Review

The Intersection of Cancer and Aging: Establishing the Need for Breast Cancer Rehabilitation

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Abstract

The increasing success of treatments for common cancers has resulted in growing awareness of the unique health care needs of cancer survivors. Cancer treatments can be toxic and have long-lasting effects on health, potentially accelerating the aging process and producing associated declines in physical function. In this synthesis of the literature, we critically examine the strength of existing evidence that breast cancer diagnosis and treatment are associated with a disproportionate decline in physical function compared with the effects of living without cancer for the same number of years. There is some observational epidemiologic evidence that women treated for breast cancer report greater declines in physical function than their peers. Discerning the factors associated with such declines and their clinical significance remains to be addressed. Physiologic, psychological, and behavioral changes associated with both aging and cancer treatment are reviewed. Parallels are proposed between existing preventive and rehabilitative programs and possibilities for similar interventions aimed at preventing, reversing, or halting declines in physical function in cancer survivors. Finally, a program of research is proposed to evaluate whether there is some subset of breast cancer survivors for whom prevention or rehabilitation of functional status declines is needed, as well as development of targeted, mechanistically driven interventions. (Cancer Epidemiol Biomarkers Prev 2007;16(5):866–72)

Introduction

There are 10 million cancer survivors alive in the United States (1) and more than 16% of U.S. adults 65 years of age or older are cancer survivors (2). The increasing success of treatments for common cancers has resulted in growing awareness of the unique health care needs of cancer survivors. Cancer treatments can be toxic and have long-lasting effects on health (1), potentially accelerating the aging process and producing associated declines in physical function. Recognizing the importance of this area, the 2006 National Cancer Institute strategic plan (3) includes a goal to expand research efforts to understand biological and physical mechanisms that affect a cancer patient's recovery from treatment. Further, a recent Institute of Medicine report (1) called for the development of a strategic care plan for adult cancer survivorship after the end of primary cancer treatment in recognition that cancer survivors have unique medical needs.

The purpose of this review is to synthesize the literature on declines in physical function in breast cancer survivors with the literature on declines in physical function with aging. We will explore whether there is evidence to support the hypothesis that breast cancer diagnosis and treatment are associated with a disproportionate decline in physical function beyond what would be expected due to normal aging. All information used in this review was identified by searching the English literature in the MEDLINE database from 1966 to 2006 using the keywords ''breast neoplasms'' or ''aging,'' crossed with the following keywords: ''functional status,'' ''physical performance,'' ''rehabilitation,'' ''activities of daily living,'' ''independent activities of daily living,'' ''quality of life,'' ''body composition,'' ''sarcopenia,'' ''inflammation,'' ''estrogens,'' ''cardiac function,'' ''pulmonary function,'' ''cognition,'' ''depression,'' ''exercise,'' ''pain,'' and ''physical symptoms,'' and by review of the reference lists of each relevant article obtained. Parallels are proposed between existing rehabilitation programs for other conditions (4) and possibilities for approaches aimed at remediation or prevention of physical function declines in cancer survivors. Finally, a program of research is proposed to identify women at highest risk for functional status declines due to breast cancer, discovery of the organ systems driving such changes, and the development of appropriate, targeted, and mechanistically driven prevention or remediation.

Although there is potential for cancer rehabilitation to be useful for multiple adult cancer diagnoses, we focus this review on breast cancer survival for several reasons. First, survivors of nonmetastatic breast cancer provide an excellent population in which to address these issues. The majority of these women will be long-term survivors: 97.5% of those with invasive malignant tumors confined to the breast and 80.4% of women with invasive malignant tumors that extend beyond the breast and include lymph involvement will survive for 5 years from diagnosis (5). Further, breast cancer survivors constitute the largest single diagnosis within the cohort of cancer survivors. Finally, the research completed thus far on long-term and late effects of cancer diagnosis and treatment, particularly effects relevant to physical function, has largely focused on breast cancer (1).

