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ARTICLE

Associations between empirically proportionate and disproportionate fears of cancer recurrence and anxiety and depression in uveal melanoma survivors: Five-year prospective study

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Abstract

Objective: Fear of cancer recurrence (FCR) may develop into elevated anxiety or depression symptoms, but few risk factors for this development are known. Objective recurrence risk estimation is possible in some cancers. Using theories of risk communication and phobias, we examined whether the proportionality of FCR to known objective recurrence risk influences the development of anxiety and depression symptoms.

Method: Uveal melanoma (UM) patients can opt for reliable prognostic testing. Patients experience either a 'good' or 'poor' prognostic outcome, whereby 10-year mortality due to metastatic disease is, respectively, low or high. In a five-year prospective study of a consecutive sample of 589 UM survivors, we used random intercept cross lagged panel analyses to examine whether proportionality differentially influences whether FCR progresses to anxiety and depression.

Results: Positive cross paths predicting anxiety from FCR were stronger in the poor prognosis group than the good prognosis and not tested groups. Prognostic group differences were not evident for depression.

Conclusions: FCR was more likely to progress to elevated anxiety symptoms when proportionate to the known objective recurrence risk. Objective evidence may play a prominent role in the development and structure of fear because it assumes a high epistemic weight that activates a wide range

of emotional and cognitive responses. Interventions that assist survivors to tolerate FCR in the presence of higher recurrence risks may be important in reducing anxiety symptoms.

KEYWORDS

anxiety, cancer, depression, fear of cancer recurrence, proportionality, prospective design

Fear of cancer recurrence or progression (FCR) is treated cancer survivors' fears of future cancer (Lebel et al., 2016). Across a range of cancers, FCR prevalence is estimated to average 59% for 'moderate' fear and 19% for 'high' fear (Luigjes-Huizer et al., 2022). FCR is itself aversive (Deimling et al., 2006), and predicts elevated anxiety and depression, sleep problems, fatigue and impaired physical and functional well-being (Brown et al., 2020; Esser et al., 2019; Koch et al., 2013; Perndorfer et al., 2022; Vanrusselt et al., 2023).

Yet, FCR is an understandable response to cancer, which does not always develop into elevated anxiety or depression symptoms (Reed et al., 2020). Severity and duration of FCR can increase the risk of anxiety or depression (Brown et al., 2020), but few other risk factors have been identified. We propose that proportionality may be a risk factor, proportionality being the concordance of FCR with known objective risk. Informed by risk perception and phobia literatures we argue that proportional FCR will be more likely to progress to anxiety and depression than FCR that is not (Elsey & Kindt, 2021).

Proportionality of FCR to objective risk is likely to become important because improvements in prognostication are providing increasingly more accurate estimates of personal risk to greater numbers of survivors (Lønning et al., 2007; Reis-Filho & Pusztai, 2011; Tan et al., 2010; Wishart et al., 2011). Uveal melanoma (UM) is a primary cancer of the eye that is treatable with little risk of local recurrence but has a 40–50% 10-year mortality rate due to metastatic melanoma (Kujala et al., 2003). A prognostic test provides reliable mortality estimates. In this paper, we examine whether FCR differentially predicts anxiety and depression in UM survivors with proportionate compared to disproportionate FCR.

PROPORTIONALITY, FCR AND ANXIETY AND DEPRESSION

FCR is not completely veridical to objective risk (Ankersmid et al., 2022). Instead, it can conceptually be seen to exist on a spectrum of proportionality (Pradhan et al., 2021). FCR can be proportionate, whereby it is concordant with objective risk; FCR has a factual basis that is coincident with, if not causal of, fear. The opposite pole is disproportionate fear, fear that is not aligned with risk. By definition, disproportionate fear is anchored in perceptions that are unlikely to be true.

We contend that proportionality is practically important. Where objective risk is high, FCR cannot be easily challenged on factual grounds, and a clinical goal is to assist people to better tolerate that risk. Where risk is low, the goal may be to challenge the evidential basis of fear. A second clinical issue could be targeting. If proportionality of FCR is a risk factor for anxiety or depression then clinicians might focus attention on survivors with fear that is proportionate to risk. This may be particularly pertinent to population-level interventions that use population data to identify and offer tailored services to survivors based on their risk profiles (Brown et al., 2022).

