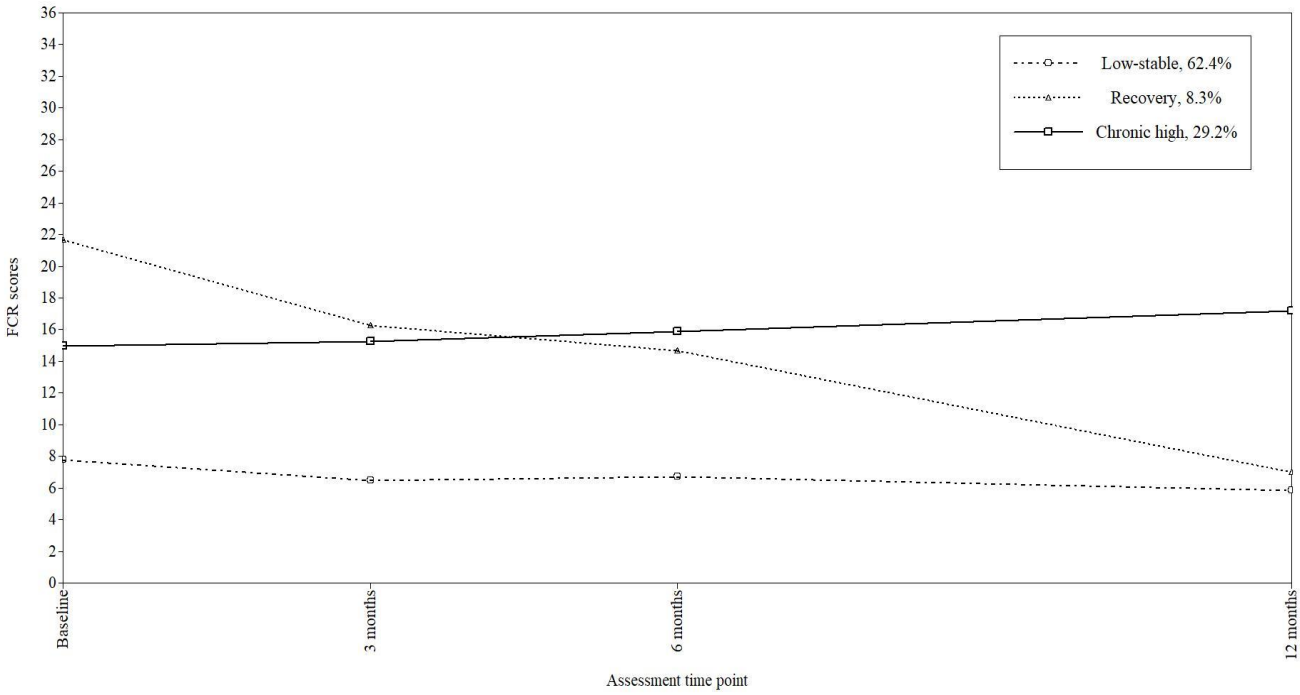


Figure 2. FCR score trajectories.

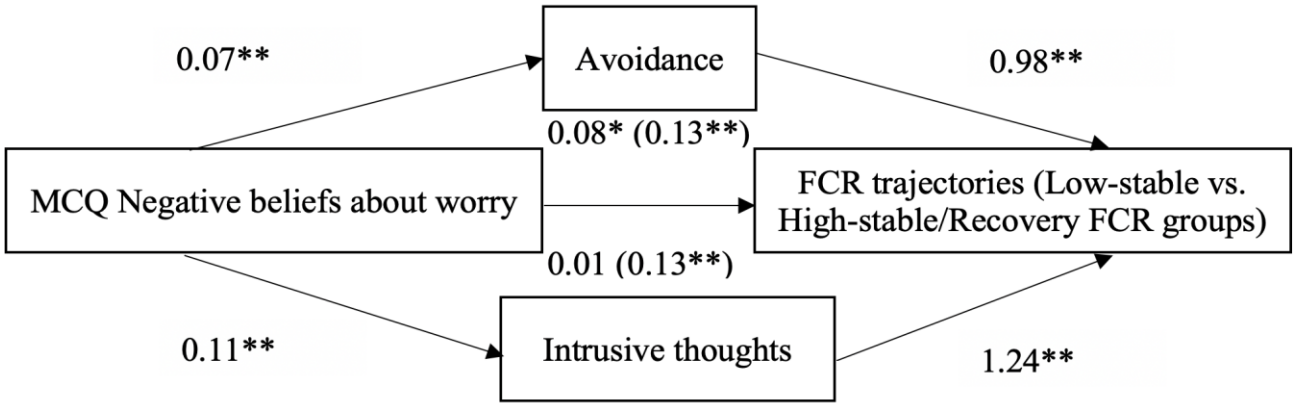


Figure 3. Direct and indirect effect of MCQ Negative beliefs about worry on FCR trajectories through avoidance or intrusive thoughts.

