Cancer Treatment as an Accelerated Aging Process: Assessment, Biomarkers, and Interventions

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OVERVIEW

An accumulating body of evidence supports the hypothesis that cancer and/or cancer treatment is associated with accelerated aging. The majority of these data come from the pediatric literature; however, a smaller yet growing body of literature points toward similar findings in the geriatric population. This is a key survivorship issue the growing number of older adults with cancer face, along with the short- and long-term impact of cancer therapy on the aging process. This article will review clinical and biologic markers of aging in older adults with cancer, use cardiovascular disease as a model of accelerated aging, and discuss potential interventions to decrease the risk.

The U.S. population is aging with the number of individuals age 65 or older anticipated to double between 2010 and 2030.[1] This growing population is at risk for cancer because the majority of cancer incidence and mortality occurs in individuals age 65 and older. Together, the aging of the U.S. population and the association of cancer and aging is culminating in a 67% increase in cancer incidence in individuals age 65 or older in the United States from 2010 to 2030.[2] However, many of these individuals will survive cancer, and the majority of cancer survivors are older adults. Presently, there are 8 million cancer survivors age 65 or older in the United States, and this number is anticipated to continue to grow to 11 million by 2020.[3]

A key survivorship issue facing these older adults is the short- and long-term impact of cancer therapy on the aging process. It has been suggested that cancer and/or its treatment may contribute to an accelerated aging phenotype.[4] The majority of these data come from the pediatric literature, in which cancer survivors are more predisposed to the development of frailty as well as chronic conditions such as myocardial infarction, congestive heart failure, and second cancers.[5-7] There is a smaller yet growing body of literature pointing toward similar findings in the geriatric population. This article will review clinical and biologic markers of aging in older adults with cancer, use cardiovascular disease as a model of accelerated aging, and discuss potential interventions to decrease the risk.

THE CLINICAL ASSESSMENT OF AGING

The aging process is unique to the individual, and chronological age is a poor descriptor of an older adult. For example, two individuals who are chronologically age 75 can have very different functional ages. At the extremes, one individual could be wheelchair-bound in a nursing home, and another may be a marathon runner; distinguishing the difference in functional age between these two individuals can be performed with the "eyeball test" from the door of the examination room. However, for most clinical situations, an individual's outward appearance can be deceiving, and an individual's functional age can be quite difficult to determine without a more detailed evaluation. There are two main ways in which an oncologist can get a better sense of the functional age of an older adult. The first is through performing a geriatric assessment, and the second is by assessing frailty. Both of these methods are discussed below.

A geriatric assessment identifies factors other than chronological age that can predict the risk of morbidity and mortality in older adults. These include functional status, cognition, comorbidity, psychological state, social support, and nutritional status. There is a growing body of literature regarding the benefits of performing a geriatric assessment in older adults with cancer.[8] In patients with cancer, this assessment can identify areas of vulnerability not otherwise detected in a routine history and physical examination, predict cancer treatment toxicity and survival, and serve as a platform for interventions to decrease toxicity risk.[8] Short geriatric assessment tools for oncologists have been developed that are feasible to implement in both daily clinical practice and among patients enrolled in clinical trials. Geriatric assessment tools that can be mailed to the patient and completed prior to the office visit, as well as computerized

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geriatric assessment tools, have also been evaluated.[9-11] Abbreviated geriatric assessment screening tools are available; however, a consensus has not been reached regarding which tool could identify those patients who would benefit from a more detailed geriatric assessment.[12]

There are compelling geriatric assessment findings in cancer survivors that support the hypothesis that cancer and its treatment may impact the aging process. Cancer survivors are more likely to report poorer physical and mental health-related quality of life compared with adults with cancer.[13,14] Older cancer survivors are more likely to have limitations in performing activities of daily living as well as mobility limitations compared with older adults without a history of cancer.[15] There is an increase in the number of comorbidities in individuals who are cancer survivors compared with those without a history of cancer.[16] Furthermore, specific comorbid conditions may be linked to the treatment the patient has received—for example, congestive heart failure (among patients receiving anthracycline-based therapies),[17] peripheral neuropathy (among patients receiving taxanes),[18] and declines in bone health (among patients receiving aromatase inhibitors).[19,20] A study of the neuropsychological function of older patients (age 60–70) with breast cancer demonstrated that those who were exposed to chemotherapy were at higher risk for posttreatment cognitive decline and factors associated with cognitive aging—such as lower cognitive capacity (low cognitive reserve) and apolipoprotein (ApoE4$^+$) status—interact with chemotherapy treatment to increase the risk of cognitive decline.[8]

