Anxiety, Depression, and Fear of Cancer Recurrence in Head and Neck Cancer

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Abstract

Objective: Patients with head and neck cancer (HNC) report some of the highest levels of psychological distress amid managing their disease as well as debilitating and disfiguring treatment side effects. Fear of cancer recurrence (FCR) is a top unmet need and concern of patients with HNC. Prior research suggests elevated symptoms of anxiety and depression are potential antecedents to FCR, but findings have been limited in HNC populations. The aim of the present study was to examine early level and change in symptoms of anxiety and depression in relation to later change in FCR among patients with HNC.

Methods: The study is a secondary analysis of data collected from 2011-2014 through the Head and Neck 5000 Study in the United Kingdom. A sample of 4891 patients completed self-report longitudinal assessments of anxiety and depression symptoms at baseline, 4, and 12 months and FCR at 4 and 12 months.

Results: Utilizing multiple indicator latent change score modeling, results revealed baseline anxiety and increases in anxiety from baseline to 4 months were both positively associated with increases in FCR from 4 to 12 months. Neither baseline depression nor change in depression from baseline to 4 months were significantly associated with FCR change.

Conclusions: Findings indicate that early level and increases in symptoms of anxiety were markers of increased FCR in patients with HNC. Future research may consider anxiety as a unique antecedent and maintaining factor of FCR and targeting anxiety early in the cancer trajectory may have downstream effects on FCR development.

Public significance statements: This study examined change in fear of cancer recurrence (FCR) as a function of early level and change in symptoms of anxiety and depression in the year after head and neck cancer diagnosis. Results indicated that early level and increases in anxiety but not depression were associated with later increases in FCR. Identifying patients with clinically elevated anxiety and ensuring early intervention may mitigate possible downstream development of FCR.

Keywords: head and neck cancer, anxiety, depression, fear of cancer recurrence, change models

Anxiety, Depression, and Fear of Cancer Recurrence in Head and Neck Cancer

Head and neck cancer (HNC) encompasses a wide range of cancers occurring within four major anatomical sites of the head and neck, including the oral cavity, sinonasal cavity, pharynx, and larynx (Chow, 2020). Globally, HNC is the seventh most common cancer group accounting for 900,000 new cases each year with a five-year survival rate of approximately 65% for all patients (Chow, 2020; Pulte & Brenner, 2010). Risk factors for HNC include tobacco and alcohol use and more recently human papillomavirus (HPV) (Chow, 2020). Surgery, radiation, and combined chemoradiation are standard treatments for HNC (Chow, 2020). Due to the anatomical location of HNC, treatments may result in highly visible disfigurement and long-term functional impairments related to eating, speaking, and breathing (Howren et al., 2013; Obeso-Benítez et al., 2021). Amid managing their disease and treatments, patients with HNC frequently report some of the highest levels of psychological distress of all cancer groups (Howren et al., 2013; Smith et al., 2017). Untreated distress may interfere with a patient's ability to cope with their disease, impede long-term quality of life, and contribute to worse physical and emotional outcomes (Alias & Henry, 2018; Campbell et al., 2000; Smith et al., 2017).

Psychological distress in cancer populations is often expressed and measured in symptoms of anxiety and depression. Anxiety and depression symptoms frequently develop or worsen in response to a cancer diagnosis and treatment, but there is great variability in reported prevalence rates (Howren et al., 2013; Linden et al., 2012). Across all cancer groups, it is typical for patients to experience higher rates of anxiety pretreatment with a steady decline over time, whereas depression tends to be lower pretreatment, peak mid-to-late treatment, and then often return near baseline levels (Hammerlid et al., 1999; Wu et al., 2016; Yi & Syrjala, 2017). In a sample of HNC patients during the first year after diagnosis, the prevalence of mild-to-severe anxiety and depression symptoms pretreatment was 30% and 15%, respectively (Neilson et al., 2010). Following treatment, about 3 months after diagnosis, the prevalence of mild-to-severe anxiety decreased to 17% and depression increased to 31% (Neilson et al.,

2010). Transient symptoms of anxiety and depression are expected with a cancer diagnosis, but some patients may experience heightened and prolonged symptoms given the complexity of HNC, its treatments, and the associated side effects (Alias & Henry, 2018; Howren et al., 2013; Nordin et al., 2001). Prolonged distress may lead to additional psychological concerns such as post-traumatic stress disorder, major depression, or fear of cancer recurrence (Alias & Henry, 2018; Archer et al., 2008; Lydiatt et al., 2009; Mirosevic et al., 2019).

