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Review

Integrating Nutrition and Exercise to Mitigate Cardiometabolic Risk and Enhance Outcomes in Lung Cancer during the Era of Immunotherapy and Targeted Therapy

Giuseppina Gallucci [1,*], Alessandro Inno [2], Stefania Fugazzaro [3], Stefania Costi [4], Silvia Di Leo [5], Debora Pezzuolo [6], Francesca Zanelli [7], Alessandro Navazio [8], Carmine Pinto [7] and Luigi Tarantini [8]

[1] Independent researcher, Melfi (Italy)
[2] Medical Oncology, IRCCS Ospedale Sacro Cuore Don Calabria, 37024 Negrar di Valpolicella, Italy
[3] Physical Medicine and Rehabilitation Unit, Azienda Sanitaria Unità Locale di Reggio Emilia, Reggio Emilia, Italy
[4] Research and EBP Unit, Health Professions Department, Azienda USL-IRCCS di Reggio Emilia, 42122 Reggio Emilia, Italy; Department of Surgery, Medicine, Dentistry and Morphological Sciences, University of Modena and Reggio Emilia, 41124 Modena, Italy
[5] Psycho-Oncology Unit, Azienda USL-IRCCS di Reggio Emilia, Via Giovanni Amendola, 2, 42122 Reggio Emilia, Italy
[6] Medicina oncologica, Ospedale di Guastalla e Correggio, Area Nord, Azienda Sanitaria Unità Locale di Reggio Emilia, Reggio Emilia, Italy
[7] Provincial Medical Oncology, Department of Oncology and Advanced Technologies, AUSL-IRCCS IN Tecnologie Avanzate e Modelli Assistenziali in Oncologia, Reggio Emilia, Italy
[8] Cardioncology Clinic - Cardiologia Ospedaliera AUSL-IRCCS Tecnologie Avanzate e Modelli Assistenziali in Oncologia, Reggio Emilia, Italy
* Correspondence: pina.gallucci@tiscali.it; Tel.: +393336337080

Abstract

Growing evidence suggests that optimized nutritional status and regular physical activity enhance immunotherapy responsiveness by modulating immunometabolism, improving T-cell function, reducing chronic inflammation, and favorably shaping the gut microbiota. Cancer-related metabolic dysfunction and treatment-induced cardiotoxicity converge to impair both skeletal and cardiac muscle energetics, thereby limiting treatment tolerance and effectiveness. Lung cancer (LC) patients frequently present with malnutrition, systemic inflammation, sarcopenia, and pre-existing cardiovascular disease (CVD), conditions that not only compromise functional status and survival but also represent significant competing risks to oncologic outcomes. By counteracting sarcopenia and malnutrition, lifestyle interventions may also reduce immune-related adverse events (irAEs) and mitigate cardiovascular (CV) toxicity, ultimately allowing patients to sustain effective treatment intensity. This narrative review examines the emerging role of targeted nutritional strategies and structured physical exercise as integral components of supportive care in LC, with a specific focus on their impact on cardiac metabolism, CV risk, and response to anticancer therapies, including immunotherapy. In this context, exercise and appropriate dietary interventions emerge as modifiable factors capable of restoring metabolic flexibility, improving mitochondrial function, and reducing systemic inflammation. These effects are particularly relevant in patients receiving immune checkpoint inhibitors (ICIs), where metabolic health and immune competence are tightly interconnected and trained immunity may be a key issue. Finally, the review discusses future challenges and perspectives, emphasizing the impact of CVD on long-term LC survivors' outcome and of allostatic load and financial toxicity on adherence to lifestyle interventions. The integration of personalized nutrition and exercise programs into cardio-oncology care pathways is proposed as a

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key strategy to enhance immunotherapy efficacy, improve cardiometabolic resilience, and translate prolonged survival into better quality of life.

