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The role of physical exercise in cancer therapy-related CV toxicity.

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Cardiovascular diseases (CVD) and cancer are among the leading causes of mortality in high-income countries [1].

In recent years, relevant improvements in managing oncologic diseases, including timely diagnosis and treatment, have led to an increase in patient's long-term survival. On the other hand, this prolonged life expectancy also determined an escalation in the prevalence of the comorbidities potentially associated with cancer therapy administration, which from a cardiovascular (CV) standpoint are comprehensively referred with the term *cancer therapy-related cardiovascular toxicity (CTR-CVT)*. According to the latest International Cardio-Oncology Society (IC-OS) consensus statement, CTR-CVT can be classified as: 1) symptomatic or asymptomatic cancer therapy-related cardiovascular dysfunction (CTRCD), 2) immune-checkpoint inhibitors (ICI) myocarditis, 3) asymptomatic or symptomatic vascular toxicity, 4) arterial hypertension, and 5) cardiac arrhythmias [2,3]. The variety and severity of CTR-CVT depends on the type and dosage of the drug administered in a specific patient, as well as the patient's basal CV risk [4]. In 2022, the latest European Society of Cardiology (ESC) guidelines on cardio-oncology defined a baseline CV toxicity risk assessment checklist, based on clinical assessment and laboratory and imaging markers, including: 1) age, sex, and genetics, 2) medical CV risk factors (CVRF) and lifestyle risk factors, 3) previous CVD and cardiotoxic therapies, 4) 12-leads electrocardiogram, transthoracic echocardiography and biomarkers abnormalities (natriuretic peptides, troponin, glycemic and lipid profile, kidney function) [3].

According to the CV toxicity assessment checklist, every patient is classified as low, moderate, high, or very high risk for CTR-CVT (class I indication according to ESC guidelines). Moreover, the Heart Failure Association-International Cardio-Oncology Society (HFA-ICOS) risk score could be a valuable tool to determine the pre-treatment risk of CTR-CVT, even if it needs further validation [2].

Keep in mind that cancer and CVD share many risk factors in common, e.g., aging and an unhealthful lifestyle, including sedentarism, smoking, alcohol consumption, and an unbalanced fat-rich diet [5,6]. Thus, a prevention approach for CTR-CVT, primarily focused on managing lifestyle changes, is mandatory, as stated in the international guidelines [3]. Every CVRF and CVD needs to be managed, and every patient should be informed and supported to develop a healthy lifestyle, as it improves body responsiveness to cancer therapies, reduces the risk of cancer recurrences, and decreases the chronic inflammatory status that is strongly related to both cancer and CVD [5].

Exercise and physical activity are often used interchangeably but represent distinct concepts. Physical activity refers to any bodily movement produced by skeletal muscles that requires energy expenditure, encompassing a wide range of activities such as walking, gardening, or household chores. In contrast, exercise is a structured, repetitive, and purposeful form of physical activity specifically aimed at improving or maintaining physical fitness, such as running, weightlifting, or attending a fitness class [7]. Physical exercise (PE) represents a potent, multitargeted, and cost-effective nonpharmacological therapy that can actively counteract anticancer treatment side effects and CVRF, substantially improving cardiorespiratory fitness (CRF), mental health, quality of life (QoL) and short and long-term cancer-related and CV outcomes. For instance, regular physical exercise can reduce the risk of cancer recurrences by improving immune function and decreasing chronic inflammation, which is strongly related to both cancer and CVD [8-11].

The model of cardio-oncology rehabilitation, 'CORE,' was introduced in 2019 by the American Cancer Society and the American Heart Association, aiming to identify a multimodality approach that includes tailored PE prescription, nutritional counseling, and CVRF assessment [12]. In this scenario, any condition potentially interfering with or limiting PE eligibility, e.g., cachexia, mobility impairment, fatigue, must be considered. Tailored PE prescription provides a therapeutic, progressive exercise program and the adherence of each patient to their PE program [11, 13]. It is important to note that PE is safe and recommended both during and after anticancer treatment. Every patient should work out for at least 150-300 min of moderate-intensity exercise or 75-150 min per week of vigorous-intensity aerobic exercise. Muscle-strengthening activities, flexibility training, and respiratory muscle training should be included in every PE program, as different PE protocols can determine different synergetic effects on cardiometabolic parameters, CRF, cancer outcomes, and mental health [3,5,12,14]. Ideally, every cancer survivor (CS) should receive a comprehensive assessment of all components of health-related physical fitness (e.g., cardiorespiratory fitness, muscle strength and endurance, body composition, and flexibility), with some considerations focused on the specific patient's health history, especially in the presence of CV or extracardiac symptoms [15]. Moreover, ensuring adherence to PE program is mandatory for improving the benefits and effectiveness of training interventions, especially in the female population, who are often less physically active than the male population for all age groups [5,16].

