Review Article on Energy Balance, Aging, Obesity, and Cancer

Sarcopenia in aging, obesity, and cancer

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Abstract: Sarcopenia, defined as loss of muscle mass, strength and physical performance, is a hallmark of aging and is invariably associated with perturbation of amino acid metabolism, increased muscle protein catabolism relative to anabolism, and loss of muscle fibers. Sarcopenia may be associated with general loss of body mass, or it may also occur along with obesity [sarcopenic obesity (SO)]. Although sarcopenia is associated with multiple comorbidities in older adults, its effects may even be more severe in patients with malignant disease where it has been shown to contribute to poor surgical outcomes, increased chemotherapy toxicity associated with both cytotoxic and targeted agents, as well as adversely impacting survival. While development of sarcopenia is a common age-related phenomenon, the associated catabolic processes appear to be promoted by physical inactivity, inadequate nutrition, and systemic low-grade inflammation, as well as intrinsic muscle and molecular changes, including mitochondrial dysfunction and impaired muscle stem cell regenerative capacity. Increased physical activity and adequate protein intake can reduce incidence and severity of sarcopenia in cancer patients, but many older cancer patients do not meet physical activity and nutrition recommendations, and cancer treatment can make it more difficult to make favorable lifestyle changes. Sarcopenia is discussed in terms of its adverse clinical consequences in older subjects and particularly, in older patients with cancer. Contributions of lifestyle, molecular, and cellular factors are likewise reviewed with suggestions for interventions to improve sarcopenia and its comorbid sequalae.

Keywords: Sarcopenia; muscle mass; aging; obesity; sarcopenic obesity (SO); cancer

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Introduction

Sarcopenia is described as a progressive, generalized muscle disorder characterized by loss of muscle mass, decreased muscle strength, and altered muscle composition (1-5). It most commonly occurs in association with aging, but may occur also with inflammatory and degenerative diseases such as rheumatoid arthritis, renal failure and congestive heart failure (1-5). Sarcopenia is commonly associated with adverse outcomes including progressive frailty, falls, fractures, physical disability and mortality (6). Sarcopenia, is usually characterized by weight loss, but it may also occur in association with obesity, in which case, it is termed sarcopenic obesity (SO). Sarcopenia is even more prevalent in older patients with cancer where it is associated with worse surgical outcomes, increased chemotherapy induced cytotoxicity, and overall worse prognosis. Targeted interventions to reduce the prevalence and severity of sarcopenia and associated comorbidities are clearly needed to improve outcomes in older adults, especially those

undergoing therapy for malignant disorders.

Sarcopenia pathophysiology

Age-dependent muscle catabolic processes leading to sarcopenia are associated with multiple systemic etiologic processes including altered energy balance, mitochondrial dysfunction, oxidative stress, and immune cell alterations leading to Senescence Associated Secretory Phenotypes (SASP) (7), extracellular matrix alterations (8) and increased fat mass, all contributing to chronic low grade inflammation which can affect all body systems and organs, particularly skeletal muscle. These proinflammatory processes such as SASP, expanded fat mass, altered extracellular matrix all promote inflammatory cytokine secretion stimulating multiple muscle catabolic processes, including upregulation of muscle atrophy f-box protein (MAF-box) and muscle ubiquitin ring finger-1 ligase (MURF-1) resulting in ubiquitination and degradation of muscle protein (9). Chronic low-grade inflammatory markers increased during normal aging process (inflammaging) include CRP, IL-1β, IL-6 and TNF (10,11).

Additionally, oxidative stress consequent to mitochondrial dysfunction can activate caspase 3 release, DNA fragmentation and myofibrillar degradation (12). Circulating F2-isoprostanes produced by reactive oxygen species (ROS) catalyzed by peroxidation of polyunsaturated fatty acids, have been identified as a reliable marker of associated oxidative stress, expanded fat mass and associated metaflammation. T cell P16INK4A has been identified as a marker of senescence and indicative of the SASP, characterized by mitotic arrest and secretion of multiple proinflammatory cytokines (discussed in detail in the accompanying article by Muss *et al.*) (13,14). Each of the above have been shown to contribute individually and collectively to muscle catabolism, suppressed muscle protein synthesis, and increased muscle protein degradation patterns (15).

The elevated inflammatory response and alterations in metabolism related to cancer and cancer treatment lead to further losses of muscle mass (16,17). Moreover, physical inactivity is linked to loss of lean body mass, and receipt of chemotherapy is related to increases in fat mass (18,19), all of which contribute to shifts in lean body/fat mass ratios. While many of these markers are noted to be upregulated during the normal aging process (9,15,20,21), their further increase in association with disease may accelerate the aging process leading to functional decline, age-associated comorbidities including sarcopenia and contribute to inter-individual variation in tolerance and response to cancer therapy (22,23).

In addition to the changes noted above, age related decreases in dehydroepiandrosterone sulfate (DHEAS) and testosterone in both men and women, have been implicated in development of sarcopenia (24,25). Multiple clinical trials employing DHEAS or testosterone supplements, usually in association with exercise, in older individuals have shown beneficial effects in muscle mass, but inconsistent impact on muscle strength and performance. In some of these studies, there was an adverse cardiovascular effect associated with testosterone administration studies (25). Studies are ongoing to improve strategies for improving hormone supplementation to prevent and mitigate development of sarcopenia while avoiding cardiovascular events (25).

Sarcopenia cell biology

Satellite cells, considered to be muscle progenitor stem cells, are located between the basal lamina and sarcolemma of muscle fibers (26). Along with macrophages, vascular components, and micro-environmental factors, satellite cells participate in muscle regeneration, especially following injury (26). They have been shown to decrease with age and can be depleted in young animals using a genetic mouse model of paired box protein Pax-7 muscle stem cell marker (Pax-7^{CreER}-Diptheria Toxin A). Mice with depleted satellite cells showed impaired regenerative capacity, but no change in age-dependent muscle atrophy compared to controls (27,28). Satellite cells in resting muscle exist in a reversible G_0 phase but can undergo activation in response to injury (29). As mice age, quiescent satellite cells transition to senescent cells, associated with increased expression of P16Ink4a, in which they lose the ability to undergo normal proliferation. They also show increased secretion of proinflammatory cytokines (29). Silencing p16 utilizing an shRNA strategy, resulted in release of satellite cells from the senescence phenotype and restoration of their activation in tissue culture and regenerative capacity upon mouse transfer (29).