Another means of assessing the aging process, which comes primarily from the geriatric literature, is measuring frailty. Frailty can be defined as a decrease in physiologic reserve that places an individual at increased risk for adverse events such as hospitalization, falls, and poorer overall survival. There are two main methods of assessing frailty in the geriatric population. The first was proposed by Fried et al[21] utilizing data from the Cardiovascular Health Study. They identified a phenotype for frailty among over 5,000 community-dwelling men and women age 65 or older (Table 1), which consists of weight loss, exhaustion, slow walking speed, weakness, and low physical activity. Patients who were defined as frail or prefrail, compared with nonfrail, were at increased risk for hospitalization, falls, decreased mobility, decline in the ability to complete activities of daily living, and mortality over the subsequent 3 and 7 years. Rockwood and Mitnitski[22] defined another method of assessing frailty that is based on the accumulation of deficits. Deficits captured in a geriatric assessment are tallied and provide a composite index of the degree of frailty. These methods of describing frailty have mainly been used as research tools rather than tools used in daily clinical practice.

TABLE 1. The Frailty Phenotype[21]

Categorizations	Criteria
Frailty Phenotype: Presents With ≥ 3 Criteria	Unintentional weight loss (≥ 10 pounds in past year)
	Self-reported exhaustion
Intermediate or Prefrail Phenotype: Presents With 1 or 2 of the Criteria	Weakness (lowest 20th percentile in grip strength)
	Slow walking speed (lowest 20th percentile on a timed walk of 15 feet)
	Low physical activity (lowest quintile of kilocalories per week)

KEY POINTS

- **Cancer and/or its treatment may contribute to an accelerated aging phenotype.**
- **A key survivorship issue facing older adults is the short- and long-term impact of cancer therapy on the aging process.**
- **Clinical (geriatric assessment) and biologic markers of aging hold great promise as independent predictors of patient outcomes including toxicity, functional reserve, and survival.**
- **Standard cancer treatment causes significant and marked impairments in global cardiovascular function, which may persist years after the cessation of primary therapy.**
- **Structured exercise training may be an effective strategy to mitigate acute and long-term impairments in cardiovascular function in patients both during and following primary adjuvant therapy.**

BIOMARKERS OF AGING AND CANCER THERAPY

Geriatric assessment is the cornerstone for assessing function in patients with cancer prior to treatment. It can be helpful in predicting survival, treatment-related toxicity, and other outcomes. However, geriatric assessment can be time consuming, and many clinicians do not have the resources to perform a geriatric assessment in daily practice. Biomarkers of aging may help fill this gap.[23] The term biomarker has many definitions; the World Health Organization has defined a biomarker as "almost any measurement reflecting an interaction between a biological system and a potential hazard, which may be chemical, physical, or biological. The measured response may be functional and physiological, biochemical at the cellular level, or a molecular interaction." A list of potential biomarkers is provided in Table 2. For this review, we will focus on several categories of potential biomarkers, including chronic inflammatory markers, markers of cellular senescence, and sarcopenia to explore how they might be further evaluated with the goal of defining markers that can independently predict outcomes in older patients with cancer. Several excellent reviews of this topic have been recently published.[23,24]

Inflammatory markers have been extensively studied, and increased levels have been shown to correlate with frailty, functional decline, and survival.[24] These markers now are receiving wide attention, as there is good evidence that chronically elevated levels may accelerate or exacerbate the

TABLE 2. Potential Biomarkers of Treatment-Related Toxicity and Aging

Marker	Source	Test	Association With Frailty/Function	Association With Mortality
Chronic Inflammatory Markers	Serum or plasma	ELISA	Yes (CRP, IL-6, TNF-α, D-dimer, IL1RA)	Yes (CRP, IL-6, D-dimer, s-VCAM)
Telomere Length	Leukocyte DNA	q-PCR or southern blot	Yes	Yes
		FISH		
		STELA		
$p16^{INK4a}$	T lymphocyte RNA	RT-qPCR	Maybe	Unknown
Sarcopenia	DEXA scan	Commercially available software for body composition analysis	Yes	Yes
	CT scan			
	Bioelectrical			
	Impedance			
Maximal Oxygen Consumption (VO_{2max})	O_2 and CO_2 of inhaled and exhaled air	Incremental exercise testing	Yes	Yes