Fear of cancer recurrence or progression (FCR) is defined as the "fear, worry, or concern relating to the possibility that cancer will come back or progress" (Lebel et al., 2016, p. 3267). FCR is widely recognized as a top concern and important unmet need among cancer patients and survivors (Lebel et al., 2016; Lee-Jones et al., 1997; Simard et al., 2013). Prior research reports that nearly half of all patients with cancer experience elevated FCR, and without intervention these levels tend to remain stable over time (Ghazali et al., 2013; Koch et al., 2013; Luigjes-Huizer et al., 2022; Savard & Ivers, 2013; Simard et al., 2013). Unmanaged FCR may cause disruptions in daily functioning and negatively influence mood, relationships, quality of life, and be associated with excessive healthcare use beyond medical benefit (Hodges & Humphris, 2009; Otto et al., 2018; Rogers et al., 2010; Simard et al., 2013; Van Liew et al., 2014).

Across all cancer groups, including HNC, characteristics such as younger age, female sex, substance use (e.g., tobacco and alcohol), psychological factors (e.g., depression, anxiety, isolation), treatment type (e.g., chemotherapy and/or radiation), and greater physical symptoms have been associated with heightened FCR (Crist & Grunfeld, 2013; Hall et al., 2017; Luigjes-Huizer et al., 2022; Savard & Ivers, 2013; Simard et al., 2013). Medical characteristics such as cancer stage, tumor site, or time since diagnosis generally have inconsistent associations with FCR (Crist & Grunfeld, 2013; Llewellyn et al., 2008; Simard et al., 2013). Patients with HNC are particularly vulnerable to experiencing FCR given their overlap with the following identified risk factors: heightened psychological distress, substance use

history, extensive treatment regimens and side effects, and greater physical symptom burden (Ghazali et al., 2013; Humphris, 2004; Rogers, Monssen, et al., 2021; Smith et al., 2017). When compared to other cancer groups, patients with HNC report high prevalence rates (>30%) of elevated FCR across the cancer trajectory (Ghazali et al., 2013; Humphris et al., 2003; Llewellyn et al., 2008; Savard & Ivers, 2013; Van Liew et al., 2014). A recent study (Mirosevic et al., 2019) of newly diagnosed HNC patients found that elevated levels of FCR were reported in 52.8% of the sample in the first year after diagnosis, and about 21% of those patients had a lifetime history of anxiety or depression.

Multiple FCR theoretical models include anxiety, depression, and distress in their frameworks suggesting the importance of psychological morbidity in the development and maintenance of FCR (Curran et al., 2017; Fardell et al., 2016). The Cognitive Processing Framework developed by Fardell et al. (2016) provides a theoretical foundation for further understanding the relationship between FCR and symptoms of anxiety and depression. The model posits that distress and worry are normal responses to a cancer diagnosis, but those who exhibit chronic and exacerbated cancer-related distress may develop unhelpful beliefs about worry and stress that can lead to a cognitive attentional syndrome including worry, rumination, self-focused attention, and threat monitoring with attempts to control, avoid, or suppress FCR (Fardell et al., 2016). To cope with this cognitive attentional syndrome, patients may engage in maladaptive coping mechanisms such as hypervigilant and/or avoidant behaviors with poor future planning. Therefore, examining early symptoms of anxiety and depression to identify those exhibiting chronic and elevated psychological distress may be a useful prognostic indicator for identifying patients who develop FCR.

Prior research examining the relationship between FCR and symptoms of anxiety and depression have revealed positive associations; however, most research has been conducted in mixed-cancer samples with a focus on baseline correlates, and research in patients with HNC has been limited to date (Crist & Grunfeld, 2013; Luigjes-Huizer et al., 2022; Simard et al., 2013). In a systematic review of 130

studies examining FCR in cancer survivors, only four investigated FCR in patients with HNC (Simard et al., 2013). Additionally, in a more recent systematic review on the prevalence rates and predictors of FCR across cancer groups, patients with HNC were not reported in the breakdown of FCR by cancer type (Luigjes-Huizer et al., 2022). In the few studies to date that have examined FCR in patients with HNC, most studies report a positive association between symptoms of anxiety and depression and FCR (Ghazali et al., 2013; Hodges & Humphris, 2009; Humphris, 2004; Llewellyn et al., 2008; Mirosevic et al., 2019; Rogers, Monssen, et al., 2021; Van Liew et al., 2014). However, the majority of these studies included small patient samples, and only a few have examined prospective relationships between symptoms of anxiety and depression and FCR. Specifically, no studies to date have examined the prospective relationship between early change in anxiety and depression in association to change in FCR in patients with HNC.

Overview of the Present Study and Hypotheses

Symptoms of anxiety and depression may be important precursors to the development of FCR, yet there is a lack of research examining the dynamic process of change in these symptoms during the first year after a cancer diagnosis and its prospective relationship to FCR. The overarching objective of the present study was to examine early change in symptoms of anxiety and depression in relation to later change in FCR throughout the first year after a HNC diagnosis. The aim of the present study was to 1) examine the baseline levels and early changes in symptoms of anxiety and depression during the early period of the first year following HNC diagnosis, and 2) determine the relationship of the baseline level and change scores in predicting later change in FCR after the completion of primary treatment and into the initial phase of survivorship. Based both in theory and past research, it was hypothesized that greater baseline levels of anxiety and depression would independently be predictive of later increases in FCR. It was further hypothesized that early increases in symptoms of anxiety and depression would be predictive of later increases in FCR following HNC diagnosis and treatment.