Zhang *et al.* (30) investigated the decreased regenerative capacity of muscle stem cells from 24-month-old mice compared to 3-month-old mice and showed lower levels of NAD+, TCA cycle and oxidative phosphorylation enzymes, increased phospho-H2AX and increased DNA strand breaks along with reduced ability to replenish muscle stem cells in a mouse model of Duchene muscle dystrophy. All of these abnormalities improved with supplementation of nicotinamide riboside (NR) which also improved endurance. The NR stimulated improvement in muscle stem cell

regeneration was abolished in Sirt 1 knockdown mice. Thus, supplementation with NR to increase NAD+ levels in association with Sirt 1 restores regenerative capacity to muscle stem cells (30).

Earlier studies have shown that PARP activation due to persistent DNA damage can deplete cellular NAD+ (31) and that decreased muscle NAD+ may contribute to mitochondrial dysfunction (32), further suggesting that strategies to target maintenance of NAD+ levels may contribute to improvement in sarcopenia (33). By preserving NAD+ pools, PARP inhibitors, commonly used in chemotherapy, can improve mitochondrial metabolism, which may preserve muscle mass (34-40).

Genetic aspects of sarcopenia

Based on observational studies, especially twin studies, that indicate heritability of muscle mass and muscle strength phenotypes, multiple studies have been initiated to identify genes predisposing to sarcopenia (41). These studies, including genome-wide linkage studies and Candidate Gene Association studies have resulted in a potential association of the vitamin D receptor gene, ciliary neurotrophic factor (CNTF) and its receptors (CNTFR), Myostatin, IGF genes, angiotensin converting enzyme 1, and alpha actinin 3 (41-43). While genes, such as myostatin, are of particular interest because of its ability to interfere with muscle growth, these studies have been overall inconsistent and no clear candidates have been identified (41,42). Moreover, none of these genes appear to account for more than 5% of differences in muscle mass (41).

Assessment muscle mass and function

A standardized, uniformly accepted definition of sarcopenia has not yet been established. The European Working Group for Sarcopenia in Older People proposed a definition focused on diminished muscle strength as the primary indicator of sarcopenia with low muscle mass as a secondary feature (6). The Working Group further defined "severe" sarcopenia as a combination of decreased muscle strength, low muscle mass, and impaired physical function. However, uptake of this classification of sarcopenia, has been limited by the fact that assessment of muscle strength and function is less regularly obtained in clinical settings, as compared to radiologic assessment of muscle volume.

Further complicating the definition of sarcopenia is the heterogeneity in the imaging modalities used to evaluate muscle mass, and the lack of clearly established cut points to define low muscle mass. Among the multiple modalities used to measure muscle mass and the different techniques (41) employed for these measurements are computerized tomography (CT), dual-energy X-ray absorptiometry (DXA), magnetic resonance imaging (MRI), and bioelectric impedance (44-46). More recently being developed is measurement of creatine (methyl-d_3) dilution in urine (47). Of these techniques, the most commonly used in the clinical setting are CT and DXA scans, with CT being considerably more costly and using more radiation than DXA (48,49). DXA measures appendicular skeletal muscle mass, whereas CT estimates muscle mass by measuring cross-sectional area (48). Assessing body composition using CT scan is accomplished using a cross-sectional CT body slice at the level of L3, which is then used to determine components of body composition and extrapolated to determine total body fat and muscle mass. Disadvantages of using CT scans to assess muscle mass or body fat include the cost and high radiation dose relative to other methods. DXA is also in common use to measure body fat percent and lean body mass. While DXA scanners are common, the cost of a DXA scan is less than for a CT scan, and DXA exposes patients to less radiologic toxicity than CT. However, there are disadvantages of DXA use in the context of measuring muscle mass. In contrast, deuterated creatine (D_3-Cr) is a promising approach to provide a more direct measure of muscle mass. This technique measures the total body creatine pool size which is 98% located in skeletal muscle. This approach requires an oral dose of a tracer followed by an equilibration period, then a urine sample several days later, in which, the dilution of the D_3-Cr is used to calculate skeletal muscle mass (50). This technique has great promise, since it measures true muscle mass as opposed to other techniques which actually measure lean body mass or fat free mass. D_3-Cr measured muscle mass has been shown to correlate with short physical performance battery (SPPB) and mobility limitation in older men (51). While the actual test is easy to administer, use of D_3-Cr dilution has been limited because of special expertise and equipment required for final measurement and by problems with inter-individual differences which have not yet been resolved (47,52).

Studies of muscle density by radiologic techniques show low muscle attenuation is indicative of fatty infiltration (myosteatosis) and is associated with decreased muscle strength (53-55). Functional tests of muscle strength usually involve hand grip and/or gait speed (45,56). Compared to subjects with normal values, those with abnormally low measurements of these parameters (lower than two standard

deviations or less than 5% of normal) are more likely to experience significant toxicity with chemotoxicity, worse outcomes, and reduced survival (57,58). Additional research is clearly needed to establish the definition of sarcopenia most predictive of adverse outcomes, especially in high-risk populations such as older individuals and individuals undergoing treatment modalities that may have an adverse impact on muscle mass and function, such as chemotherapy.

Age-related sarcopenia

Age-related loss of muscle mass and function is common in older adults; losses in skeletal muscle mass and strength begin in mid-life and progress linearly with increasing age (59). In otherwise normal adults over age 50, muscle strength declines at 12–14% per decade in association with decreased muscle mass (60-62). Age-related sarcopenia has a multifactorial origin, involving lifestyle factors, hormonal changes, age-dependent biological changes, such as chronic inflammation, mitochondrial abnormalities, and loss of neuromuscular junctions. Sarcopenia can also be accelerated by a number of disease states, and as a response to medications, such as steroids and chemotherapeutic agents. Sarcopenia in older patients is also often accompanied by increases in adiposity, leading to SO (63). Gain of fat mass is associated with upregulation of circulating inflammatory factors and increased oxidative stress, which may further contribute to progression of sarcopenia (63). Recent reports suggest prevalence of sarcopenia in the range of 1–29% in community dwelling individuals, 14–33% among institutionalized patients and as high as 50% in those over 80 years of age (16,64). Several studies have shown a slight preponderance of sarcopenia among men compared to women, but others have not (65-67). For example, a study in Connecticut, of healthy community dwelling adults age >65, showed sarcopenia in 22.6% women and 26.8% in men. In another study performed in Shanghai, women > age 60 showed 8.5% sarcopenia, while men showed 19.2% (66). In contrast, studies performed in Singapore, showed 24.8% sarcopenia in women and 25.4% in men (67). Sarcopenia in older adults has been linked to functional impairment, disability, loss of independence, and mortality (68-70).

