European Heart Journal Supplements (2024) **26** (Supplement 2), ii252–ii263
The Heart of the Matter
https://doi.org/10.1093/eurheartjsupp/suae030

ESC
European Society
of Cardiology

Cardio-oncology rehabilitation: are we ready?

Irma Bisceglia[1†*], Elio Venturini[2†], Maria Laura Canale[3], Marco Ambrosetti[4], Carmine Riccio[5], Francesco Giallauria[6], Giuseppina Gallucci[7], Maurizio G. Abrignani[8], Giulia Russo[9], Chiara Lestuzzi[10], Raffaella Mistrulli[11], Giovanni De Luca[12], Fabio Maria Turazza[13], Gianfrancesco Mureddu[14], Stefania Angela Di Fusco[15], Fabiana Lucà[16], Leonardo De Luca[17], Andrea Camerini[18], Geza Halasz[19], Massimiliano Camilli[20,21], Vincenzo Quagliariello[22], Nicola Maurea[22], Francesco Fattirolli[23], Michele Massimo Gulizia[24], Domenico Gabrielli[19,25], Massimo Grimaldi[26], Furio Colivicchi[15], and Fabrizio Oliva[27]

[1]Integrated Cardiology Services, Cardio-Thoracic-Vascular Department, Azienda Ospedaliera San Camillo Forlanini, C.ne Gianicolense, 87 00152 Rome, Italy; [2]Department of Cardiac Rehabilitation, Cecina Civil Hospital, Via Montanara, 52, 57023 Cecina (LI), Italy; [3]Division of Cardiology, Azienda USL Toscana Nord-Ovest, Versilia Hospital, Via Aurelia, 335, 55041 Lido di Camaiore (LU), Italy; [4]Unità Operativa Complessa di Riabilitazione Cardiologica, ASST Crema Ospedale Santa Marta, Rivolta D'Adda, 26027 Cremona, Italy; [5]Dipartimento Cardio-Vascolare, AORN Sant'Anna e San Sebastiano, Caserta, Italy; [6]Department of Translational Medical Sciences, University of Naples Federico II, Naples, Italy; [7]Cardio-oncologist, Melfi, 85025 Potenza, Italy; [8]U.O di Cardiologia, P.O. 'P. Borsellino', Marsala, ASP Trapani, Italy; [9]SC Patologie Cardiovascolari, Ospedale Maggiore, Via Slataper, 9, 34125 Trieste, Italy; [10]Centro Medico Esperia, Porcia, PN, Italy; [11]Cardiology Unit, Department of Clinical and Molecular Medicine, Faculty of Medicine and Psychology, Sapienza University of Rome, Sant'Andrea Hospital, Rome, Italy; [12]Health Activities and Epidemiologic Observatory Division, Health Department, Sicily Region, Piazza O. Ziino, 24, 90145 Palermo, Italy; [13]Director of Cardiology, IRCCS Foundation, National Cancer Institute, via G Venezian, 1, 20133 Milano, Italy; [14]Cardiology Division, S. Giovanni Hospital, Via dell'Amba Aradam, 8, 00184 Rome, Italy; [15]Clinical and Rehabilitation Cardiology Unit, San Filippo Neri Hospital, Via Martinotti, 20, 00135 Roma, Italy; [16]Cardiology Department, Grande Ospedale Metropolitano, GOM, AO Bianchi Melacrino Morelli, 89129 Reggio di Calabria, Italy; [17]SC Cardiologia, Fondazione IRCCS San Matteo, Viale Camillo Golgi, 19, 27100 Pavia Italy; [18]Department of Medical Oncology, Azienda USL Toscana Nord-Ovest, Versilia Hospital,Via Aurelia, 335, 55041 Lido di Camaiore (LU), Italy; [19]Dipartimento Cardio-Toraco-Vascolare, U.O.C. Cardiologia, Azienda Ospedaliera San Camillo-Forlanini, C.ne Gianicolense, 87, 00152 Rome, Italy; [20]Department of Cardiovascular Medicine, Fondazione Policlinico Universitario A. Gemelli, IRCCS, L.go A. Gemelli, 1, 00168 Rome, Italy; [21]Department of Cardiovascular and Pulmonary Sciences, Catholic University of the Sacred Heart, L.go Francesco Vito, 00168 Rome, Italy; [22]Division of Cardiology, National Cancer Institute, Sen. Pascale Foundation, via Mariano Semmola, 80131 Napoli, Italy; [23]Azienda Ospedaliero - Universitaria Careggi, Largo Brambilla, 3, 50134 Firenze, Italy; [24]Cardiothoracic Department, Garibaldi Nesima Hospital, 95122 Catania, Italy; [25]Fondazione per il Tuo cuore—Heart Care Foundation, Firenze, Via A. La Marmora, 36, 50121 Firenze, Italy; [26]Regional General Hospital F. Miulli, Strada Prov. 127 Acquaviva - Santeramo Km, 4, 100.70021 Acquaviva delle Fonti (BARI), Italy; and [27]Cardiologia 1-Emodinamica Dipartimento Cardiotoracovascolare 'A. De Gasperis', ASST Grande Ospedale Metropolitano Niguarda, 20162 Milan, Italy

*Corresponding author: Email: irmabisceglia@gmail.com
†These authors share first authorship

KEYWORDS
Cardiac rehabilitation;
Cardio-oncology rehabilitation (CORE);
Reverse cardio-oncology;
Core components of CORE;
Telehealth in rehabilitation;
Geriatric oncologic patients

Cardio-oncology rehabilitation (CORE) is not only an essential component of cancer rehabilitation but also a pillar of preventive cardio-oncology. Cardio-oncology rehabilitation is a comprehensive model based on a multitargeted approach and its efficacy has been widely documented; when compared with an 'exercise only' programme, comprehensive CORE demonstrates a better outcome. It involves nutritional counselling, psychological support, and cardiovascular (CV) risk assessment, and it is directed to a very demanding population with a heavy burden of CV diseases driven by physical inactivity, cancer therapy-induced metabolic derangements, and cancer therapy-related CV toxicities. Despite its usefulness, CORE is still underused in cancer patients and we are still at the dawning of remote models of rehabilitation (tele-rehabilitation). Not all CORE is created equally: a careful screening procedure to identify patients who will benefit the most from CORE and a multidisciplinary customized approach are mandatory to achieve a better outcome for cancer survivors throughout their cancer journey. The aim of this paper is to provide an updated review of CORE not only for cardiologists dealing with this peculiar population of patients but also for oncologists, primary care providers, patients, and caregivers. This multidisciplinary team should help cancer patients to maintain a healthy and active life before, during, and after cancer treatment, in order to improve quality of life and to fight health inequities.

Introduction

Cardiovascular disease (CVD) and cancer are competing causes of mortality in cancer patients.[1] Multiple shared risk factors coupled to cancer therapy-induced metabolic derangements and cardiovascular (CV) toxicities increase the probability of the coexistence of the two diseases.[2] Cancer patients should be considered 'survivors' ever since the diagnosis of cancer, a crucial moment that marks the beginning of a proactive preventive process that should last for the whole life. In this 'cancer continuum' cardio-oncology rehabilitation (CORE) has a pivotal role. It employs the multimodality approach of cardiac rehabilitation (CR) and thus includes a complete structured exercise, associated with comprehensive nutritional counselling, psychological support, and thorough CV risk assessment.[3] Cardio-oncology rehabilitation has three phases: a *pre-habilitation* phase that lasts from the cancer diagnosis till the beginning of cancer therapy, a *habilitation* phase during the cancer treatment and a *rehabilitation* phase that starts at the end of cancer treatment.[4] Both CORE and CR have the goal of increasing the cardiorespiratory fitness (CRF) of patients in order to improve psychosocial well-being and reduce CV risk, hospitalization, and CV morbidity and mortality.[5,6] Cardio-oncology rehabilitation must follow a customized pathway that takes into account patient's CV risk at baseline, the scheduled oncologic treatment, and the end of treatment evaluation.[7] A vital issue is to identify patients who will benefit the most from a rehabilitation programme. This is of paramount importance to avoid the loss of patients after treatment (*from cancer patient to cancer survivor: lost in transition*).[8]

Digital medicine should help in the baseline evaluation of CV risk and during the monitoring process of both patients and their CRF parameters. Remote monitoring should also improve the compliance of patients who have some difficulties in reaching the hub centres. New technologies will soon overcome the current limitations of a virtual visit and a virtual monitoring process.[9,10]

The aim of this paper is to raise the awareness of the urgent need of a multimodal rehabilitation programme that has to start when a cancer diagnosis is made and that has to stand in close proximity of the oncologic treatment throughout the survivorship care. A concomitant psychological treatment is crucial to increase the compliance of patients to the CORE programme. In 2017, the WHO has launched the programme 'Rehabilitation 2030—a call for action', the goal was 'to draw attention to the increasing unmet needs for rehabilitation'[11] in patients with non-communicable diseases; in this scenario, oncology patients should be considered a priority population.

Cancer and cardiovascular diseases

Epidemiology and risk factors

There are robust data to support the concept of a multifaceted relationship between cancer and CVD. The reduction of mortality rates both for cancer and CVD with strict adherence to the recommendations for the reduction of CV risk factors is a demonstration of the close link between the two diseases.

