

# Prevalence and Causes of Fatigue After Cancer Treatment: The Next Generation of Research

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The presence of fatigue in cancer patients is now well documented. Fatigue is recognized as the most common and distressing side effect of cancer treatment, occurring among patients undergoing radiation, chemotherapy, and treatment with biologic response modifiers.<sup>1</sup> Furthermore, there is evidence that fatigue may persist for months or years after completion of successful treatment in a substantial minority of patients.<sup>2</sup> Qualitative reports indicate that cancer-related fatigue differs from normal fatigue related to lack of rest or overexertion as it involves more severe and enduring mental, physical, and emotional domains.<sup>3</sup> As such, cancer-related fatigue has a particularly detrimental effect on quality of life.<sup>4</sup>

Although research on cancer-related fatigue has become increasingly sophisticated, few longitudinal studies have been conducted that assess patients before and after treatment completion. Clearly, knowledge of a patient's status before treatment onset (and ideally, during treatment) is critical for an accurate understanding of post-treatment fatigue. The study by Nieboer et al<sup>5</sup> in this issue of the *Journal of Clinical Oncology* represents an important advance in this literature in its evaluation of breast cancer patients before and at yearly intervals after randomization to treatment with standard- or high-dose chemotherapy. The study is also notable for the size of the sample (N = 430) and the number of post-treatment assessments. The key findings from the study are as follows. First, the authors found that fatigue remained stable over the assessment period. That is, fatigue levels before treatment were comparable with those observed 1, 2, and 3 years after random assignment (all patients had completed treatment with chemotherapy and radiation therapy at the 1-year assessment). Second, women treated with standard- and high-dose chemotherapy reported comparable levels of fa-

tigue. Third, approximately 20% of women were classified as fatigued at each assessment point. This categorization was based on women's scores on the SF-36 vitality scale; if they scored  $\leq 46$  on this scale (at least one standard deviation below the mean score for Dutch women in the general population), they were classified as fatigued. Fourth, fatigue was strongly correlated with mental health and with muscle and joint pain, but not with hemoglobin or menopausal status.

Overall, these findings offer hope for breast cancer survivors, suggesting that most patients will recover their energy within 1 year after treatment onset and that the incidence of post-treatment fatigue is relatively low. Before these conclusions can be drawn, it is important to compare findings from the study by Nieboer et al with previous research. Studies conducted with breast cancer patients have shown consistently that fatigue levels increase during chemotherapy,<sup>6</sup> but few have followed patients into the post-treatment period. In one report, fatigue declined to baseline levels after completion of treatment with chemotherapy and radiotherapy among women with early-stage breast cancer.<sup>7</sup> These results are consistent with Nieboer et al, who found that fatigue levels 1 year after treatment onset were comparable with pretreatment levels among women treated with chemotherapy and radiation therapy. In contrast, previous cross-sectional studies have shown that breast cancer patients treated with radiation or chemotherapy report higher levels of fatigue than women treated with surgery alone 1 year after diagnosis.<sup>2</sup> In addition, there is considerable variability in fatigue levels both during and after treatment, suggesting that some patients may experience a slower (or faster) course of recovery. Because Nieboer et al did not evaluate patterns of change in fatigue over time, it is unclear whether certain patients experienced more severe or more persistent fatigue.

The percentage of patients who were categorized as fatigued in the report by Nieboer et al was quite low, and

mean levels of fatigue were comparable with Dutch population norms. These results might lead one to conclude that fatigue is not a significant problem among disease-free breast cancer survivors. However, earlier studies of breast cancer survivors (in both the United States and the Netherlands) have shown that 31% to 38% report significant fatigue.<sup>2,8,9</sup> These estimates are comparable to a recent population-based study of cancer survivors in the United States, which found that 37% of the 379 patients surveyed reported at least 2 weeks of fatigue in the last month.<sup>10</sup> Moreover, studies using more comprehensive fatigue inventories have demonstrated that cancer survivors report significantly higher levels of fatigue than age-matched controls.<sup>4,11,12</sup> The reason for these discrepancies is unclear, but may be related to unique characteristics of the sample examined by Nieboer et al. Unlike previous reports, women in this study were participants in a clinical trial and may not be representative of the broader population of cancer patients. In addition, the cut point used to classify fatigued patients in this study was more stringent than that used in previous research,<sup>2</sup> which may have restricted the size of the fatigued group.

The correlates of fatigue identified by Nieboer et al are consistent with those found in previous research. In particular, earlier studies have shown that psychological factors (particularly depressed mood) and pain are strongly correlated with fatigue in cancer patients and survivors, whereas hemoglobin is not.<sup>13</sup> Results based on menopausal status are more equivocal; previous research has shown a modest association between menopausal symptoms (such as hot flashes and night sweats) and fatigue in breast cancer survivors.<sup>2,4</sup> Should we conclude that cancer-related fatigue is largely attributable to psychological distress? A more careful examination of results from Nieboer et al suggests that we should not; although mental health was strongly correlated with fatigue, only 30% to 35% of the variance in fatigue scores could be accounted for by mental health status (along with muscle and joint pain, hemoglobin level, treatment group, and menopausal status). Moreover, scores for fatigue and mental health followed a different trajectory over time, with fatigue remaining constant and mental health improving from pre- to post-treatment. Overall, results from this and other research suggest that psychological distress may contribute to (or result from) fatigue, but does not fully explain the occurrence of fatigue in cancer patients.<sup>14</sup>

What is the next step for research on cancer-related fatigue? Clearly, longitudinal studies that assess patients before, during, and after treatment are required to determine more accurately the prevalence of fatigue in cancer patients and survivors and to identify different trajectories of fatigue symptoms. This research will enable us to calculate how many patients begin treatment with significant fatigue, how many develop fatigue during treatment, and

how many experience persistent fatigue after treatment completion, and also to identify those most at risk for severe or enduring fatigue. This type of inquiry will require the use of reliable, valid measures of fatigue as well as more sophisticated statistical methods that take repeated measures over time into account. Future studies should also include a more comprehensive assessment of potential mechanisms, recognizing that cancer-related fatigue is likely caused by multiple factors (which may differ for different patients). A number of promising mechanisms have been identified, including alterations in immune and neuroendocrine function,<sup>15-18</sup> disturbances in sleep and circadian rhythms,<sup>19</sup> catastrophizing coping style,<sup>20</sup> psychological distress, pain, and other symptoms.<sup>2,4</sup> Other factors that may increase one's risk for fatigue, such as genetic factors, personality characteristics, and pre-existing medical conditions, have been examined only rarely. Identifying the causes of and contributors to cancer-related fatigue will elucidate the pathophysiology of this complex symptom and will also facilitate the development of targeted interventions. In addition, identifying risk factors for fatigue will enable us to deliver these interventions to those most in need, improving the efficacy and cost effectiveness of the intervention. Given the adverse effects of fatigue on quality of life, this research is critical for maintaining physical and emotional well-being in the growing population of cancer survivors.

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### Author's Disclosures of Potential Conflicts of Interest

The author indicated no potential conflicts of interest.

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