Much psychological theory suggests that proportionality might not be important. It is almost axiomatic to psychologists that individuals' subjective, as much as objective, realities influence psychological states. For example, appraisal-based theories of FCR imply that FCR is partly a product of cognitive biases. Potential sources of bias contributing to FCR (Pradhan et al., 2021) include catastrophic cognitions about the likelihood, impact and controllability of recurrence (Curran et al., 2020; Lebel et al., 2018),

and over-reliance on personal experience, intuition or emotion in risk appraisal (Brown et al., 2021; Fielden et al., 2017). Thus, challenging unfounded beliefs forms the cornerstone of influential models and successful treatments for FCR (Curran et al., 2020; Lebel et al., 2018; Simonelli et al., 2016). An implication of this focus on subjectivity is that fears based on falsehoods carry similar implications to those based on truths. Empirically, disproportionately high FCR can be demonstrated by studies showing high rates of FCR in cancers where the population risk of recurrence is low (e.g., Ankersmid et al., 2022; Bell et al., 2017; Maguire et al., 2018; Magnani et al., 2022; Smith et al., 2018). In one of these studies, disproportionately high fear is associated with poorer quality of life (Maguire et al., 2018).

However, we argue, using theories from risk communication and the development of clinical phobias, that FCR occurring in the presence of known objective risk is qualitatively different from FCR that does not, and that unique attributes of objectively-founded FCR might facilitate progress to anxiety or depression. Communication theories (Chaiken & Ledgerwood, 2012; Kruglanski et al., 2006) argue that objective evidence augments persuasion because it carries an epistemic weight that engenders greater conviction than non-evidence based beliefs; hence, it is more elaborately processed, creating strong mental representations. Clinical theories of phobias emphasize the impact of objective evidence of risk because it confirms or disconfirms intuitive fear responses (Brewin, 2006; Stott, 2007). Some research suggests that people's fears based in objective evidence differ qualitatively from non-evidence-based fears because they represent a wider range of emotional and cognitive responses. Experimental manipulations emphasizing objectively presented threats have powerful effects on both perceptions of the likelihoods of negative events and emotional arousal, whereas manipulations that do not emphasize evidence are less likely to do this because they primarily influence perceptions of threat severity (Elsey & Kindt, 2021; Klemm et al., 2019). In terms of cancer, FCR and anxiety and depression are greater in cancers objectively known to carry a higher recurrence risk (Ankersmid et al., 2022; Brown et al., 2021; Gormley et al., 2021; Savard & Ivers, 2013). However, there is little evidence to suggest that FCR is more likely to develop into anxiety and depression in those who know that they are objectively at greater recurrence or progression risk.

CURRENT STUDY

Based on a genetic marker, UM survivors may be partitioned into three prognostic groups; no mutation with little likelihood of recurrence or progression ('good' prognosis), genetic mutation resulting in a high 10-year likelihood of death ('poor' prognosis) and not tested (or tests failed) with unknown individual likelihood ('unknown' prognosis; Damato et al., 2020). Patients are informed of their prognostic group. The largest study available (Brown et al., 2021) suggests that a poor prognosis precedes moderate anxiety and depression lasting at least five years, although smaller studies suggest that prognostication does not influence outcomes (Beran et al., 2009; Lieb et al., 2020). The influence of proportionality on the development of anxiety or depression from prior FCR can be established through the relative magnitude of prospective prediction in each group. A stronger positive prediction of anxiety or depression from FCR in the poor than the good or unknown prognosis group would suggest that proportionate FCR constitutes a risk factor for progression to anxiety and depression.

METHOD

Transparency and openness

We conducted a secondary analysis of data from an audit of patient-reported outcomes, approved by the [redacted] Central Ethics Committee (03/06/072/A). STROBE guidelines were followed in this report (von Elm et al., 2007). Written consent was sought for research use of data but not publication of individuals' data. The dataset can be obtained by written request from the first author. A list of publications already taken from this dataset, with a statement of how this study adds additional value, can be found in Appendix 1: Data S1.