Note: *p<0.05; **p<0.001; MCQ= metacognition; FCR= Fear of cancer recurrence.

Table 1. Summary of demographic and clinical characteristics

	Participants (%) n = 270
Demographic characteristics	
Gender	
Male	67 (24.8)
Female	203 (75.2)
Age at diagnosis (year) mean ± standard deviation (SD)	59.86 ± 10.22
Time since cancer diagnosis (months) mean ± SD	2.12 ± 2.65
Marital status	
Married/ cohabited	191 (70.7)
Single/ divorced/ separated/ widowed	79 (29.3)
Educational level	
No formal/ primary education	84 (31.1)
Secondary/ tertiary	186 (68.9)
Occupation status	
Employed (full-time/part-time)	101 (37.4)
Retired	84 (31.1)
Housewife	50 (18.5)
Unemployed	35 (13.0)
Monthly household income (HK$)[a]	
No income	34 (12.6)
< HK$ 10, 000 – 30,000	140 (51.9)
HK$ 30001 or above	84 (31.1)
Missing	12 (4.4)
Clinical characteristics	
Cancer type	
Breast cancer (BC)	163 (60.4)
Colorectal cancer (CRC)	107 (39.6)
Stage	
Stage 0	53 (19.6)
Stage I	84 (31.1)

Stage II	86 (31.9)
Stage III	47 (17.4)
Active treatment at baseline	
Chemotherapy	1 (0.4)
Radiotherapy	0 (0)
Target therapy	1 (0.4)
Hormonal therapy	12 (4.4)
No active treatment	256 (94.8)
Missing	0 (0)
Active treatment at FU1	
Chemotherapy	89 (33.0)
Radiotherapy	15 (5.6)
Target therapy	9 (3.3)
Hormonal therapy	48 (17.8)
No active treatment	101 (37.4)
Missing	27 (10.0)
Active treatment at FU2	
Chemotherapy	39 (14.4)
Radiotherapy	9 (3.3)
Target therapy	13 (4.8)
Hormonal therapy	76 (28.1)
No active treatment	120 (44.4)
Missing	26 (9.6)
Active treatment at FU3	
Chemotherapy	5 (1.9)
Radiotherapy	0 (0)
Target therapy	9 (3.3)
Hormonal therapy	72 (26.7)
No active treatment	166 (61.5)
Missing	23 (8.5)
Surgery type	
Breast cancer	
Modified radical mastectomy	62 (23.0)

Modified radical mastectomy plus reconstruction	17 (6.3)
Breast-conserving therapy	84 (31.1)
Colorectal cancer	
Open surgery	25 (9.3)
Laparoscopic surgery	76 (28.1)
Both	6 (2.2)
Plus colostomy	18 (6.7)

Note: [a] US $1 = HK$7.8; FU1= Follow-up 1 (3-months post-baseline); FU2= Follow-up 1 (6-months post-baseline); FU3= Follow-up 3 (12-months post-baseline); N/A= not applicable.