Abbreviations: ELISA, enzyme-linked immunosorbent assay; CRP, C-reactive protein; TNF-α, tumor necrosis factor α; IL1RA, IL-1 receptor agonist; s-VCAM, soluble vascular cell adhesion molecule; q-PCR, quantitative polymerase chain reaction; FISH, fluorescent in situ hybridization; STELA, single telomere length analysis; RT-qPCR, quantitative reverse transcription polymerase chain reaction; DEXA, dual-energy x-ray absorptiometry.
Modified from Hubbard et al.[23]

aging process. These markers, which include interleukins, tumor necrosis factors, and others, have been studied extensively in frail patients in whom they independently correlate with other measures of physical function. Interleukin-6 (IL-6) has probably been the most extensively studied cytokine and has been shown to predict functional decline, including a diminution in the ability to perform activities of daily living, poor ambulation, and decreased mobility.[25] There also appears to be a major relationship between inflammatory markers and cell senescence. Senescent cells are viable and capable of secreting proinflammatory markers that have led to the definition of a senescence-associated secretory phenotype.[26] To date, however, none of these markers has assumed a major role in clinical care or further studies designed to see if any single marker or combination might have an independent role in the management of the older patient with cancer. These studies would test whether such markers could be independent predictors of treatment tolerance, including acute and chronic toxicities, functional loss, and cognitive decline.

Telomere length as well as the proteins that play a role in telomere length are also of great interest as markers that may predict survival, functional status, and toxicity,[27,28] and studies are underway to further define the potential role of telomere length as a predictor of cancer-related outcomes. Another emerging marker of great potential benefit as a predictor of toxicity and outcomes is *p16ink4a.* This gene, in which expression increases 10-fold with aging, codes for a protein that blocks cyclin-dependent kinase, which leads to cell senescence.[29] In animal models, there is a clear direct relationship between *p16ink4a* expression and organ age.[30] In addition, human studies have shown a strong association of *p16ink4a* expression and T-cell aging in patients infected with HIV,[31] senescence of human mesenchymal stem cells,[32] and hospital stay after coronary artery bypass.[33]

Other markers of potential interest include the measurement of sarcopenia; recent data show the utility of using CT scans of the abdomen as a valid measure of muscle mass and a tool to predict cancer clinical outcomes.[34] This is of great interest, as CT scans are widely used in management of patients with cancer. The role of maximum oxygen consumption (VO_{2max}) as a biomarker of aging and treatment effect is discussed elsewhere in this review.

THE EFFECT OF CANCER TREATMENT ON BIOMARKERS OF AGING

There is little doubt that the treatment of cancer, especially radiation therapy and chemotherapy, greatly accelerates aging.[35,36] A recent overview of survivors of childhood cancer showed that these individuals were at greatly increased risk for substantial comorbidity and premature death.[35] Data from one of the large cohorts described in this review demonstrated the cumulative prevalence for a serious or life-threatening chronic condition of 81% by age 45; in addition, there was an extremely high incidence of second neoplasms that was directly related to the radiation dose. In another study of survivors of childhood cancer, the prevalence of prefrailty and frailty were 31.5 and 13.1% among women and 12.9 and 2.7% among men, respectively. This prevalence of frailty among young adult survivors of cancer with a mean age of 34 years was similar to that of adults age 65 or older.[37]

Operative procedures result in a cascade of cytokine and acute-phase responses including IL-6, white cell count, and C-reactive protein. In a systematic review that included 164 studies involving 14,362 patients, IL-6 and C-reactive protein responses were clearly associated with the magnitude and invasiveness of the operative procedure. Colorectal cancer

surgery resection was associated with the highest acute increase in cytokines.[38] Although of concern in the short run, it is not likely that surgical procedures directly accelerate aging. Radiation therapy is clearly related to the formation of proinflammatory cytokines and may result in progressive and long-term tissue damage.[39] As shown in survivors of childhood cancer, radiation is associated with the accelerated development of second malignancies as well as other comorbidities. Studies testing how biomarkers might be used to predict radiation toxicity in individual patients and possible interventions to ameliorate radiation effects are needed. As the childhood cancer survivorship studies show, chemotherapy also is a major cause of accelerated aging. This has been well demonstrated in vitro[40] and in animal models.[30] Chemotherapy has a major effect on telomere length[41] and has been associated with telomere shortening in hematopoietic stem cells[42] as well as in peripheral blood mononuclear cells in patients given repetitive standard-dose chemotherapy for solid tumors.[43] Furthermore, telomere shortening was shown to be greater in older patients given combined chemotherapy and radiation for head and neck cancer when compared with younger patients.[44]

p16ink4a has major promise as a biomarker of chemotherapy toxicity. *p16ink4a* expression increases approximately 10-fold between ages 20 and 80, and this dynamic range provides for a more robust marker as a predictor of molecular aging. In one study of women receiving adjuvant chemotherapy for early-stage breast cancer, *p16ink4a* expression measured in peripheral blood T cells increased by almost one $\log_2$ order of magnitude immediately after treatment and remained elevated 12 months after treatment.[45] This change corresponds to almost a 15-year increase in chronologic age. In this study, the cytokines VEGFA and monocyte chemotactic protein-1 also significantly increased and remained elevated at 12 months, but telomere length was not affected. In a cross-sectional cohort of patients in the same study, prior chemotherapy exposure was independently associated with increased *p16ink4a* expression comparable to 10 years of chronologic aging. Current studies are underway exploring the potential role of *p16ink4a* as a predictor of toxicity and subsequent comorbidity in patients receiving chemotherapy.