Design

Prospective five-year cross-lagged design with observations of FCR and anxiety/depression at 6, 12, 24, 36, 48 and 60 months. Primary treatment was completed within 3 months for all participants, and those who opted for testing received their prognosis before the six-month observation. Prognoses were provided either by the team or the patients' general practitioners or oncologists.

Participants

We approached a consecutive series of adult patients from England and Wales treated for posterior (choroid or ciliary body) UM between April 1st 2008 and August 31st 2012 at Liverpool Ocular Oncology Centre (LOOC). LOOC is the main referral centre for Northwest England and North Wales, because LOOC is the main UK provider of prognostic testing. Those agreeing to participate were surveyed using a printed questionnaire over the six observations. Patients who gave written consent were posted questionnaires with postage-paid return envelopes before each timepoint. We excluded all participants who did not provide at least two observations. Re-entry into the study after missed observations was permitted. As this was a secondary analysis, we did not aim for a specific sample size.

Participants underwent either ruthenium plaque radiotherapy, proton beam radiotherapy, trans-scleral local resection, trans-retinal endoresection or enucleation (eye removal; Damato & Heimann, 2013). All patients are offered psychological support as part of their routine care. UM is associated with an approximately 40–50% 10-year survival rate, with death mainly attributable to metastatic melanoma. The 0.4–0.5 probability of death by metastatic melanoma is largely, although not solely, determined by monosomy 3 (M3), a mutation involving the loss of one of the chromosome 3 pair (Damato et al., 2020). Disomy 3 (D3) is normal. The prognosis was not ameliorable at the time because treatments for metastatic melanoma rarely prolong life, and currently, treatments may only do so for a small subgroup.

Patients are offered prognostic testing, of which about 60% accept. Prognostic results are communicated as an individualized risk of developing life-threatening metastatic disease over 10 years. UM survivors are partitioned into three groups; 'good' prognosis being no genetic mutation with almost no likelihood of cancer progression; 'poor' prognosis being genetic mutation with over 90% 10-year likelihood of death; and 'not tested' (or in a small number, their test failed) with about 50% individual likelihood. Patients are informed of their prognostic results, including their prognostic groups, by ocular oncology clinicians. Qualitative analyses suggest that patients understand the life-expectancy implications of their prognoses (Brown et al., 2022; Hope-Stone et al., 2015). A prospective study showed that a poor prognosis precedes moderately elevated anxiety, depression and FCR over five years (Brown et al., 2023). Patients in the poor or no prognosis groups are usually offered surveillance programmes of regular testing for metastatic melanoma. Proportionality can be clearly established;[1] higher FCR in the poor prognosis group and lower FCR in the good prognosis group are approaching proportionality, and vice versa for disproportionate FCR. Treatments were completed, and test results were communicated before the 6-month observation.

Measures

We used a three-item FCR scale embedded in the European Organization for Research and Treatment for Cancer Ophthalmic Quality of Life questionnaire (EORTC QLQ-OPT 30; Brandberg et al., 2004). FCR is operationalized as worry about local and secondary recurrence (Cronbach alphas across the nine timepoints ranged from .82 to .86). This scale was developed and used in this study before much of

[1]Proportionality is linear, because the outcomes in the good and poor prognosis groups are absolutes in terms of risk (close to zero and 90%) and thus roughly aligned with extreme scores on FCR scales ('Not at all' and 'Very much').

the FCR literature appeared, but it carries substantial similarities to current FCR measures (Humphris et al., 2018). The three items are: 'Were you worried about your health in the future?'; 'Were you worried about the tumour recurring in the treated eye?' and 'Were you worried about the tumour recurring in other areas of your body?' Response format was 'Not at all', 'A little', 'Quite a bit' and 'Very much', scored 1–4, respectively. A fourth item on concern about loss of the eye was excluded because it was not relevant to enucleated patients. Scale scores are item means.

Anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) anxiety and depression subscales (Zigmond & Snaith, 1983). Subscales have seven items scored from 0 to 3, with higher scores signifying greater symptomology (range = 0–21, Cronbach alphas across the nine timepoints; anxiety .87–.88, depression .83–.87). Both predict diagnosed cases with good sensitivity and specificity, with a clinical cut-off of ≥7 (Vodermaier & Millman, 2011).

Age, gender, treatment (enucleation versus other treatments (Hope-Stone et al., 2019)) and chromosome 3 status (M3, D3, not tested/test failed) were taken from patient records.

Analysis plan

Preparatory analyses examined summary statistics for all variables and means and intercorrelations between FCR and outcome variables in the full sample and within each prognostic group. Prospective relationships between FCR and outcomes (anxiety, depression and QoL) were assessed using random intercept cross-lagged panel models (RI-CPLM) with predicted cross-lagged paths (FCR → Anxiety/Depression) compared between the good, poor and not tested groups (Mund & Nestler, 2019). The RI-CPLM provides a stricter hypothesis test than traditional CPLM by partitioning within and between person variances to allow cross-lagged prediction independently of participants' trait FCR, anxiety or depression; trait scores are represented by mean scores over all timepoints (Orth et al., 2021). Chi-square, CFI and RMSEA were used to evaluate model fit, with good fitting models defined as CFI > .95 and RMSEA < .06.

Predicted between group differences in cross-paths (i.e., that FCR → anxiety/depression paths will be more strongly positive in the poor prognosis group) were tested by comparing an unconstrained three-group model with a model that constrained FCR → anxiety/depression cross-paths to equality across groups. Differences between the unconstrained and constrained models were assessed for significance using the chi-square difference test (Muthén & Muthén, 2017). Where a difference was observed, additional two-group comparisons were made with the first comparing the poor prognosis group with the good prognosis group and the second comparing the poor prognosis with the not tested group. We note the rule of thumb that 180 participants are required to accurately estimate parameters in SEM (Wolf et al., 2013) and point to the smaller size of our good and poor prognosis groups. Thus, the analyses were possibly underpowered, and readers are recommended to the 95% confidence intervals surrounding parameter estimates in Appendix 3: Data S1.

Age and gender were statistically controlled. To assess the effects of impending death on observations prior to death, a Kaplan-Meier estimate of mortality likelihood across the study was computed for each participant. Mortality likelihood did not predict outcomes on any occasion. Preparatory analyses were conducted using SPSS v28 and cross-lagged analyses using MPlus version 8.4.

Data replacement

The median number of completed observations per participant was 5 (Interquartile range from 4 to 6), with 79.37% overall completion. Summary statistics, correlations and comparisons of means were computed using the available data without data replacement. Cross-lagged analyses were based on imputed data. Unfortunately, 119 participants died during the study (ascertained by matching participants' names and dates of birth to the England and Wales death registry), missing a median of

two timepoints (Interquartile range 2–4). Data from these participants requires removal for timepoints after their deaths. We used five multiple imputations in SPSS, based on the estimations of all study variables. Based on Wen and Terrera (2018), the Kaplan-Meier estimate of mortality likelihood was used as a covariate for missing data estimation. We then deleted the imputations made after a participant had died. Covariance matrices and mean scores based on the imputed data were used for the cross-lagged analysis.

RESULTS

Entry criteria were met by 589 survivors. Table 1 shows the participants' demographic characteristics. In total, 143 received a good prognosis, 155 received a poor prognosis and 291 did not have a test-based prognosis because they did not consent to a test ($n = 253$) or they did but their test failed ($n = 38$). Before combining the 253 who did not consent to testing with the 38 whose prognosis failed into a single group

TABLE 1 Sample parameters of demographic, clinical and chromosome 3 status variables.