Method

The present study is a secondary analysis of data collected as part of the Head and Neck 5000 Study (H&N5000). The H&N5000 is a large prospective observational study undertaken in the United Kingdom (UK) aimed at creating a clinical cohort of HNC patients to explore survival trends and predictors. Through the UK National Health Services (NHS), the H&N5000 study was reviewed and given a favorable opinion by the Office for Research Ethics Committees Northern Ireland and the Integrated Research Application System (#211454). The parent study was monitored by the Research and Development Department in the University Hospitals Bristol NHS Foundation Trust. The present study was approved with exempt determination (#1897577) in April 2022 by the Institutional Review Board at the University of Delaware.

Participants and Procedures

Participants were recruited from head and neck clinics across the UK from April 2011 to December 2014. Patients were identified at multidisciplinary team meetings and asked to participate by their clinical team. Research nurses provided study information leaflets and approached patients at planned clinic appointments to further explain the study and obtain written informed consent. Patients were recruited shortly after diagnosis and prior to the start of any cancer treatments. All patients > 18 years of age and newly diagnosed with head and neck cancer (e.g., pharynx, mouth, larynx, salivary, or thyroid) were eligible to participate. Patients were excluded from participating if they had lymphoma, skin cancer, a recurrence of a previous HNC, did not have HNC, or were considered to not have the mental capacity to provide informed consent. Participants did not receive compensation for their time and effort in the study.

The final enrolled cohort included 5,511 patients from 11,158 eligible patients yielding an enrollment rate of approximately 49% (Ness et al., 2015). Original data collection included three assessments in the first year after diagnosis: baseline, 4 months, and 12 months following diagnosis.

These timepoints were selected to map on to the typical HNC treatment trajectory where baseline captures the experience of diagnosis, 4 months is near the end of primary treatment, and 12 months is the beginning of survivorship. The H&N5000 team added additional follow-up assessments to observe the cohort into long-term survivorship, but for the purposes of this study only longitudinal data assessments from the first year are used in analyses. Additional information on recruitment, data collection procedures, a CONSORT diagram, and missingness of data are detailed in previous reports of the parent study (Ness et al., 2014, 2015).

Measures

Fear of Cancer Recurrence. The Fear of Cancer Recurrence-4 (FCR-4) measured FCR at the 4- and 12-month timepoints. The FCR-4 is a brief unidimensional self-report measure including four questions capturing fear and worry of cancer recurrence that has demonstrated strong reliability (α = .93) in past research (Humphris et al., 2018). Within the current study the FCR-4 also demonstrated strong reliability at the 4- (α = .94) and 12-month (α = .94) timepoints. Scores range from 4-20 with higher scores signifying greater FCR burden, with scores ≥ 10 considered moderate and scores ≥ 15 considered severe FCR (Humphris et al., 2018). The items include, "*I am afraid that my cancer may recur*," "*I am worried or anxious about the possibility of cancer recurrence*," "*How often have you worried about the possibility of getting cancer again,*" and "*I get waves of strong feelings about the cancer coming back*." Responses were reported on a Likert scale ranging from 1 (*Not at all*) to 5 (*All the time*).

Anxiety and Depression. The Hospital Anxiety and Depression Scale (HADS) assessed symptoms of anxiety and depression at all timepoints. The HADS is a 14-item self-report measure specifically used with medical populations to screen for distress expressed in symptoms of anxiety and depression (Bjelland et al., 2002; Zigmond & Snaith, 1983). Scores on the HADS range from 0-21 on each anxiety and depression subscale with higher scores denoting greater symptom presentation. Within the current

study, the anxiety subscale at baseline (α = .87) and 4 months (α = .88) and the depression subscale at baseline (α = .85) and 4 months (α = .87) demonstrated good reliability. Anxiety subscale items include language concerning worries, restlessness, and fear. An example item is "*I get sudden feelings of panic*". Depression items include language regarding symptoms of anhedonia and hopelessness. An example reverse-coded item is "*I look forward with enjoyment to things*". All items included Likert scale responses ranging from 0 (*Definitely*) to 3 (*Not at all*) with certain responses reverse coded.

Covariates. Demographic and clinical characteristics were collected via self-report questionnaires and through medical record review at baseline. Age, sex, disease stage, cancer site, and type of planned treatment were variables considered as covariates in analyses based on associations with the main variables of interest in the present study. Sex and age were collected via self-report measures, and a trained research nurse performed medical record reviews at baseline to capture disease stage, cancer site, and planned treatment.

