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Pain and cancer survival: a cognitive-affective model of symptom appraisal and the uncertain threat of disease recurrence.

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## 1. Introduction

Forty years ago, three quarters of adults and children diagnosed with cancer died. Today, almost half of adults [77] and three quarters of children survive [17,70]. Survival, however, is rarely psychologically simple. Life after cancer can be characterised by an altered relationship with bodily perception: in particular an anxious uncertainty about the meaning of new or recurrent sensations such as pain [87]. Cancer survival is an altered context in which pain can make one fear the worst [25]. To date, research on the experience of pain in cancer survival has existed largely within a biological frame. That is, pain is studied as the result of tissue damage from the cancer itself or from surgery, chemotherapy, or radiotherapy [13,43]. Yet, if there is one inescapable fact of pain science it is that tissue damage cannot alone explain pain and pain-related behaviour. In this review we discuss the threat associated with pain in cancer survival, specifically how one manages the inherent uncertainty of pain as a potential symptom of cancer recurrence. We recognize that the word 'survivor' is contentious [82]; and here we principally use 'survival' to identify the post-treatment, disease-free stage that individuals experience. We introduce a cognitive-affective model of pain appraisal and experience applied to a survival context, stressing both the clinical and research opportunities it provides.

## 2. 'Better Safe than Sorry'

Following successful cancer treatment, the communication that potentially life-shortening disease is no longer active is often accompanied by an instruction or desire to monitor and be vigilant for potential symptoms of recurrence [40,61]. This desire primes for attention toward altered and new physical sensations, and can be accompanied by the suggestion to take a '*better safe than sorry*' strategy in appraising sensations as threatening [9,56]. The challenge of this caring message is that pain is a common feature of cancer survival [15,43,49,58,72]. Reviews suggest that up to 40% of those living beyond cancer are in pain [10], and 5% to 10% have chronic severe pain that interferes with functioning [43]. In addition, 21% of those who survive childhood cancer report pain that they attribute to their previous cancer experience [59]. Importantly, pain is also a normal part of leading an active, healthy life.

There are, however, almost no studies on the unique experience of acute, everyday pain in cancer survival. We know very little about whether and how habits of attending, interpreting, and reporting on pain are established, maintained, or extinguished, or how these habits influence subsequent pain experience. We also know very little about whether habitual attending to and negative interpreting of pain – known as cognitive biases – are associated with the gross behaviours we measure in clinical studies such as clinic attendance and medication use, as well as coping behaviours such as emotion-regulation, avoidance, and help-seeking.

## 3. Cognitive biases in psychopathology, trauma, and chronic non-cancer pain

In the absence of direct evidence, we review the indirect evidence. Cognitive bias is a feature of most psychopathological models of behaviour [63]. At the heart of these models is the core assumption that biases in attention and interpretation – the tendency to selectively attend to threatening information, and to habitually interpret ambiguous information as threatening – are unrelated to any 'real' danger. From

paranoia to generalized anxiety disorder, the defining feature of a psychopathological model is that the demonstrated fear is 'abnormal': either unwarranted [60,62], exaggerated [8,90], or functioning to promote maladaptive behaviour [23,69]. Whilst it may be evolutionarily advantageous to selectively attend to and appraise threat in situations with real danger, the habitual employment of these cognitive biases is considered abnormal and maladaptive. Unlike primary psychopathological disorders, the cognitive biases inherent in cancer survival are better considered a 'normal' response to a real threat [38]. However, the mechanisms by which cognition is biased towards threat are common to both cases, so our understanding of pain in cancer survival can be guided by the much more populated research on primary anxiety disorders, trauma, and chronic non-cancer pain.