While there is great inter-individual variation in the development of sarcopenia, the major contributing lifestyle factors in older adults, appear to be insufficient dietary protein intake and reduced physical activity (71-74). In one cross sectional review of 900 men and women over age 50, 77% had lower than recommended protein intake. Recent studies of circulating amino acids have shown a seven amino acid signature (methionine, lysine, phenylalanine, threonine and three branch chain amino acids, including leucine, isoleucine and valine) to be negatively associated with sarcopenia (69). In addition, methionine, isoleucine and leucine levels are positively associated with increased muscle function, highlighting the importance of adequate intake of high-quality protein in muscle strength and volume (70-76).

Regular physical exercise has been shown to be protective for many conditions including sarcopenia, cardiovascular disorders, and cancer (77,78). It is noteworthy that protein intake and physical activity appear to be the major anabolic stimuli for muscle protein synthesis and building muscle mass (17,74,79). Resistance exercise has generally been employed to promote increased muscle volume, however, differences among individuals demonstrate that both aerobic and resistance exercises promote synthesis of myokines, such as myostatin and follistatin, with consequent impact on muscle growth (80). In addition, aerobic exercise has been shown to increase muscle vascularity (81,82). Moreover, combined nutrition emphasizing protein content and quality and exercise have been shown to have a synergistic effect to increase muscle mass, strength and function (71-74).

Sarcopenic obesity

While the image of the older, frail, sarcopenic individual is usually one of low body mass, it is important to emphasize that low muscle mass is not always associated with low BMI. The increasing prevalence of obesity in the population at large, and particularly in older adults, results in its combined occurrence with sarcopenia in a condition identified as SO. Moreover, since obesity has been associated with at least 13 malignancies (83), it is expected that there will be an increased association of SO with many malignancies especially those having been determined to be obesity-associated. Similar to sarcopenia itself, difficulties exist in defining SO due to lack of consensus and specific measurements of sarcopenia. Sarcopenia alone has been described as low weight, low/normal fat mass, low appendicular lean mass, low body mass index, and low/normal waist circumference. In contrast, SO is characterized as normal to high weight, high fat mass, low appendicular lean mass, normal to high body mass and normal to high waist circumference (63).

Depending on technique and criteria used to define sarcopenia, SO has been identified in 0–41% of the older population (63). Some series indicate slightly greater prevalence in men compared to women, while other series

suggest the opposite (63).

From a clinical viewpoint, individuals with SO have been reported to have difficulty with physical function, such as walking and stair climbing and are more prone to develop disability, as compared to individuals without SO (84-86). From a pathophysiologic viewpoint, obesity and sarcopenia have overlapping and probably interacting components. Obesity is a chronic low grade inflammatory disorder (metaflammation) generating altered levels of cytokines and adipokines, including increased IL-6, MCP-1, TNFα, leptin, and decreased adiponectin (87), all of which may contribute to general muscle inflammation (88,89). Obesity also leads to insulin resistance and leptin resistance, each of which can impair muscle metabolism and lead to fatty infiltration of muscle (myosteatosis) (86,90). Obesity also contributes to decreased physical activity, which may further promote sarcopenia. Loss of muscle mass may likewise promote decreased physical activity, further promoting obesity. Whether sarcopenia and obesity are separate but mutually reinforcing processes or part of a single age-associated process remains to be determined. Nonetheless, their combination increases morbidity and mortality. However, both sarcopenia and obesity are the result of potentially modifiable lifestyle factors and thus lifestyle modification needs to be the focus of further basic research and clinical trials.

Sarcopenia and treatment toxicity in cancer patients

Sarcopenia has been linked to treatment toxicity and poor quality of life in mixed-age groups of cancer patients (91). One study looked at the relationship between lean body mass and other measures of muscle volume and toxicity in 151 women with early-stage breast cancer receiving anthracycline and taxane-based chemotherapy regimens and demonstrated that low lean body mass was associated with a higher risk of grade 3/4 toxicities (RR: 1.48, P=0.002). Low muscle volume was found to predict for higher rates of hematologic toxicity (RR: 2.2, P=0.02), gastrointestinal toxicity (RR: 6.49, P=0.02) and hospitalization (RR: 1.91, P=0.05) (91). Another study looked at the relationships amongst quality of life, muscle mass, and muscle function in 200 inactive breast cancer patients receiving adjuvant chemotherapy and found that both sarcopenia and dynapenia (poor muscle function compared to age- and sex-based norms) were associated with poor quality of life (92). Sarcopenia has also been associated with toxicity in the setting of advanced breast cancer; a meta-analysis including four observational studies evaluating the relationship between sarcopenia and outcomes in women with advanced cancer receiving chemotherapy demonstrated that patients with metastatic disease with sarcopenia had a two-fold risk of grade 3–5 toxicity as compared to patients who were not sarcopenic (RR: 2.17, 95% CI: 1.4–3.34, P=0.0005) (93).

Sarcopenia in older cancer patients

Studies have demonstrated that cancer and cancer treatment can have a significant impact on body composition, leading to loss of lean muscle mass, often in combination with gains in fat mass. These changes may be especially common and problematic in older individuals with cancer, where cancer progression and treatment effects can lead to increased frailty and loss of independence (22,94). Notably, loss of muscle mass can become an escalating issue in patients, as the elevated inflammatory response related to cancer and aging, as well as alterations in metabolism related to cancer cachexia, lead to on-going loss of muscle mass (16,17). However, there are very limited data prospectively evaluating treatment-related changes in muscle mass and body composition in older cancer patients. One study investigated the association between sarcopenia and decline in physical function in 131 cancer patients ≥65 years who were initiating chemotherapy for stage I–IV cancers and found that 26.2% of patients had sarcopenia at baseline. Individuals with sarcopenia had a non-significant trend toward increased risk of functional decline during chemotherapy (95).