Analytic Approach

Data were analyzed using structural equation modeling in version 8 of Mplus (Muthén & Muthén, 2017). As a first step, confirmatory factor analyses were conducted to construct and evaluate separate error-free unidimensional latent variables of anxiety, depression, and FCR. A latent factor of FCR was created with the four observed items of the FCR-4 measure. Latent factors of anxiety and depression were created utilizing seven observed items each from the HADS measure relating to anxiety and depression, respectively. Model fit was examined with model chi-square values, comparative fit index (CFI), root mean square error of approximation (RMSEA), and standardized root mean squared residual (SRMR). Although a chi-square p-value > 0.05 is preferred as an indicator of model fit, chi-square is known to be increasingly sensitive to small residuals as sample size increases, therefore chi-square p-values will not be interpreted (Kline, 2016).

To ensure a three-factor model was appropriate for analyses, a model with anxiety and depression as one latent factor of "distress" was examined but demonstrated poor fit ($\chi 2$ (134) = 4413.49 , $p < 0.001$.; RMSEA = 0.098 (90% CI: 0.096, 0.101); CFI = 0.891; SRMR = 0.063), suggesting that these constructs are distinct and should remain as individual factors. Additionally, given the potential overlap of anxiety and FCR, a model with both constructs as one latent factor was estimated but also demonstrated poor fit ($\chi 2$ (134) = 8789.56 , $p < 0.001$; RMSEA = 0.140 (90% CI: 0.137, 0.142); CFI = 0.780; SRMR = 0.103). Ultimately, a three-factor model of anxiety, depression, and FCR as separate latent constructs demonstrated acceptable fit ($\chi 2$ (132) = 2231.18, $p < 0.001$; RMSEA = 0.069 (90% CI: 0.067, 0.072); CFI = .947; SRMR = .046) and was used in the final analyses. Coefficient omega (McDonald, 2013) a factor-based index of internal consistency was acceptable for each factor across all timepoints: baseline anxiety (ω = .88), change in anxiety (ω = .89), baseline depression (ω = .98), change in depression (ω = .98), 4-month FCR (ω = .94), and 12-month FCR (ω = .95).

A multiple indicator latent change score model was estimated using full information maximum likelihood (FIML) to make use of all participants' data at all available waves in the H&N5000 sample, including participants who only completed one timepoint (Kievit et al., 2018; McArdle, 2009). Additionally, the multiple indicator latent change score model allowed change to be modeled over time with multiple latent variables constructed from multiple items rather than modeling change with observed indicators. Specifically, the model was used to create error-free latent level and change factors for anxiety and depression at baseline and from baseline to 4 months (early change), as well as estimate latent level and change in FCR from 4 to 12 months (later change). Then, later change in FCR from 4 to 12 months was estimated as a function of early level and change in anxiety and depression. Two-tailed significance tests of parameters were conducted using an alpha of .05 and variable distributions were examined to verify that model assumptions were met. In the final model, latent FCR change scores were regressed simultaneously on baseline latent anxiety, baseline latent depression, anxiety latent change,

and depression latent change. Patients were only excluded from analyses if they had completely missing data that is data missing at all timepoints. Patient age, sex, disease stage, cancer site, and type of treatment were included as covariates in the model.

Results

The final analyses in the present study included 4891 patients with HNC. Table 1 shows sociodemographic and clinical characteristics of study participants. The mean age at diagnosis was 61 years old (range =18-96, *SD* = 12) with 91.4% identifying as White British, 72.8% identifying as male, and 57% being married. Slightly more than half (55.4%) of participants reported an annual household income less than £22,999 and nearly half (46.9%) reported that their highest level of education completed was primary or secondary school. The majority of participants were current or former tobacco users (75.4%), and participants drank alcohol 2.85 (*SD* = 2.6) days a week and consumed about 30.32 (*SD* = 29.16) drinks per week on average. The most common HNC cancers were of the pharynx region followed by oral cavity and larynx. Most participants were diagnosed with stage I-III disease (53.8%) and received surgery followed by radiation and/or combined chemoradiation. When considering health co-morbidities, half of participants (50.5%) had mild or moderate decompensation relating to other health ailments outside of their current HNC diagnosis. At the 4-month timepoint, 1.5% of patients had a recurrence of HNC and at 12 months this increased to nearly 10% of patients with recurrent disease.

When examining descriptive change in symptoms of depression and anxiety from baseline to 4 months, 34.2% of patients exhibited increases in anxiety, 13.8% had no change in their anxiety, 59.3% showed increases in depression, and 17.3% showed no change in depressive symptoms, respectively. Prior literature in other medical populations determined a cut point of at least 1.5 points on the HADS to signify a minimal clinically important score difference (Lemay et al., 2019; Puhan et al., 2008). Based on this cut point, among the subset of patients exhibiting increases in symptoms, approximately 67% and

74% of patients reported clinically significant increases in their anxiety and depression from baseline to 4 months, respectively.