Keywords: lung cancer; nutrition; exercise; cardiac metabolism; sarcopenia; malnutrition; cardiovascular risk; therapy response; lifestyle intervention; inflammation; immune system; immunotherapy; targeted therapy

1. Introduction

LC remains a leading cause of cancer mortality worldwide and is frequently complicated by pre-existing or therapy-induced CVD [1–4]. Malnutrition, systemic inflammation, and sarcopenia further exacerbate this vulnerability, contributing to cardiometabolic stress and increased risk of heart failure (HF), arrhythmias, and ischemic events [5–9]. Addressing these overlapping risks is crucial, today, especially considering the improvement in patient survival resulting from the widespread use of current screening programs and new immunological and targeted therapies [10]. Unfortunately, the improved survival is threatened by competing causes of mortality, among which CVD is particularly relevant, affecting 30–50% of cases [11,12] and contributing to increased mortality (~30%) when coexisting with LC [4]. CVD is the second leading cause of death in LC patients, following cancer progression [13], and its impact on treatment decisions is well known [14]. The strong bidirectional relationship between LC and CVD is indeed documented by the increasing trend of CVD-related hospitalizations among LC patients, the higher incidence of LC in individuals with pre-existing CVD [15,16] and the shared risk factors, such as smoking and airborne environmental contaminants (AECs) [17]. Moreover, lifestyle-related CV risk factors, such as physical inactivity and unhealthy diet are well-known contributors to LC risk [18,19]. In the UK Biobank cohort (416,588 participants, 1782 LC cases), a diet rich in fruits, vegetables, whole grains, and fiber—but low in red and processed meats—was associated to reduced LC incidence. LC was indeed more frequent in older males with lower socioeconomic status, higher smoking and alcohol use, and poorer education [20]. In addition, active smokers commonly exhibit unhealthy lifestyle habits that adversely affect immuno-cardio-metabolic balance [21,22]. Tailored nutritional strategies and structured exercise interventions not only counteract cachexia and metabolic dysfunction but also preserve cardiac function, improve tolerance to anticancer therapy, and reduce the likelihood of competing CV events [23,24]. This review explores the mechanisms linking diet, exercise, and cardiac metabolism in LC, emphasizing clinical applications for improving therapy response and survivorship.

2. Metabolic and Cardiovascular Alterations in Lung Cancer

2.1. Systemic Inflammation and Cardiometabolic Risk

As Libby pointed out "inflammation is a common contributor to cancer, aging, and cardiovascular diseases" [25]. Major drivers of atherosclerosis are indeed age, low-density lipoprotein (LDL) cholesterol, hypertension, diabetes mellitus, smoking and obesity; many pathogenic processes (e.g. endothelial-mesenchimal transition, smooth muscle cell and macrophage proliferation, dysregulated cell death, defective efferocytosis, leukocyte infiltration, plaque angiogenesis, extracellular matrix remodeling, rupture and erosion) and numerous mediators such as fibroblast growth factor (FGF), matrix metalloproteinase (MMP), platelet derived growth factor (PDGF), transforming growth factor beta (TGF-b) and vascular endothelial growth factor (VEGF) are implicated in both oncogenesis and atherogenesis [26]. The release of adipokines from the adipose tissue (an immunologically active organ) orchestrates metabolic inflammation that links obesity to cardiometabolic risk [26]. The dynamic inflammatory process of atherosclerotic plaque begins with high levels of oxidized LDLs and remnants of triglyceride-rich lipoproteins that gain access to the subendothelial space, and elicit a danger signal that activates the NOD [nucleotide oligomerization domain]-containing, LRR [leucine-rich repeat]-containing, and PYD [pyrin domain]-containing