Although data regarding the impact of cancer treatment on body composition in older cancer patients are lacking, a few small studies have demonstrated that chemotherapy treatment leads to an increase in fat mass, reduction in lean body mass, and decreased strength in mixed-age populations of cancer patients (96). For example, a cross sectional study evaluating muscle function in 225 women with breast cancer and 26 healthy controls demonstrated that patients who received chemotherapy had significantly lower muscle strength in the upper and lower extremities and also experienced muscle fatigue more quickly as compared to age-matched healthy women (96). More information is needed looking at the impact of therapy on body composition in larger groups of cancer survivors.

Sarcopenia and treatment toxicity in older cancer patients

While sarcopenia is associated with multiple comorbidities

in patients with cancer, its effects may be even more severe in older patients with cancer (34). In different series, sarcopenia has been identified before therapeutic intervention in 14% to 74% of cancer patients (34,97-99) where it has been shown to be associated with increased surgical complications, increased chemotherapy toxicity, and poorer outcomes, including poorer survival in multiple malignancies, including lung, breast, colorectal, renal cell, ovarian, hepatocellular cancer, and lymphoma (34,44,58,93,100-104). Older cancer patients with sarcopenia have been shown to experience increased toxicity with multiple chemotherapeutic agents including 5FU, capecitabine, cisplatin, anthracyclines, taxanes, etoposide, and cyclophosphamide (34,99-105). In addition, sarcopenia has been associated with increased toxicity of targeted agents such as sorafenib and sunitinib (106-109). Notably, many of these chemotherapeutic agents cause oxidative stress in muscle, resulting in progressive sarcopenia and increased fat deposition in muscle (34,110). This sets up a vicious cycle in which therapeutic agents induce sarcopenia, and sarcopenia results in increased chemotoxicity. Chemotherapy may also further contribute to sarcopenia through contributing to nausea, which may lead to lower protein intake.

Sarcopenia and cancer mortality

Observational studies also suggest that sarcopenia and SO may be associated with poorer outcomes in cancer patients. A recent analysis looked at the relationship between body composition, evaluated through single-slice CT scan at the L3 vertebral body, and mortality in 3,241 women with early-stage breast cancer (111). Thirty-four percent of patients had sarcopenia, and 6% had both sarcopenia and high total adipose tissue. Women with SO had the highest risk of overall mortality (HR: 1.89, 95% CI: 1.30–2.73). Sarcopenia alone was also linked to higher mortality (HR: 1.41, 95% CI: 1.18–1.69). These data and several other reports were included in a recent meta-analysis by Aleixo and colleagues looking at the relationship between muscle mass and outcomes in women receiving chemotherapy for early-stage (four studies) and advanced (four studies) breast cancer (93). The overall prevalence of sarcopenia reported in these studies was 39.8% (range, 25–66.9%). Sarcopenia, as measured by skeletal muscle index, was associated with poorer overall survival in breast cancer patients (HR: 1.68, 95% CI: 1.09–2.59, 5 studies, P=0.02). Notably, in women with advanced disease, time to progression on chemotherapy was 71 days shorter in women who were sarcopenic versus those who were not (P=0.007). However, there is currently limited data evaluating the relationship between sarcopenia or other elements of body composition in older women with breast cancer.

Another study of 3,262 early-stage (stage I–II) patients with colorectal cancer evaluated the relationship of SO and mortality. Women with SO had a 64% higher risk of overall mortality as compared to women with lower adiposity and adequate muscle (HR: 1.64, 95% CI: 1.05–2.57). Additionally, women with sarcopenia alone also had increased mortality as compared to women with adequate muscle and lower adiposity (HR: 1.27, 95% CI: 1.09–1.48) (112).

Physical activity, muscle mass, and functional status in older cancer patients

A number of trials have evaluated the impact of physical activity interventions on muscle strength and mass in older cancer patients. One study demonstrated that a resistance training intervention led to an increase in total body muscle mass, strength and power (all P<0.001) in 19 men over age 65 with prostate cancer who were receiving androgen deprivation therapy (ADT) (113). Another study demonstrated that men with prostate cancer over age 65 who were randomized to a resistance training intervention during radiation preserved muscle mass compared with men randomized to aerobic exercise or usual care control (114). Studies have suggested that interventions employing only aerobic exercise have been less successful in maintaining muscle mass in older cancer survivors. For example, a French study randomized 301 cancer patients over the age of 70 who were initiating treatment (surgery, chemotherapy or radiation) to a 12-month telephone-based aerobic physical activity intervention or usual care control (115). After 1 year, there was no difference in SPPB scores between groups (P=0.772). Subgroup analyses suggested an improvement in SPPB scores in breast cancer patients randomized to the intervention group at 2 years (P=0.006), but falls, hospitalization, institutionalization, and death rates were similar in both groups, suggesting that aerobic training alone was not sufficient to maintain muscle strength and function.

Data regarding the impact of physical activity interventions on muscle mass and function in older breast cancer patients are currently lacking. A few studies have evaluated the impact of physical activity interventions on body composition in mixed-age groups of breast cancer patients and have demonstrated that interventions that

incorporate resistance training exercise lead to increased muscle mass and prevention of clinically significant decline during and after cancer treatment (92,116,117). Aerobic exercise alone, however, has not been shown to result in increased muscle mass or strength, suggesting a critical role for resistance training in building and maintaining muscle mass during cancer treatment (92). In studies of greater than 2,100 women (1,220 newly diagnosed breast cancer, 900 mammographic controls) only 30.5% of women over the age of 65 met American Cancer Society guidelines of 2.5 hours/week combined strenuous and moderate physical activity, underscoring the need for interventions to increase physical activity in this population at risk for sarcopenia (118). Overall, there is a clear need for interventions focused on improving nutrition and increasing physical activity to prevent and reverse sarcopenia.

The question of timing and dose of exercise and diet to address sarcopenia in older adults with cancer remains unanswered. There is compelling evidence that prehabilitation interventions among esophagogastric, colorectal, lung and liver cancer patients result in improved functional outcomes (119-122). Early recovery after surgery (ERAS) protocols also suggest that movement soon after surgery improves function as well, as part of a comprehensive protocol, of which movement is just one part (123-125). The potential to improve body composition, or prevent worsening, by exercise interventions during chemotherapy is an area of active investigation in two ongoing NCI funded R01s (R01 CA206196, R01 CA207753), but neither of these studies focuses on older adults. It is important not to assume that interventions for younger adults will work in older adults with cancer, in whom there may be unique needs regarding sarcopenia and unique barriers to exercise. Exercise trials have documented improved body composition after treatment completion (126,127), but very few have focused specifically on older adults. The potential remains to alter outcomes with exercise and dietary interventions designed to address sarcopenia before, during or after cancer therapy.