In the past decades, cardiologists and oncologists have proved that cancer itself and cancer treatments can have damaging effects on the CV system; as a consequence, the management of cancer patients may be extremely challenging. On the other hand, there is the intriguing hypothesis that CVD may represent a pro-oncogenic condition, giving birth to the concept of 'reverse cardio-oncology'.[12-14]

Cancer induces a prothrombotic status with an increased risk of venous and arterial thrombosis,[15,16] radiotherapy and chemotherapy (CT) can induce CVD.[17-19] It is widely

known that anthracyclines may lead to asymptomatic left ventricular dysfunction or heart failure that can be irreversible, human epidermal growth factor receptor 2 antagonists can cause left ventricular dysfunction that may be reversible,[18,19] and vascular endothelial growth factor inhibitors can cause hypertension, thromboembolism, and left ventricular dysfunction, can prolong the QT interval and induce atrial fibrillation (AF).[20] Immune checkpoint inhibitor's treatment has been causally related to CV complications. Myocarditis is the most threatened event for its high mortality rates (20–50% of cases).[21]

As far as reverse cardio-oncology is concerned, there are many studies documenting an increased incidence of cancer in patients with heart failure complicating acute myocardial infarction or pre-existing heart failure.[22-24] Preclinical studies have documented an increased intestinal tumour load in mice with heart failure due to a large anterior myocardial infarction.[25] More recently, a large population study has shown a significantly higher incidence of cancer in patients with CVD, especially atherosclerotic CVD, compared with patients without CVD and this was independent of traditional CV risk factors.[26]

Atrial fibrillation, too, may be associated with cancer. The Women's Health Study has documented that 10% of patients with a new-onset AF were diagnosed with a tumour.[27] The link may be attributed to many different molecular mechanisms such as hypoxia with its pro-oncogenic effect and inflammation that is causally related to both cancer and CVD. Interleukin (IL)-1 and IL-6 have indeed a role in promoting cancer and AF through the production of reactive oxygen species.[28-31]

An intriguing issue in the cancer/CVD relationship is the possibility of unmasking an occult cancer in patients with AF treated with oral anticoagulants. A study has analysed the data of a Retrospective Observational Registry of Patients with Atrial Fibrillation from Vigo's Health Area (Cardio CHUVI-AF) documenting that gastrointestinal bleeding was associated with a 13-fold higher risk of new gastrointestinal cancer diagnosis, genitourinary bleeding was associated with an 18-fold higher risk of new genitourinary cancer diagnosis, and bronchopulmonary bleeding was associated with a 15-fold higher risk of new bronchopulmonary cancer diagnosis.[32]

The relationship between cancer and CVD is reinforced by shared risk factors such as smoking, alcohol, diabetes mellitus, obesity, and a sedentary lifestyle. As a consequence, the shared risk factor can cause CVD, cancer, or even both diseases in the same patient.[13] From all these data, De Boer *et al.* have suggested a new classification of the cardio-oncology syndromes (COSs). COS Type I is characterized by the mechanisms linking the abrupt onset or progression of cancer to CV dysfunction. COS Type II includes the mechanisms of cancer therapy-induced chronic CVD. COS Type III is characterized by the pro-oncogenic milieu created by CV dysfunction through the release of cardiokines and high oxidative stress. COS Type IV includes CVD treatment and diagnostic procedures that promote or unmask cancer. COS Type V is characterized by factors that cause systemic and genetic predisposition to both CVD and cancer.[33]

For the authors, this characterization of COSs should facilitate cancer care and optimize CV health through a personalized COS-type-guided treatment.

Components of cardio-oncology rehabilitation

Due to the protective effect of physical activity in cancer patients with respect to coexisting CVD, it seems reasonable to hypothesize an active role for CR, which in this mode of application is more appropriately called CORE. As noted by Dittus *et al.*,[34] the affinities between 'classic' CR and CORE are remarkable, and CORE itself could theoretically be implemented from the existing professional network of CR, appropriately integrated by other figures such as the oncologist and the cardio-oncologist. In 2019, the American Heart Association produced an important statement on CORE[3] with the endorsement of the American Cancer Society; the European guidelines of the European Society of Cardiology (ESC) on cardio-oncology, although not specifically addressing CORE, underline how CR *should be considered* (Class IIa) in subjects at high CV risk.[35] The CORE should therefore be defined as a multidisciplinary intervention applicable to cancer patients which, through the prescription of a structured training programme, strict control of risk factors, wise nutritional advice, and valid psychosocial support, plays a central role in reducing CV risk with a positive impact on overall outcome.

Referral to core

Patients eligible for CORE[3] have 'historically' been defined according to ASCO guidelines' criteria[36] that identified as being at increased risk for cardiac dysfunction: (1) patients treated with high doses of anthracyclines (e.g. doxorubicin $\geq$ 250 mg/m^2, epirubicin $\geq$ 600 mg/m^2) or high-dose radiotherapy ($\geq$30 Gy) with the heart in the treatment field or lower-dose anthracyclines (e.g. doxorubicin $<$ 250 mg/m^2, epirubicin $<$ 600 mg/m^2) in combination with lower-dose radiotherapy ($<$30 Gy); (2) patients treated with lower-dose anthracyclines or trastuzumab alone and the presence of any of the following risk factors: multiple CV risk factors ($\geq$2 risk factors that include smoking, hypertension, diabetes mellitus, obesity, and dyslipidaemia), during or after completion of therapy; advanced age ($\geq$60 years) at the time of cancer treatment; or compromised cardiac function [history of myocardial infarction, borderline or low (50–55%) left ventricular ejection fraction, and moderate or more severe valvular disease]; (3) patients treated with sequential treatment with lower-dose anthracyclines and trastuzumab. Following the ESC guidelines,[35] the cardiologist should plan to initiate the CORE in patients at high CV risk according to the newly proposed criteria, which allow risk stratification into low, intermediate, high, and very high using a number of domains such as history of CVD, baseline ejection fraction, and/or presence of structural changes of the left ventricle, biomarkers (troponin and *N*-terminal pro-brain natriuretic peptide), age, and CV risk factors, as well as previous exposure to cardiotoxic therapies or radiotherapy. The adoption of these criteria also provides for applicability to newer treatments such as tyrosine kinase inhibitors, proteasome inhibitors, immunotherapy, and androgen deprivation therapies.

Based on data from the literature, candidate cancers for CORE include breast, colorectal, prostate, and

Table 1 Core components of cardio-oncology rehabilitation as an extension of cardiac rehabilitation interventions

CR	CORE
Clinical and functional evaluation	Evaluation of oncological therapies and their side effects Evaluation of clinical conditions influencing the possibility of carrying out a training programme Evaluation of the presence of lymphoedema, stomas, and infectious risks Evaluation of the presence of bone metastases and their impact on training risk Blood cell count evaluation Screening for depression, fatigue, and quality of life Global assessment of functional capacity: CPET is the gold standard. Other exercise tests may be used if CPET is not available
Physical activity counselling	Reducing the level of sedentariness caused by cancer diseases and cancer therapies (e.g. chemotherapy sessions)
Training programme	Both aerobic and strength training in patients with cancer Provide adequate supervision during the training programme
Nutritional intervention/ counselling	Evaluation and management of cancer-related nutritional aspects Dietitian with experience in oncology
Weight management	Consider cancer-related issues: weight loss, lean/fat mass ratio
Blood pressure management	Consider concomitant cancer therapy-induced hypertension
Management of dyslipidaemia	Pay attention to treatment goals in primary prevention for possible underestimation of traditional risk scores in cancer patients
Management of diabetes	Consider concurrent antineoplastic therapy as a potential cause of dysglycaemia
Smoking cessation	Promote anti-smoking programmes for cancer patients
Psychosocial support	Promote work and psychiatric support programmes dedicated to patients with cancer

CR, cardiac rehabilitation; CORE, cardio-oncology rehabilitation; CPET, CardioPulmonary Exercise Test.

lymphoproliferative disorders. More recently, it has been observed that, in lung cancer, pre-habilitation may offer advantages in the management of perioperative complications and length of post-operative hospital stay.[37] However, there is currently no evidence available to support the individualization of exercise as precision medicine to tailor training to new treatments and cancer types.

The referral of patients to CORE must include communication between the oncologist and the rehabilitation cardiologist; the presence of a cardio-oncologist is also essential for choosing the ideal time to start CORE in the individual cancer continuum: before ('prehabilitation'), during ('habilitation') or after oncological therapy ('rehabilitation') and, finally, the preparation and adoption of an intra-hospital diagnostic-therapeutic-assistance path.[38]

Cardio-oncology rehabilitation components

The components of CORE, derived and remodelled from those of CR,[39] are summarized in *Table 1*. Before starting CORE, an initial assessment[35] of the patient is mandatory, starting with a careful review of the antineoplastic treatment and its potential side effects. Then a careful evaluation of the presence of lymphoedema, surgical outcomes, infection risk, and other conditions (muscle wasting, sarcopenia, and obesity) that may affect the training programme must be carried out.

It is also fundamental to consider the risk of metastases, especially bone metastases, due to the risk of pathological fractures. The functional evaluation, using the cardiopulmonary exercise test if available, or alternatively, other validated direct tests, must be preceded by the execution of a blood cell count in order to exclude some of the main contraindications to training (severe anaemia, thrombocytopenia, and leukopoenia). Physical training—which will be discussed in detail in the next chapter—is an essential component of the CORE (as well as of the classic CR), but not the only one.

Cancer has a significant emotional impact that can change the patient's life: the psychological suffering is extensive and ranges from concerns about health, family affection, and the side effects of therapies to the discomfort caused by the possible withdrawal from work and the loss of social function. This is why psychological support is the cornerstone of CORE, capable of improving the quality of life (QOL), increasing therapeutic adherence and reducing anxiety and depression. In selected cases, psychiatric intervention may be useful. Communication must be clear, empathetic and modulated on the patient's perceptions and cultural level; the doctor's verbal and non-verbal language must adapt to the degree of psychological suffering, as must the choice of behavioural change techniques to adopt.