Table 2. Regression analyses of predictors of the FCR trajectories

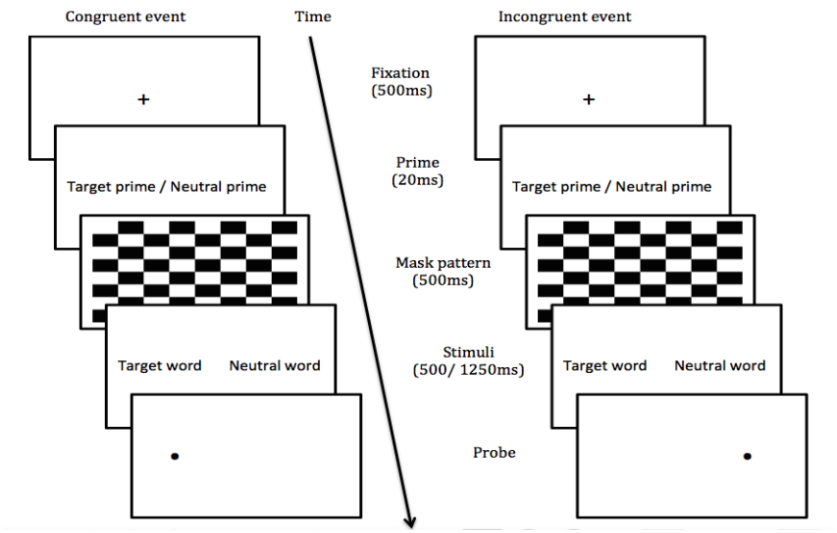
	Model 1		**Model 2**			**Model 3**						**Model 4**	
FCR trajectories (ref; Low-stable)	High-stable FCR	Recovery FCR	Avoidance	Intrusive thoughts	-/prime/500	High-stable FCR	Recovery FCR	High-stable FCR	Recovery FCR	High-stable FCR	Recovery FCR	High-stable FCR	Recovery FCR
	OR [95% CI]	OR [95% CI]	β [95% CI]	β [95% CI]	β [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]	OR [95% CI]
Age	0.95* [0.92, 0.98]	0.96 [0.91, 1.01]				0.96* [0.93, 0.99]	0.97 [0.93, 1.02]	NS	NS	0.95* [0.93, 0.98]	0.96 [0.92, 1.01]	NS	NS
Gender (1=male, ref; 0=female)	NS	NS				0.41* [0.18, 0.92]	0.32 [0.07, 1.52]	NS	NS	0.37* [0.17, 0.82]	0.26 [0.06, 1.21]	NS	NS
Cancer type (1=BC, ref; 0=CRC)	NS	NS				NS	NS	2.74* [1.41, 5.34]	1.82 [0.65, 5.14]	NS	NS	2.74* [1.41, 5.34]	1.82 [0.65, 5.14]
Physical symptoms distress	NS	NS				NS	NS	NS	NS	2.25* [1.16, 4.36]	1.97 [0.72, 5.38]	NS	NS
Metacognition													
Positive beliefs about worry	NS	NS											

Negative beliefs about worry	1.08 [0.99, 1.16]	1.13* [1.01, 1.27]	0.06** [0.04, 0.08]	0.10** [0.08, 0.12]	-3.86* [-7.03, -0.69]						NS	NS
Cognitive confidence	1.12* [1.04, 1.21]	1.03 [0.91, 1.17]	-0.01 [-0.02, 0.01]	0.01 [-0.01, 0.03]	1.66 [-1.21, 4.53]						NS	NS
Cognitive self-consciousness	NS	NS										
Need to control thoughts	NS	NS										
Avoidance						2.36* [1.53, 4.14]	3.54* [1.72, 7.32]				NS	NS
Intrusive thoughts								3.12** [1.99, 4.87]	3.77** [2.06, 6.91]		3.12** [1.99, 4.87]	3.77** [2.06, 6.91]
Attentional bias												
Negatively-valenced stimuli												
Stimulus/Prime/Duration												
+ or -/prime or neutral/500ms or 1250ms												
-/prime/500ms										NS	NS	
Model statistics												
χ^2	38.31					44.11		53.14		34.86		53.14
$R^{2\,a}$	0.14	0.25	0.40	0.062		0.16		0.19		0.13		0.19

p-value	<0.001**	<0.001**	<0.001**	0.006*	0.001**	<0.001**	<0.001**	<0.001**

Note: [a]Pseudo R^2 (Cox and Snell) for multinomial logistic regression; *p<0.05; **p<0.001; NS= non-significant; FCR= Fear of cancer recurrence.

Supplemental materials:

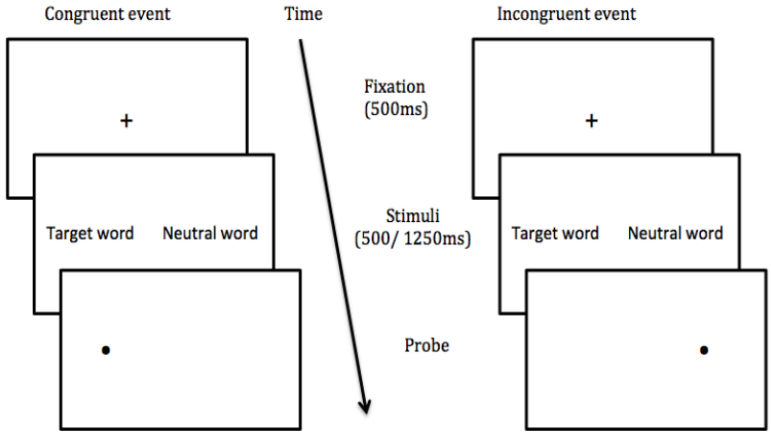


Supplementary Figure 1. Dot-probe task using negatively-valenced words.