Women face a range of multifaceted barriers to participating in physical activity (PA) and sports, which can be broadly categorized into three areas: economic and socio-cultural, practical, and knowledge-related barriers. Economic and socio-cultural barriers include

deeply ingrained misconceptions that sports are inherently masculine and exclusive, low self-esteem among women, parental opposition to sports participation, concerns about academic performance, and responsibilities related to family care and housework [17]. Practical barriers encompass poverty, limited financial resources, insufficient leisure time, and a lack of accessible, safe, and suitable facilities [18,19]. Lastly, knowledge-related barriers arise from insufficient awareness of the physical and mental health benefits associated with PA [15].
Potential sex differences in psychosocial correlates of physical activity identified self-efficacy, social support, and motivation as those constructs most researched [17,18,19].
There appears to be a strong connection between being male, possessing higher levels of self-efficacy, and engaging in greater physical activity across the lifespan [17]. Future research in this area would benefit from more detailed examinations of sex-specific differences in barrier-related self-efficacy, as well as identifying which activity-promotion strategies—such as vicarious experiences, verbal encouragement, or mastery experiences—are more commonly utilized to support males, potentially contributing to their higher levels of physical activity [17,19].
Both aerobic (including moderate-intensity continuous exercise or high-intensity interval training) and resistance exercise programs have been shown to be safe, well tolerated in most patients, and effective at preventing and treating CVD, CV risk factors, and CTR-CVT risk. They are frequently combined to increase their effectiveness on physical and mental health.
The characteristics of the training sessions, in terms of frequency, duration, and intensity, should progressively increase across the entire program, considering each subject's response to the training, to ensure adequate patient adherence. Appropriate patient supervision strategies (heart rate and respiratory responses monitoring, oxygen saturation, ratings of perceived effort, exercise-related adverse events), personalized on patient's basal health status, should be always considered during exercise training [20,21,22].
Among cancer survivors (CS), childhood cancer survivors (CCS) represent a population at high risk for CTR-CVT, low quality of life (QoL), poor mental health, and frailty, with the cumulative incidence of CV events being inversely correlated with the increase in the reported PE levels. Exercise guidelines for CCS following antineoplastic treatments have been published, but compared to evidence from the literature in adults, cardioprotective properties of PE in CCS have received less attention, with a significant heterogeneity among the available studies. Nevertheless, all reports suggested the benefit of PE in mitigating CTR-CVT risk in CCS [23].

The role of PE in reducing CTR-CVT risk is still under evaluation. The preliminary results are promising, but further studies are needed to identify the best type, intensity, and frequency of exercise and to understand whether, in some types of anticancer therapy, the responses to the beneficial effects of PE are attenuated. The current evidence about the role of PE as a primary, secondary, and tertiary prevention strategy of CTR-CVT is still significantly heterogeneous. Moreover, the role of PE in each of these clinical contexts may be different.

In the primary prevention scenario, when CV adaptations to cancer therapy are unavoidable, PE may preserve or avoid severe treatment-induced adverse effects. On the other hand, PE as a secondary prevention strategy may determine improvements in cardiorespiratory fitness in terms of VO2 peak, but the right amount and type of PE essential to get the best improvement in CTR-CVT risk is currently under analysis. Finally, evidence regarding PE’s role in tertiary prevention are scarce and limited to preclinical data, with much of the current knowledge resumed by non-cancer CVD populations [24]. It is important to acknowledge that developing an exercise prescription requires careful consideration of the individual’s physical and physiological status at the time of treatment. Research indicates that factors such as prior physical activity levels, current physical and mental capabilities, comorbidities, and the effects of ongoing treatments significantly influence the success of exercise interventions [25,26]. For example, individuals recovering from chronic conditions like cardiovascular disease or cancer may have reduced capacity for high-intensity activity, while those with mental health challenges may benefit from activities that are less structured but still promote engagement and consistency [27,28]. Studies have consistently shown that even low levels of physical activity—such as 10-minute bouts of light to moderate exercise—can yield meaningful health benefits, particularly for individuals transitioning from sedentary lifestyle [29]. However, the specific type, intensity, frequency, and duration of exercise must be carefully personalized. High-intensity regimens may benefit some individuals, enhancing cardiorespiratory fitness and strength, but may be unsuitable or even harmful for others, particularly those with significant limitations or heightened treatment-related fatigue. This variability underscores the importance of tailoring exercise prescriptions to the individual. In practice, this means prioritizing flexibility in design and recognizing that 'any' movement is better than none. Providing detailed guidelines on how to adapt activity levels incrementally and align them with the individual’s evolving capabilities and health status would enhance the applicability of exercise interventions across diverse populations [30, 31].

As stated by Campbell et al., in the future, exercise prescription in cardio-oncology should ideally become tailored to the specific characteristics of every patient's cancer, moving toward the same target as precision oncology. This ongoing research presents an exciting opportunity for the healthcare community to contribute to developing personalized exercise interventions in cardio-oncology [15].

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