Strict control of risk factors is essential in patients with coexisting CVD and in those who have experienced cardiotoxicity. Abstinence from tobacco is a strong predictor of survival after cancer diagnosis[40] and must be pursued even with interventions that are not particularly complex: a 'simple' telephone consultation lasting 12 weeks, co-ordinated by a nurse, associated with a free supply of anti-smoking drugs, has been shown to significantly increase the number of quitters.[41]

The Mediterranean diet, low in red meat, and with a low inflammatory index, especially if accompanied by regular use of extra virgin olive oil, has demonstrated not only a reduction in CV events but also a lower incidence of breast cancer in women with diabetes or at high CV risk.[42]

In colon cancer survivors, a diet rich in vegetables, fruits, and whole grains and reduced alcohol intake have demonstrated a beneficial effect,[43] probably mediated by the modification of the microbiota, with low bacterial fermentation leading to reduced production of pro-atherogenic and carcinogenic toxins.[44] Therefore, during the CORE, an accurate assessment of the patient's bad eating habits and their prompt correction are essential issues.

Closely connected to diet is weight control; its evaluation is fundamental at the start of CORE and must include the definition of body composition, the role that adipose tissue has in carcinogenesis and the tailoring of physical training (continuous or interval aerobic training, with or without strength training). In a meta-analysis of 82 studies in breast cancer patients, all-cause and cancer-specific mortality were higher in obese women, both in pre-menopause (relative risk [RRs] 1.75) and in post-menopause (RRs 1.34),[45] so it appears essential to avoid weight gain and promote its reduction in breast cancer survivors. The rehabilitation programme, associated with dietary support and counselling, can achieve this goal and, at the same time, reduce the main metabolic markers.

Blood pressure control is essential in patients with a pre-existing hypertension, as well as in those who are treated with oncological therapies capable of determining it (e.g. anti-angiogenic drugs). It is also useful in the search for orthostatic hypotension induced by concomitant therapies, as well as subclavian artery stealing in patients treated with surgery or radiotherapy for neck or mediastinal tumours.[35] Among the antihypertensive drugs, those with proven cardioprotective action (beta-blockers and ACE inhibitors) are preferable.

The lipid targets in secondary prevention of CVD do not differ in cancer patients if compared with non-cancer patients, while particular attention must be paid in primary prevention to the calculation of the individual risk using the scores currently in force (e.g. SCORE2 and SCORE2-OP), for a possible underestimation. Among cancer patients, some are more susceptible to dyslipidaemia: those with prostate cancer undergoing androgen deprivation therapy and women with breast cancer, especially if post-menopausal, obese, and being treated with tamoxifen or aromatase inhibitors. Lymphoma survivors, especially those with anamnestic radiotherapy of the mediastinum that accelerates coronary atherosclerosis, also represent a group at increased risk.[7] Statins are the cornerstone of lipid-lowering therapies with fewer interactions with current CTs. Proprotein convertase subtilisin/kexin 9 inhibitors are a promising therapy, not only for their lipid-lowering effects but also for their potential to improve the anti-tumour functions of immune checkpoint inhibitors.[46]

Diabetes and metabolic syndrome can precede the diagnosis of neoplasia, as well as be favoured by the metabolic alterations induced by anticancer therapies such as antiandrogens, antiestrogens, and orchiectomies.[7] On the other hand, the complications of diabetes (peripheral arterial disease, neuropathy, and orthostatic hypotension) must be evaluated both as markers of CV damage and as influencers of the training programme.

New hypoglycaemic drugs may be useful, in particular, gliflozins (with documented anti-proliferative effects on some types of tumours)[47] or glucagon-like peptide-1 (GLP-1) receptor agonists (with antiatherosclerotic and anti-obesity effects).[48]

Core: the training programme

The prescription of the training programme, as in CR, must be based on the FITT acronym (frequency, intensity, time, and type)[39] with appropriate attention to some typical aspects of CORE. In particular, the presence of anxiety and/or depression related to the neoplasm, the lack of family support, the social and economic context, the local transportation system (for outpatients' programmes), and work constraints must be highlighted, as they may constitute a barrier difficult to overcome when organizing the exercise programme.

In the planning phase, it is necessary to assess the cancer progression, the presence of metastases, lymphoedema, cicatricial retraction, osteoporosis, or sarcopenia. A study conducted on more than 500 elderly cancer patients demonstrated, compared with subjects of the same age without cancer, a greater severity of the markers of sarcopenia: reduced walking speed (gait speed), hand-grip strength, and lean mass of the limbs.[49] In these subjects, the use of strength training may be able to improve the indices of sarcopenia and the risk of death. Always in the preparatory evaluation phase for training, particular attention must always be paid to the frailty, cardiometabolic, and cognitive statuses of the patient.

The CORE training session should last at least 60 min (warm-up, plateau, and cool-down), at least three times a week, including aerobic and resistance exercises[50] and prescribing an exercise intensity using the usual CR methods (from indirect ones, based on a scale of subjective perception of fatigue to direct ones based on the calculation of training heart rates through physical exercise or cardiopulmonary tests).[51] Generally, a gradual approach with a progressive increase in workload is preferred, especially in patients with metastases, osteoporosis, or recent surgical interventions. The protocol should last for at least 24 sessions, but in subjects with compromised contractile function, it is reasonable to reach 36 sessions in total. Moreover, it is known, at least for the CR, that the improvement in functional capacity is progressive and constant with the increase in the number of sessions at least until the 36th session.[51]

High-intensity interval training (HIIT) appears to be a very useful tool in CORE: a meta-analysis on 2515 patients demonstrated that this exercise modality is able to increase cardiorespiratory capacity to a greater level than continuous aerobic exercise training, especially when performed before oncological therapy, with a session duration of at least 20 min and for at least 8 weeks.[52]

Moreover, some patients with neoplasia (e.g. advanced breast cancer) seem to be more adherent to an aerobic protocol including HIIT,[53] and this once again underlines the importance of personalizing training through cross-talk between oncologists, cardio-oncologists, and rehabilitation cardiologists. Strength training can be beneficial, and it is complementary to aerobic exercise, with a frequency of 2–3 times/week, starting with low intensity [<30% 1 repetition max (RM)], and gradually increasing the load

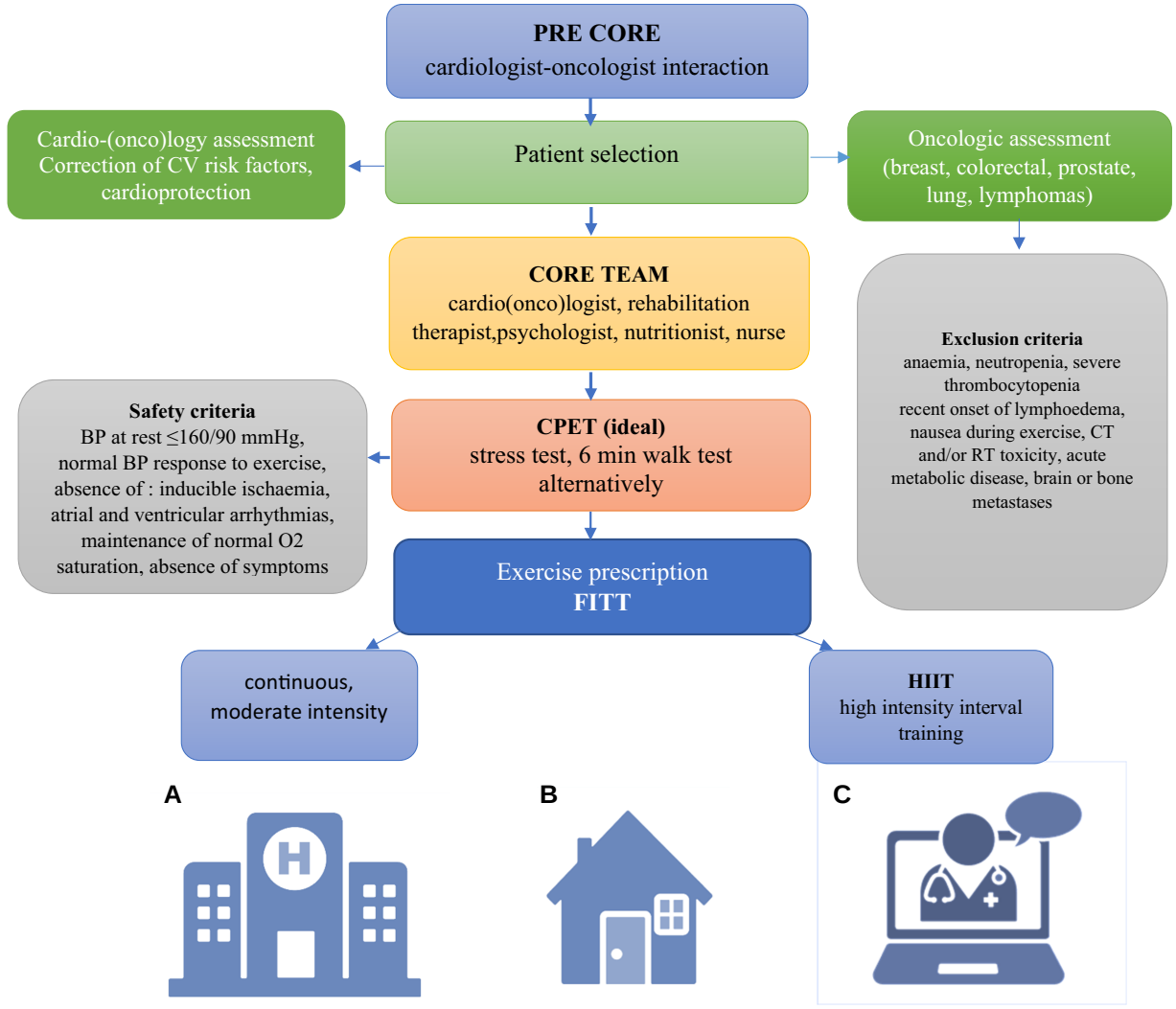

Figure 1 Cardio-oncology rehabilitation operating flow chart.

with a concomitant progressive reduction in the number of repetitions (RMs from 12-25 to 8-15).[7] With regard to the CORE setting, in selected populations (young people, greater information technology skills, absence of frailties, and less impairment of functional capacity), the use of home rehabilitation treatment, with tele-rehabilitation technique, can be safe and effective,[54] facilitating, at the same time, the maintenance of the training programme over time.[55]

The absolute contraindications to exercise consist of dizziness or pre-syncope, cyanosis, or O_2 saturation at rest <88% (with careful evaluation of lower values in chronic obstructive pulmonary disease). It is not indicated to start exercise if the systolic blood pressure is >200 mm Hg and/or the diastolic blood pressure is higher than 110 mm Hg and if the basal heart rate is >120/min after two measurements taken 5 min apart. Some contraindications are specific to cancer patients: leukopoenia (leukocytes <2000 and neutrophils <1500) increases the risk of infection, just as thrombocytopenia (platelets < 50 000) increases the risk of bleeding. Finally, significant anaemia (Hb < 8 g/dL), which is common in oncohaematological neoplasms, constitutes a contraindication to the exercise programme.[56]

Figure 1 shows a CORE operational flow chart.