Six principal patterns of cognitive bias common in psychopathology are relevant: (1) The individual's response to ambiguity, in particular how one negatively interprets [2,38,44,67], (2) infers causality [46], and (3) emotionally responds to ambiguous situations and information [33]. Also relevant is the extent to which one (4) automatically shifts attention towards threat [53,73], (5) has difficulty disengaging attention from threat [4,14,41,54], and, at later stages (6) avoids attending to threat [42,55,68,73]. A vigilance-avoidance pattern of threat attending has been identified as particularly potent in maintaining fear and anxiety [55,68,83]. These six primary biases do not operate in isolation. Attention and interpretation biases are proposed to interact to maintain one another over time [3,88]. Once a threat is identified, behavioural avoidance can also maintain anxiety by preventing contact with evidence that allows threat disconfirmation and re-appraisal [57,85].

Trauma, both psychological and physical, often has a lasting effect on subsequent threat awareness and appraisal. Unlike the literature on generalised anxiety, the cause of cognitive biases towards threat in post-traumatic stress disorder (PTSD) and panic disorder is often known. Particularly relevant for the context of survivorship is the focus on persistent and catastrophic misinterpretation of benign physical sensations as symptomatic of severe threat (e.g., an impending heart attack), in turn, making them intrusive and difficult to ignore [21]. Cognitive models of panic disorder and PTSD propose that catastrophic misinterpretation of bodily sensation plays a central role in the onset and maintenance of physical and emotional distress [22]. Interoception can also be readily conditioned to otherwise unrelated cues of possible danger associated with the original trauma, making gastro-intestinal discomfort, pain, or itch all possible conditioned stimuli of further trauma [92]. Indeed, in the classic PTSD model, pain is believed to be evidence of impending further trauma [64].

Attentional bias to physical sensations in chronic non-cancer pain and disease states has also attracted research. For many chronic pain patients, pain is no longer a reliable signal of tissue damage. Despite this, many patients are complexly disabled [28,84], anxious [65], depressed [81], and maintain a strong belief that pain is a sign of danger [51,86]. We have argued that because pain functions to capture attention and motivate escape [34], when escape is technically impossible, worry will flourish [35]. Indeed, attention bias to pain and bodily threat has been identified in multiple studies [27,79], and is particularly associated with fear and worry about pain [6], even in community samples [48,52]. Biases are strongest when stimuli are personally relevant [30] and related to sensory qualities of pain [79]. Interpretation bias, with an emphasis on pain as related to illness or injury, has also been identified in chronic pain samples

[36,75,76]. As in psychopathological models of behaviour, this biased cycle is argued to maintain pain and hinder recovery [26,74].

#### 4. A cognitive-affective model of symptom appraisal and uncertainty in cancer survival

Cognitive bias after cancer, in the context of *'better safe than sorry'*, is similar but different to all three abnormal contexts, and should be understood as a particular problem of managing *uncertainty* in the face of an improbable but potentially life-threatening danger. In survival, one is motivated to believe that the pain is non-threatening, but can find it hard to continually judge a true from a false alarm. It is a context defined by the uncertainty of threat, and a lack of easy access to objective threat assessment. Such environments are high risk for the development of anxiety and maladaptive coping [24,32,66]. In Figure 1 we propose the Cancer Threat Interpretation Model, a cognitive-affective model of the appraisal and experience of pain in the context of cancer survival. Our model builds on other models proposed in non-cancer pain fields [19,29,34,35,37,63,80,85].

### Figure one

The Cancer Threat Interpretation Model has a number of research implications; of which we highlight just three. (1) If cognitive biases do underpin both threat appraisal and coping following pain, then it begins with interpretation. It will be important to identify the extent to which the style of interpreting pain as threatening becomes habitual in survival. It is likely driven by the individual's experience of pain at diagnosis and during treatment, the clinical instruction received at remission, and trait-like individual differences. (2) Relatedly, although we know a lot about the mechanisms of attending to experimentally-induced and chronic non-cancer pain [1,27,29,34,35,48], we do not know to what extent cancer-related pain captures and holds attention. It will be useful to employ cognitive tasks that have been developed to measure threat-related attending within psychopathology and chronic non-cancer pain populations to now examine attention bias in cancer survival populations (e.g., [5,20]). (3) It will also be important to measure the behavioural consequences of threat appraisal, including clinic attendance, demand for diagnostic tests, and avoidance, as well as cognitive coping strategies such as emotion regulation and re-appraisal. Whilst previous research has focused on measuring the incidence of chronic pain in survival populations [15], it will also be important to capture acute episodes of pain and intense worry. We predict that acute episodic experiences will be most guided by threat-related biases, and will have an equal impact on help-seeking.