Effects of Anxiety and Depression on FCR Change

Table 2 shows the descriptive statistics and bivariate correlations for key study variables. The final multiple indicator latent change score model including covariates demonstrated acceptable fit: $\chi 2$ (801) = 6039.83, p = 0.00; RMSEA = 0.037 (90% CI: .036, .037); CFI = 0.934; SRMR = 0.041 and produced a converged solution. Figure 1 shows the reduced path model with key standardized parameter estimates. Baseline anxiety was positively associated with FCR change (*b* =.426, *SE*=.072, *p* < .001), indicating that a one-unit increase in baseline anxiety was associated with a .426-unit increase in FCR from 4 to 12 months. Anxiety latent change from baseline to 4 months was also positively associated with FCR change (*b* = .241, *SE* = .076, *p* = .002), indicating that a one-unit increase in anxiety from baseline to 4 months was associated with a .241-unit increase in FCR from 4 to 12 months. Neither baseline depression (*b* = .059, *SE* = .058, *p* = .312) nor change in depression from baseline to 4 months (*b* = .014, *SE* = .057, *p* = .802) were significantly associated with FCR change from 4 to 12 months. No covariates included in the model were significantly associated with FCR change. The explained variance of the model yielded an R^2 of .20, indicating that 20% of the variance in FCR change was accounted for in the final model.

The model was rerun with the addition of baseline alcohol and tobacco use to which the results did not change, and covariates remained not significant within the model. Further exploratory analyses examined this model separately in early (stage I and II) and advanced stage (stage III and IV) patients. Results revealed no significant difference in model results in the advanced stage sample (all *p* < .05), indicating that early level and increases in anxiety from baseline to 4 months were still significantly associated with change in FCR from 4 to 12 months. In the early stage sample, baseline level anxiety remained a significant predictor (*p* < .001); however, change in anxiety from baseline to 4 months was

no longer significantly associated (p = .20) with change in FCR and younger age become a significant covariate (b = -.005, SE = .002, p = .007) associated with increases in FCR from 4 to 12 months.

Discussion

The current study sought to investigate change in FCR during the first year following HNC diagnosis and treatment as a function of early level and change in symptoms of anxiety and depression in a large clinical patient cohort. Results of this prospective study indicated that baseline anxiety and change in anxiety were each uniquely associated with later change in FCR. Specifically, findings support the proposed hypotheses that greater baseline anxiety and increases in anxiety from baseline to 4 months were predictive of increases in FCR from 4 to 12 months. Counter to study hypotheses, neither baseline depression nor change in depressive symptoms were associated with later change in FCR. Results provide empirical evidence for a path between symptoms of anxiety and FCR and underscores the need for psychological symptom monitoring and intervention early and throughout the cancer care trajectory. Findings align with existing literature and contribute to the greater understanding of FCR development while emphasizing several important areas for clinical and research intervention.

The observed effects of anxiety in the current study are consistent with current literature and FCR models where anxiety-related processes have been closely linked to FCR (Curran et al., 2017; Fardell et al., 2016; Simard et al., 2013). Symptoms of anxiety are a common response to a threat such as cancer and may be adaptive for managing appointments, treatment, and healthcare decision-making; but, at some point, anxiety may become maladaptive (Fardell et al., 2016; Stark & House, 2000; Yi & Syrjala, 2017). Model results explained nearly one-fifth of the variance in FCR change and provide support for the Cognitive Processing Framework proposed by Fardell et al. (2016), that when symptoms of anxiety are not managed properly early in the cancer continuum, maladaptive anxiety may develop and manifest into FCR. The two assessments of anxiety in the current study provide unique information, in that baseline anxiety may reflect the initial spike in anxiety at diagnosis or patients who are

predisposed to anxiety, however the following increases in anxiety among nearly a third of patients may reflect a more chronic condition that is linked to FCR development. FCR is best conceptualized as a multidimensional construct with significant cognitive, affect, and behavioral components (Fardell et al., 2016; Lee-Jones et al., 1997). The significance of anxiety in the development of FCR may reflect the importance of cognitive worry for patients. Particularly, patients may see worry as a way to be 'prepared' for recurrence through vigilance and self-monitoring of physical symptoms (Fardell et al., 2016). As proposed in the Cognitive Processing Framework (Fardell et al., 2016), unhelpful beliefs around worry can lead to the development of a cognitive attentional syndrome with continuous worry, rumination, hypervigilance, and self-monitoring that may result in maladaptive behaviors to manage and suppress uncontrollable thoughts related to FCR.

Findings revealed that depression was not a significant predictor of change in FCR, adding to the growing literature of inconsistent results between depression and FCR (Simard et al., 2013). In the current sample, about a third of patients exhibited increases in anxiety and over half showed increases in depressive symptoms from baseline to 4-months, demonstrating that depression was a prevalent symptom among patients. However, the lack of observed effects suggest that depression may not be a unique psychological antecedent to FCR, and further supporting the overlap between anxiety and FCR. However, prior literature has noted a significant link between depression and FCR in the context of rumination (Liu et al., 2018). While depressive rumination may be an important factor in FCR development, the current study was limited to the HADS depression subscale. The subscale greatly relies on symptoms of anhedonia and does not capture the full range of depressive symptoms such as sleep disturbance, suicidal ideation, or rumination (Coyne & van Sonderen, 2012; Smith et al., 2017). Future research should consider measures that capture a range of anxiety and depressive symptoms experienced by patients with HNC and specifically explore depressive rumination and cognitive worry in relation to the development and maintenance of FCR.

