Cancer & Accelerated Aging ADVANCING RESEARCH FOR HEALTHIER SURVIVORS

Strategies to Prevent or Remediate Cancer- and Treatment-Associated Aging

Background for Think Tank

MOTIVATION

- There has been an extraordinary increase in the number of older cancer patients and survivors in the U.S. and worldwide. In 2016, 62% of the estimated 16 million US cancer survivors were ≥ 65 years.[1] This is a significant demographic shift in the U.S. with a growth in the number of older adults with cancer, and the unique issues faced by this population have been underrepresented in research studies to date. Expanding studies focusing on survivorship issues faced by older adults was identified as a key research priority by the IOM, the American Society of Clinical Oncology, and the Cancer and Aging Research Group.[2–4]
- Improvements in cancer detection, cancer therapies, and a rapidly aging population all contribute to a higher prevalence of cancer patients and survivors.[5] However, this success comes at a cost. Emerging data indicates that a subgroup of cancer survivors exhibit increased comorbidities, functional dependence, frailty, and poorer overall survival.[5,6] There is a pressing need to accelerate the implementation and dissemination of efficacious interventions to this vulnerable population.
- Another motivation is to address the needs of the complex patient with multiple geriatric conditions. A typical older adult lives with two or more comorbid conditions. The addition of active cancer treatment, or recovery from treatment, to this burden adds another layer of complexity to an aging system, creating an ongoing need for innovative survivorship programs.
- Recently, the National Cancer Policy Forum of the National Academies of Sciences, Engineering, and Medicine convened a meeting to improve the speed at which evidence-based knowledge is translated into clinical practice to address the long-term and delayed effects of cancer treatment.[7]
- The NCI 2015-2025 research agenda calls for access to interventions for all cancer survivors, evaluation of implementation and dissemination of programs, and focus on demonstrating value and feasibility of health behavior change interventions at multiple levels, including the survivor, clinician, and healthcare payer.[8]

EXERCISE INTERVENTIONS

- Physical activity after a cancer diagnosis decreases the risk of overall mortality[9,10] and cancer-specific mortality[10,11] and recurrence,[11] and is associated with fewer and less severe adverse side effects[11] and improved global health-related quality of life (HRQoL) and specific HRQoL domains (body image/self-esteem, emotional well-being, sexuality, sleep disturbance, social functioning, anxiety, fatigue, and pain at varying follow-up periods).[12]
- The benefits of physical activity are well established in the geriatrics and gerontology literature, with routine engagement attenuating most of the hallmarks of aging (Figure 1).[13–15]
- Exercise interventions have been found to counteract chemotherapy-induced peripheral neuropathy and improve balance and strength in stage IV colorectal cancer survivors.[16]
- Pilot study evidence suggests that resistance training interventions lower plasma and tissue-specific inflammation, which in turn is related to reduced fatigue and improved physical and behavioral functioning in postmenopausal breast cancer survivors.[17]

- A systematic review found that exercise improved muscle strength in older adults with sarcopenic obesity.[18] The LIFE study demonstrated that a structured physical activity intervention was effective at preventing major mobility disability in older adults.[19]

Physical Activity Recommendations for Cancer Survivors

- Physical activity is recommended for all cancer survivors, regardless of cancer type.[20] Several reviews suggest benefits of physical activity before, during, and after treatment.[12,21] Despite these positive benefits, the majority of cancer survivors do not meet the minimal amounts of physical activity required for health benefits (e.g., 150 minutes of at least moderate intensity activity per week or 75 minutes of vigorous activity per week).[22]
- ACSM 2009 roundtable discussion provides recommendations for medical assessments and exercise testing, as well as a review of the evidence of exercise interventions for breast, colon, prostate, adult hematologic, adult HSCT, and gynecologic cancers. The panel reported exercise training-related improvements in aerobic fitness, muscular strength, QOL, and reduced fatigue in breast, prostate, and hematologic cancer survivors, and concluded that physical activity is safe and offers many benefits for cancer survivors[22]
- It is recommended that oncology clinicians counsel cancer survivors to avoid inactivity and understand the consequences of sedentary behaviors.[23]

Limitations

- Current ACSM guidelines should be re-examined, because many cancer patients cannot meet them because of side effects from treatment. Additionally, the guidelines do not include alternative types of activity (e.g., yoga) because of insufficient data.[23]
- Recommendations need to be more specific to different cancer types and/or treatments. There needs to be significant heterogeneity across exercise programs.[12]
- Most published studies in the literature are focused on breast cancer survivors.