There is no doubt that chemotherapy and radiation therapy accelerate aging. This is an especially concerning observation in younger patients, for whom the dramatically improved survival rates for many childhood cancers are now associated with the early development of comorbidities and an increased risk of second cancers, and in older patients, in whom such changes may result in the development of new comorbidities or accelerate previous noncancer-related illness. Several biomarkers of aging are now available that might prove to identify those patients most vulnerable to cancer treatment and allow for the earlier testing of interventions that might minimize treatment related toxicity.

ACCELERATED AGING IN PATIENTS WITH CANCER: CARDIOVASCULAR AGING AS A MODEL

As described in the preceding sections, older patients with cancer are subject to the deleterious effects associated with normal aging but experience the confounding effects of cancer treatment that can lead to an accelerated aging phenotype, characterized by a notable impairment in physical functioning and other parameters. In current practice, the extent of functional decline or physical functioning is typically assessed using performance status scoring systems, evaluated either by the Karnofsky Performance Scale (KPS) or the Eastern Cooperative Oncology Group (ECOG) scale. However, performance status scoring systems are subjective and lack sensitivity to discriminate between individuals, particularly those defined as having a good (i.e., KPS $>$ 70; ECOG 0 to 1) performance status.[46,47]

As a result, performance status measurements are often supplemented with the use of other more objective measures of overall physical functioning such as the comprehensive geriatric assessment or measurement of cardiac and lung function via resting assessment of left ventricular ejection fraction and pulmonary function testing, respectively. Although these tools provide valuable information regarding physical functioning, treatment eligibility, and risk stratification, they do not provide evaluation of global cardiovascular function and reserve. Indeed, cardiac function is only one organ component that contributes to the integrative capacity of the cardiovascular and musculoskeletal system to transport and use oxygen (O_2) for adenosine triphosphate resynthesis.[48] The efficiency of O_2 transport and utilization determines an individual's cardiovascular performance (or exercise capacity). An incremental cardiopulmonary exercise test with gas-exchange measurement, to assess peak oxygen consumption (VO_{2peak}), provides the gold-standard assessment of exercise capacity. VO_{2peak} is inversely correlated with cardiovascular and all-cause mortality in a broad range of adult populations.[49-53] On this basis, several groups have started to examine whether the cardiopulmonary exercise test provides a marker of physiologic aging in the oncology setting both during and following primary adjuvant therapy.

Cancer Therapy-Induced Changes in Exercise Capacity

No prospective, observational studies have examined longitudinal changes in exercise capacity during and following adjuvant therapy in patients with solid tumors; nevertheless, it is possible to glean initial data in the context of randomized controlled trials of exercise training among patients assigned to the usual care condition. For example, Courneya et al[54] performed an exercise randomized controlled trial among 242 operable patients with breast cancer receiving standard adjuvant chemotherapy. Among the 82 women assigned to usual care (i.e., chemotherapy only), exercise capacity as measured by VO_{2peak} declined approximately 5% from baseline (following the first cycle of chemotherapy) to following the completion of chemotherapy (median 17 weeks). Similarly, van Waart et al[55] reported that exercise capacity,

as measured by a maximal cycle ergometer test, decreased approximately 18% from prechemotherapy to immediately postchemotherapy. Finally, Hornsby et al[56] reported that 12 weeks of standard neoadjuvant chemotherapy was associated with a 9.5% decline in VO_{2peak} from prechemotherapy to postchemotherapy. The impairment in exercise capacity also appears to extend to other tumor sites receiving other anticancer regimens. For example, Segal et al[57] reported that 6 months of androgen deprivation therapy with or without radiation therapy was associated with an approximately 10% decline in VO_{2peak} among men with advanced prostate cancer. Similarly, West et al[58] found that standard neoadjuvant chemoradiation in patients with rectal cancer caused a 16% decline in VO_{2peak}. The long-term clinical importance of this decline is not known; however, VO_{2peak} typically declines 10% every decade in healthy women, indicating that short-term chemotherapy may cause the equivalent of a decade of physiological aging.[59]