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protein3 (NLRP3) inflammasome [27,28] in innate immune cells. The activation of inflammasome induces a cascade of inflammatory cytokines such as interleukin 1 (IL-1 and interleukin 6 (IL-6) and upregulates high-sensitivity C-reactive protein (hs-CRP) in the liver eventually leading to atherosclerotic lesions that disrupt the integrity of endothelial cells (ECs) and their atheroprotective role (e.g. secretion of vasoactive substances affecting vasodilatation, platelet function, and monocyte infiltration). The activated ECs enhance the process of tissue inflammation by steering the recruited immune cells towards a proinflammatory phenotype [29,30]. Sustained stimulation of ECs may also be involved in the endothelial-to-mesenchymal transition that leads to fibrosis [31]. Immune cells (monocytes, macrophages, dendritic cells, neutrophils, T cells, and B cells) are deeply committed in the inflammatory scenario of atherosclerosis [32]. In LC, chronic inflammation, mediated by cytokines such as IL-6, tumour necrosis factor-α (TNF-α), and interleukin-1β (IL-1β), drives proteolysis, lipolysis, and mitochondrial dysfunction [33–36]. The key role of mitochondria in atherogenesis has been recently highlighted in a study that has determined the expression levels of mitochondrial DNA (mtDNA) in atherosclerotic lesions revealing a novel mechanism by which mtDNA arranges mitochondrial function–related gene expression in macrophages and promotes atherosclerosis [37]. All these effects of inflammation compromise skeletal and cardiac muscle energetics, promote endothelial dysfunction, and CV morbidity [38–43] while the systemic inflammatory milieu directly contributes to sarcopenia, reduced exercise capacity, and decreased tolerance to anticancer therapy [44]. Moreover, epidemiologic data suggest a close link between social determinants of health (SDOH) and HF [45]; systemic inflammation (defined by hs-CRP) and traditional cardiovascular-kidney-metabolic (CKM) risk (defined by the AHA PREVENT HF risk score) seem to underline the relationship between SDOH and incident HF and this association is likely independent of subclinical atherosclerosis and myocardial injury. The hypothesis is confirmed by a recent study among MESA cohort participants without HF at baseline in which inflammation and traditional CKM risk explained approximately one-third of the associations between SDOH and HF, thus conferring a key role to inflammation in the complex SDOH/HF relationship and emphasizing the need of addressing social/ biological intersections to prevent HF in **vulnerable** populations [46].

2.2. Cancer Cachexia and Sarcopenia

Cancer cachexia, characterized by ongoing loss of skeletal muscle mass and function, is prevalent in up to 70% of patients with advanced lung cancer [47,48]. Mechanisms include increased resting energy expenditure, hormonal dysregulation, mitochondrial impairment, and chronic inflammation [49,50]. Sarcopenia, identified by low muscle strength and low muscle mass [51], is associated with poor response to therapy, increased toxicity, and higher risk of CV events, highlighting the interplay between metabolic derangements and competing CV risk [52–55].

2.3. Cancer Therapy-Induced Cardiac Metabolic Dysfunction

Chemotherapy, targeted therapy, radiotherapy, and immunotherapy exacerbate cardiac metabolic stress via mitochondrial injury, oxidative stress, and impaired substrate utilization [56–67] eliciting the Cancer Treatment-induced Metabolic Syndrome (CTMS), a key driver of CV risk. Immune check point inhibitors (ICIs) and targeted therapies have indeed transformed the therapeutic landscape of NSCLC, but their use has been increasingly burdened by cardiometabolic complications [59,60]. Targeted therapies for LC include Epithelial growth factor receptors (EGFR) inhibitors, anaplastic lymphoma kinase/c-ros oncogene 1 (ALK/ROS1) inhibitors, V-Raf murine sarcoma viral oncogene homolog B/ mitogen-activated extracellular signal-regulated kinase (BRAF/MEK) inhibitors, Rearranged during Transfection (RET) inhibitors, and Vascular endothelial growth factor (VEGF) pathway agents. First-generation EGFR-I such as erlotinib and gefitinib are associated with ischemic events and hypomagnesemia-mediated cardiac dysfunction. Overall cardiac risk is lower in third-generation agents such as Osimertinib and Lazertinib [68,69]. Among ALK/ROS1 inhibitors Lorlatinib is uniquely associated with pronounced hypercholesterolemia, hypertriglyceridemia, weight gain and hypertension. Grade 3-4 hypertriglyceridemia and hypercholesterolemia are