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Physical Function Status: The Disablement Model

To understand whether cancer therapy accelerates aging and functional decline, it is first necessary to define ''physical functional status'' and the progression of aging expected in the absence of cancer. Gerontologists have defined several domains of physical functional status pertinent to studying aging, independent living, frailty, and disability. These domains include functional mobility (ability to walk independently at a functional pace, for functional distances, and ability to climb stairs), upper extremity function (ability to put things up on shelves or pick things up off the floor), complex tasks called instrumental activities of daily living (e.g., shopping, preparing meals), and basic tasks called activities of daily living (e.g., toileting, dressing, feeding oneself; ref. 6). Physical function in each of these four domains is a major determinant of functional independence (6, 7). The first of these domains to change in the long-term aging trajectory toward physical function decline is functional mobility. Changes in upper extremity function may occur concurrently with or sequentially after changes in functional mobility in the common model used to describe the aging trajectory toward disability. At the point of observing changes in instrumental activities of daily living or activities of daily living, an individual has entered a part of the aging trajectory that includes functional disability. At this point, remediation of functional limitations is needed to reestablish ability to participate in life roles or to develop strategies to overcome incurable limitations. The functional changes resulting from the interaction of breast cancer and aging may include the development of functional declines that predispose women to disability (thus needing intervention to avoid disability) or frank disability (thus needing remediation), depending on preexisting conditions and severity of disease and treatment.

Integration and coordination of multiple physiologic and psychological systems are required for optimal physical function (8). The physiologic determinants include muscular strength and endurance, cardiorespiratory endurance, flexibility, coordination, balance, and dexterity. The psychological determinants include cognitive function, symptom experience, and depression. Figure 1, derived from Nagi (9), depicts the multiple physiologic, psychological, and behavioral changes noted to occur both with aging and in association with breast cancer treatment that are predictive of a decline in functional mobility and upper extremity function (10).

Observational Evidence that Breast Cancer Treatment Accelerates Aging or Functional Decline

There are two cohort studies that have measured physical functional status in women before cancer diagnosis and that were large enough to discern whether breast cancer diagnosis and treatment resulted in differential declines. Prior studies on this topic did not assess physical function before cancer diagnosis and many did not include a comparison group without cancer. These factors both limit causal inference. Thus, the self-reported data from the Nurses' Health Study and the Iowa Women's Health Study offer the best available observational evidence on this topic to date.

The Iowa Women's Health Study assessed upper extremity function (ability to do heavy household chores, ability to prepare meals) and functional mobility (ability to go out, ability to walk half a mile, or ability to climb stairs; ref. 11). Observations included that 32.7% of postmenopausal cancer survivors 5 years out from diagnosis reported an inability to do heavy household chores compared with 20.5% of women with no cancer history. After adjustment for pre-illness function, this comparison is associated with an odds ratio of 1.75. In a subanalysis specific to breast cancer, postmenopausal survivors were 40% more likely to report at least one additional functional limitation compared with women who had not had the disease, 5 years after the diagnosis, and adjusting for pre-illness function.

The Nurses' Health Study used the SF-36 (12) to assess long-term physical functional changes associated with breast cancer. This survey includes questions regarding functional mobility (walking 1 mile, walking one block, climbing stairs, vigorous and moderate intensity activities) and upper extremity functions (lifting or carrying groceries). Thirty percent of nurses who had been diagnosed with breast cancer reported difficulties with life roles due to physical problems, compared with 25% of women with no history of breast cancer. After adjustment for baseline functional status, this was associated with a relative risk of 1.58.

Whether declines in physical function with breast cancer treatment are large enough to affect participation in life roles remains unclear. One study observed a statistically significant decrease in self-reported physical function over ~5 years of follow-up in 763 breast cancer survivors 5 to 10 years after diagnosis (13). However, the difference was not only very small but also seemed to be age related, and function was in the ''excellent'' range for most women (13). Further, multiple studies observed no sustained physical functional status differences between breast cancer survivors and healthy controls (14, 15). The two large cohort studies mentioned above also found that many cancer survivors were free of functional limitations; however, both studies were able to detect greater risk for limitations in physical function among breast cancer survivors than in women without cancer. Comparing findings between these two and other studies is difficult (16) due to variability both in the operational definition of physical function and in the surveys used to