In the current study further analyses reveled that change in anxiety from baseline to 4 months was no longer predictive of change in FCR from 4 to 12 months for those with early stage HNC, suggesting that although early stage patients may still be experiencing anxiety, it is no longer associated with FCR. Notably, in this early stage model, younger age become a significant covariate associated with change in FCR. In a number of prior studies, younger age has been associated with greater levels of FCR across cancer groups (Crist & Grunfeld, 2013; Luigjes-Huizer et al., 2022; Simard et al., 2013). In the current study, the early stage sample may consist of a greater proportion of younger patients, thus age may be accounting for more of the variance in FCR change than increases in anxiety for this group. Furthermore, the main study findings held significance in the advanced stage sample, perhaps reflective of the psychological distress and uncertainty experienced by patients living with advanced stage HNC and facing greater rates of recurrence (Alias & Henry, 2018; Lang et al., 2013). Conceptual models of FCR suggest that patients who see their disease as more chronic rather than an acute concern may experience greater symptoms of FCR; yet disease stage is not consistently associated with FCR and research remains limited on the experience of FCR in advanced stage samples (Curran et al., 2017; Lee-Jones et al., 1997).

In recent decades HNC has evolved with the emergence of HPV-related disease as well as treatment advancements such as the combined use of chemotherapy and radiation and the integration of multidisciplinary teams, resulting in better overall prognosis and survival with a growing number of patients in survivorship or living with HNC (Chow, 2020). These advancements should be considered when interpreting the current study findings as these data were collected nearly 10 years ago. The presentation of psychological symptoms and FCR among patients today may differ with improved outcomes and perhaps reductions in comorbidities, recurrence rates, and death when compared to the current sample. However, HNC and its associated treatments continue to leave many patients with long-term side effects and functional impairments that may be key components in the anxiety and FCR

experienced by patients (Alias & Henry, 2018; Nguyen & Ringash, 2018). Unique HNC survivorship considerations include disfigurement and physical symptom burden as well as important health behaviors such as continued tobacco and alcohol use (Alias & Henry, 2018; Hall et al., 2017; Howren et al., 2013; Nguyen & Ringash, 2018). Further research is needed to investigate the psychosocial experience of patients amid the changing HNC landscape, with considerations of demographic and medical factors in relation to psychological morbidity and FCR development.

Results from the current study highlight the importance for frequent psychological screening procedures in outpatient cancer settings as recommended by the American Society of Clinical Oncology (Andersen et al., 2014). Importantly, screening procedures ensure effective and efficient use of resources when followed by a stepped-care model to connect patients with appropriate care based on their symptom severity and clinical presentation (Andersen et al., 2023; Prins et al., 2022). Regular monitoring of psychological symptoms can help to identify patients who demonstrate chronically elevated anxiety and ensure early intervention and referral to supportive care services to mitigate the possible downstream development of FCR (Prins et al., 2022). ln a recent systematic review and meta-analysis of interventions for FCR across all cancer groups, small but significant and lasting intervention effects were found, and larger effects were demonstrated by a number of factors including the use of more contemporary cognitive behavioral therapies that have a greater focus on cognitions (Tauber et al., 2019). Clinical and research interventions focused on cognitive flexibility such as acceptance and commitment therapy or metacognitive therapy may help to support patients in reducing the importance of cognitive worry and aid in managing uncertainty while living with HNC (Curran et al., 2017; Hayes et al., 2006). Additionally, mind-body interventions including cognitive behavioral therapies, meditation, and relaxation strategies have demonstrated small-to-medium effects for reducing FCR, and may assist patients in challenging unhelpful worry, managing triggers, and reducing self-monitoring behaviors (Hall et al., 2018). Psychological interventions specifically for patients with HNC is a growing area of research

(Richardson et al., 2019), and only one intervention to date has targeted FCR in patients with HNC where effects were not maintained at follow-up (Humphris & Rogers, 2012). Nevertheless, recent research has demonstrated interventional benefit with the integration of self-report measures specific to patients' physical and emotional concerns such as the Patients Concerns Inventory (PCI) in outpatient medical settings (Rogers, Allmark, et al., 2021; Rogers et al., 2009). Utilizing tools to tailor medical consults and referrals for unmet needs, such as FCR, may benefit patients with HNC who experience high emotional and physical symptom burden. Taken together, considering the antecedents and mechanisms underlying FCR may aid in the development and enhancement of effective interventions and clinical services for patients.