NUTRITIONAL INTERVENTIONS

- A Western lifestyle, including high-calorie diets and sedentariness, can accelerate aging (e.g., alter the hallmarks of aging, including systemic inflammation, dysregulation of adipokines, insulin resistance, dysbiosis, and immune system alterations) and have detrimental metabolic effects. Caloric restriction intervals, reduced overall caloric and animal protein intake, and a shift to a Mediterranean diet coupled with physical activity may have substantial anti-aging effects.[24]

Caloric restriction interventions

- The results of long-term caloric restriction studies in humans are similar to those of animal studies, which show that caloric restriction improves longevity.[25]

- The CALERIE trial randomized N = 220 non-obese adults to 25% caloric restriction or to maintain current diet for 2 years and showed that caloric restriction slowed biological aging using both the Klemera-Doubal Method and homeostatic dysregulation.[26]

- Recently, the WHO put forth a framework that emphasizes the need to better understand an individual's intrinsic capacity, functional abilities at various life stages, and the impact of the environment and mental and physical health.[27]

Intermittent Fasting

- Animal models show that a 24-hour fast every other day or twice a week slows or reverses cancer, CVD, diabetes, and neurodegenerative disorders.[28–30]
- A study of 107 overweight or obese women in middle adulthood using either continuous caloric restriction (~6,276 kJ per day for 7 days/week) or intermittent fasting two days per week (~2,710 kJ on fasted days) had

similar weight loss and reductions in CRP, total and LDL cholesterol, triglycerides, insulin, insulin resistance, and blood pressure. This suggests that both intermittent fasting and caloric restriction can reduce markers of aging in overweight/obese persons.[30,31]

Weight Loss Interventions

- Several weight loss interventions among cancer survivors show significant reductions in weight, serum biomarkers, and improvements in QOLs.[32–35]

- The ENERGY Trial, conducted in 692 overweight/obese early-stage breast cancer survivors, found significant reductions in weight, decreased blood pressure, and improvements in QOL. Greater effects were seen among older women.[36,37]

- Research suggest that weight loss interventions among cancer survivors should provide adequate protein intake to prevent/reduce a loss of muscle mass and improve treatment response. A study of 533 overweight nonmetastatic colon cancer patients receiving chemotherapy found that patients in the lowest vs. highest tertile of muscle mass were more likely to experience chemotherapy toxicities, and treatment-related poor adherence and dose reductions.[38]

COGNITIVE INTERVENTIONS

Environmental Enrichment

- Animal studies show that environmental enrichment improves cognitive function and reduces anxiety-related behaviors.[39]
- Longitudinal evidence consistently shows that engaging in a stimulating lifestyle and being socially engaged predicts maintenance of cognitive skills.[40]
- Physical activity (aerobic exercise in particular) enhances older adults' cognitive function.[40]

SUPPORTIVE CARE INTERVENTIONS (PSYCHOSOCIAL, BEHAVIORAL, INTEGRATIVE MEDICINE)

Psychological/Behavioral

- Psychosocial interventions (PSI), including information provision, support, coping skills, training, and psychotherapy, significantly improved QoL (β = 0.14,95%CI = 0.06;0.21), emotional function (β = 0.13,95%CI = 0.05;0.20), and social function (β = 0.10,95%CI = 0.03;0.18). Significant differences in effects of different types of PSI were found, with largest effects from psychotherapy. The effects of coping skills training were moderated by age, treatment type, and targeted interventions.[41]