Of importance, the decline in exercise capacity may not recover, even years following the cessation of primary therapy. For example, Jones et al[59] found that despite normal resting cardiac function (i.e., left ventricular ejection fraction $\geq$ 50%), VO_{2peak} was, on average, 22% below that of age-matched sedentary women in 140 patients with early-stage breast cancer a mean of 27 months following the completion of primary adjuvant therapy. In corroboration, Khouri et al[60] found that VO_{2peak} was, on average, 20% below that of age-matched sedentary women in 57 patients with early-stage breast cancer a mean of 26 months following the completion of primary therapy. The persistent impairment in exercise capacity also appears to extend beyond operable breast cancer to other cancer sites. For example, Adams et al[61] performed a study of survivors with Hodgkin disease (48 patients, mean of 14 years after diagnosis) and found that VO_{2peak} was significantly reduced in 30% of survivors. Again, the clinical and prognostic importance of these decrements is currently not known, but because exercise capacity is a strong independent predictor of both cardiovascular as well as all-cause mortality in noncancer populations, the observed impairments are alarming and create a strong rationale for the development and testing of interventions to prevent and/or treat the observed impairments.

Efficacy of Exercise Training Countermeasures

Aerobic (exercise) training is the most effective therapy to improve VO_{2peak} in healthy individuals given that it improves the reserve capacity of all O_2 transport organs, which together lead to favorable improvements in exercise capacity,[48] although fewer trials have examined the efficacy of exercise on exercise capacity, as measured by VO_{2peak}, in patients with cancer, with the vast majority of work to date in women with early-stage breast cancer. In a recent meta-analysis of six exercise training randomized controlled trials (involving 571 patients) that assessed the effects of exercise training in adults with cancer, exercise training led to a significant improvement in VO_{2peak} (mean weighted difference = +2.90 mL $\cdot$ $kg^{-1}min^{-1}$; 95% CI, 1.16–4.64), compared with nonexercising sedentary control participants.[62] However, the data from individual studies are more heterogeneous. For instance, Courneya et al[54] reported that supervised aerobic training was superior to usual care (chemotherapy only) for improving VO_{2peak} in 242 patients with operable breast cancer receiving standard adjuvant chemotherapy. Interestingly, aerobic training was associated with a nonsignificant improvement in VO_{2peak} (+0.5 mL $\cdot$ $kg^{-1}min^{-1}$) but completely abrogated the VO_{2peak} decline observed in the usual-care group. Further work from this group found that supervised exercise training following standard (i.e., three times per week, at 25 to 30 minutes/session), higher volume (i.e., three times per week, at 50 to 60 minutes/session), or combined (i.e., three times per week of combined aerobic and resistance training) prescriptions did not mitigate the considerable declines in VO_{2peak} among 301 patients with breast cancer receiving conventional adjuvant therapy. In contrast, Jones et al[63] tested the efficacy of supervised aerobic training consisting of three sessions per week at 55%–100% of VO_{2peak} for 20–60 min per session following a nonlinear prescription in patients with breast cancer receiving neoadjuvant chemotherapy; specifically, in nonlinear prescriptions, aerobic training sessions are sequenced in such a fashion that training-induced physiologic stress is continually altered in terms of intensity and duration in conjunction with appropriate rest and recovery sessions to optimize cardiovascular adaptation. Attendance and adherence rates to aerobic training were 82 and 66%, respectively. Intention-to-treat analysis indicated that VO_{2peak} increased by 2.6 $\pm$ 3.5 ml/kg/min (+13.3%) in the chemotherapy plus aerobic training group, whereas it decreased by 1.5 $\pm$ 2.2 ml/kg/min ($-$8.6%) in the chemotherapy only group (between-group difference, p = .001). In the oncology setting, approximately five additional studies, both during and following adjuvant therapy, have examined the safety, tolerability, and preliminary efficacy of nonlinear aerobic training, compared with a usual care (no exercise training) control group. Overall, exercise prescriptions adhering to a nonlinear approach appear to be safe (low adverse event rate), tolerable (mean adherence $\geq$ 75% of prescribed sessions both during and after primary adjuvant therapy), and efficacious, conferring favorable improvements in VO_{2peak}, quality of life, and other physiologic outcomes.[64]

In summary, the extant evidence indicates that patients with cancer experience considerable and marked impairments in exercise capacity during cancer therapy that appear to persist even years following the completion of primary treatment—such decrements are consistent with an accelerated cardiovascular aging phenotype and may, in part, contribute to the increased risk of cardiovascular disease, frailty, and functional dependence in certain cancer populations. Based on current data, supervised aerobic exercise training appears to be a safe, tolerable, and efficacious intervention strategy to potentially offset as well as recover impaired cardiopulmonary function in a broad range

of patients with cancer. The mechanisms, optimal timing, type, and schedule of exercise training, as well as the long-term clinical implications of declines and/or improvements in exercise capacity, are a high research priority in geriatric oncology.