	Frequency or mean
Age	69.27 (SD 12.33)
Gender	
Male	305 (51.8%)
Female	284 (48.2%)
Employment status	
Employed	220 (37.4%)
Homemaker	19 (3.2%)
Retired	291 (49.4%)
Sick leave/Medically retired	9 (1.5%)
Other	42 (7.1%)
Not known	8 (1.4%)
Marital status	
Married or co-habiting	439 (79.6%)
Separated	39 (6.6%)
Widowed	74 (12.6%)
Single	36 (6.1%)
Not known	2 (0.3%)
Eye	
Left	289 (49.1%)
Right	300 (50.9%)
Treatment	
Enucleation	159 (27.00%)
Plaque radiotherapy	257 (46.6%)
Proton beam radiotherapy	125 (21.2%)
Resection	32 (5.4%)
Other	16 (2.7%)
Chromosome 3 status	
Poor prognosis (M3 – mutation)	155 (26.3%)
Good prognosis (D3 – non-mutation)	143 (24.3%)
Not tested/fail	291 (49.4%)

TABLE 2 Means and SDs for study variables at each observation.

	6 months $n=589$[a]	12 months $n=523$	24 months $n=488$	36 months $n=434$	48 months $n=402$	60 months $n=361$
Full sample						
FCR	2.44 (0.91)	2.24 (0.78)	2.11 (0.80)	2.00 (0.76)	2.00 (0.78)	1.99 (0.77)
Anxiety	5.39 (4.19)	5.15 (4.25)	4.96 (4.00)	5.01 (4.13)	4.86 (3.98)	5.03 (4.10)
Depression	3.22 (3.36)	3.27 (3.50)	3.06 (3.36)	3.22 (3.68)	3.17 (3.28)	3.22 (3.59)
Poor prognosis						
FCR	2.62 (0.85)	2.38 (0.85)	2.31 (0.79)	2.14 (0.73)	2.12 (0.78)	2.13 (0.75)
Anxiety	6.02 (4.59)	5.61 (4.51)	5.18 (4.28)	5.42 (4.15)	5.32 (4.19)	5.20 (4.02)
Depression	3.67 (3.50)	3.59 (3.66)	3.47 (3.76)	3.50 (3.75)	3.26 (3.31)	3.04 (3.33)
Good prognosis						
FCR	2.25 (0.90)	2.07 (0.81)	1.96 (0.74)	1.92 (0.83)	1.94 (0.79)	1.97 (0.81)
Anxiety	4.88 (3.96)	4.56 (4.04)	4.67 (4.07)	4.47 (4.25)	4.46 (3.98)	4.57 (4.05)
Depression	2.55 (2.69)	2.53 (3.09)	2.62 (3.13)	2.64 (3.31)	2.78 (3.23)	2.92 (3.61)
Not tested/Failed						
FCR	2.44 (0.94)	2.24 (0.90)	2.07 (0.82)	1.96 (0.73)	1.97 (0.76)	1.95 (0.76)
Anxiety	5.31 (4.06)	5.17 (4.17)	4.99 (3.74)	5.15 (4.00)	4.89 (3.84)	5.28 (4.17)
Depression	3.37 (3.53)	3.47 (3.56)	3.06 (3.17)	3.45 (3.85)	3.42 (3.28)	3.54 (3.69)

[a]Means reflect non-imputed data and numbers are those who provided data at each observation.

for analysis, we compared the two groups on all study variables at baseline. We found no differences; thus, we combined the two groups for subsequent analyses. There were 5 (3.5%) deaths in the good prognosis group, 31 (20.0%) in the poor prognosis group and 25 (8.59%) in the not tested group. Participants' 3-month summary statistics are provided in Table 1 and mean scores of study variables at each timepoint in Table 2. FCR generally abated over time and was greater in the 'poor' prognosis group. Anxiety and depression were consistently higher in the 'poor' prognosis group but moderated slightly over time.

Correlation analyses

Appendix 2: Data S1 shows moderate positive correlations between FCR and anxiety and depression, within and between observations, in all prognostic groups. Some violations of autoregressive assumptions occurred. The autoregressive paths for FCR did not decrease monotonically over time lags. Anxiety and depression showed better adherence to autoregressive assumptions, but again, their decrease over successive time lags was not monotonic. Prospective prediction by FCR of depression and anxiety did not monotonically decrease as time lags lengthened.