As noted above, under Cell Biology, PARP inhibitors can improve mitochondrial function and may preserve muscle mass (34-40). Thus, PARP inhibitors need to be further evaluated for impact on sarcopenia, especially in malignancies where they are already part of the therapeutic armamentarium such as breast, ovarian, pancreas, and some cases of prostate cancer (128-131). Interestingly, dietary supplementation of NAD+ and/or its precursors is currently undergoing extensive investigation to promote healthy aging (132,133), although specific information on sarcopenia is not available.

Conclusions

Sarcopenia is common in older adults with cancer and unfavorably impacts treatment tolerance and long-term outcomes. Sarcopenia can be mitigated through increased physical activity, especially resistance exercise, and adequate protein intake, but studies suggest that many older cancer survivors do not meet nutrition and physical activity goals. There is thus a clear need for a transdisciplinary, mechanistic, and clinical approach involving regenerative cell therapy with targeted metabolic strategies along with pharmacologic, and lifestyle modifications of nutrition and physical activity, including both aerobic and resistance exercise to increase muscle mass and prevent, reverse, and reduce impact of sarcopenia, and improve outcomes in older patients, with and without malignancies.

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References

1. Lang T, Streeper T, Cawthon P, et al. Sarcopenia: etiology, clinical consequences, intervention, and assessment. Osteoporos Int 2010;21:543-59.
2. Bozzetti F. Forcing the vicious circle: sarcopenia increases toxicity, decreases response to chemotherapy and worsens with chemotherapy. Ann Oncol 2017;28:2107-18.
3. Calvani R, Picca A, Marini F, et al. A distinct pattern of circulating amino acids characterizes older persons with physical frailty and sarcopenia: results from the BIOSPHERE study. Nutrients 2018;10:1691.
4. Fujita S, Volpi E. Amino acids and muscle loss with aging. J Nutr 2006;136:277S-80S.
5. Walston JD. Sarcopenia in older adults. Curr Opin Rheumatol 2012;24:623-7.
6. Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019;48:16-31.
7. Campisi J. Senescent cells, tumor suppression, and organismal aging: good citizens, bad neighbors. Cell 2005;120:513-22.
8. Tlsty TD, Gascard P. Stromal directives can control cancer. Science 2019;365:122-3.
9. Pérez-Baos S, Prieto-Potin I, Román-Blas JA, et al. Mediators and patterns of muscle loss in chronic systemic inflammation. Front Physiol 2018;9:409.
10. Beyer I, Mets T, Bautmans I. Chronic low-grade inflammation and age-related sarcopenia. Curr Opin Clin Nutr Metab Care 2012;15:12-22.
11. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. Mech Ageing Dev 2007;128:92-105.
12. Powers SK, Kavazis AN, McClung JM. Oxidative stress and disuse muscle atrophy. J Appl Physiol (1985) 2007;102:2389-97.
13. Liu JY, Souroullas GP, Diekman BO, et al. Cells exhibiting strong p16 (INK4a) promoter activation in vivo display features of senescence. Proc Natl Acad Sci U S A 2019;116:2603-11.
14. Zanni F, Vescovini R, Biasini C, et al. Marked increase with age of type 1 cytokines within memory and effector/cytotoxic CD8+ T cells in humans: a contribution to understand the relationship between inflammation and immunosenescence. Exp Gerontol 2003;38:981-7.
15. Bano G, Trevisan C, Carraro S, et al. Inflammation and sarcopenia: a systematic review and meta-analysis. Maturitas 2017;96:10-5.
16. von Haehling S, Morley JE, Anker SD. An overview of sarcopenia: facts and numbers on prevalence and clinical impact. J Cachexia Sarcopenia Muscle 2010;1:129-33.
17. Yanai H. Nutrition for sarcopenia. J Clin Med Res 2015;7:926-31.
18. Pedersen B, Delmar C, Bendtsen MD, et al. Changes in weight and body composition among women with breast cancer during and after adjuvant treatment: a prospective follow-up study. Cancer Nurs 2017;40:369-76.
19. Nissen MJ, Shapiro A, Swenson KK. Changes in weight and body composition in women receiving chemotherapy for breast cancer. Clin Breast Cancer 2011;11:52-60.
20. Bian AL, Hu HY, Rong YD, et al. A study on relationship between elderly sarcopenia and inflammatory factors IL-6 and TNF-alpha. Eur J Med Res 2017;22:25.
21. Rong YD, Bian AL, Hu HY, et al. Study on relationship between elderly sarcopenia and inflammatory cytokine IL-6, anti-inflammatory cytokine IL-10. BMC Geriatr 2018;18:308.
22. Vasto S, Candore G, Balistreri CR, et al. Inflammatory networks in ageing, age-related diseases and longevity. Mech Ageing Dev 2007;128:83-91.
23. Hubbard JM, Cohen HJ, Muss HB. Incorporating biomarkers into cancer and aging research. J Clin Oncol 2014;32:2611-6.
24. Sakuma K, Yamaguchi A. Sarcopenia and age-related endocrine function. Int J Endocrinol 2012;2012:127362.
25. Maggio M, Lauretani F, Ceda GP. Sex hormones and sarcopenia in older persons. Curr Opin Clin Nutr Metab Care 2013;16:3-13.
26. Naranjo JD, Dziki JL, Badylak SF. Regenerative medicine approaches for age-related muscle loss and sarcopenia: a mini-review. Gerontology 2017;63:580-9.