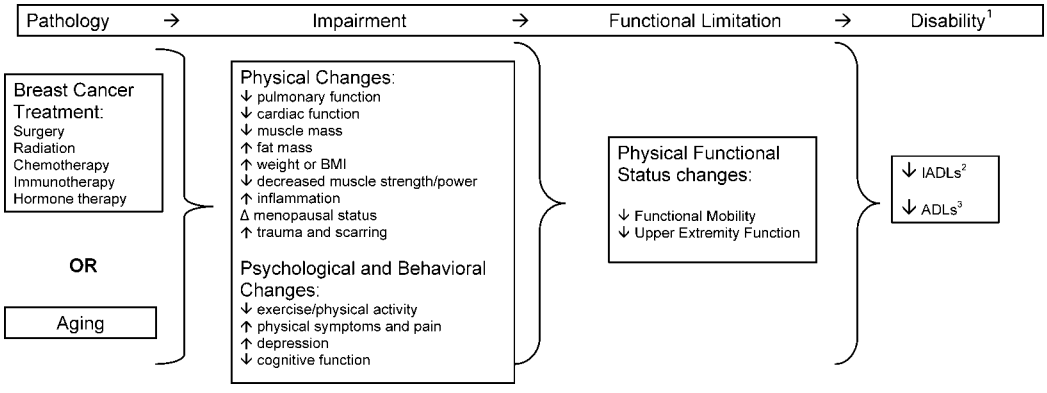

Figure 1. Effects of aging or breast cancer treatments on physical functional status and disability. *1,* this conceptual model was originally presented by Nagi (9). *2,* IADLs, instrumental activities of daily living. *3,* ADLs, activities of daily living.

measure it. Further, the clinical relevance of the reports of functional limitations in cancer survivors is difficult to interpret, given the lack of a clearly defined threshold for clinical significance with self-report measures of physical function. The large cohort studies provided statistical power to detect significant differences between cancer survivors and others, but still are consistent with a conclusion that many long-term cancer survivors seem to be unaffected by functional limitations related to their disease and treatment. On the other hand, the pathway linking predisability functional limitations to higher risk of disability and death has been shown in prospective studies on the topic of aging (6, 17). Therefore, for some subset of cancer survivors, functional declines are a potentially serious outcome.

Establishing Who Needs Rehabilitation

Targeting rehabilitation services to individuals with the greatest need is essential for ensuring both efficacy and cost-effectiveness. Studies of noncancer disease events that are common among the elderly have resulted in well-established trajectories toward loss of independence that occur in certain subgroups of elders. Within the field of aging, there is a concept of ''frailty'' that precedes the development of frank disability (18), which has been defined as ''diminished ability to carry out important practiced social activities of daily living.'' Frailty has been conceptualized as a predisposition for disability that may be reversible with appropriate intervention and is distinct from frank disability (18). For example, hip fracture leads to decreased functional mobility (19). Without adequate rehabilitation to regain function, this may lead to frank disability and loss of independence in some, but not all, elders (20). Similar to other health events that occur more frequently with aging, not all women diagnosed with breast cancer will develop frailty or experience declines large enough to be considered functional disability. However, if clinicians could predict which of their patients are most likely to experience such effects, targeted interventions to prevent or reverse the functional declines could also become a standard part of breast cancer therapy, analogous to cardiac rehabilitation and exercise prescriptions after certain cardiovascular diagnoses, procedures, and events.

Four possible trajectories for the effects of breast cancer treatment on functional status can be hypothesized. First, it is possible that there are women for whom breast cancer treatment does not have any major effect on physical functional status beyond what would be anticipated if there had been no cancer diagnosis or treatment. Second, there are women who will experience a measurable but transient effect on physical functional status, with a near return to baseline after some period of recovery. Third, there are likely some women for whom breast cancer treatment results in a measurable decline in physical functional status that does not return to baseline with time. The magnitude of the decline might be defined as ''frailty'' (predisposition to disability) or ''functional disability'' (severe enough to limit her ability to carry out life roles). Finally, it is also possible that there are women for whom breast cancer results in a transient decline in physical functional status, followed by a return to baseline levels, but with subsequent delayed declines that may be directly attributable to some other condition but that may be potentiated by changes associated with breast cancer treatment. This last trajectory could be likened to a post–polio syndrome (21). With post–polio syndrome, the late-onset disability after early recovery seems to be related to the degeneration of individual nerve terminals in the motor units that sprouted to compensate for the loss of innervation (22). With breast cancer, one possible parallel is the effect of radiation on the cardiovascular system that increases risk for cardiovascular outcomes years later (23).