As the number of people living beyond cancer grows, so there emerges a new population of patients not achieving full recovery—living with uncertainty. Novel treatment methods are needed for these individuals. First, methods to identify those most at risk of suffering with uncertainty about pain could make early intervention possible. Better identification of at-risk individuals would be useful at the end of treatment, and during long-term follow-up clinics, or when a patient presents with a new pain complaint. Second, it will be important to consider the impact of physician-patient communication at the end of treatment, including on the patients' cancer-related knowledge regarding the prevalence of pain following cancer and its usefulness as a sign of recurrence. We also do not currently know how often the *'better*

*safe than sorry*' message is portrayed. We do not know if this message is deleterious to a large proportion of people, or whether it may lead a small, but important group to experience worry, distress, and associated disability. The potential risks of abandoning this message, especially for those who are not distressed by it, are also unknown. A consideration of the practical ethics of reducing vigilance for signs of recurrence, particularly for those experiencing decreased quality of life, is warranted. Third, novel training tools that directly target biased patterns of attending and interpreting have provided early promise for psychopathology [7,47] and for chronic non-cancer pain [18,31], and may be useful for survivorship populations. There are also opportunities in e-health innovations that reduce the '*waiting*' for reassurance that may influence the development of cognitive bias, and provide opportunities for delivering pain education to improve cancer-related knowledge. Finally, understanding how individuals successfully adapt to pain in cancer survival, and do not experience uncertainty, will be useful for identifying protective mechanisms that could be employed in treatments.

Whilst we draw primarily from the non-cancer cognitive bias literature in this review, our proposed research must also fit within a growing literature on fear of cancer recurrence (FCR). Many models of FCR already incorporate uncertainty and interpretation of physical symptoms (e.g., [39,45,71,78,89]). Our model may also indeed be relevant for understanding other interoception in the context of the threat of recurrence, for example fatigue. However, there already exist a number of excellent studies on the experience and treatment of fatigue in cancer survival (e.g., [11,12,91]). Less studied is how uncertainty and threat-perception alter the experience of pain in particular. Also less studied are the mechanisms of cognitive bias, for example differentiating hypervigilance from difficulty in disengaging, that may be useful for developing interventions. In addition, whilst coping with physical symptoms is a component of some ongoing FCR intervention studies (e.g., [16]), pain is rarely studied as an outcome.

## 5. Conclusion

People living with and beyond cancer inhabit an environment of symptom uncertainty, which can make the experience of pain a salient cue of threat, promoting fear and worry about disease recurrence. Symptom uncertainty and anxiety are likely to drive cognitive bias toward threat, and then help-seeking behaviour. Understanding how normal cognitive biases operate to prioritise threat in cancer survival can not only enhance our understanding of the role of cognition in pain more generally, but also provide a basis for the development of treatments designed to prevent secondary anxiety following cancer, and help people achieve optimal recovery.