CONCLUSION

An accumulating body of evidence is supporting the hypothesis that cancer and/or cancer treatment is associated with accelerated aging; however, several gaps in knowledge remain, and future research is needed to understand the implications of these findings, as well as ways to decrease the risk. This unmet need formed the basis for a research conference of the Cancer and Aging Research Group, National Institute on Aging, and National Cancer Institute, titled "Design and Implementation of Intervention Studies to Improve or Maintain Quality of Survivorship in Older and/or Frail Adults with Cancer," in which gaps in knowledge and research priorities to fill these gaps were recommended. Among the key recommendations was the need to expand studies focusing on the survivorship issues facing older adults with cancer, the impact of cancer on the aging process, as well as interventions to decrease the risk. Inclusion of a geriatric assessment and biomarkers of aging in research studies will be needed to accomplish these goals. Interventions are needed to halt or modify the accelerated aging phenotype seen in survivors of cancer. The compelling data with regard to exercise can serve as a model for future studies in the years to come.

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References

1. Howlader N, Noone AM, Krapcho M, et al. SEER Cancer Statistics Review, 1975-2012, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2012/, based on November 2014 SEER data submission, posted to the SEER web site, April 2015.
2. Smith BD, Smith GL, Hurria A, et al. Future of cancer incidence in the United States: burdens upon an aging, changing nation. *J Clin Oncol*. 2009;27:2758-2765.
3. Parry C, Kent EE, Mariotto AB, et al. Cancer survivors: a booming population. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1996-2005.
4. Henderson TO, Ness KK, Cohen HJ. Accelerated aging among cancer survivors: from pediatrics to geriatrics. *Am Soc Clin Oncol Educ Book*. 2014;34:e423-e430.
5. Mulrooney DA, Yeazel MW, Kawashima T, et al. Cardiac outcomes in a cohort of adult survivors of childhood and adolescent cancer: retrospective analysis of the Childhood Cancer Survivor Study cohort. *BMJ*. 2009;339:b4606.
6. Oeffinger KC, Mertens AC, Sklar CA, et al; Childhood Cancer Survivor Study. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006;355:1572-1582.
7. Mohile SG, Xian Y, Dale W, et al. Association of a cancer diagnosis with vulnerability and frailty in older Medicare beneficiaries. *J Natl Cancer Inst*. 2009;101:1206-1215.
8. Wildiers H, Heeren P, Puts M, et al. International Society of Geriatric Oncology consensus on geriatric assessment in older patients with cancer. *J Clin Oncol*. 2014;32:2595-2603.
9. Ingram SS, Seo PH, Martell RE, et al. Comprehensive assessment of the elderly cancer patient: the feasibility of self-report methodology. *J Clin Oncol*. 2002;20:770-775.
10. Hurria A, Lichtman SM, Gardes J, et al. Identifying vulnerable older adults with cancer: integrating geriatric assessment into oncology practice. *J Am Geriatr Soc*. 2007;55:1604-1608.
11. McCleary NJ, Wigler D, Berry D, et al. Feasibility of computer-based self-administered cancer-specific geriatric assessment in older patients with gastrointestinal malignancy. *Oncologist*. 2013;18:64-72.
12. Decoster L, Van Puyvelde K, Mohile S, et al. Screening tools for multidimensional health problems warranting a geriatric assessment in older cancer patients: an update on SIOG recommendations. *Ann Oncol*. 2015;26:288-300.
13. Reeve BB, Potosky AL, Smith AW, et al. Impact of cancer on health-related quality of life of older Americans. *J Natl Cancer Inst*. 2009;101:860-868.
14. Weaver KE, Forsythe LP, Reeve BB, et al. Mental and physical health-related quality of life among U.S. cancer survivors: population estimates from the 2010 National Health Interview Survey. *Cancer Epidemiol Biomarkers Prev*. 2012;21:2108-2117.
15. Keating NL, Nørredam M, Landrum MB, et al. Physical and mental health status of older long-term cancer survivors. *J Am Geriatr Soc*. 2005;53:2145-2152.
16. Baker F, Haffer SC, Denniston M. Health-related quality of life of cancer and noncancer patients in Medicare managed care. *Cancer*. 2003;97:674-681.
17. Pinder MC, Duan Z, Goodwin JS, et al. Congestive heart failure in older women treated with adjuvant anthracycline chemotherapy for breast cancer. *J Clin Oncol*. 2007;25:3808-3815.
18. Lichtman SM, Hurria A, Cirrincione CT, et al; Cancer and Leukemia Group B. Paclitaxel efficacy and toxicity in older women with metastatic breast cancer: combined analysis of CALGB 9342 and 9840. *Ann Oncol*. 2012;23:632-638.
19. Eastell R, Adams JE, Coleman RE, et al. Effect of anastrozole on bone mineral density: 5-year results from the anastrozole, tamoxifen, alone or in combination trial 18233230. *J Clin Oncol*. 2008;26:1051-1057.
20. Choksi P, Williams M, Clark PM, et al. Skeletal manifestations of treatment of breast cancer. *Curr Osteoporos Rep*. 2013;11:319-328.
21. Fried LP, Tangen CM, Walston J, et al; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146-M156.
22. Rockwood K, Mitnitski A. Frailty in relation to the accumulation of deficits. *J Gerontol A Biol Sci Med Sci*. 2007;62:722-727.
23. Hubbard JM, Cohen HJ, Muss HB. Incorporating biomarkers into cancer and aging research. *J Clin Oncol*. 2014;32:2611-2616.
24. Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. *J Gerontol A Biol Sci Med Sci*. 2014;69(Suppl 1):S4-S9.
25. Ferrucci L, Penninx BW, Volpato S, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. *J Am Geriatr Soc*. 2002;50:1947-1954.