To make the most of limited rehabilitation resources, the influence of comorbidities and age at diagnosis on breast cancer treatment–related physical function declines needs to be defined. Preexisting comorbidities have been linked to greater self-reported physical function declines in some, but not all, studies (16), particularly in older breast cancer survivors (2, 24). Multiple observations suggest that older age at diagnosis is associated with greater self-reported physical functional declines, including functional mobility and upper extremity function (25-27). Older age may interact with more aggressive treatment to produce significant self-reported physical function decline (26), as observed in older women between 3 and 15 months after diagnosis (24). In the Nurses' Health Study cohort, a much smaller percentage of older women (20.1%) compared with their younger counterparts (79.2% of women <40 years, 48.6% of women 41-64 years) received chemotherapy (28), a variable that has been independently related to greater physical function declines in women with breast cancer (13, 24, 29, 30) and Nurses' Health Study data indicated that younger women experienced declines in self-reported physical functional status that were greater than expected with age, whereas older women diagnosed with breast cancer had declines similar to those expected with age (28).

Physical function declines may also be correlated with severity of disease, as well as treatment intensity and modality (e.g., more extensive surgery, cardiotoxic chemotherapeutic agents, such as Adriamycin, or radiotherapy to the chest wall). Again, studies that have addressed this with subjective measures have provided conflicting results. The Nurses' Health Study reported greater declines in SF-36 physical function subscale scores among women with larger tumors and with a greater number of lymph nodes removed (16). By contrast, data from the Iowa Women's Health Study indicate no meaningful differences in the effect of breast cancer on self-reported functional status according to stage at diagnosis, extent of surgery, chemotherapy (yes versus no), or hormonal therapy (yes versus no; ref. 11). Several other studies have reported that breast cancer survivors 1 to 10 years after chemotherapy self-report poorer physical functional status than those who were not treated with chemotherapy (13, 24, 29-31). Recent trends toward less extensive surgery may have resulted in decreased upper extremity functional morbidity (32, 33). However, with less extensive surgery, radiation may also be added, along with the risk for radiation-induced upper extremity functional morbidity (34). The incidence of upper extremity functional morbidity is thought to vary by surgical procedures, radiation dose, and fractionation, as well as by functional assessment methods (35). Greater treatment-related side effect and symptom burden have also been linked to greater physical function decline (36, 37). If severity of disease and intensity of therapy are associated with worse physical function declines, the specific magnitude of these differences is unclear (35, 38).

Physical Functional Decline Due to Cancer Treatment: Mechanisms

In this section, we review the evidence that breast cancer treatment may accelerate the aging process in women in a manner that alters the long-term trajectory from full function, through frailty (predisposition for disability), toward physical disability and loss of independence. This hypothesis is supported by the observation that physiologic, psychological, and behavioral mechanisms known to underlie physical function declines with aging are congruent with changes observed among breast cancer survivors.

Physiologic Changes

Body Composition, Hormones, and Inflammation. Sarcopenia is the aging-associated loss of muscle mass (39-41). With a loss of muscle mass, associated losses of muscle strength, functional mobility, and upper extremity function are expected as well (42-46). Lower muscle mass and strength are associated with reduced objectively measured functional mobility (gait speed), even among middle-aged women (47). Sarcopenic obesity (40, 41, 48), a state in which there is insufficient muscle mass with an excess of fat, may also predict loss of functional mobility, as there may be insufficient muscle strength for mobility. Breast cancer treatment is associated with muscle mass loss and increased fat mass, particularly among those who undergo chemotherapy (49-53). There have been observations of reduced muscle strength or power among breast cancer survivors as well (54, 55). The proposed mediators of body composition changes in breast cancer survivors include decreases in physical activity (51), inflammation associated with chemotherapies (56), and hormonal changes (50, 51). The aromatase inhibitors (anastrazole, exemestane, and letrozole), now first-line adjuvant hormonal treatment in postmenopausal women whose breast cancer is hormone-dependent (approximately two thirds of all breast cancers), can also lead to reductions in bone mineral density, osteopenia, and osteoporosis, and increased incidence of fractures (57-61), which could, in turn, lead to pain, decreased physical activity, and related declines in functional mobility. Additionally, oophorectomy, chemotherapy, and hormonal therapy can lead to premature menopause in premenopausal and perimenopausal women with breast cancer (62), which can independently or jointly contribute to the accelerated aging effects of breast cancer treatments. Elevated inflammatory markers have also been shown to be associated with a decline in functional mobility (gait speed) and upper extremity function (grip strength), perhaps acting through muscle wasting (63-66). The majority of observations regarding inflammatory responses to breast cancer treatment have focused on transient or acute effects during treatment (67, 68). However, there is evidence of a long-term elevation of inflammatory markers among breast cancer survivors as well (56). These changes may contribute to muscle mass and strength loss, further accelerating the aging process.