- A literature review of psychosocial interventions (defined as any intervention aimed at improving psychosocial well-being and including technology-based, counseling, psychoeducational, physical activity, rehab, yoga, and multicomponent interventions) in AYA cancer populations showed that the standardized mean difference between intervention and control conditions was 0.13 (95% CI: -0.16 to 0.42) for quality of life, 0.27 (95% CI: -0.22 to 0.76) for cancer-related knowledge, and -0.16 (95% CI: -0.73 to 0.42) on psychological distress, suggesting that the effects of interventions improving mental health are small and relatively statistically insignificant.[42]

Environmental Enrichment (EE)

- In 10-month-old mice, the effects of six-week EE showed adipose remodeling, decreased age-related liver steatosis, reduced hepatic glucose production, and increased glucose uptake by liver and adipose tissue contributing to the improved glycemic control. EE down-regulated the expression of inflammatory genes in the brain, adipose, and liver. EE initiated at 18 months of age significantly improved glycemic control and showed a

trend of positive impact on mean lifespan. These data suggest that EE induces metabolic and behavioral adaptations that are shared by factors known to increase healthspan and lifespan.[43]

Yoga or other CAM/Meditation-based Modalities

- Major Depressive Disorder is associated with accelerated aging. One study found an association between changes in biomarkers of cellular aging and clinical improvement in MDD after yoga and meditation.[44]
- After 12 weeks of a yoga and lifestyle intervention targeting cellular aging, there were significant improvements in both the biomarkers of cellular aging and the metabotrophic biomarkers influencing cellular aging compared to baseline values. The mean levels of 8-OH2dG, ROS, cortisol, and IL-6 were significantly lower and mean levels of TAC, telomerase activity, β-endorphin, BDNF, and sirtuin-1 were significantly increased post-intervention, suggesting that the intervention reduced the rate of cellular aging.[45]
- A yoga and meditation-based intervention was shown to decrease depression severity in MDD patients and was associated with improved systemic biomarkers of neuroplasticity, providing evidence that yoga and meditation interventions can be considered as potential therapeutic interventions for MDD management.[45]
- Systematic review of 18 studies with clinical and non-clinical samples indicates that mind-body interventions (e.g., mindfulness, yoga, Tai Chi, Qigong, relaxation response, and breath regulation) are associated with a downregulation of nuclear factor kappa B pathway – opposite of the effects of chronic stress on gene expression. This suggests that Mind-Body Intervention practices may lead to a reduced risk of inflammation-related diseases.[46]
- Systematic review and meta-analysis showed short-term effects on global health-related quality of life and functional, social, and spiritual well-being in breast cancer survivors, but these studies had either an unclear risk or high risk of selection bias. Short-term effects on psychological health also were found: anxiety, depression, perceived stress, and psychological distress. Subgroup analyses revealed evidence of efficacy only for yoga during active cancer treatment but not after completion of active treatment.[47]
- A yoga intervention in breast cancer survivors showed that fatigue was lower, vitality was higher, and IL-6, TNF-α, and IL-1β were lower for yoga participants compared with the control group three months post-treatment. The frequency of yoga practice had stronger associations with fatigue and vitality than simple group assignment; more frequent practice produced larger changes. At three months post-treatment, increasing yoga practice also led to a decrease in IL-6 and IL-1β production, but not in TNF-α.[48]

MULTICOMPONENT/TRANSLATIONAL INTERVENTIONS

- Synthesized compounds and nutraceuticals such as calorie restriction mimetics, autophagy inductors, senolytics and others have been identified as having potential for anti-aging intervention through their possible effects on basic processes underlying aging.[49]
- Effects of lifestyle interventions remain unclear in gynecological cancer survivors. A meta-analysis showed that two RCTs found no effect of lifestyle interventions on total QoL or individual domains of QoL.[50]

OTHER INTERVENTIONS

- Obesity is linked to telomere shortening, and bariatric surgery has been shown to cause a recovery in telomere length.[51]

MEASUREMENT & DESIGN CONSIDERATIONS

- Most studies are centered on breast cancer survivors, and the literature is limited on childhood cancer survivors.
- There are generalizability issues if some populations (older, comorbid patients) are left out of clinical trials.