Random intercept cross-lagged panel models

Table 3 shows model fit and between-group comparisons (full model parameters in Appendix 3: Data S1, MPlus code Appendix 4: Data S1). Model fit was only moderate for the unconstrained models for anxiety ($X^2=453.45$, $df=175$; REMSA = .093; CFI = .938) and depression ($X^2=412.29$, $df=175$; REMSA = .086; CFI = .942), possibly attributable to the above-described violations in autoregressive assumptions. Group comparisons showed the unconstrained anxiety model ($X^2=26.27$, $df=10$, $p<.01$), but not the depression model ($X^2=5.31$, $df=10$, $p=.870$), to have a better fit than the constrained models. Additional two-group comparisons for anxiety showed both unconstrained models to be better

TABLE 3 Model fit, group comparison and standardized coefficients for lagged FCR/Anxiety and FCR/Depression paths.

	Model fit, group comparison and standardized coefficients		
Anxiety			
Unconstrained model fit	$X^2 = 453.45$, $df = 175$; REMSA = .093; CFI = .938		
Constrained model fit	$X^2 = 479.71$, $df = 185$; REMSA = .093; CFI = .935		
Fit difference	$X^2 = 26.27$, $df = 10$, $p < .01$		
Fit difference (Good vs. Poor prognosis)	$X^2 = 12.79$, $df = 5$, $p < .01$		
Fit difference (Good vs. Not tested)	$X^2 = 19.17$, $df = 5$, $p < .01$		
	Good prognosis	**Poor prognosis**	**No test**
T1 FCR/T2 anxiety	−.15	.27*	−.23*
T2 FCR/T3 anxiety	.03	.10	.03
T3 FCR/T4 anxiety	.08	−.17	−.28*
T4 FCR/T5 anxiety	.05	.03	.07
T5 FCR/T6 anxiety	.05	.15	.10
RI corr. FCR/anxiety	.51	.67	.66
Depression			
Unconstrained model fit	$X^2 = 412.29$, $df = 175$; REMSA = .086; CFI = .942		
Constrained model fit	$X^2 = 417.60$, $df = 1851$; REMSA = .082; CFI = .943		
Fit difference	$X^2 = 5.31$, $df = 10$, $p = .870$		
	Good prognosis	**Poor prognosis**	**No test**
T1 FCR/T2 depression	.11	.10	.08
T2 FCR/T3 depression	.02	.03	−.19
T3 FCR/T4 depression	−.04	−.02	−.12
T4 FCR/T5 depression	.08	.03	.00
T5 FCR/T6 depression	.06	.07	.13
RI corr. FCR/depression	.43	.55	.44

* indicate significant at p <.05.

fit than constrained models (Good versus poor prognosis, $X^2 = 12.79$, $df = 5$, $p < .01$; Good prognosis vs. not tested, $X^2 = 19.17$, $df = 5$, $p < .01$). Table 3 shows that the poor prognosis group differed from the other two groups in that cross-lagged standardized coefficients from FCR → anxiety were more positive in the poor prognosis group. In particular, 12-month anxiety was significantly predicted by 6-month FCR. No positive prospective links were significant in the good prognosis or no test groups. We also noted significant negative paths from 6 and 24-month FCR to 12 and 36-month anxiety, respectively, in the no test group.

Retention analysis

A logistic regression was performed to compare the T1 variables of those retained in the study at T6 and those who dropped out. The model was significant ($X^2 = 49.18$, $df = 7$, $p < .01$; Cox-Snell $R^2 = .083$; Nagelkerke $R^2 = .112$). Unsurprisingly, membership of the poor prognosis group increased the risk of dropout (standard coefficient = 3.67 (95%C.I 2.22, 6.08)). Lower depression scores were also associated with dropout (standard coefficient = 0.91 (95%C.I 0.85, 0.98)).

DISCUSSION

Our key finding was that FCR is more likely to develop into elevated anxiety symptoms when proportionate to higher recurrence risk. Specifically, FCR was most strongly predictive of anxiety amongst participants in the poor prognosis group, who knew that they were at high risk of progression. Three-month FCR significantly predicted six-month anxiety. Indeed, this was the only prognostic group to show any significant positive prediction of anxiety or depression. There was no evidence that FCR prospectively predicted depression.