A word set comprised by 32 negative (e.g. “suicide”) and 32 positive (e.g. “happiness”) two-character Chinese compound words in which have been validated previously [1-3] were used. Each target word was paired with a neutral word (e.g. “height”). Each trial began with a fixation for 500ms. A priming condition, subliminal exposure of a two-character Chinese compound words either “cancer” (target prime) or “sky” (neutral prime) for 20ms [4] was then incoporated to examine the effect of cancer-related context on attentional bias [5]. Following a pattern mask for 500ms, a pair of word stimuli comprised by one target word and one neutral word (e.g. negative-neutral word pair) appeared side-by-side on the screen for either a subliminal (500ms) [6] or supraliminal (1250ms) [7] duration in order to assess automatic and later strategic attentional processing. After the offset of the paired stimuli, a probe (i.e. a dot) appeared at the location that previously occupied by one of the paired words. Participants were asked to indicate the location of the probe as quickly as possible by pressing the corresponding keys. Reaction latency was recorded. The priming condition, exposure duration, location of the target word, and probe location were counterbalanced generating 64 trials. Four practice trials were given preceding the test trials.

Reaction time from correct trials were included for analysis. Reaction time <200ms and >3000ms, and more than 3 SDs above each participants’ mean were discarded as outliners [8]. It

has been assumed that individuals who demonstrate attentional bias towards target words would have reaction time advantage when in response to probes replacing negative or positive words (i.e. congruent trials) compared to probes replacing neutral words (i.e. incongruent trials) [9, 10]. Hence, attentional bias is inferred from mean difference of reaction time between congruent and incongruent trials. Bias index was calculated by using the formula [11]: Bias Index=((trpl-tlpl)+(tlpr-trpr))/2



Supplementary Figure 2. Dot-probe task using cancer-related words.

In this task, in order to examine thematically-specific nature of attentional bias, 32 Cancer-related Chinese compound words, rather than negatively-valenced words, were used as target words [5]. As such, there was no priming condition. Otherwise, the setting and procedure were identical to the described one. Cancer-related or positive two-character Chinese compound words were paired with neutral words respectively to produce 64 trials.

Reference:

1. Lee TM, Chan CC. Stroop interference in Chinese and English. J Clin Exp Neuropsychol. 2000;22(4):465-71.
2. Leung K-K, Lee TM, Xiao Z, Wang Z, Zhang JX, Yip PS, et al. Neural activities for negative priming with affective stimuli: An fMRI study. Neurosci Lett. 2008;433(3):194-8.
3. Leung K-K, Lee TM, Yip P, Li LS, Wong MM. Selective attention biases of people with depression: Positive and negative priming of depression-related information. Psychiat Res. 2009;165(3):241-51.
4. Bullock AB, Bonanno GA. Attentional bias and complicated grief: a primed dot-probe task with emotional faces. J Exp Psychopathol. 2013;4(2):194-207.
5. Lam WW, Ng D, Wong S, Lee T, Kwong A, Fielding R. The role of cognitive bias in relation to persistent distress among women diagnosed with breast cancer. Psycho-Oncology. 2018;27:983-989.
6. Williams JMG, Watts FN, MacLeod C, Mathews A. Cognitive psychology and emotional disorders: John Wiley & Sons; 1988.
7. Mogg K, Bradley B, Miles F, Dixon R. Brief report time course of attentional bias for threat scenes: testing the vigilance-avoidance hypothesis. Cogn Emot. 2004;18(5):689-700.
8. Mogg K, Bradley BP, De Bono J, Painter M. Time course of attentional bias for threat information in noclinical anxiety. Behav Res Ther. 1997;35(4):297-303.
9. Bar-Haim Y, Lamy D, Pergamin L, Bakermans-Kranenburg MJ, van IMH. Threat-related attentional bias in anxious and nonanxious individuals: a meta-analytic study. Psychol Bull. 2007;133(1):1-24.
10. Cisler JM, Koster EH. Mechanisms of attentional biases towards threat in anxiety disorders: An integrative review. Clin Psychol Rev. 2010;30(2):203-16.
11. Butow P, Kelly S, Thewes B, Hruby G, Sharpe L, Beith J. Attentional bias and metacognitions in cancer survivors with high fear of cancer recurrence. Psycho-Oncology. 2015;24(4):416-23.

Supplementary Table 1. Fit indices for one- to four-class growth mixture models (unconditional)

Fit indices	Growth mixture model			
	One class	Two class	Three class	Four class
AIC	6312.02	6267.25	6228.80	6219.50
BIC	6344.41	6310.43	6282.78	6284.27
SSBIC	6315.87	6272.38	6235.22	6227.20
Entropy		0.81	0.84	0.82
LRT p-value		0.10	0.0002	0.57
BLRT p-value		< 0.001	<0.001	0.58

AIC: Akaike information criterion; BIC: Bayesian information criterion; SSBIC: sample size adjusted Bayesian information criterion; LRT: Lo-Mendell-Rubin test; BLRT: bootstrap likelihood ratio test.