Strengths and Limitations

A significant strength of this study was the design that was derived from a large prospective clinical cohort recruited from multiple sites across the UK, with three timepoints during the first year after HNC diagnosis. The size of the cohort allowed us to make robust inferences with the use of the multiple indicator latent change score model utilizing error-free latent change variables. However, due to the observational nature of the parent study, causation cannot be determined but temporal sequence may be inferred given the longitudinal design. Additionally, the sample was homogeneous in sociodemographic data and heterogenous in clinical presentation. While the study sample is reflective of the UK population that was reported to be 85% White British in 2019 (Office for National Statistics, 2021), these results may not generalize to individuals of other races, ethnicities, or geographic regions. Furthermore, these data were collected nearly 10 years ago, with the ever evolving advancements in HNC these data may not fully capture the current experience of patients with HNC. This study included a variety of HNCs that each carry unique risks, treatment plans, and diagnostic experiences that may contribute to differences in distress and FCR. Importantly, patients with HNC have a significant risk for recurrence and 480 patients in the current study had a recurrence between the 4- and 12-month

timepoints. Although the greatest number of recurrences was noted at 12 months, the authors were unable to determine who died from their recurrence or to differentiate timing of when patients completed the FCR measure and when they experienced a recurrence. As a result, patients may have completed the FCR measure after experiencing a recurrence which may have complicated their interpretation and responses. Future research on FCR in patients with HNC should consider the rates of recurrence in their study design and analysis, and perhaps consider measures that directly assess fears associated with recurrence and progression.

The results of the study are limited to data from self-report measures which may have been influenced by recall bias and over-or-under reporting of symptoms. The FCR-4 is only four-items resulting in low participant burden, optimized completion in a large sample, and reduced missing data. However, the measure assessed general FCR severity and excludes other areas of FCR such as death anxiety that may be prominent in HNC given the rates of recurrence and advanced disease (Curran et al., 2017). In addition, FCR was not captured at baseline limiting our understanding of this construct at diagnosis and change of FCR over time, thus future research should focus on elucidating the timeline for FCR emergence in the HNC care trajectory. Additionally, the HADS demonstrated strong reliability in the current study, but recent research suggests the measure may be inconsistent in differentiating symptoms of anxiety from depression (Coyne & van Sonderen, 2012; Norton et al., 2012). The HADS is a commonly used measure in medical settings worldwide, but recent research has noted issues with cultural sensitivity in question wording, a strong reliance on anhedonia in the depression subscale, and a lack of questions targeting somatic symptoms across both subscales (Coyne & van Sonderen, 2012; Norton et al., 2012). Finally, analyses did not consider additional key variables that may be related to differences in FCR, such as changes in tobacco and alcohol use, physical symptoms, coping, or social support (Hall et al., 2017; Humphris, 2004; Van Liew et al., 2014). Future research should consider these

unique psychosocial components in relation to anxiety and FCR to better understand factors that modulate the maintenance of FCR in patients with HNC.

Taken together, results indicated that early symptoms of anxiety and increases in anxiety near the end of treatment were associated with later increases in FCR for patients with HNC. Findings highlight the need for psychological symptom monitoring as an important tool for identifying those who may experience chronic or increasing anxiety to coordinate appropriate intervention and supportive care services. Future research should consider anxiety as a unique antecedent and maintaining factor of FCR, and targeting anxiety early in the cancer trajectory may have downstream effects on FCR development.

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Table 1

Baseline Participant Characteristics

Sociodemographic Characteristics	No. or Mean	% or SD
Age at diagnosis, years	61	12
Sex		
Male	3908	72.8%
Female	1463	27.2%
Race		
White British	4908	91.5%
Asian	98	1.7%
White Other	128	2.6%
Black	37	0.7%
Relationship status		
Married	2266	57.1%
Single	487	12.3%
Living with a Partner	437	11%
Divorced/Separated	498	12.5%
Widowed	278	7%
Annual Household Income		
£<11,999	1013	29.6%
£12,000-22,999	886	25.8%
£23,000-34,999	696	20.3%
£>35,000	836	24.4%
Highest Level of Education		
Primary or Secondary School	1776	46.9%
College Sixth Form or FE	988	26%
University or polytechnical or other	710	27%
Tobacco Use		
Former User	2131	56%
Current User	739	19.4%
Never User	937	24.6%
Alcohol Use		

Days per week alcohol consumed	2.85	2.6
Units of alcohol consumed/week	30.32	29.16
Medical Characteristics		
HNC Cancer Type		
Pharynx	2294	42.7%
Oral Cavity	1330	24.8%
Larynx	1078	20.1%
Other	669	12.4%
Stage		
Stage I	1186	22.8%
Stage II	900	17.3%
Stage III	710	13.7%
Stage IV	2405	46.2%
Treatment Type		
Surgery	3860	71.9%
Radiation	1758	32.7%
Combined Chemoradiotherapy	1708	31.8%
Chemotherapy	601	11.2%
Co-morbidity Index		
No co-morbidity	2286	42.6%
Mild decompensation	1768	32.9%
Moderate decompensation	945	17.6%
Severe decompensation	254	4.7%
Recurrence at 4 months	79	1.5%
Deceased patients with a recurrence	63	79.7%
Recurrence at 12 months	480	9.6%
Deceased patients with a recurrence	364	75.8%
All-Cause Mortality at 12 months	1250	23.3%