27. Fry CS, Lee JD, Mula J, et al. Inducible depletion of satellite cells in adult, sedentary mice impairs muscle regenerative capacity without affecting sarcopenia. Nat Med 2015;21:76-80.
28. Snijders T, Parise G. Role of muscle stem cells in sarcopenia. Curr Opin Clin Nutr Metab Care 2017;20:186-90.
29. Sousa-Victor P, Gutarra S, Garcia-Prat L, et al. Geriatric muscle stem cells switch reversible quiescence into senescence. Nature 2014;506:316-21.
30. Zhang H, Ryu D, Wu Y, et al. NAD(+) repletion improves mitochondrial and stem cell function and enhances life span in mice. Science 2016;352:1436-43.
31. Berger NA. Poly(ADP-ribose) in the cellular response to DNA damage. Radiat Res 1985;101:4-15.
32. Gomes AP, Price NL, Ling AJ, et al. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell 2013;155:1624-38.
33. Sanchis-Gomar F, Pareja-Galeano H, Mayero S, et al. New molecular targets and lifestyle interventions to delay aging sarcopenia. Front Aging Neurosci 2014;6:156.
34. Davis MP, Panikkar R. Sarcopenia associated with chemotherapy and targeted agents for cancer therapy. Ann Palliat Med 2019;8:86-101.
35. Barreiro E, Gea J. PARP-1 and PARP-2 activity in cancer-induced cachexia: potential therapeutic implications. Biol Chem 2018;399:179-86.
36. Mohamed JS, Wilson JC, Myers MJ, et al. Dysregulation of SIRT-1 in aging mice increases skeletal muscle fatigue by a PARP-1-dependent mechanism. Aging (Albany NY) 2014;6:820-34.
37. Chacon-Cabrera A, Mateu-Jimenez M, Langohr K, et al. Role of PARP activity in lung cancer-induced cachexia: Effects on muscle oxidative stress, proteolysis, anabolic markers, and phenotype. J Cell Physiol 2017;232:3744-61.
38. Pirinen E, Canto C, Jo YS, et al. Pharmacological Inhibition of poly(ADP-ribose) polymerases improves fitness and mitochondrial function in skeletal muscle. Cell Metab 2014;19:1034-41.
39. Conrad MF, Albadawi H, Stone DH, et al. Local administration of the Poly ADP-Ribose Polymerase (PARP) inhibitor, PJ34 during hindlimb ischemia modulates skeletal muscle reperfusion injury. J Surg Res 2006;135:233-7.
40. Migliavacca E, Tay SKH, Patel HP, et al. Mitochondrial oxidative capacity and NAD(+) biosynthesis are reduced in human sarcopenia across ethnicities. Nat Commun 2019;10:5808.
41. Roth SM. Genetic aspects of skeletal muscle strength and mass with relevance to sarcopenia. Bonekey Rep 2012;1:58.
42. Tan LJ, Liu SL, Lei SF, et al. Molecular genetic studies of gene identification for sarcopenia. Hum Genet 2012;131:1-31.
43. Garatachea N, Lucía A. Genes and the ageing muscle: a review on genetic association studies. Age (Dordr) 2013;35:207-33.
44. Kumar A, Moynagh MR, Multinu F, et al. Muscle composition measured by CT scan is a measurable predictor of overall survival in advanced ovarian cancer. Gynecol Oncol 2016;142:311-6.
45. Dhillon RJ, Hasni S. Pathogenesis and management of sarcopenia. Clin Geriatr Med 2017;33:17-26.
46. Iliopoulos D, Hirsch HA, Struhl K. An epigenetic switch involving NF-kappaB, Lin28, Let-7 MicroRNA, and IL6 links inflammation to cell transformation. Cell 2009;139:693-706.
47. Clark RV, Walker AC, Miller RR, et al. Creatine (methyl-d3) dilution in urine for estimation of total body skeletal muscle mass: accuracy and variability vs. MRI and DXA. J Appl Physiol (1985) 2018;124:1-9.
48. Kim TN, Park MS, Lee EJ, et al. Comparisons of three different methods for defining sarcopenia: an aspect of cardiometabolic risk. Sci Rep 2017;7:6491.
49. Lee K, Shin Y, Huh J, et al. Recent Issues on Body Composition Imaging for Sarcopenia Evaluation. Korean J Radiol 2019;20:205-17.
50. Evans WJ, Hellerstein M, Orwoll E, et al. D(3) -Creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. J Cachexia Sarcopenia Muscle 2019;10:14-21.
51. Cawthon PM, Orwoll ES, Peters KE, et al. Strong relation between muscle mass determined by D3-creatine dilution, physical performance, and incidence of falls and mobility limitations in a prospective cohort of older men. J Gerontol A Biol Sci Med Sci 2019;74:844-52.
52. Clark RV, Walker AC, O'Connor-Semmes RL, et al. Total body skeletal muscle mass: estimation by creatine (methyl-d3) dilution in humans. J Appl Physiol (1985) 2014;116:1605-13.
53. Messina C, Maffi G, Vitale JA, et al. Diagnostic imaging of osteoporosis and sarcopenia: a narrative review. Quant Imaging Med Surg 2018;8:86-99.
54. Biltz NK, Meyer GA. A novel method for the quantification of fatty infiltration in skeletal muscle. Skelet Muscle 2017;7:1.
55. Addison ML, Rissman EF. Sexual dimorphism of growth

