Many gaps remain in understanding fatigue across the phases of the cancer experience. These include determining the extent to which fatigue is a presenting or continuing symptom of cancer or a side effect of cancer treatment, identifying those at highest risk of fatigue, defining factors that differentiate between those who do and do not experience fatigue, and characterizing fatigue in special populations such as those with advanced cancer, children, and elders. This article reviews current knowledge of who experiences fatigue, the relationship of fatigue to cancer treatment, and the phenomenon of persistent fatigue following treatment. Critical elements in the research agenda that need to be addressed include the relationship of fatigue to other symptoms of cancer or side effects of treatment, mechanisms underlying fatigue and the development of mechanism-specific approaches to preventing and managing this troublesome symptom. [J Natl Cancer Inst Monogr 2004;32:72–5]

Interest in the study of fatigue in people with cancer is relatively recent. Although the first research paper that focused on cancer treatment–related fatigue was published in 1979, most reports of fatigue seen over the next 15 years were either incidental findings from studies of the psychosocial effects of cancer or brief comments in reports of cancer treatment trials (1–3). In the mid-1990s, tests of interventions to treat fatigue began to appear in the literature (4–6). The development of a body of knowledge about fatigue in cancer has revealed a number of gaps in the knowledge about fatigue in people with cancer, which need to be addressed to support clinical practice (7). These gaps include identifying those at highest risk for fatigue, defining factors that differentiate between those who do and those who do not experience fatigue, determining whether fatigue is a symptom of cancer or a result of other problems caused by cancer and cancer treatment, establishing the prevalence of persistent fatigue among those who have completed cancer treatment, and exploring the experience of fatigue in children with cancer.

**Fatigue Measures**

The traditional approach to presenting results of treatment toxicity studies is to report the number of subjects experiencing a specific toxicity by grouping the subjects into either two (absent/present) or three (absent, mild/moderate, severe) categories. The predominant model used in the work on fatigue is drawn from behavioral science and tends to report results as mean scores computed for fatigue scales or for single-item fatigue measures. This approach provides an advantage in terms of potential sensitivity and responsiveness, but it does not present information on the number or percentage of subjects in a given study who are judged to have fatigue. The consistent finding across studies is that the level of fatigue is above zero, is higher than noncancer controls, and declines over the first few months after cancer treatment is completed (8,9).

**Is Fatigue a Presenting Symptom of Early-Stage Cancer?**

Although fatigue is widely viewed as a symptom of cancer, there are no published studies of symptoms preceding diagnosis of local or regional cancer. Studies that report on symptoms before the initiation of cancer treatment only include people who have already been diagnosed with cancer, most of whom have undergone surgery and various other diagnostic procedures. Both the procedures and the psychosocial burden of being diagnosed with a life-threatening illness are potential sources of confounds with fatigue as a presenting symptom, and recall bias is an issue in retrospective studies. When there is a plausible cancer-related mechanism such as anemia resulting from bleeding (colon cancer or cancer of the uterine cervix), hypoxia (lung cancer with obstruction), or infection (leukemia), fatigue may be a presenting symptom. However, the current limited body of research does not support the idea that fatigue is a common symptom in relatively early stage cancers.

**Is Fatigue a Side Effect of Cancer Treatment?**

The evidence that fatigue is a common side effect of cancer treatment is strongest in longitudinal studies of people undergoing various forms of cancer treatment. Treatments studied include surgery, radiation treatment, chemotherapy, high-dose chemotherapy followed by stem cell or bone marrow transplantation (BMT), biologic response modifiers, and hormone manipulation. Most studies address either radiation treatment or chemotherapy. The radiation treatment studies show a treatment-related pattern, with fatigue increasing during the weeks of treatment and declining after treatment ends (1,3,10–19). The studies of chemotherapy treatment regimens delivered on cyclic schedules show a cyclic pattern of fatigue (20–31). In general, fatigue peaks within days after chemotherapy treatment and declines until the next treatment is administered.

High-dose alfa interferon used to treat malignant melanoma produces debilitating fatigue in a pattern that is tied to administration of this biologic response modifier (32–36). Studies of hormone manipulation, primarily antiestrogen agents used in breast cancer treatment and drugs used to establish androgen blockade in prostate cancer treatment, show some association with fatigue, but the long-term, continuous dosing used in the treatment regimen does not provide information on variations in fatigue in relation to the beginning and ending of treatment.
The few studies of surgery show that fatigue is common following surgery, but there are few longitudinal studies specific to cancer (39). It appears that many people with cancer begin radiation treatment or chemotherapy treatment without having recovered from the fatigue-inducing effects of surgery, raising concern about interpreting results of fatigue measures collected just before initiating radiation treatment or chemotherapy treatment as representing a “baseline” or “usual” level of fatigue.