We based the proportionality hypothesis on risk communication and phobia literature. Both suggest that objective evidence plays a particular role in the development and structure of fear because it assumes a high epistemic weight that activates a wider range of emotional and cognitive responses than less evidence-based fear processes (Chaiken & Ledgerwood, 2012; Elsey & Kindt, 2021; Klemm et al., 2019; Kruglanski et al., 2006). In this way, a poor personal prognosis might fortify fear responses, contributing to the development of anxiety symptoms. However, it is unclear from our study exactly *why* or *how* prognoses influenced the FCR anxiety link.

One reason *why* FCR might have caused anxiety in the 'poor' prognosis group is that reliable prognosis increases the certainty of a poor outcome. We provided a prognosis that was both scientifically valid (and therefore more certain) and carried a high likelihood of death. Normally, uncertainty, not certainty, is thought to be aversive to survivors and a risk factor for FCR (Lebel et al., 2018). However, compared to the poor prognosis group, whose fates were largely fixed, uncertainty may confer benefits – members of the not tested group faced potential loss but also the possibility of a good outcome (Han et al., 2021). A large social psychology literature suggests that people can exploit uncertainty to develop and hold self-enhancing or self-preserving interpretations of reality (Brown et al., 2013; Han et al., 2021). Evidence from UM suggests that survivors seek and exploit uncertainty to build personal hope (Hope-Stone et al., 2015). Greater prognostic certainty in the poor prognosis group reduces the scope to build this hope.

Nor do the findings show *how* objective risk information is processed. Our FCR measure did not examine fear as a multidimensional construct thus, we cannot determine whether specific aspects of FCR, such as emotional distress, perceptions of vulnerability, outcome likelihood or severity, were differentially influenced by proportionality. Research is needed to examine the range of responses that may be activated by proportional FCR, and particularly to test the hypothesis that higher objective risk is associated with greater emotional arousal and higher expectations of recurrence likelihood (Elsey & Kindt, 2021; Klemm et al., 2019).

Interestingly, the risk of FCR developing into anxiety in the poor prognosis group appeared to be confined to the year after diagnosis, with the only significant path being from 6-month FCR to 12-month anxiety. This finding suggests a developmental process whereby participants become tolerant of, or desensitized to, FCR over time. Processes that might confer tolerance could involve an active process of spontaneous improvements in emotional processing as survivors adjust to cancer (Darabos et al., 2021) or post-traumatic growth (Wang et al., 2023). Alternatively, the impact of a poor prognosis on the development of anxiety from FCR may simply passively decrease as a function of the time elapsed since the prognosis.

The two unexpected negative cross-paths between FCR and subsequent anxiety in the not tested group may be attributable to the uncertainty inherent in this prognostic outcome. An implication of not knowing a prognosis is that the passage of time between observations becomes a meaningful survival indicator. Survived time reduces the overall likelihood of chromosome 3 mutation and thus could provide relief. We speculate that participants with greater initial FCR experienced proportionally higher levels of relief upon staying healthy. Relief is inimical to anxiety (Papalini et al., 2021), and greater relief in fearful participants could explain the negative cross-paths.

One implication for FCR research is that models might focus more strongly on how survivors can better accept and tolerate fear in the presence of higher objective risk. Third-wave approaches, such as mindfulness (Hughes et al., 2021), acceptance and commitment therapy (Graham et al., 2016) and

metacognitive therapy (Wells, 2000, 2009), focus on the processes by which individuals respond to commonly occurring negative thoughts, rather than their content. In this way, they may be uniquely suited to the needs of patients who are faced with immutable realities, such as a 'poor' prognosis. These approaches are becoming more prominent in the FCR and general fear literature but current FCR-specific approaches are still largely focussed on appraisal processes and modification of false beliefs (Curran et al., 2020; Lebel et al., 2018; Simonelli et al., 2016; Tauber et al., 2019). We acknowledge that appraisal-based approaches are probably important to the aetiology of FCR itself, but emphasize that third-wave approaches may be more relevant to explaining and potentially preventing its development into anxiety.