Cardiac and Pulmonary Function. Aging is associated with decreases in cardiovascular and pulmonary function (69-72), which then predict declines in objectively measured functional mobility, including assessments from treadmill exercise tests (73-79). There are aspects of breast cancer treatment that result in altered cardiovascular and pulmonary function. Radiation therapy has been shown to have long-term effects on both the heart and lungs (80-85). There is also strong evidence that commonly used chemotherapeutic agents are toxic for the heart and lungs as well (83, 86-89). Trastuzumab, a monoclonal antibody, has recently been incorporated into standard adjuvant treatment regimens for women whose breast cancer overexpresses the *Her-2-neu* oncogene, a subpopulation that comprises ~25% of all women with breast cancer (90). The use of trastuzumab leads to a greater incidence of both subclinical declines in left ventricular ejection fraction. In one study, 34% of women exposed to trastuzumab experienced at least one episode of cardiac dysfunction (a drop of ≥10% points in left ventricular ejection fraction and an absolute left ventricular ejection fraction score <55%) over 52 weeks, compared with 17% in the control group (91). Congestive heart failure occurred in ~4% of women treated with this agent in clinical trials (90, 91). The combination of radiation therapy and cardiotoxic drugs seems to have a potentiating effect, increasing risk for long-term cardiovascular toxicities (86, 92). Thus, breast cancer treatment with several types of agents may contribute to loss of functional mobility through effects on the cardiovascular and pulmonary systems.

Trauma and Scarring. Changes in upper extremity function also occur with age, and mediators of these age-associated changes likely include sarcopenia, loss of muscle strength, and overuse or traumatic injuries. These upper extremity changes and their antecedents also occur among breast cancer survivors (1, 55) and are among the most commonly reported long-term physical function changes among breast cancer survivors (1). They are likely the result of trauma from surgery (32, 33) and radiation therapy (34). Hayes et al. (55) noted objectively and subjectively assessed decreases in upper extremity function 6 months after breast cancer treatment, including an objective assessment of upper body strength and endurance, as well as the Disability of the Arm, Shoulder, and Hand questionnaire. There are multiple ongoing observational studies that are focusing in this direction with breast cancer survivors (Jane Armer, University of Missouri, Columbia 5R01NR005342-05; Sandra Norman, University of Pennsylvania, 5R01CA065422-09).

Psychological Changes

Depression, Cognition, and Physical Symptoms/Pain. Aging is associated with an increase in the prevalence of depression (93), cognitive changes (94), and an increase in physical symptoms, including pain (95). Each of these highly correlated age-associated changes has been shown to negatively affect functional mobility and upper extremity function, as measured by self-report, gait speed, and the Physical Performance Test, a battery of objective measures that assess functional mobility and upper extremity physical function (76, 77, 95-97). Breast cancer surgery, radiation therapy, chemotherapy, and hormonal therapies can independently and collectively (possibly synergistically) lead to a cycle of depression, cognitive changes, increased symptoms, fatigue, and musculoskeletal problems(1, 13, 35, 37, 56, 68, 83, 98, 99). These changes may continue long after the end of treatment, although there are conflicting observations regarding the transience of these effects (1, 29, 100). The cognitive changes reported in association with chemotherapy include deficits in memory, concentration, and executive function (organizing or coordinating activities; refs. 1, 101). Executive function has been specifically noted to correlate with functional status measures, including self-reports of instrumental activities of daily living, functional mobility assessments (gait speed), and the Physical Performance Test (77, 96, 102, 103). Finally, up to 50% of women who undergo breast surgery experience long-term chronic pain (83), which may directly affect functional mobility. If severe enough, this pain may have an indirect effect on functional mobility as well, through depression, fatigue, and reduced physical activity.

Behavioral Changes

Physical Activity Changes. Physical activity declines with age (42, 104, 105) and lower physical activity is associated with declines in functional mobility measures (including gait speed), even among relatively healthy individuals (46, 76, 104). There have been several observations of decreased physical activity among breast cancer survivors (51, 106). However, in one of these studies, physical activity levels only declined for a short time and returned to prediagnosis levels by several years posttreatment (106). The effect of this transient decline of physical activity on objectively assessed functional mobility is unknown among breast cancer survivors. This is surprising, given the number of aerobic exercise intervention studies that have been completed among breast cancer survivors (107).