Table 2

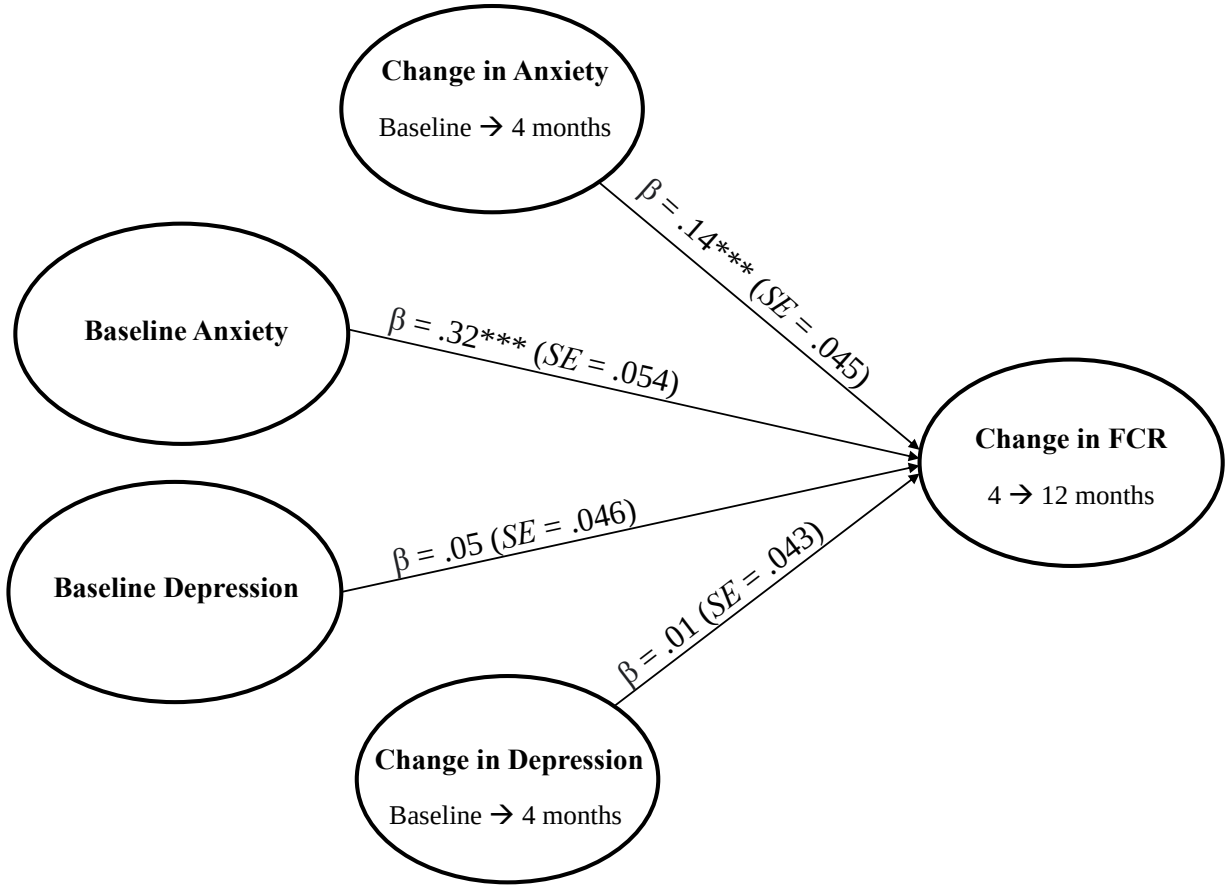
Bivariate Correlations, Means, and Standard Deviations of Key Study Variables

	1	2	3	4	5	6
1. Baseline Anxiety	(1)					
2. 4-month Anxiety	0.63*	(1)				
3. Baseline Depression	0.65*	0.51*	(1)			
4. 4-month Depression	0.40*	0.68*	0.55*	(1)		
5. 4-month FCR	0.50*	0.64*	0.37*	0.48*	(1)	
6. 12-month FCR	0.49*	0.56*	0.40*	0.44*	0.69*	(1)
Means	6.73	5.94	4.18	5.69	10.96	10.69
SDs	4.39	4.36	3.92	4.45	3.98	4.02
N	3919	3186	3938	3216	3195	2731

Note. Anxiety and Depression = HADS subscale composites and FCR = FCR-4 composites
*Correlation is significant at the 0.01 level (2-tailed).

Figure 1

Simplified Path Model with Standardized Parameters



Note: Latent Constructs derived from multiple indicator latent change score model. Although not depicted, patient age, sex, disease stage, cancer site, and treatment type included as covariates. *** $p \leq .001$, ** $p \leq .01$, * $p < .05$