Core effectiveness

Effects on cardiorespiratory fitness and quality of life

The functional capacity of cancer patients is largely reduced, with negative consequences for QOL. In women with breast cancer, cardiopulmonary function is reduced, with an average peak VO_2 value that is 27% lower than that of similarly aged women, and comparable to that of women 20-30 years older. The lowest values are found in patients with metastatic disease.[57] Functional capacity is also a predictor of survival. A study conducted on 1631 patients undergoing stress testing after cancer diagnosis with a follow-up of over 4 years demonstrated a direct correlation between the increase in functional capacity and the reductions in all-cause, CV, and cancer-specific mortality, with RRs of 0.17, 0.41, and 0.16, respectively,

comparing the high functional capacity group (metabolic equivalent of task [MET]: 10.7–22.0) with the low functional capacity group (MET: 1.9–7.6).[58] Furthermore, each MET increase in CRF appears to be associated with a 25% reduction in all-cause and cancer-specific mortality and a 14% reduction in CV mortality. Therefore, the stress test is mandatory for the selection of patients on which to maximize the CORE intervention.

A supervised exercise programme 3 times a week at an intensity of 40–80% of peak heart rate in patients with breast cancer, colon cancer, and lymphoma is able to increase aerobic capacity (ΔVO_2peak + 2.91 mL/kg/min) compared with usual care,[59] resulting in improved QOL.[60,61] A randomized trial of 104 women with Stages I–III breast cancer under treatment with anthracyclines has demonstrated that a 12-month physical exercise programme can improve functional capacity and cardiac reserve, preventing a state of disability in adherent patients.[62] The protocol consisted of a mixture of continuous resistance exercises, HIIT, and high-intensity resistance exercises, supervised for the first 3 months during CT and for the immediately following quarter, and then at home with weekly monitoring by the centre. At the end of the study, the increase in VO_2max was 3.5 mL/kg/min and was associated with both increased systolic volume and increased right and left ventricular ejection fractions. The protective effect of exercise was also confirmed by the lower increase in troponin after CT. Finally, a systematic review conducted on 25 randomized controlled trials involving 1434 adult patients undergoing haematopoietic stem cell or bone marrow transplantation demonstrated that a training programme is able to improve aerobic capacity and muscle strength, with a benefit also on the psychoemotional profile of patients and on the QOL.[63]

With regard to pre-habilitation programme, an intervention before abdominal oncological surgery was associated with an improvement in preoperative functional capacity [measured with the 6-min walk test (6MWT)] and a shorter hospital stay, but not with a reduction in complications or mortality (probably due to the heterogeneity and small number of studies conducted).[64] Therefore, exercise should be encouraged in all cancer patients, although in some subgroups the cost-effectiveness seems to be better. A meta-analysis of 34 randomized trials showed that the benefit was greater in patients who complained of greater baseline fatigue and had more severe impairment of physical function, while aerobic capacity improved significantly only in patients with less impairment at baseline. However, the beneficial effects on muscle strength and QOL appeared to be independent of baseline values.[65]

Effects on cardiovascular risk profile

In cardio-oncology patients, CORE significantly reduces CV risk. In a study of 62 testicular cancer survivors, a 12-week exercise programme (a mix of continuous aerobic exercise and HIIT) not only significantly increased functional capacity but also reduced levels of LDL cholesterol, C-reactive protein, arterial stiffness and intima-media thickness, and increased parasympathetic tone. The final result was a 0.6% reduction in the CV risk profile according to the Framingham Risk Score (FRS).[66] In sedentary, overweight, or obese women with Stages I–III breast cancer, a 16-week, 3-week supervised aerobic and resistance training programme was able to reduce the risk profile based on FRS (−11%) compared with usual care. The greater effect on FRS may be due to the physiological advantage of resistance exercise combined with aerobic exercise in a population at high risk of obesity. The categories used to define CV risk were age, systolic blood pressure, LDL-C, HDL-C, diabetes, and smoking habits, and, for each of these, exercise produced a significant improvement.[67]

Effects on cancer progression

The ERASE (Exercise During Active Surveillance for Prostate Cancer) study[68] represents a paradigm shift, as, for the first time, the effect of an exercise programme on cancer progression was analysed. The trial was conducted in 52 men with localized, intermediate-to-low-risk prostate cancer under active surveillance, who underwent a 12-week exercise programme using HIIT (supervised treadmill sessions on a treadmill with loads ranging from 85% to 95% of VO_2peak). Compared with the control group, the intervention arm showed a predictable increase in functional capacity (+0.9 mL/kg/min), with improvements in upper body strength and lower body flexibility. At the same time, an unexpected reduction in the rate of increase (or biochemical progression) of prostate-specific antigen, and in the growth of LNCaP cells (cells derived from prostate tumours) incubated with the patient's serum was also demonstrated, indicating an anti-proliferative effect. These effects seem to indicate a suppressive effect of exercise on neoplastic growth ('survival of the fittest'). Furthermore, they provide a pathophysiological basis for the use of training in the pre-habilitation phase. Given the limited number of subjects enrolled, the study was not able to evaluate the effect on survival, which will instead be the objective of the ongoing *Intense Exercise for Survival Among Men with Metastatic Prostate Cancer* (*INTERVAL-GAP4*) trial, currently in progress.[69]

Organizational issues: crosstalk between cardio-oncologist and rehabilitation cardiologist and organizational models

The CORE programme is inspired by the rehabilitation programme of the general cardiology patient, which over the years has demonstrated its effectiveness in terms of outcomes in the holistic approach to the patient with CVD. The prescription of physical exercise requires careful assessment, not only of the patient's physical capacity but also of the extent of the neoplasm. The location of the disease, its local and distant spread, cancer therapy (with possible cardiovasculotoxicity), and the patient's co-morbidities are important issues. Therefore, the relationship between the rehabilitation cardiologist and the cardio-oncologist is fundamental in correctly prescribing the physical activity programme.

The whole process, from the selection to the management to the prescription of physical activity, implies a close collaboration between the different figures involved in the CORE (oncologist, cardiologist, nurses, physiotherapists, psychologist, and nutritionist), with the cardio-oncologist acting as the conductor: there is thus a process of information exchange between all the actors in a perfect multidisciplinary approach.[7,70] Furthermore,

during CORE, it is not only essential to maintain close contact between medical figures for possible adjustments of therapy based on the response to treatment (think of the increase in CRF or QOL or ventricular function) but also to plan adequate follow-ups. Among the tasks of the cardio-oncologist, there is the correct selection of the subjects to be sent to the rehabilitation process: all patients can benefit from CORE, but the greater effectiveness of the CORE has been demonstrated in some types of cancer during active therapy (breast, prostate and lung cancers, lymphomas, and other haematological diseases) and in case of multiple CV risk factors or previous CV pathology. Adult patients who have survived paediatric cancer should also be able to access this path in relation to previous oncological treatments.[3]

Furthermore, if care takes place in 'expert and dedicated' centres capable of fully responding to the patient's needs, the level of adherence to the CORE is higher, at least in women affected by breast cancer.

Increasing the prescriptions of physical activity among cancer patients is an ambitious goal. Precisely for this reason, it is therefore necessary to create, within one's own structures or regions, specific rehabilitation programmes/paths for cancer patients. The use of tele-rehabilitation techniques, already successfully tested during the pandemic period, could increase the offer of CORE prescribing centres. In fact, tele-rehabilitation has been shown to improve pain tolerance and QOL, reduce the length of hospital stay in cancer patients with advanced disease,[54] improve the general state of health and cognitive functions, and reduce post-operative upper limb complications in patients with early breast cancer who have undergone surgery.[71]

Despite the evidence, rehabilitation centres for cancer patients are not widespread at a national level. A collective, scientific, and political effort ('a call to action') is desirable to ensure that physical exercise becomes an essential 'therapy' in future oncology programmes.