hormone in the hypothalamus: regulation by estradiol. Endocrinology 2012;153:1898-907.
56. Rogers BH, Brown JC, Gater DR, et al. Association between maximal bench press strength and isometric handgrip strength among breast cancer survivors. Arch Phys Med Rehabil 2017;98:264-9.
57. Abellan van Kan G, Houles M, Vellas B. Identifying sarcopenia. Curr Opin Clin Nutr Metab Care 2012;15:436-41.
58. Ataseven B, Luengo TG, du Bois A, et al. Skeletal muscle attenuation (sarcopenia) predicts reduced overall survival in patients with advanced epithelial ovarian cancer undergoing primary debulking surgery. Ann Surg Oncol 2018;25:3372-9.
59. Larsson L, Degens H, Li M, et al. Sarcopenia: aging-related loss of muscle mass and function. Physiol Rev 2019;99:427-511.
60. Lindle RS, Metter EJ, Lynch NA, et al. Age and gender comparisons of muscle strength in 654 women and men aged 20-93 yr. J Appl Physiol (1985) 1997;83:1581-7.
61. Lord SR, Ward JA, Williams P, et al. Physiological factors associated with falls in older community-dwelling women. J Am Geriatr Soc 1994;42:1110-7.
62. Kostek MC, Delmonico MJ, Reichel JB, et al. Muscle strength response to strength training is influenced by insulin-like growth factor 1 genotype in older adults. J Appl Physiol (1985) 2005;98:2147-54.
63. Cauley JA. An overview of sarcopenic obesity. J Clin Densitom 2015;18:499-505.
64. Cruz-Jentoft AJ, Landi F, Schneider SM, et al. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). Age Ageing 2014;43:748-59.
65. Iannuzzi-Sucich M, Prestwood KM, Kenny AM. Prevalence of sarcopenia and predictors of skeletal muscle mass in healthy, older men and women. J Gerontol A Biol Sci Med Sci 2002;57:M772-7.
66. Du Y, Wang X, Xie H, et al. Sex differences in the prevalence and adverse outcomes of sarcopenia and sarcopenic obesity in community dwelling elderly in East China using the AWGS criteria. BMC Endocr Disord 2019;19:109.
67. Tay L, Ding YY, Leung BP, et al. Sex-specific differences in risk factors for sarcopenia amongst community-dwelling older adults. Age (Dordr) 2015;37:121.
68. Hurley BF, Redmond RA, Pratley RE, et al. Effects of strength training on muscle hypertrophy and muscle cell disruption in older men. Int J Sports Med 1995;16:378-84.
69. Lu Y, Karagounis LG, Ng TP, et al. Systemic and metabolic signature of sarcopenia in community-dwelling older adults. J Gerontol A Biol Sci Med Sci 2020;75:309-17.
70. De Martinis M, Franceschi C, Monti D, et al. Inflammation markers predicting frailty and mortality in the elderly. Exp Mol Pathol 2006;80:219-27.
71. Scott D, Blizzard L, Fell J, et al. Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort Study. J Am Geriatr Soc 2010;58:2129-34.
72. Farsijani S, Morais JA, Payette H, et al. Relation between mealtime distribution of protein intake and lean mass loss in free-living older adults of the NuAge study. Am J Clin Nutr 2016;104:694-703.
73. Pencharz PB, Elango R, Wolfe RR. Recent developments in understanding protein needs - how much and what kind should we eat? Appl Physiol Nutr Metab 2016;41:577-80.
74. Kobayashi H. Amino acid nutrition in the prevention and treatment of sarcopenia. Yakugaku Zasshi 2018;138:1277-83.
75. 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;50:1947-54.
76. Ferrucci L, Harris TB, Guralnik JM, et al. Serum IL-6 level and the development of disability in older persons. J Am Geriatr Soc 1999;47:639-46.
77. Fiuza-Luces C, Santos-Lozano A, Joyner M, et al. Exercise benefits in cardiovascular disease: beyond attenuation of traditional risk factors. Nat Rev Cardiol 2018;15:731-43.
78. Fiuza-Luces C, Garatachea N, Berger NA, et al. Exercise is the real polypill. Physiology (Bethesda) 2013;28:330-58.
79. Genaro PS, Pinheiro Mde M, Szejnfeld VL, et al. Dietary protein intake in elderly women: association with muscle and bone mass. Nutr Clin Pract 2015;30:283-9.
80. He Z, Tian Y, Valenzuela PL, et al. Myokine response to high-intensity interval vs. resistance exercise: an individual approach. Front Physiol 2018;9:1735.
81. Padilla J, Simmons GH, Bender SB, et al. Vascular effects of exercise: endothelial adaptations beyond active muscle beds. Physiology (Bethesda) 2011;26:132-45.
82. Joyner MJ, Casey DP. Regulation of increased blood flow (hyperemia) to muscles during exercise: a hierarchy of competing physiological needs. Physiol Rev 2015;95:549-601.
83. Lauby-Secretan B, Scoccianti C, Loomis D, et al. Body fatness and cancer--viewpoint of the IARC working group. N Engl J Med 2016;375:794-8.
84. Baumgartner RN, Wayne SJ, Waters DL, et al. Sarcopenic obesity predicts instrumental activities of daily living

disability in the elderly. Obes Res 2004;12:1995-2004.
85. Lim S, Kim JH, Yoon JW, et al. Sarcopenic obesity: prevalence and association with metabolic syndrome in the Korean Longitudinal Study on Health and Aging (KLoSHA). Diabetes Care 2010;33:1652-4.
86. Levine ME, Crimmins EM. The impact of insulin resistance and inflammation on the association between sarcopenic obesity and physical functioning. Obesity (Silver Spring) 2012;20:2101-6.
87. Berger NA. Obesity and cancer pathogenesis. Ann N Y Acad Sci 2014;1311:57-76.
88. Dalle S, Rossmeislova L, Koppo K. The role of inflammation in age-related sarcopenia. Front Physiol 2017;8:1045.
89. Iyengar NM, Gucalp A, Dannenberg AJ, et al. Obesity and cancer mechanisms: tumor microenvironment and inflammation. J Clin Oncol 2016;34:4270-6.
90. Hamrick MW, McGee-Lawrence ME, Frechette DM. Fatty infiltration of skeletal muscle: mechanisms and comparisons with bone marrow adiposity. Front Endocrinol (Lausanne) 2016;7:69.
91. Shachar SS, Deal AM, Weinberg M, et al. Body composition as a predictor of toxicity in patients receiving anthracycline and taxane-based chemotherapy for early-stage breast cancer. Clin Cancer Res 2017;23:3537-43.
92. Adams SC, Segal RJ, McKenzie DC, et al. Impact of resistance and aerobic exercise on sarcopenia and dynapenia in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. Breast Cancer Res Treat 2016;158:497-507.
93. Aleixo GFP, Williams GR, Nyrop KA, et al. Muscle composition and outcomes in patients with breast cancer: meta-analysis and systematic review. Breast Cancer Res Treat 2019;177:569-79.
94. Vinel C, Pereira O, Dupuy A, et al. Isoprostanes as markers for muscle aging in older athletes. Biochim Open 2017;6:1-8.
95. Klassen O, Schmidt ME, Ulrich CM, et al. Muscle strength in breast cancer patients receiving different treatment regimes. J Cachexia Sarcopenia Muscle 2017;8:305-16.
96. Rahman M, Temple JR, Breitkopf CR, et al. Racial differences in body fat distribution among reproductive-aged women. Metabolism 2009;58:1329-37.
97. Miyake M, Owari T, Iwamoto T, et al. Clinical utility of bioelectrical impedance analysis in patients with locoregional muscle invasive or metastatic urothelial carcinoma: a subanalysis of changes in body composition during neoadjuvant systemic chemotherapy. Support Care Cancer 2018;26:1077-86.
98. Daly LE, Ni Bhuachalla EB, Power DG, et al. Loss of skeletal muscle during systemic chemotherapy is prognostic of poor survival in patients with foregut cancer. J Cachexia Sarcopenia Muscle 2018;9:315-25.
99. Vega MC, Laviano A, Pimentel GD. Sarcopenia and chemotherapy-mediated toxicity. Einstein (Sao Paulo) 2016;14:580-4.
100. Stene GB, Helbostad JL, Amundsen T, et al. Changes in skeletal muscle mass during palliative chemotherapy in patients with advanced lung cancer. Acta Oncol 2015;54:340-8.
101. Miyamoto Y, Baba Y, Sakamoto Y, et al. Sarcopenia is a negative prognostic factor after curative resection of colorectal cancer. Ann Surg Oncol 2015;22:2663-8.
102. Shachar SS, Williams GR, Muss HB, et al. Prognostic value of sarcopenia in adults with solid tumours: a meta-analysis and systematic review. Eur J Cancer 2016;57:58-67.
103. Rutten IJ, Ubachs J, Kruitwagen RF, et al. The influence of sarcopenia on survival and surgical complications in ovarian cancer patients undergoing primary debulking surgery. Eur J Surg Oncol 2017;43:717-24.
104. Lanic H, Kraut-Tauzia J, Modzelewski R, et al. Sarcopenia is an independent prognostic factor in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Leuk Lymphoma 2014;55:817-23.
105. Prado CM, Baracos VE, McCargar LJ, et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009;15:2920-6.
106. Antoun S, Baracos VE, Birdsell L, et al. Low body mass index and sarcopenia associated with dose-limiting toxicity of sorafenib in patients with renal cell carcinoma. Ann Oncol 2010;21:1594-8.
107. Antoun S, Birdsell L, Sawyer MB, et al. Association of skeletal muscle wasting with treatment with sorafenib in patients with advanced renal cell carcinoma: results from a placebo-controlled study. J Clin Oncol 2010;28:1054-60.
108. Antonelli G, Gigante E, Iavarone M, et al. Sarcopenia is associated with reduced survival in patients with advanced hepatocellular carcinoma undergoing sorafenib treatment. United European Gastroenterol J 2018;6:1039-48.
109. Huillard O, Mir O, Peyromaure M, et al. Sarcopenia and body mass index predict sunitinib-induced early dose-limiting toxicities in renal cancer patients. Br J Cancer 2013;108:1034-41.
110. Waltz TB, Fivenson EM, Morevati M, et al. Sarcopenia,