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common at 5-year follow up [70]. Alectinib causes visceral adiposity and sarcopenic obesity with a risk of metabolic syndrome in patients with substantial weight gain [71]. Selpercatinib, a RET inhibitor, is associated with hypertension [59]. As far as VEGF inhibitors are concerned, bevacizumab, ramucirumab and multi-kinase inhibitors (cabozantinib, lenvatinib) are associated with hypertension linked to reduced NO bioavailability, endothelin-1 upregulation and capillary rarefaction [59,72]. Cancer therapy-induced metabolic syndrome is a key modifiable driver of CVD and combines with pre-existing CV risk, making cardiotoxicity a major competing cause of morbidity and mortality. Subclinical left ventricular dysfunction, arrhythmias, and endothelial damage may limit patients' ability to tolerate optimal oncologic therapy.

3. Nutritional Status and Energy Requirements

3.1. Assessment of Nutritional Risk

Early screening for malnutrition and sarcopenia is essential [73,74]. Tools such as Nutritional risk score (screening)-2002 (NRS-2002) [75], Patient-Generated Subjective Global Assessment (PG-SGA) [76], Malnutrition Universal Screening Tool (MUST) [77] and Controlling Nutritional Status (CONUT) score [78], complemented by body composition assessment [dual-energy X-ray absorptiometry (DEXA), computed tomography (CT) and bioimpedance analysis (BIA)] [79,80], allow timely identification of patients at risk. This is critical not only to prevent weight loss but also to reduce cardiovascular stress and improve therapy response [48,53].

3.2. Energy and Protein Requirements

Energy intake should generally be 25–30 kcal/kg/day, with protein at 1.2–1.5 g/kg /day, adjusted for hypercatabolism or sarcopenia [81–84]. Adequate nutrition supports cardiac and skeletal muscle function, immune response, and mitochondrial efficiency.

3.3. Macronutrient Composition and Dietary Patterns

High-quality proteins, complex carbohydrates, and unsaturated fats enhance metabolic flexibility and reduce inflammation [85]. CVD is a common comorbidity in LC patients, therefore fiber-rich food and high-quality carbohydrates associated, in the CARDIA study, with lower left ventricular mass index, improved global longitudinal strain, better left ventricular ejection fraction and improved diastolic function, should be recommended [86], even though the small differences in echocardiographic parameters question the power of the evidence [87]. Diets that emphasize the use of fruits, vegetables, whole grains, healthy fats and lean proteins such as the Dietary Approaches to Stop Hypertension (DASH) and the Mediterranean dietary patterns are indeed broadly considered to be beneficial [88,89]. Mediterranean-style diets improve endothelial function and cardiac efficiency, which is particularly important for patients with elevated cardiovascular risk [90,91]. In a preclinical study with rats, a high fat diet induced cardiac fibrosis and left ventricular dysfunction through an up-regulation of the microRNA expressions of fibrotic markers such as connective tissue growth factor (CTGF), collagen-1α1 (Col1α1), collagen 3α1 (Col3α1), and collagen4α1 (Col4α1) and a concomitant up-regulation of the protein levels of CTGF, collagen-II, and collagen-IV [92], thus confirming the deleterious effect of a high fat diet on cardiac remodeling.

It has been shown that the use of fish oil improves body fat, lean body mass, pain, appetite and quality of life in pancreatic and LC patients with cachexia [93,94]. Metabolomic-based studies have hypothesized that the tryptophan–kynurenine pathway metabolites might explain the beneficial effects of Mediterranean diet (MD) on CVD [95]. The 2026 Dietary Guidance to improve cardiovascular health summarize the features of a heart-healthy diet in 8 items that include the choice of plenty of vegetables and fruits, of whole grain food, of unsaturated fats and minimally processed food, of a minimum intake of added sugars in beverages and foods and of a reduced amount of sodium and avoidance of alcohol consumption [96]

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3.4. Micronutrients

Deficiencies in vitamin D, selenium, zinc, and magnesium impair muscle, immune, and cardiac function [97–101]. Correction of these deficiencies can improve both oncologic and cardiovascular outcomes. Routine antioxidant supplementation during active therapy is discouraged due to potential interference with treatment efficacy. A review from Polanski et al. has documented a beneficial antioxidant effect of vitamin A, vitamin C, Vitamin E, selenium and zinc in the preoperative setting in which immune-nutrition improves perioperative nutritional status and reduces postsurgical complications [102].