Future perspectives: from comprehensive cardio-oncology rehabilitation model to telehealth interventions and mobile applications

Even though the feasibility and efficacy of CORE have been extensively documented, many barriers (old age, frailties, rural living, long distance, digital illiteracy, poor adherence, etc.) limit its implementation. Telehealth can overcome these barriers and should be included in the preventive strategies of the cancer care continuum due to its usefulness, feasibility, and safety.[72-74]

Telehealth decentralizes care by bringing providers to the patient; this goal can be achieved through both telehealth visits that encompass phone or video approaches, and remote patient monitoring that exploits smartphone sensors (e.g. accelerometers and gyroscopes) and wearable sensors of heart rate, electrocardiogram, blood pressure, body weight, glycaemia, etc.[75] In the near future, wearable devices that allow somatosensory sensations will become available.[76] Mobile technologies, besides, enable a more objective evaluation of patients. There is a wide literature background supporting the implementation of telehealth in cancer patients,[9,77-80] but a few papers specifically addressed the issue of tele-rehabilitation in all phases of the cancer continuum.[81-84] A remote *pre-habilitation* programme (including physiotherapy, dietetics, psychological support, and patient blood values management) has been tested by Gonella *et al.* before oncologic surgery during the COVID-19 lockdown.[81] Phone counselling and home delivery of the pre-habilitation diary were the tools to promote physical activities and healthy lifestyles. The authors documented the feasibility of such a programme, which was enthusiastically received by the patients.[81]

A remote *habilitation* programme (8-week customized exercise programme delivered through a Web-based system) was performed during CT in 34 breast cancer patients and compared with a control group of 34 patients. The outcome was a proxy of functional capacity, the 6MWT. The walking distance increased in the intervention group and decreased in the control group.[82]

As far as remote *post-habilitation* programmes are concerned, a review pointed out the positive impact of telemedicine on cancer-related psychosocial and physical effects in a population of post-treatment survivors,[78] whereas another review reported a favourable experience of more than 3600 patients enrolled in a remote exercise programme[83]; besides, an 8-month tele-rehabilitation programme, administered to 175 post-treatment cancer patients, improved self-reported physical activity, with no adverse events.[84] Moreover, there are many ongoing trials with the aim of defining the efficacy of a telehealth programme in all phases of cancer.[85,86] Telehealth has been described by cancer survivors as a convenient and reassuring modality of care, reducing the subjective impact of cancer treatment.[87-90] We know from the application of CORE to cancer patients that some of them benefit the most from rehabilitation[3]; this principle holds true for tele-rehabilitation, too, which has been proven to be as effective as face-to-face rehabilitation.[79] There are other factors that must be assessed: best timing (phase of tele-rehabilitation with the greatest benefits), best method (home-based vs. satellite health centre-based), best markers of efficacy, e.g. CRF vs. 6MWT, and cost-effectiveness. To obtain a true 'tailored' rehabilitation programme, age and sex-oriented differences must also be considered.

In conclusion, CORE must rely on telehealth and mobile technologies to become more extensively implemented; multitarget telehealth interventions (and exercise) are pivotal tools in cancer survivorship care. A *patient-centred* approach in cancer care continuum, including *decentralized* visits, adds another component to the precision medicine algorithm 'the right treatment, for the right patient, at the right time', which becomes 'the right treatment, for the right patient, at the right time, *in the right place*'.[91] The psychosocial issues should not be neglected to make telehealth an essential and valuable tool in order to ban health care inequity.[92,93]

We still need, however, more, larger, controlled randomized trials to recommend this modality of rehabilitation.

The elderly cardio-oncology patient: specificities of assessment and intervention

Advanced age is one of the major risk factors for the development of chronic diseases.[94] The incidence and

prevalence of cancer mainly affect the geriatric population; 60% of all cancer cases and 70% of cancer-related deaths occur in patients aged 65 years and over.[95] Cancer therapies have had a very significant impact prolonging survival or even enabling good outcomes in patients with advanced cancer.[96,97] The increase in elderly patients with multiple comorbidities and associated clinical complexity (e.g. frailty) has led to an increased focus on stratification methods to improve individualized treatment in CORE, albeit with mixed results.[98,99] A multidimensional model of care approaching the geriatric patient is the best strategy to move beyond the survival and disease model by focusing on QOL.[7] Cardio-oncology rehabilitation in older cancer patients would have the specificity of guiding the patient towards integrated pathways.

Specificity of evaluation

Ageing is characterized by low-grade inflammation (inflamm-ageing), an important driver of age-related diseases such as CVD and cancer.[100] These chronic diseases share similar pathophysiological underpinnings and risk factors and often may coexist. The burden of comorbidities lowers the threshold for cardiotoxic effects of cancer therapies. Geriatric assessment is useful in recognizing the unique vulnerabilities and complexity of this specific population but improving the appropriateness of care requires a multidisciplinary approach.[101] Prevention of CV risk factors, dietary advice, weight management, and psychological management are key elements that properly guide the approach to older cancer patients. In addition, exercise training is a key component of multidimensional cardio-oncology strategies that can be used at any stage of cancer, especially in frail patients.[102–104] Notably, approaching the elderly population highlights several aspects that should be carefully considered: frailty, social isolation, malnutrition, cognitive decline, dementia, disability, other geriatric syndromes, and overall QOL.[102,103]

Specificity of the intervention

Exercise training can be challenging in older patients. Rehabilitation modalities need to be adapted according to clinical stability and functional capacity, individual ability, and frailty status. Disability, cognitive impairment, fall risk, sarcopenia, and visual and hearing impairment can also have a significant impact on exercise modalities. There is growing evidence that telemedicine in cardio-oncology is effective and well tolerated, even in older patients.[105–107] Telemedicine approaches are effective and safe in older cancer patients, with increasing use of artificial intelligence.[108–110] However, patients' social skills and social networks, especially in the last decades of life and in independent patients, need to be carefully assessed. Stronger social networks have been shown to be valuable strategies for delaying loss of autonomy.[111] In this context, exercise has been shown to be effective in improving mood disorders, anxiety, and social functioning in older cancer patients.[112,113] However, carers of older cancer/heart patients may be particularly burdened by the worry, anxiety, and stress that often accompany cancer diagnosis and treatment. Interestingly, some studies have shown that exercise improved physical and cognitive parameters in couples with cancer.[114,115] The geriatric relevance of these early findings is very important, as improved sociality and reduced mood disturbance play a crucial role in preventing disability.[116]

Conclusions

Cardiovascular disease and cancer are not to be purely considered as an epidemiologic association, being also an 'operating field' where the clinical and rehabilitative needs of affected patients require optimal responses. In this perspective, the CORE represents a specific discipline, which has a great deal of technical expertise from the CR setting, especially for physical training, nutritional intervention, and psychosocial support. However, detailed strategies need to be identified for this patient population, namely, appropriate criteria and priorities for referral, outcome measures, and quality standards of intervention. In the future, the appropriate use of tele-rehabilitation and digital health will be valuable tools. Last but not least, there is a need for strong political commitment and adequate policies and laws for CORE delivery, as far as an increased awareness by the general population.

Funding

This paper was published as part of a supplement financially supported by Centro Servizi ANMCO SrL - Società Benefit.

Conflict of interest: none declared.

Data availability

No new data were generated or analysed in support of this research.

Disclaimer

This Position Paper was originally published in the Italian language as 'Position paper ANMCO in collaborazione con ITACARE-P: Riabilitazione cardio-oncologica. "Are we ready?"', in the official journal of the Italian Federation of Cardiology (IFC) 'Giornale Italiano di Cardiologia', published by Il Pensiero Scientifico Editore. This paper was translated by a representative of the Italian Association of Hospital Cardiologists (ANMCO) and reprinted with permission of IFC and Il Pensiero Scientifico Editore.

References

1. Wang Z, Fan Z, Yang L, Liu L, Sheng C, Song F *et al.* Higher risk of cardiovascular mortality than cancer mortality among long-term cancer survivors. *Front Cardiovasc Med* 2023;**10**:1014400. PMID: 36760569; PMCID: PMC9905625.
2. Zullig LL, Sung AD, Khouri MG, Jazowski S, Shah NP, Sitlinger A *et al.* Cardiometabolic comorbidities in cancer survivors: JACC: CardioOncology state-of-the-art review. *JACC CardioOncol* 2022;**4**: 149–165. PMID: 35818559; PMCID: PMC9270612.
3. Gilchrist SC, Barac A, Ades PA, Alfano CM, Franklin BA, Jones LW *et al.* Cardio-oncology rehabilitation to manage cardiovascular outcomes in cancer patients and survivors: a scientific statement from the American Heart Association. *Circulation* 2019;**139**:e997–e1012. PMID: 30955352; PMCID: PMC7603804.
4. Rickard JN, Eswaran A, Small SD, Bonsignore A, Pakosh M, Oh P *et al.* Evaluation of the structure and health impacts of exercise-based cardiac and pulmonary rehabilitation and prehabilitation for individuals with cancer: a systematic review and meta-analysis. *Front Cardiovasc Med* 2021;**8**:739473.