Supplementary Table 2. Demographic and clinical characteristics between different FCR trajectories

	Low-stable (%) n=165	High-stable (%) n=74	χ2/ t	p-value	Recovery (%) n=21	χ2/ t	p-value
Demographic characteristics							
Gender			11.68	0.001*		4.97	0.026*
Male	55 (33.3)	9 (12.2)			2 (9.5)		
Female	110 (66.7)	65 (87.8)			19 (90.5)		
Age at diagnosis (year) mean ± standard deviation (SD)	61.75 ± 9.40	55.92 ± 10.82	-4.22	<0.001**	56.71 ± 9.27	-2.31	0.022*
Time since cancer diagnosis (months) ± SD	2.14 ± 2.55	2.30 ± 3.30	0.41	NS	1.57 ± 0.68	-1.01	NS
Marital status			0.039	NS		0	NS
Married/ cohabited	118 (71.5)	52 (70.3)			15 (71.4)		
Single/ divorced/ separated/ widowed	47 (28.5)	22 (29.7)			6 (28.6)		
Educational level			1.62	NS		0.87	NS
No formal/ primary education	56 (33.9)	19 (25.7)			5 (23.8)		
Secondary/ tertiary	109 (66.1)	55 (74.3)			16 (76.2)		
Occupation status			5.59	NS		7.41	NS
Employed (full-time/part-time)	65 (39.4)	30 (40.5)			4 (19.0)		
Retired	59 (35.8)	18 (24.3)			6 (28.6)		
Housewife	25 (15.2)	12 (16.2)			6 (28.6)		
Unemployed	16 (9.7)	14 (18.9)			5 (23.8)		
Monthly household income (HK$)[a]			4.84	NS		2.91	NS

No income	25 (15.2)	8 (10.8)			1 (4.8)		
< HK$ 10, 000 – 30,000	87 (52.7)	35 (47.3)			13 (61.9)		
HK$ 30001 or above	46 (27.9)	30 (40.5)			5 (23.8)		
Missing	7 (4.2)	1 (1.4)			2 (9.5)		
Clinical characteristics							
Cancer type			15.34	<0.001**		2.97	NS
Breast cancer (BC)	85 (51.5)	58 (78.4)			15 (71.4)		
Colorectal cancer (CRC)	80 (48.5)	16 (21.6)			6 (28.6)		
Stage			1.32	NS		5.22	NS
Stage 0	35 (21.2)	13 (17.6)			2 (9.5)		
Stage I	48 (29.1)	26 (35.1)			7 (33.3)		
Stage II	56 (33.9)	22 (29.7)			5 (23.8)		
Stage III	26 (15.8)	13 (17.6)			7 (33.3)		
Undergoing active treatment at baseline							
Chemotherapy	1 (0.6)	0 (0)	0.45	NS	0 (0)	0.13	NS
Radiotherapy	0 (0)	0 (0)	-	-	0 (0)	-	-
Target therapy	1 (0.6)	0 (0)	0.45	NS	0 (0)	0.13	NS
Hormonal therapy	6 (3.6)	3 (4.1)	0.025	NS	3 (14.3)	5.59	0.032*
No active treatment	157 (95.2)	71 (95.9)	0.073	NS	18 (85.7)	2.98	NS
Surgery type							
Breast cancer			1.71	NS		2.42	NS
Modified radical mastectomy	33 (38.8)	20 (34.5)			7 (46.7)		

Modified radical mastectomy plus reconstruction	12 (14.1)	5 (8.6)			0 (0)		
Breast-conserving therapy	40 (47.1)	33 (56.9)			8 (53.3)		
Colorectal cancer			2.50	NS		0.41	NS
Open surgery	21 (26.3)	2 (12.5)			2 (33.3)		
Laparoscopic surgery	55 (68.8)	14 (87.5)			4 (66.7)		
Both	4 (5.0)	0 (0)			0 (0)		
Plus colostomy	12 (15.0)	5 (31.3)	2.42	NS	0 (0)	1.05	NS
Physical symptom distress mean ± SD	0.36 ± 0.41	0.53 ± 0.46	2.88	0.004*	0.50 ± 0.52	1.39	NS

Note: *p<0.05; **p<0.001; [a] US $1 = HK$7.8; NS= non-significant.