aging and prospective interventional strategies. Curr Med Chem 2018;25:5588-96.
111. Caan BJ, Cespedes Feliciano EM, Prado CM, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. JAMA Oncol 2018;4:798-804.
112. Caan BJ, Meyerhardt JA, Kroenke CH, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS study). Cancer Epidemiol Biomarkers Prev 2017;26:1008-15.
113. Hanson ED, Sheaff AK, Sood S, et al. Strength training induces muscle hypertrophy and functional gains in black prostate cancer patients despite androgen deprivation therapy. J Gerontol A Biol Sci Med Sci 2013;68:490-8.
114. Alberga AS, Segal RJ, Reid RD, et al. Age and androgen-deprivation therapy on exercise outcomes in men with prostate cancer. Support Care Cancer 2012;20:971-81.
115. Arrieta H, Astrugue C, Regueme S, et al. Effects of a physical activity programme to prevent physical performance decline in onco-geriatric patients: a randomized multicentre trial. J Cachexia Sarcopenia Muscle 2019;10:287-97.
116. Dieli-Conwright CM, Courneya KS, Demark-Wahnefried W, et al. Effects of aerobic and resistance exercise on metabolic syndrome, sarcopenic obesity, and circulating biomarkers in overweight or obese survivors of breast cancer: a randomized controlled trial. J Clin Oncol 2018;36:875-83.
117. Brown JC, Schmitz KH. Weight lifting and physical function among survivors of breast cancer: a post hoc analysis of a randomized controlled trial. J Clin Oncol 2015;33:2184-9.
118. Thompson CL, Owusu C, Nock NL, et al. Race, age, and obesity disparities in adult physical activity levels in breast cancer patients and controls. Front Public Health 2014;2:150.
119. Minnella EM, Awasthi R, Loiselle SE, et al. Effect of exercise and nutrition prehabilitation on functional capacity in esophagogastric cancer surgery: a randomized clinical trial. JAMA Surg 2018;153:1081-9.
120. Dunne DF, Jack S, Jones RP, et al. Randomized clinical trial of prehabilitation before planned liver resection. Br J Surg 2016;103:504-12.
121. Bhatia C, Kayser B. Preoperative high-intensity interval training is effective and safe in deconditioned patients with lung cancer: a randomized clinical trial. J Rehabil Med 2019;51:712-8.
122. Minnella EM, Bousquet-Dion G, Awasthi R, et al. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol 2017;56:295-300.
123. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for perioperative care in elective colorectal surgery: enhanced recovery after surgery (ERAS(®)) society recommendations: 2018. World J Surg 2019;43:659-95.
124. Tanaka R, Lee SW, Kawai M, et al. Protocol for enhanced recovery after surgery improves short-term outcomes for patients with gastric cancer: a randomized clinical trial. Gastric Cancer 2017;20:861-71.
125. Temple-Oberle C, Shea-Budgell MA, Tan M, et al. Consensus review of optimal perioperative care in breast reconstruction: enhanced recovery after surgery (ERAS) society recommendations. Plast Reconstr Surg 2017;139:1056e-71e.
126. Schmitz KH, Ahmed RL, Troxel A, et al. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med 2009;361:664-73.
127. Ingram C, Courneya KS, Kingston D. The effects of exercise on body weight and composition in breast cancer survivors: an integrative systematic review. Oncol Nurs Forum 2006;33:937-47; quiz 48-50.
128. Robson M, Im SA, Senkus E, et al. Olaparib for metastatic breast cancer in patients with a germline BRCA mutation. N Engl J Med 2017;377:523-33.
129. Coleman RL, Fleming GF, Brady MF, et al. Veliparib with first-line chemotherapy and as maintenance therapy in ovarian cancer. N Engl J Med 2019;381:2403-15.
130. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline BRCA-mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317-27.
131. Virtanen V, Paunu K, Ahlskog JK, et al. PARP inhibitors in prostate cancer—the preclinical rationale and current clinical development. Genes (Basel) 2019;10:565.
132. Imai S, Guarente L. NAD+ and sirtuins in aging and disease. Trends Cell Biol 2014;24:464-71.
133. Mitchell SJ, Bernier M, Aon MA, et al. Nicotinamide improves aspects of healthspan, but not lifespan, in mice. Cell Metab 2018;27:667-76.e4.

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