5. Bisceglia I, Canale ML, Silvestris N, Gallucci G, Camerini A, Inno A *et al*. Cancer survivorship at heart: a multidisciplinary cardio-oncology roadmap for healthcare professionals. *Front Cardiovasc Med* 2023; **10**:1223660. Erratum in: *Front Cardiovasc Med* 2023;**10**:1309921. PMID: 37786510; PMCID: PMC10541962.
6. Taylor RS, Dalal HM, McDonagh STJ. The role of cardiac rehabilitation in improving cardiovascular outcomes. *Nat Rev Cardiol* 2022;**19**: 180–194.
7. Venturini E, Gilchrist S, Corsi E, Di Lorenzo A, Cuomo G, D'Ambrosio G *et al*. The core components of cardio-oncology rehabilitation. *Panminerva Med* 2021;**63**:170–183. PMID: 33528152.
8. Hewitt M, Greenfield S, Stovall E, eds. *From Cancer Patient to Cancer Survivor: Lost in Transition*. Washington, DC: National Academies Press; 2006. p151–153
9. Chang P, Zheng J. Updates in cancer rehabilitation telehealth. *Curr Phys Med Rehabil Rep* 2022;**10**:332–338. PMID: 36408472; PMCID: PMC9643960.
10. Melillo A, Chirico A, De Pietro G, Gallo L, Caggianese G, Barone D *et al*. Virtual reality rehabilitation systems for cancer survivors: a narrative review of the literature. *Cancers (Basel)* 2022;**14**:3163. PMID: 35804933; PMCID: PMC9264833.
11. Gimigliano F, Negrini S. The World Health Organization "rehabilitation 2030: a call for action". *Eur J Phys Rehabil Med* 2017;**53**:155–168. PMID: 28382807.
12. Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. *Cardiovasc Res* 2019;**115**:844–853.
13. de Boer RA, Meijers WC, van der Meer P, van Veldhuisen DJ. Cancer and heart disease: associations and relations. *Eur J Heart Fail* 2019;**21**:1515–1525. PMID: 31321851; PMCID: PMC6988442.
14. Bertero E, Canepa M, Maack C, Ameri P. Linking heart failure to cancer. *Circulation* 2018;**138**:735–742.
15. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV *et al*. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol* 2017;**70**:926–938. PMID: 28818202; PMCID: PMC5667567.
16. Brenner B, Bikdeli B, Tzoran I, Madridano O, López-Reyes R, Suriñach JM *et al*. Arterial ischemic events are a major complication in cancer patients with venous thromboembolism. *Am J Med* 2018;**131**: 1095–1103. PMID: 29807000.
17. Herrmann J, Yang EH, Iliescu CA, Cilingiroglu M, Charitakis K, Hakeem A, *et al*. Vascular toxicities of cancer therapies: the old and the new–an evolving avenue. *Circulation* 2016;**133**:1272–1289.
18. Chang HM, Moudgil R, Scarabelli T, Okwuosa TM, Yeh ETH. Cardiovascular complications of cancer therapy: best practices in diagnosis, prevention, and management: part 1. *J Am Coll Cardiol* 2017;**70**:2536–2551. Erratum in: *J Am Coll Cardiol* 2018;**71**:587.
19. Bisceglia I, Mistrulli R, Cartoni D, Matera S, Petrolati S, Canale ML. Cardiac toxicity of chemotherapy for breast cancer: do angiotensin-converting enzyme inhibitors and beta blockers protect? *Eur Heart J Suppl* 2023;**25**:B25–B27.
20. Brown SA, Nhola L, Herrmann J. Cardiovascular toxicities of small molecule tyrosine kinase inhibitors: an opportunity for systems-based approaches. *Clin Pharmacol Ther* 2017;**101**:65–80.
21. Thuny F, Naidoo J, Neilan TG. Cardiovascular complications of immune checkpoint inhibitors for cancer. *Eur Heart J* 2022;**43**: 4458–4468.
22. Hasin T, Gerber Y, Weston SA, Jiang R, Killian JM, Manemann SM *et al*. Heart failure after myocardial infarction is associated with increased risk of cancer. *J Am Coll Cardiol* 2016;**68**:265–271. PMID: 27417004; PMCID: PMC4947209.
23. Bertero E, Robusto F, Rulli E, D'Ettorre A, Bisceglia L, Staszewsky L *et al*. Cancer incidence and mortality according to Pre-existing heart failure in a community-based cohort. *JACC CardioOncol* 2022; **4**:98–109. PMID: 35492831; PMCID: PMC9040106.
24. Hasin T, Iakobishvili Z, Weisz G. Associated risk of malignancy in patients with cardiovascular disease: evidence and possible mechanism. *Am J Med* 2017;**130**:780–785.
25. Meijers WC, Maglione M, Bakker SJL, Oberhuber R, Kieneker LM, de Jong S *et al*. Heart failure stimulates tumor growth by circulating factors. *Circulation* 2018;**138**:678–691. PMID: 29459363.
26. Bell CF, Lei X, Haas A, Baylis RA, Gao H, Luo L *et al*. Risk of cancer after diagnosis of cardiovascular disease. *JACC CardioOncol* 2023; **5**:431–440. PMID: 37614573; PMCID: PMC10443115.
27. Conen D, Wong JA, Sandhu RK, Cook NR, Lee IM, Buring JE *et al*. Risk of malignant cancer among women with new-onset atrial fibrillation. *JAMA Cardiol* 2016;**1**:389–396. PMID: 27438314; PMCID: PMC4957657.
28. Hu YF, Chen YJ, Lin YJ, Chen SA. Inflammation and the pathogenesis of atrial fibrillation. *Nat Rev Cardiol* 2015;**12**:230–243. PMID: 25622848.
29. Gottschlich A, Endres S, Kobold S. Therapeutic strategies for targeting IL-1 in cancer. *Cancers (Basel)* 2021;**13**:477.
30. Nguyen MLT, Bui KC, Scholta T, Xing J, Bhuria V, Sipos B *et al*. Targeting interleukin 6 signaling by monoclonal antibody siltuximab on cholangiocarcinoma. *J Gastroenterol Hepatol* 2021;**36**: 1334–1345. PMID: 33091158.
31. Moloney JN, Cotter TG. ROS signalling in the biology of cancer. *Semin Cell Dev Biol* 2018;**80**:50–64.
32. Roubín SR, Assi EA, Pardal CB, Fernandez MC, Pousa IM, Paz RC *et al*. New cancer diagnosis after bleeding in anticoagulated patients with atrial fibrillation. *J Am Heart Assoc* 2020;**9**:e016836. PMID: 33140676; PMCID: PMC7763724.
33. de Boer RA, Aboumsallem JP, Bracun V, Leedy D, Cheng R, Patel S *et al*. A new classification of cardio-oncology syndromes. *Cardiooncology* 2021;**7**:24. PMID: 34154667; PMCID: PMC8218489.
34. Dittus KL, Lakoski SG, Savage PD, Kokinda N, Toth M, Stevens D *et al*. Exercise-based oncology rehabilitation: leveraging the cardiac rehabilitation model. *J Cardiopulm Rehabil Prev* 2015;**35**:130–139. PMID: 25407596; PMCID: PMC4342296.
35. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J *et al*. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229–4361. Erratum in: *Eur Heart J* 2023;**44**:1621. PMID: 36017568.
36. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N *et al*. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2017;**35**:893–911. PMID: 27918725.
37. Voorn MJJ, Franssen RFW, Hoogeboom TJ, van Kampen-van den Boogaart VEM, Bootsma GP, Bongers BC *et al*. Evidence base for exercise prehabilitation suggests favourable outcomes for patients undergoing surgery for non-small cell lung cancer despite being of low therapeutic quality: a systematic review and meta-analysis. *Eur J Surg Oncol* 2023;**49**:879–894. PMID: 36788040.
38. Canale ML, Camerini A, Magnacca M, Del Meglio J, Lilli A, Donati S *et al*. Applicazione di un percorso diagnostico-terapeutico assistenziale di cardioncologia per la rilevazione e la gestione del danno cardiaco da trattamenti oncologici in ambito ospedaliero [Application of a shared interdisciplinary and multiprofessional cardio-oncology in-hospital pathway]. *G Ital Cardiol (Rome)* 2017; **18**:760–763. Italian. PMID: 29105670.
39. Ambrosetti M, Abreu A, Corrà U, Davos CH, Hansen D, Frederix I *et al*. Secondary prevention through comprehensive cardiovascular rehabilitation: from knowledge to implementation. 2020 update. A position paper from the secondary prevention and rehabilitation section of the European Association of Preventive Cardiology. *Eur J Prev Cardiol* 2021;**28**:460–495. PMID: 33611446.
40. Karam-Hage M, Cinciripini PM, Gritz ER. Tobacco use and cessation for cancer survivors: an overview for clinicians. *CA Cancer J Clin* 2014; **64**:272–290.
41. Goldstein AO, Shoenbill KA, Jolly TA. Intensive smoking cessation counseling for patients with cancer. *JAMA* 2020;**324**:1401–1143.
42. Toledo E, Salas-Salvadó J, Donat-Vargas C, Buil-Cosiales P, Estruch R, Ros E *et al*. Mediterranean diet and invasive breast cancer risk among women at high cardiovascular risk in the PREDIMED trial: a randomized clinical trial. *JAMA Intern Med* 2015;**175**:1752–1760. Erratum in: *JAMA Intern Med* 2018;**178**:1731–1732. PMID: 26365989.
43. Van Blarigan EL, Fuchs CS, Niedzwiecki D, Zhang S, Saltz LB, Mayer RJ *et al*. Association of survival with adherence to the American Cancer Society nutrition and physical activity guidelines for cancer survivors after colon cancer diagnosis: the CALGB 89803/alliance trial. *JAMA Oncol* 2018;**4**:783–790. Erratum in: *JAMA Oncol* 2019;**5**:579. PMID: 29710284; PMCID: PMC6145685.
44. Windey K, De Preter V, Verbeke K. Relevance of protein fermentation to gut health. *Mol Nutr Food Res* 2012;**56**:184–196.