Prevention and Rehabilitation: Defining Cause of Impairments and Appropriate Interventions

In general, rehabilitation targets a specific organ system in need of remediation or teaches the patient strategies or

adaptations that allow for improved function when the impairment cannot be eliminated. For example, persons receiving cardiac rehabilitation have defined impairments that can be remediated by exercise to improve physical performance (32). If specific functional impairments or physical activity limitations are defined in breast cancer survivors, today's Medicare reimbursement guidelines allow for provider reimbursement. Further, if documented functional impairment or physical activity limitation due to low cardiopulmonary fitness is the primary issue for breast cancer survivors, rehabilitation should also be available. However, the treatments and preexisting conditions associated with such declines are not clear. Further, there may be more mild impairments that precede the development of changes in participation in life roles that could be the target of interventions to prevent functional disability after breast cancer treatment. For such interventions to be most useful, it will be important to identify those at highest risk for functional declines, the specific organ systems in need of prevention or remediation, and the development of interventions targeting the appropriate organ system. Such targeted interventions may restore physical function and full participation in life roles so that loss can be prevented and function can be restored sooner.

In a recent meta-analysis, Schmitz et al. (107) observed that aerobic exercise interventions can increase cardiopulmonary fitness among cancer survivors, including five studies done during treatment and seven studies done posttreatment. Several studies have also shown the usefulness of interventions to improve upper extremity function among breast cancer survivors (108-111), although issues such as lymphedema risk continue to create confusion on the part of survivors and clinicians as to what modes and intensities of exercise are safe (111). Given the current lack of clarity regarding which breast cancer survivors are at greatest risk for functional declines and the mechanisms that should be the target of these efforts, exercise interventions have yet to achieve their maximal effect.

Future Directions

Before endorsing policies and recommendations for programs to prevent or reverse functional disability among breast cancer survivors, bodies such as the Institute of Medicine and the National Cancer Institute will require evidence of persistent declines in physical function are clearly related to cancer treatment, within a defined subset of patients. Functional mobility emerges as the most appropriate domain of physical functional status to evaluate the occurrence of such functional declines. Functional mobility measures also allow for assessment of decreases in physical functional status among younger women who function far above the threshold required for instrumental activities of daily living or activities of daily living but who may be predisposed to earlier functional disability due to breast cancer treatment.

Measuring Functional Status in Future Studies. It is easier and less expensive to administer self-report measures of physical function that to measure function objectively. The major limitation of self-report measures is vulnerability to influence by a predisposed opinion of the respondent (6). Objective performance-based measures are less likely to be influenced by affective, social, economic, and cognitive factors, and may enhance the potential to identify small declines in function as well as the mechanisms for those declines (77). Further, self-report data have been observed to differ from results of objectively measured physical function testing, including upper extremity function and functional mobility assessments (55, 74, 112). One explanation for differences in self-report and objective measures in aging populations could be that self-report of functional difficulty is related to a number of medical comorbidities. The severity of these comorbidities might lead the patient either to modify physical tasks or to cease performing them without assistance, thereby masking the independent association of physiologic measures with self-report of limitations in physical function (113). For these reasons, we propose that studies using both self-report and objective measures of physical function are essential to build this evidence base.

Summary of Future Directions. Based on the evidence reviewed herein, the following research should be undertaken to discern the need for functional status prevention and rehabilitation among breast cancer survivors and most appropriate intervention methods and targets:

1. Observational, long-term follow-up studies of cancer survivors and women who have not been diagnosed with breast cancer designed to assess whether and to what extent cancer interacts with aging to accelerate functional decline. Future studies should use a broad range of subjective and objective physical function assessments, including measures before treatment. Characteristics of those who are most likely to experience functional declines that lead to either a predisposition to disability or frank disability need to be defined. The inclusion of objective measures is particularly important for younger and more physically fit women diagnosed with breast cancer, for whom self-reported surveys such as those used in the Iowa Women's Health Study and the Nurses' Health Study may not detect subtle physical function declines at the proximal end of the trajectory toward disability.
2. Elucidation of mechanisms by which cancer diagnosis and treatments accelerate functional decline, toward the goal of developing interventions specifically targeted to the correct subset of survivors and mechanisms.
3. Studies of interventions, based on the identified mechanisms and within the subset of survivors that are most likely to benefit, designed to assess the efficacy of exercise to prevent a decline or to restore lost physical function among cancer survivors.

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