

# Defining cancer-related fatigue for biomarker discovery

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Cancer-related fatigue (CRF) is a prominent and distressing symptom for cancer patients that can impair their overall health-related quality of life [1]. CRF is often described as a complex and multidimensional concept consisting of physical, cognitive, affective, spiritual, psychosocial, and environmental factors [1, 2]. Assessment of CRF is obtained from responses on various valid, self-report questionnaires established from several theoretical models of CRF. The complexity of CRF as a concept and the variability in the method of CRF assessment pose a challenge to investigators attempting to understand the etiology of CRF. Establishing a clear definition of a phenomenon, such as CRF, is an essential starting point for phenotypic characterization and biomarker discovery [3]. Therefore, this commentary aims to increase our awareness of the need for better definition and clearer phenotypic characterization of CRF.

Several organizations have proposed definitions for CRF such as the National Comprehensive Cancer Network (NCCN), the American Society of Clinical Oncology (ASCO), and the Pan Canadian Practice Guidelines [2, 4, 5]. However, a recent review conducted by the Multinational Association of Supportive Care in Cancer Fatigue Study Group–Biomarker Working Group found that CRF is defined in various ways [6]. Some studies referenced a specific definition used by national organizations such as the National Comprehensive Cancer Network [2], while other studies defined CRF using specific cancer treatment-related tools, such as the

National Cancer Institute Common Toxicity criteria, as well as diagnostic criteria from a proposed ICD-10 definition of CRF [7, 8]. The lack of a consistent operational definition for CRF in the empirical literature makes it challenging to develop a CRF phenotype, which in turn poses a major obstacle for researchers investigating the biological mechanisms of CRF [9]. Therefore, consistent use of an agreed upon definition would be of benefit for biomarker discovery.

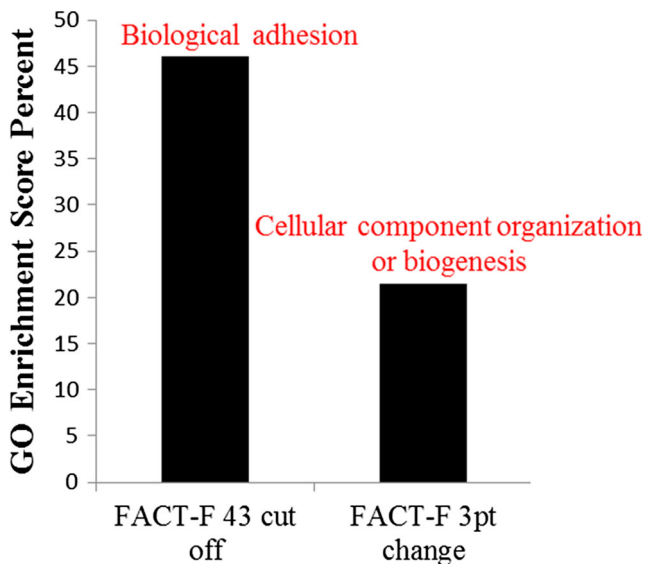
In addition to the variability in the definition of CRF, numerous questionnaires were reported in the reviewed articles to assess CRF. In fact, 23 different questionnaires were used to assess CRF in the 47 articles reviewed. Even when the same questionnaire was used, different scoring rubrics were often applied to phenotype CRF or to determine its clinical relevance [10, 11]. The significance of this variability when investigating different biologic pathways to determine molecular correlates of CRF is pronounced. For example, we recently assessed genetic correlates of CRF using two different cut-off scores on the Functional Assessment of Cancer Therapy–Fatigue (FACT-F) questionnaire (<http://www.facit.org/FACITOrg/Questionnaires>) in the same group of men with prostate cancer who received radiation therapy. The FACT-F subscale is a 13-item widely-used, readily available questionnaire validated to explore fatigue symptoms in the oncology population. Our unpublished findings revealed that different functional biologic pathways were found when different approaches were utilized to phenotype CRF patients using previously reported FACT-F cut-off scores (Fig. 1).

Investigating causal relationships of CRF with specific physiologic mechanisms will remain difficult, unless the complex concept of CRF is better defined, and clearly phenotyped. Perhaps, describing the disease and/or treatment associated with the CRF experience can better define the construct, especially if the intention is for biomarker discovery. CRF is often believed to be induced by the tumor itself and/or the

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**Fig. 1** This figure highlights the various biological pathways identified when different cut-off scores were applied to the Functional Assessment of Cancer Therapy-Fatigue (FACT-F) questionnaire. Gene ontology (GO) enrichment analysis is a way to assign significantly expressed genes into biologically meaningful GO categories; it is a method of biological interpretation. The higher the enrichment score, the more over-represented this functional group is in the gene list

mode of treatment [12]. Specifying the proposed inducer of CRF may place into perspective the physiologic mechanisms that may be involved. For example, a preclinical study demonstrated that an inflammatory response with corresponding fatiguing behavior was observed in a murine model of lung cancer while receiving a chemotherapeutic agent, etoposide; however, neither the behavioral or inflammatory responses were observed when using non-treated lung cancer mice [13]. In contrast, clinical studies have observed that some tumors (i.e., human papillomavirus (HPV)-related head and neck cancers) strongly induce pro-inflammatory responses [14]. Ionizing radiation, even partial body exposure, has been shown to induce pronounced neuroinflammation and consequent fatiguing behavior in a preclinical model [15]. Although more research is needed, there is also evidence that chemotherapy can influence pro-inflammatory mechanisms in pre-clinical and clinical models [16, 17]. However, the evidence for fatigue mechanisms during concurrent chemoradiation therapy is not well developed. Therefore, the use of descriptive terms such as “radiation-related fatigue,” “chemotherapy-related fatigue,” “tumor-related fatigue,” or “survivorship” should be included along with descriptors of the clinical population being investigated to add perspective and context to the CRF definition, so a more precise CRF phenotype can be characterized.

Fatigue has been hypothesized to be influenced by several contributing factors, including stage of the disease, treatment status, or comorbid conditions [12]. For example, increases in inflammatory mechanisms have been observed in both acute

and persistent fatigue related to cancer therapy; however, the mechanism of acute fatigue is often attributed to treatment-related anemia, whereas the mechanism of persistent fatigue following cancer therapy remains elusive [1, 18]. In another study, it was observed that women with advanced stage ovarian cancer had higher inflammatory markers compared to women with early-stage disease [19].

Not only is the disease status of the clinical population important to describe when investigating CRF, it is also necessary to explain the effect of comorbid symptoms, such as depression and sleep disturbance. The occurrence of comorbid symptoms can complicate the identification of biological pathways of CRF. For example, depression is linked to increased inflammatory markers [20]. Depression often clusters with CRF. The occurrence of depression and CRF together creates a more complicated mechanism in which to delineate distinct biological pathways for each symptom. Therefore, it is imperative to fully describe the population of interest, including the disease status and presence of comorbidities [9], in order to clearly define the CRF experience, characterize its clinically-relevant phenotype, and describe the biological mechanisms associated with the CRF phenotype.

In conclusion, in order to advance our understanding of the etiology of CRF, it is critical that we address the challenges mentioned in this commentary. An agreed upon operational definition of CRF, consistent use of an assessment tool and scoring criteria, and full descriptions of the context of CRF are necessary to move the CRF biomarker discovery forward. Operationally defining CRF will allow for optimal phenotypic characterization and will greatly enhance and advance the scientific base of CRF. Hence, specific terms such as “radiation-related fatigue,” “chemotherapy-related fatigue,” or “tumor-related fatigue” might be more useful when reporting biologic correlates or proposing etiologic mechanisms of CRF.

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