45. Chan DSM, Vieira AR, Aune D, Bandera EV, Greenwood DC, McTiernan A *et al*. Body mass index and survival in women with breast cancer-systematic literature review and meta-analysis of 82 follow-up studies. *Ann Oncol* 2014;**25**:1901–1914. PMID: 24769692; PMCID: PMC4176449.
46. Quagliariello V, Bisceglia I, Berretta M, Iovine M, Canale ML, Maurea C *et al*. PCSK9 inhibitors in cancer patients treated with immune-checkpoint inhibitors to reduce cardiovascular events: new frontiers in cardioncology. *Cancers (Basel)* 2023;**15**:1397. PMID: 36900189; PMCID: PMC10000232.
47. Dutka M, Bobiński R, Francuz T, Garczorz W, Zimmer K, Ilczak T *et al*. SGLT-2 inhibitors in cancer treatment-mechanisms of action and emerging new perspectives. *Cancers (Basel)* 2022;**14**:5811. PMID: 36497303; PMCID: PMC9738342.
48. Sauter RE. Obesity, metabolic and bariatric 1 surgery, and cancer prevention: what do we need to learn and how do we get there? *Surg Obes Relat Dis* 2023;**19**:781–787.
49. Williams GR, Chen Y, Kenzik KM, McDonald A, Shachar SS, Klepin HD *et al*. Assessment of sarcopenia measures, survival, and disability in older adults before and after diagnosis with cancer. *JAMA Netw Open* 2020;**3**:e204783.
50. Sweegers MG, Altenburg TM, Brug J, May AM, van Vulpen JK, Aaronson NK *et al*. Effects and moderators of exercise on muscle strength, muscle function and aerobic fitness in patients with cancer: a meta-analysis of individual patient data. *Br J Sports Med* 2019;**53**: 812. PMID: 30181323.
51. Haeny T, Nelson R, Ducharme J, Zuhl M. The influence of exercise workload progression across 36 sessions of cardiac rehabilitation on functional capacity. *J Cardiovasc Dev Dis* 2019;**6**:32. PMID: 31489917; PMCID: PMC6787655.
52. Lavín-Pérez AM, Collado-Mateo D, Mayo X, Humphreys L, Liguori G, James Copeland R *et al*. High-intensity exercise to improve cardiorespiratory fitness in cancer patients and survivors: a systematic review and meta-analysis. *Scand J Med Sci Sports* 2021; **31**:265–294. PMID: 33098219.
53. Courneya KS, Segal RJ, Gelmon K, Mackey JR, Friedenreich CM, Yasui Y *et al*. Predictors of adherence to different types and doses of supervised exercise during breast cancer chemotherapy. *Int J Behav Nutr Phys Act* 2014;**11**:85. PMID: 24997476; PMCID: PMC4110703.
54. Cheville AL, Moynihan T, Herrin J, Loprinzi C, Kroenke K. Effect of collaborative telerehabilitation on functional impairment and pain among patients with advanced-stage cancer: a randomized clinical trial. *JAMA Oncol* 2019;**5**:644–652. PMID: 30946436; PMCID: PMC6512772.
55. Witlox L, Hiensch AE, Velthuis MJ, Steins Bisschop CN, Los M, Erdkamp FLG *et al*. Four-year effects of exercise on fatigue and physical activity in patients with cancer. *BMC Med* 2018;**16**:86. PMID: 29879968; PMCID: PMC5992660.
56. D'Ascenzi F, Anselmi F, Fiorentini C, Mannucci R, Bonifazi M, Mondillo S. The benefits of exercise in cancer patients and the criteria for exercise prescription in cardio-oncology. *Eur J Prev Cardiol* 2021; **28**:725–735. PMID: 31587570.
57. Jones LW, Courneya KS, Mackey JR, Muss HB, Pituskin EN, Scott JM *et al*. Cardiopulmonary function and age-related decline across the breast cancer survivorship continuum. *J Clin Oncol* 2012;**30**: 2530–2537. PMID: 22614980; PMCID: PMC3397786.
58. Groarke JD, Payne DL, Claggett B, Mehra MR, Gong J, Caron J *et al*. Association of post-diagnosis cardiorespiratory fitness with cause-specific mortality in cancer. *Eur Heart J Qual Care Clin Outcomes* 2020;**6**:315–322. PMID: 32167560; PMCID: PMC9989596.
59. Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, Hornsby WE *et al*. Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. *Oncologist* 2011;**16**:112–120. Erratum in: *Oncologist* 2011;**16**:260. PMID: 21212429; PMCID: PMC3228052.
60. Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP, Prud'Homme DG *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. PMID: 19064985.
61. Thomas GA, Cartmel B, Harrigan M, Fiellin M, Capozza S, Zhou Y *et al*. The effect of exercise on body composition and bone mineral density in breast cancer survivors taking aromatase inhibitors. *Obesity (Silver Spring)* 2017;**25**:346–351. PMID: 28026901; PMCID: PMC5450163.
62. Foulkes SJ, Howden EJ, Haykowsky MJ, Antill Y, Salim A, Nightingale SS *et al*. Exercise for the prevention of anthracycline-induced functional disability and cardiac dysfunction: the BREXIT study. *Circulation* 2023;**147**:532–545. PMID: 36342348.
63. Morales Rodríguez E, Lorenzo Calvo J, Granado-Peinado M, Pérez-Bilbao T, San Juan AF. Effects of exercise programs on psychoemotional and quality-of-life factors in adult patients with cancer and hematopoietic stem cell transplantation or bone marrow transplantation: a systematic review. *Int J Environ Res Public Health* 2022;**19**:15896. PMID: 36497971; PMCID: PMC9735672.
64. Waterland JL, McCourt O, Edbrooke L, Granger CL, Ismail H, Riedel B *et al*. Efficacy of prehabilitation including exercise on postoperative outcomes following abdominal cancer surgery: a systematic review and meta-analysis. *Front Surg* 2021;**8**:628848. PMID: 33816546; PMCID: PMC8017317.
65. Buffart LM, Sweegers MG, May AM, Chinapaw MJ, van Vulpen JK, Newton RU *et al*. Targeting exercise interventions to patients with cancer in need: an individual patient data meta-analysis. *J Natl Cancer Inst* 2018;**110**:1190–1200. PMID: 30299508; PMCID: PMC6454466. Inizio modulo.
66. Adams SC, DeLorey DS, Davenport MH, Stickland MK, Fairey AS, North S *et al*. Effects of high-intensity aerobic interval training on cardiovascular disease risk in testicular cancer survivors: a phase 2 randomized controlled trial. *Cancer* 2017;**123**:4057–4065. PMID: 28708930.
67. Lee K, Tripathy D, Demark-Wahnefried W, Courneya KS, Sami N, Bernstein L *et al*. Effect of aerobic and resistance exercise intervention on cardiovascular disease risk in women with early-stage breast cancer: a randomized clinical trial. *JAMA Oncol* 2019;**5**: 710–714. PMID: 30920602; PMCID: PMC6512455.
68. Kang DW, Fairey AS, Boulé NG, Field CJ, Wharton SA, Courneya KS. Effects of exercise on cardiorespiratory fitness and biochemical progression in men with localized prostate cancer under active surveillance: the ERASE randomized clinical trial. *JAMA Oncol* 2021; **7**:1487–1495. PMID: 34410322; PMCID: PMC8377605.
69. Newton RU, Kenfield SA, Hart NH, Chan JM, Courneya KS, Catto J *et al*. Intense Exercise for Survival among Men with Metastatic Castrate-Resistant Prostate Cancer (INTERVAL-GAP4): a multicentre, randomised, controlled phase III study protocol. *BMJ Open* 2018;**8**: e022899. PMID: 29764892; PMCID: PMC5961562.
70. Canale ML, Camerini A, Orso F, Misuraca L, Carluccio M, Talini E *et al*. Modello organizzativo e di un percorso clinico per la gestione cardiologica ambulatoriale del paziente oncologico: una proposta congiunta ANMCO e AIOM toscana [A clinical cardio-oncology pathway for the cardiology management of cancer outpatients: a joint proposal by ANMCO and AIOM Tuscany]. *G Ital Cardiol (Rome)* 2022;**23**:437–443. Italian. PMID: 35674034.
71. Galiano-Castillo N, Cantarero-Villanueva I, Fernández-Lao C, Ariza-García A, Díaz-Rodríguez L, Del-Moral-Ávila R *et al*. Telehealth system: a randomized controlled trial evaluating the impact of an internet-based exercise intervention on quality of life, pain, muscle strength, and fatigue in breast cancer survivors. *Cancer* 2016;**122**:3166–3174.
72. Knudsen KE, Willman C, Winn R. Optimizing the use of telemedicine in oncology care: postpandemic opportunities. *Clin Cancer Res* 2021; **27**:933–936. PMID: 33229457; PMCID: PMC7887011.
73. Butel-Simoes LE, Ngo DTM, Sverdlov AL. Digital technologies to help delivery of cardio-oncology care. *Heart Lung Circ* 2021;**30**:1271–1273. PMID: 34219023.
74. Rocco P, Finkelstein J. Telerehabilitation for patients with cancer: a scoping review. *Stud Health Technol Inform* 2022;**290**:543–546. PMID: 35673075.
75. Jones AK, Yan CL, Rivera Rodriquez BP, Kaur S, Andrade-Bucknor S. Role of wearable devices in cardiac telerehabilitation: a scoping review. *PLoS One* 2023;**18**:e0285801. PMID: 37256878; PMCID: PMC10231816.
76. Sun Z, Zhu M, Shan X, Lee C. Augmented tactile-perception and haptic-feedback rings as human-machine interfaces aiming for immersive interactions. *Nat Commun* 2022;**13**:5224. PMID: 36064838; PMCID: PMC9445040.
77. Cox A, Lucas G, Marcu A, Piano M, Grosvenor W, Mold F *et al*. Cancer survivors' experience with telehealth: a systematic review and thematic synthesis. *J Med Internet Res* 2017;**19**:e11. PMID: 28069561; PMCID: PMC5259589.