High-dose chemotherapy treatment (with or without radiation treatment) and BMT are associated with high levels of fatigue. There are few published longitudinal studies of fatigue occurring immediately after BMT, perhaps because of the initial acuity of the population of patients receiving BMT and the number of complex, fatigue-inducing problems experienced following BMT (e.g., infection, anemia, dehydration, fever, mucositis pain, sleep disruption).

**Fatigue as a Persistent Side Effect of Cancer Treatment**

Estimates of the percentage of people who experience persistent fatigue for months and years following the completion of cancer treatment range from 10% to 30% (40–43). Information on persistent fatigue is difficult to obtain because there are few longitudinal studies of people following completion of treatment. Most studies are of women with breast cancer, and associated factors such as individual differences and other symptoms are not always examined. Fatigue at the end of radiation treatment, sleep problems at 6 months following radiation treatment, and trait negative affectivity measured 2 weeks before the end of radiation treatment accounted for 26% of the variance in fatigue at 6 months following radiation treatment in a sample of women with localized breast cancer (n = 234) (Nail LM: unpublished data). Age, stage of disease, and depression at the end of radiation treatment did not predict fatigue at 6 months post-radiation treatment. In long-term survivors of BMT, persistent fatigue is a major problem that has kept survivors from resuming their pretreatment roles in family care, work, and the community (44–46).

**Fatigue in Advanced Cancer**

Fatigue is common in advanced cancer and palliative care, and reports of the prevalence of fatigue range from 40% to 78% (47–52). Similar to the studies of persistent fatigue, most of the studies of people with advanced cancer are cross-sectional and contain limited information on factors that may relate to fatigue such as the use of narcotic analgesics, level of physical activity, muscle mass loss, and individual differences.

**Special Populations**

Studies of fatigue in children with cancer are beginning to appear. Significant instrumentation problems and controversies over the use of parents as proxies for reporting fatigue have limited research in this area. Published work demonstrates that fatigue is a problem for children undergoing cancer treatment and that children exhibit changes in behavior in response to fatigue (53–57).

Elders represent a large proportion of the participants in studies of fatigue in people with cancer. In general, when age is examined in relation to fatigue intensity, there is either no relationship or a weak negative relationship between age and fatigue intensity (8). Some possible explanations of the weak negative relationship include prior experience with a fatigue-inducing illness among elders leading to more effective self-care, possible age-related differences in basic physiologic processes interacting with cancer treatment to produce differences in side effect severity, and differences in demand for activity between retired and working populations. Additional research is needed to explore the influence of age on symptom perception and symptom experience.

**Fatigue in Relation to Other Symptoms**

Longitudinal studies of fatigue and depression in people with cancer demonstrate that these symptoms do not exhibit the pattern that would be expected if the fatigue reported by people with cancer was a symptom of depression (58,59). Studies of antidepressant therapy in people with cancer have improved depressed mood and related symptoms without improving fatigue (60,61). However, the results of longitudinal studies of people undergoing cancer treatment indicate that unresolved symptoms, including fatigue, are related to subsequent negative outcomes such as depressed mood. The relationship of fatigue to other symptoms, such as sleep disruption and pain, is a growing area of investigation (62). Understanding these relationships is important both in directing work on fatigue mechanisms and in defining targets for interventions to prevent or alleviate fatigue.

**Effect of Fatigue**

The results of descriptive studies and fatigue intervention studies demonstrate an inverse relationship between fatigue and various indicators of quality of life (63–65). Descriptive studies of perceptions of the effects of fatigue also show that people with cancer attribute a variety of functional limitations and emotional responses to fatigue (66).

**Conclusions**

Fatigue is characterized as the most common side effect of radiation treatment, chemotherapy treatment, selected hormonal therapies, and some biologic response modifiers. It is often seen in advanced cancer and palliative care and may be a presenting symptom of some specific cancers or advanced-stage cancer. Fatigue is seen across all age groups. Most of the knowledge about fatigue is derived from cancer treatment studies. Across studies, the pattern of increasing and decreasing fatigue is linked to the scheduling of treatment. There is much less information about fatigue as a persistent side effect of cancer treatment and about fatigue in people with advanced cancer who are not undergoing treatment.

Existing research shows that fatigue is a major burden for people undergoing cancer treatment, persists among a significant minority of people who have completed treatment, is a common problem in advanced cancer, and has an adverse effect on quality of life. Developing effective approaches to preventing and treating this troublesome symptom is an important area for further research.
REFERENCES


NOTES

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