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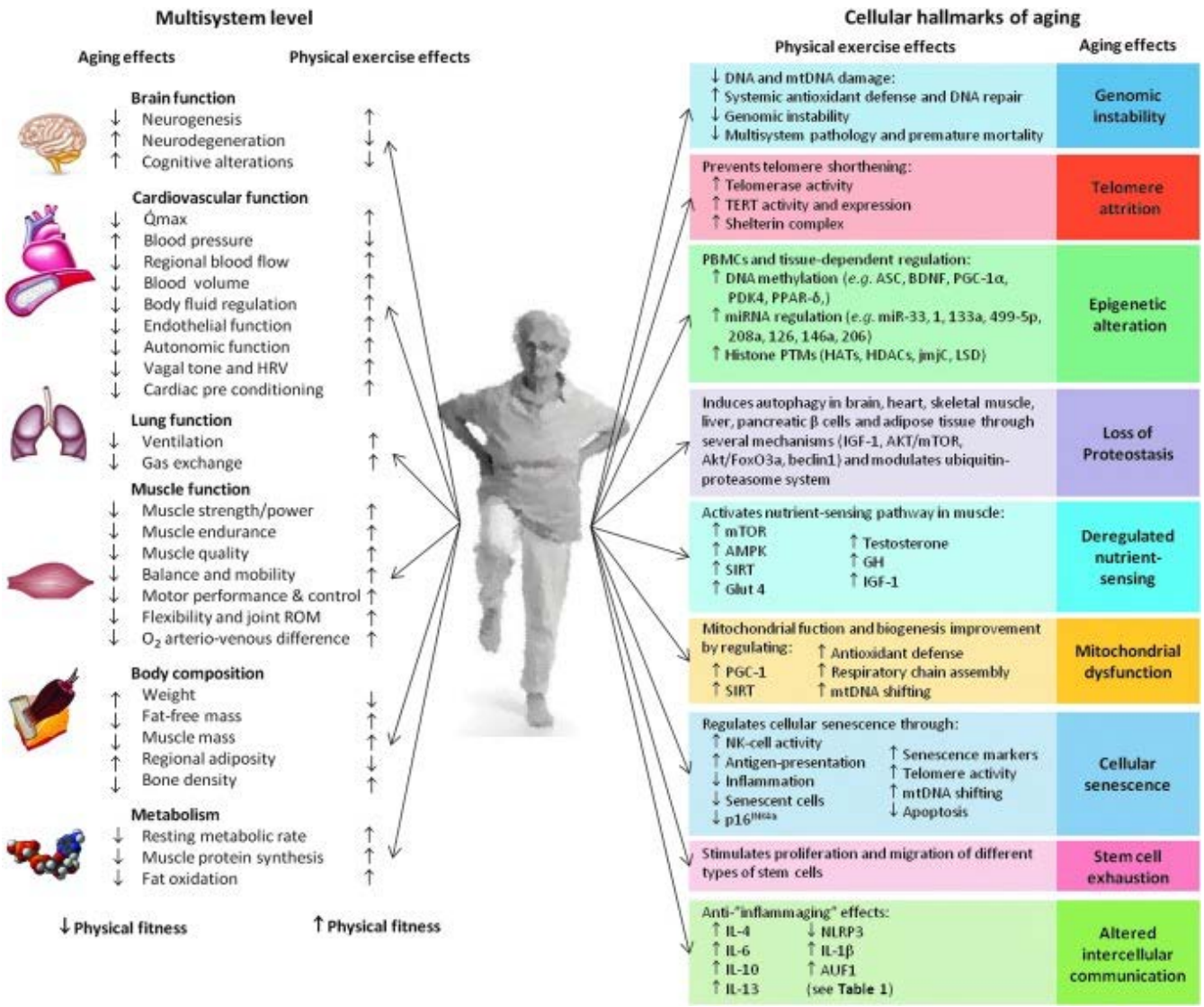

Figure from Garatachea N, Pareja-Galeano H, Sanchis-Gomar F, et al. Exercise attenuates the major hallmarks of aging. Rejuvenation Res. 2015;18(1):57-89. doi:10.1089/rej.2014.1623