78. Chan RJ, Crichton M, Crawford-Williams F, Agbejule OA, Yu K, Hart NH *et al*. The efficacy, challenges, and facilitators of telemedicine in post-treatment cancer survivorship care: an overview of systematic reviews. *Ann Oncol* 2021;**32**:1552–1570. PMID: 34509615.
79. Batalik L, Filakova K, Radkovcova I, Dosbaba F, Winnige P, Vlazna D *et al*. Cardio-oncology rehabilitation and telehealth: rationale for future integration in supportive care of cancer survivors. *Front Cardiovasc Med* 2022;**9**:858334.
80. Chang P, Asher A. Cancer telerehabilitation. *Phys Med Rehabil Clin N Am* 2021;**32**:277–289. PMID: 33814058.
81. Gonella F, Massucco P, Perotti S, Monasterolo S, Vassallo D, Laezza A *et al*. Telemedicine prehabilitation as a result of COVID-19: disruptive technological solutions. *Br J Surg* 2021;**108**:e215–e216. PMID: 33693459; PMCID: PMC7989587.
82. Ariza-Garcia A, Lozano-Lozano M, Galiano-Castillo N, Postigo-Martin P, Arroyo-Morales M, Cantarero-Villanueva I. A web-based exercise system (e-CuidateChemo) to counter the side effects of chemotherapy in patients with breast cancer: randomized controlled trial. *J Med Internet Res* 2019;**21**:e14418. PMID: 31342907; PMCID: PMC6685131.
83. Morrison KS, Paterson C, Toohey K. The feasibility of exercise interventions delivered via telehealth for people affected by cancer: a rapid review of the literature. *Semin Oncol Nurs* 2020;**36**:151092.
84. Dennett A, Harding KE, Reimert J, Morris R, Parente P, Taylor NF. Telerehabilitation's safety, feasibility, and exercise uptake in cancer survivors: process evaluation. *JMIR Cancer* 2021;**7**:e33130.
85. He Y, Han X, Zou W, Liu X, Sun N, Zhou F. Telerehabilitation programs for patients with cancer and survivors: a protocol for a systematic review. *BMJ Open* 2022;**12**:e058981. PMID: 35393328; PMCID: PMC8991069.
86. Dennett AM, Harding KE, Peiris CL, Shields N, Barton C, Lynch L *et al*. Efficacy of group exercise-based cancer rehabilitation delivered via telehealth (TeleCaRe): protocol for a randomized controlled trial. *JMIR Res Protoc* 2022;**11**:e38553. PMID: 35849441; PMCID: PMC9345024.
87. Tang LH, Kikkenborg Berg S, Christensen J, Lawaetz J, Doherty P, Taylor RS *et al*. Patients' preference for exercise setting and its influence on the health benefits gained from exercise-based cardiac rehabilitation. *Int J Cardiol* 2017;**232**:33–39.
88. Lafaro KJ, Raz DJ, Kim JY, Hite S, Ruel N, Varatkar G *et al*. Pilot study of a telehealth perioperative physical activity intervention for older adults with cancer and their caregivers. *Support Care Cancer* 2020; **28**:3867–3877.
89. Mendoza JA, Baker KS, Moreno MA, Whitlock K, Abbey-Lambertz M, Waite A *et al*. A Fitbit and Facebook mHealth intervention for promoting physical activity among adolescent and young adult childhood cancer survivors: a pilot study. *Pediatric Blood Cancer* 2017;**64**:e26660.
90. Snyder S, Silva RF, Whisenant MS, Milbury K. Videoconferenced yoga interventions for cancer patients and their caregivers during the COVID-19 pandemic: a report from a clinician's perspective. *Integr Cancer Ther* 2021;**20**:15347354211019112.
91. Binder AF, Handley NR, Wilde L, Palmisiano N, Lopez AM. Treating hematologic malignancies during a pandemic: utilizing telehealth and digital technology to optimize care. *Front Oncol* 2020;**10**:1183. PMID: 32676459; PMCID: PMC7333768.
92. Kuziemsky C, Hunter I, Udayasankaran JG, Ranatunga P, Kulatunga G, John S *et al*. Telehealth as a means of enabling health equity. *Yearb Med Inform* 2022;**31**:60–66. PMID: 35654429; PMCID: PMC9719760.
93. Yee V, Bajaj SS, Stanford FC. Paradox of telemedicine: building or neglecting trust and equity. *Lancet Digit Health* 2022;**4**:E480–E481.
94. Ferrucci L, Giallauria F, Guralnik JM. Epidemiology of aging. *Radiol Clin North Am* 2008;**46**:643–652. PMID: 18922285; PMCID: PMC2692491.
95. Cinar D, Tas D. Cancer in the elderly. *North Clin Istanb* 2015;**2**:73–80. PMID: 28058345; PMCID: PMC5175057.
96. Chen RC, Royce TJ, Extermann M, Reeve BB. Impact of age and comorbidity on treatment and outcomes in elderly cancer patients. *Semin Radiat Oncol* 2012;**22**:265–271. PMID: 22985808.
97. Koroukian SM, Murray P, Madigan E. Comorbidity, disability, and geriatric syndromes in elderly cancer patients receiving home health care. *J Clin Oncol* 2006;**24**:2304–2310. PMID: 16710028.
98. Venturini E, Iannuzzo G, D'Andrea A, Pacileo M, Tarantini L, Canale ML *et al*. Oncology and cardiac rehabilitation: an underrated relationship. *J Clin Med* 2020;**9**:1810. PMID: 32532011; PMCID: PMC7356735.
99. Sayed A, Munir M, Addison D, Abushouk AI, Dent SF, Neilan TG *et al*. The underutilization of preventive cardiovascular measures in patients with cancer. An analysis of the behavioural risk factor surveillance system, 2011–2022. *Eur J Prev Cardiol* 2023;**30**: 1325–1332. PMID: 37158488.
100. Liberale L, Badimon L, Montecucco F, Lüscher TF, Libby P, Camici GG. Inflammation, aging, and cardiovascular disease: JACC review topic of the week. *J Am Coll Cardiol* 2022;**79**:837–847.
101. Bisceglia I, Canale ML, Camilli M, Gallucci G, Laudisio A, Lestuzzi C *et al*. F. Cardio-oncogeriatrics: ANMCO position paper on cardio-oncology management of elderly patients. *G Ital Cardiol (Rome)* 2022;**23**:878–891.
102. Giallauria F, Testa C, Cuomo G, Di Lorenzo A, Venturini E, Lauretani F *et al*. Exercise training in elderly cancer patients: a systematic review. *Cancers (Basel)* 2023;**15**:1671. PMID: 36980559; PMCID: PMC10046194.
103. Shultz AM, Squires RW, Shin JY, Durani U, Pophali PA. Cardio-oncology rehabilitation (CORE) exercise prescription and programming: a practical guide. *J Cardiopulm Rehabil Prev* 2021;**41**:341–344. PMID: 34461622.
104. Giallauria F, Di Lorenzo A, Venturini E, Pacileo M, D'Andrea A, Garofalo U *et al*. Frailty in acute and chronic coronary syndrome patients entering cardiac rehabilitation. *J Clin Med* 2021;**10**:1696. PMID: 33920796; PMCID: PMC8071180.
105. Wei M, Meng D, Guo H, He S, Tian Z, Wang Z *et al*. Hybrid exercise program for sarcopenia in older adults: the effectiveness of explainable artificial intelligence-based clinical assistance in assessing skeletal muscle area. *Int J Environ Res Public Health* 2022;**19**:9952. PMID: 36011588; PMCID: PMC9407935.
106. Sagarra-Romero L, Butragueño J, Gomez-Bruton A, Lozano-Berges G, Vicente-Rodríguez G, Morales JS. Effects of an online home-based exercise intervention on breast cancer survivors during COVID-19 lockdown: a feasibility study. *Support Care Cancer* 2022;**30**: 6287–6297. PMID: 35471614; PMCID: PMC9039602.
107. Morey MC, Snyder DC, Sloane R, Cohen HJ, Peterson B, Hartman TJ *et al*. Effects of home-based diet and exercise on functional outcomes among older, overweight long-term cancer survivors: RENEW: a randomized controlled trial. *JAMA* 2009;**301**:1883–1891. PMID: 19436015; PMCID: PMC2752421.
108. Brown SA, Patel S, Rayan D, Zaharova S, Lin M, Nafee T *et al*. A virtual-hybrid approach to launching a cardio-oncology clinic during a pandemic. *Cardiooncology* 2021;**7**:2.PMID: 33441188; PMCID: PMC7803880.
109. Netz Y, Argov E, Yekutieli Z, Ayalon M, Tchelet K, Ben-Sira D *et al*. Personalized multicomponent exercise programs using smartphone technology among older people: protocol for a randomized controlled trial. *BMC Geriatr* 2021;**21**:605. PMID: 34702168; PMCID: PMC8547559.
110. Ciccarelli M, Giallauria F, Carrizzo A, Visco V, Silverio A, Cesaro A *et al*. Artificial intelligence in cardiovascular prevention: new ways will open new doors. *J Cardiovasc Med (Hagerstown)* 2023;**24**: e106–e115. PMID: 37186561.
111. Bernabei R, Landi F, Calvani R, Cesari M, Del Signore S, Anker SD *et al*. Multicomponent intervention to prevent mobility disability in frail older adults: randomised controlled trial (SPRINTT project). *BMJ* 2022;**377**:e068788. PMID: 35545258; PMCID: PMC9092831.
112. Loh KP, Kleckner IR, Lin PJ, Mohile SG, Canin BE, Flannery MA *et al*. Effects of a home-based exercise program on anxiety and mood disturbances in older adults with cancer receiving chemotherapy. *J Am Geriatr Soc* 2019;**67**:1005–1011. PMID: 31034591; PMCID: PMC6544022.
113. Cheng KKF, Lim YTE, Koh ZM, Tam WWS. Home-based multidimensional survivorship programmes for breast cancer survivors. *Cochrane Database Syst Rev* 2017;**8**:CD011152. PMID: 28836379; PMCID: PMC6483678.
114. Winters-Stone KM, Lyons KS, Dobek J, Dieckmann NF, Bennett JA, Nail L *et al*. Benefits of partnered strength training for prostate cancer survivors and spouses: results from a randomized controlled trial of the exercising together project. *J Cancer Surviv* 2016;**10**:633–644. PMID: 26715587.
115. Winters-Stone KM, Lyons KS, Beer TM, Skiba MB, Hung A. A pilot feasibility study of Exercising Together© during radiation therapy for prostate cancer: a dyadic approach for patients and spouses. *Pilot Feasibility Study* 2021;**7**:216. PMID: 34879873; PMCID: PMC8653603.
116. Blaney J, Lowe-Strong A, Rankin J, Campbell A, Allen J, Gracey J. The cancer rehabilitation journey: barriers to and facilitators of exercise among patients with cancer-related fatigue. *Phys Ther* 2010;**90**: 1135–1147.