26. Campisi J, Robert L. Cell senescence: role in aging and age-related diseases. *Interdiscip Top Gerontol*. 2014;39:45-61.

27. Chiodi I, Mondello C. Telomere and telomerase stability in human diseases and cancer. *Front Biosci (Landmark Ed)*. 2016;21:203-224.

28. Jia H, Wang Z. Telomere Length as a Prognostic Factor for Overall Survival in Colorectal Cancer Patients. *Cell Physiol Biochem*. 2016;38:122-128.

29. Liu Y, Sanoff HK, Cho H, et al. Expression of p16(INK4a) in peripheral blood T-cells is a biomarker of human aging. *Aging Cell*. 2009;8:439-448.

30. Krishnamurthy J, Torrice C, Ramsey MR, et al. Ink4a/Arf expression is a biomarker of aging. *J Clin Invest*. 2004;114:1299-1307.

31. Nelson JA, Krishnamurthy J, Menezes P, et al. Expression of p16(INK4a) as a biomarker of T-cell aging in HIV-infected patients prior to and during antiretroviral therapy. *Aging Cell*. 2012;11:916-918.

32. Shang J, Yao Y, Fan X, et al. miR-29c-3p promotes senescence of human mesenchymal stem cells by targeting CNOT6 through p53-p21 and p16-pRB pathways. *Biochim Biophys Acta*. 2016;1863:520-532.

33. Pustavoitau A, Barodka V, Sharpless NE, et al. Role of senescence marker p16(INK4a) measured in peripheral blood T-lymphocytes in predicting length of hospital stay after coronary artery bypass surgery in older adults. *Exp Gerontol*. 2016;74:29-36.

34. Kazemi-Bajestani SM, Mazurak VC, Baracos V. Computed tomography-defined muscle and fat wasting are associated with cancer clinical outcomes. *Semin Cell Dev Biol*. Epub 2015 Sep 3.

35. Bhatia S, Armenian SH, Armstrong GT, et al. Collaborative Research in Childhood Cancer Survivorship: The Current Landscape. *J Clin Oncol*. 2015;33:3055-3064.

36. Armstrong GT, Kawashima T, Leisenring W, et al. Aging and risk of severe, disabling, life-threatening, and fatal events in the childhood cancer survivor study. *J Clin Oncol*. 2014;32:1218-1227.

37. Ness KK, Krull KR, Jones KE, et al. Physiologic frailty as a sign of accelerated aging among adult survivors of childhood cancer: a report from the St Jude Lifetime cohort study. *J Clin Oncol*. 2013;31:4496-4503.

38. Watt DG, Horgan PG, McMillan DC. Routine clinical markers of the magnitude of the systemic inflammatory response after elective operation: a systematic review. *Surgery*. 2015;157:362-380.

39. Kim JH, Jenrow KA, Brown SL. Mechanisms of radiation-induced normal tissue toxicity and implications for future clinical trials. *Radiat Oncol J*. 2014;32:103-115.

40. Buttiglieri S, Ruella M, Risso A, et al. The aging effect of chemotherapy on cultured human mesenchymal stem cells. *Exp Hematol*. 2011;39:1171-1181.