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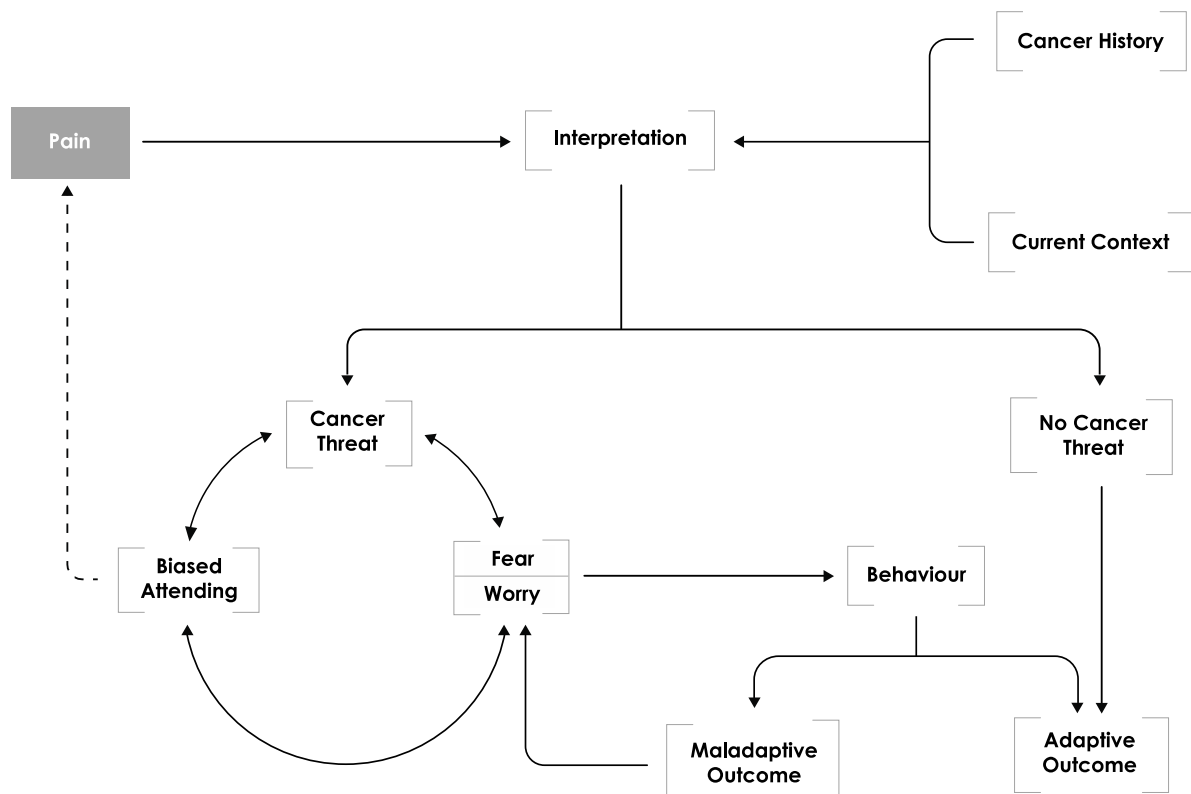


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**Figure 1. The Cancer Threat Interpretation Model.** The model begins with pain, which demands interpretation (cancer threat or no cancer threat). This interpretation depends on the individual's cancer history (e.g., was pain a key feature of diagnosis?), the current context (e.g., is there a clear cause of the pain?), and the interaction between the two (e.g., is the current pain similar to the previous cancer pain?). It is also in the current context, and its interaction with cancer history, where uncertainty emerges. If no cancer threat is determined, there can be an adaptive outcome. Of note, our model refers only to cancer-specific outcomes, and we recognise that non-cancer related maladaptive outcomes can result from pain outside of this context. If a cancer threat is determined, there will be biased attending (hypervigilance, monitoring, difficulty disengaging), fear, and worry, which will maintain one another, and in turn amplify the experience of pain. To alleviate fear and worry, behaviours will be selected. We include here behaviours typically measured in clinical studies (e.g., help-seeking, clinic attendance, avoidance), as well as cognitive coping strategies (e.g., emotion regulation). The choice of behaviour, whether adaptive or maladaptive, will lead to recovery or will enhance fear and worry, maintaining the cycle of biased cognition and fear.