It is notable that FCR was associated with anxiety but not depression. This may be attributable to differences in the aetiology of depression versus anxiety. Depression can be conceptualized as a response to loss or harm, with negative cognitions focussed on the meanings of past experiences and their implications. Anxiety, on the other hand, can be conceptualized as fears of future loss or harm (Eysenck et al., 2006). The possibility of cancer recurrence or progression is a future-oriented concern (Fardell et al., 2016) that might render people vulnerable to anxiety in particular (Hay et al., 2005).

Strengths and limitations

The strengths of the study are the consecutive sampling and prospective repeated observation design, which allow stronger interpretations of cause and temporal patterns in relationships between FCR and anxiety and depression. One limitation is that the implications of UM prognostication changed during the study, with new and trial treatments for metastatic melanoma being introduced. Whilst life expectancy benefits were not forthcoming, it is reasonable for participants to have drawn encouragement from this activity that effective treatments may emerge in the future. A limitation to internal validity is that memberships of prognostic groups were not random. A particular problem is that a poor prognosis is more likely in advanced tumours, which are more likely to be treated by enucleation (eye-removal), with adverse effects of loss of binocular vision, socket complaints, difficulties with prosthesis and phantom eye syndrome (Hope-Stone et al., 2015). We note, though, that FCR rates appear to be similar across enucleation and localized radiotherapy groups[2] (Hope-Stone et al., 2019). In addition to the prognostic grouping, findings may be influenced by the procedural implications of the prognosis; participation by patients with a poor prognosis in metastatic melanoma surveillance programmes could influence FCR and its progression to anxiety. A limitation to the transferability of findings is that UM prognostication is unique in its reliability and irreversibility. Further, prognosis or other forms of risk information in other cancers may be more nuanced in terms of being dimensional rather than categorical, less certain and contingent on fully or partially effective treatment.

Clinical implications

A key clinical goal in FCR is to prevent the development of anxiety and possibly depression. Our findings have several implications. First, aside from severe and prolonged FCR, objectively high recurrence risk is one of the few known risk factors defining sub-groups needing to be monitored and possibly treated. Second, as mentioned earlier, we see key treatment goals as helping survivors to understand and accept the unfortunate reality of higher recurrence risk and to tolerate that risk. We point to metacognitive therapy as a third-wave approach where research in cancer care has established

[2]The vast majority of patients with a poor prognosis are treated with enucleation but very few good prognosis patients. The close alignment between prognosis and treatment mean that statistical control is problematic.

theoretical underpinnings and clinical efficacy (Cherry et al., 2019; Fisher et al., 2019). In particular, a recent small-scale trial has shown acceptance and commitment of interventions to benefit people with late-stage cancer (Serfaty et al., 2018).

Reliable risk information is becoming more freely available in cancer and other areas of medical care. Health professionals could assist patients to make informed choices about whether they wish to receive potentially confronting information or not by explaining the possibility of adverse psychological consequences (Brown & Salmon, 2019). We have identified a need for resilience in cancer survivors who receive confronting predictions of recurrence risk. Currently, minimal contact interventions are being developed to promote resilience against FCR in patients (Tauber et al., 2019). Some use metacognitive and mindfulness principles, which as argued earlier, could be effective at reducing links between FCR and cancer in those who know that they are at a high objective risk of recurrence.

AUTHOR CONTRIBUTIONS

Stephen L. Brown: Conceptualization; investigation; writing – original draft; methodology; validation; visualization; writing – review and editing; software; formal analysis; project administration; data curation; supervision. **Laura Hope-Stone:** Writing – review and editing; project administration; visualization. **Nicola van der Voort:** Writing – review and editing; project administration. **Rumana Hussain:** Writing – review and editing. **Heinrich Heimann:** Writing – review and editing. **William L. Coventry:** Formal analysis. **Mary Gemma Cherry:** Conceptualization; methodology; writing – review and editing; visualization.

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CONFLICT OF INTEREST STATEMENT

The authors do not have conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are not publicly available because participants did not provide permission for publication of individual data. Data can be obtained from the first author.

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