41. Beeharry N, Broccoli D. Telomere dynamics in response to chemotherapy. *Curr Mol Med*. 2005;5:187-196.

42. Diker-Cohen T, Uziel O, Szyper-Kravitz M, et al. The effect of chemotherapy on telomere dynamics: clinical results and possible mechanisms. *Leuk Lymphoma*. 2013;54:2023-2029.

43. Yoon SY, Sung HJ, Park KH, et al. Telomere length shortening of peripheral blood mononuclear cells in solid-cancer patients undergoing standard-dose chemotherapy might be correlated with good treatment response and neutropenia severity. *Acta Haematol*. 2007;118:30-37.

44. Unryn BM, Hao D, Glück S, et al. Acceleration of telomere loss by chemotherapy is greater in older patients with locally advanced head and neck cancer. *Clin Cancer Res*. 2006;12:6345-6350.

45. Sanoff HK, Deal AM, Krishnamurthy J, et al. Effect of cytotoxic chemotherapy on markers of molecular age in patients with breast cancer. *J Natl Cancer Inst*. 2014;106:dju057.

46. Jones LW, Cohen RR, Mabe SK, et al. Assessment of physical functioning in recurrent glioma: preliminary comparison of performance status to functional capacity testing. *J Neurooncol*. 2009;94:79-85.

47. Abernethy AP, Shelby-James T, Fazekas BS, et al. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care*. 2005;4:7.

48. Jones LW, Eves ND, Haykowsky M, et al. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. *Lancet Oncol*. 2009;10:598-605.

49. Kavanagh T, Mertens DJ, Hamm LF, et al. Prediction of long-term prognosis in 12 169 men referred for cardiac rehabilitation. *Circulation*. 2002;106:666-671.

50. Kavanagh T, Mertens DJ, Hamm LF, et al. Peak oxygen intake and cardiac mortality in women referred for cardiac rehabilitation. *J Am Coll Cardiol*. 2003;42:2139-2143.

51. Kubozono T, Itoh H, Oikawa K, et al. Peak VO(2) is more potent than B-type natriuretic peptide as a prognostic parameter in cardiac patients. *Circ J*. 2008;72:575-581.

52. Aaronson KD, Mancini DM. Is percentage of predicted maximal exercise oxygen consumption a better predictor of survival than peak exercise oxygen consumption for patients with severe heart failure? *J Heart Lung Transplant*. 1995;14:981-989.

53. Jones LW, Watson D, Herndon JE II, et al. Peak oxygen consumption and long-term all-cause mortality in nonsmall cell lung cancer. *Cancer*. 2010;116:4825-4832.

54. Courneya KS, Segal RJ, Mackey JR, et al. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. *J Clin Oncol*. 2007;25:4396-4404.

55. van Waart H, Stuiver MM, van Harten WH, et al. Effect of low-intensity physical activity and moderate- to high-intensity physical exercise during adjuvant chemotherapy on physical fitness, fatigue, and chemotherapy completion rates: results of the PACES randomized clinical trial. *J Clin Oncol*. 2015;33:1918-1927.

56. Hornsby WE, Douglas PS, West MJ, et al. Safety and efficacy of aerobic training in operable breast cancer patients receiving neoadjuvant chemotherapy: a phase II randomized trial. *Acta Oncol*. 2014;53:65-74.

57. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J Clin Oncol*. 2009;27:344-351.

58. West MA, Loughney L, Lythgoe D, et al. Effect of prehabilitation on objectively measured physical fitness after neoadjuvant treatment in preoperative rectal cancer patients: a blinded interventional pilot study. *Br J Anaesth*. 2015;114:244-251.

59. Jones LW, Courneya KS, Mackey JR, et al. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol*. 2012;30:2530-2537.

60. Khouri MG, Hornsby WE, Risum N, et al. Utility of 3-dimensional echocardiography, global longitudinal strain, and exercise stress echocardiography to detect cardiac dysfunction in breast cancer patients treated with doxorubicin-containing adjuvant therapy. *Breast Cancer Res Treat*. 2014;143:531-539.

61. Adams MJ, Lipsitz SR, Colan SD, et al. Cardiovascular status in long-term survivors of Hodgkin's disease treated with chest radiotherapy. *J Clin Oncol*. 2004;22:3139-3148.

62. Jones LW, Liang Y, Pituskin EN, et al. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. *Oncologist*. 2011;16:112-120.

63. Jones LW, Fels DR, West M, et al. Modulation of circulating angiogenic factors and tumor biology by aerobic training in breast cancer patients receiving neoadjuvant chemotherapy. *Cancer Prev Res (Phila)*. 2013;6:925-937.

64. Sasso JP, Eves ND, Christensen JF, et al. A framework for prescription in exercise-oncology research. *J Cachexia Sarcopenia Muscle*. 2015;6:115-124.