3.5. Meal Timing and Chrononutrition

Aligning meal timing with circadian rhythms improves metabolic processes and reduces cardiometabolic risk, thus conferring a relevant role to the concept of chrononutrition. The combination of MD and meal timing/chrononutrition improves the beneficial effects of the diet alone [103]. Time-restricted eating (TRE) improves quality of life and has a beneficial impact on body mass index, adiposity, glucose regulation and inflammation [104]. Chrononutrition restores circadian synchrony, reduces hyperinsulinemia and increases metabolic resilience [105].

3.6. The Role of Trained Immunity

Innate immune cells are key regulators of atherosclerosis, given their capacity of a durable pro-inflammatory phenotype after external or endogenous inflammatory stimuli (e.g. oxidized LDL or high glucose) [106–108]. This long-term enhanced response may be modified by dietary components; preclinical studies in mice have documented an epigenetic reprogramming of myeloid progenitor cells after "intermittent" administration of high-fat diets driven by activation of the NLRP3 inflammasome [109]. According to Lavillegrand et al., the intermittent high-fat diet-induced trained immunity is responsible for the enhanced plaque growth during a second 4-week period of a high fat diet when compared with the effects of an 8 consecutive week high-fat diet [110]. On the contrary, there are clinical data documenting the role of MD in attenuating maladaptive trained immunity and systemic inflammation, primarily through its well-known anti-inflammatory effects, diet-induced modulation of the gut microbiota, and improved immune function [111–113].

4. Exercise

4.1. The Multitargeted Effects of Exercise: From Myokines to Exerkines

Robust data support the importance of exercise in the prevention and treatment of noncommunicable diseases (NCD), such as CVD, obesity, type 2 diabetes mellitus, cognitive decline and many cancers [114,115]. Aerobic training, encompassing moderate-intensity continuous training and high-intensity interval training (HIIT), enhances mitochondrial biogenesis and oxidative capacity in skeletal muscle and improves myocardial energetics, while resistance training drives a different mitochondrial remodeling with a modest effect on mitochondrial biogenesis, oxidative capacity and myocardial energetics. High-intensity aerobic exercise training has indeed a favorable impact on cardiometabolic health (e.g. insulin sensitivity) [116]. A synergistic effect on mitochondrial remodeling can be obtained combining resistance and endurance training [117]. Exercise mitigates systemic inflammation [116], improves endothelial function [118] and strengthens cardiac and skeletal muscle [119,120], thus reducing the risk of therapy-induced cardiotoxicity [121,122]. Exerkines are molecules modified in response to acute and chronic exercise that mediate the systemic adaptations to exercise [123]; they are the drivers of the beneficial effects of exercise, given their important signaling effects through endocrine, paracrine and/or autocrine pathways. While muscle-secreted hormones (myokines such as IL-6) were initially considered the main source of signaling activities, now the panel of cytokines has broadened to include exercise-induced humoral factors from the heart (cardiokines), the liver (hepatokines), the white adipose tissue (WAT adipokines), the

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brown adipose tissue (BAT batokines) and the nervous system (neurokines) [124]. A meta-analysis of 30 randomized controlled trials (RCTs) with 2,484 participants across different cancer types found an improvement in VO2 peak, resting diastolic blood pressure and resting heart rate after exercise-based interventions [123]. Preclinical studies have documented a positive impact of low-intensity exercise on ICI-induced dilated cardiomyopathy preventing left ventricular dilatation and fractional shortening decline through a regulatory effect on dysfunctional metabolism and autophagy [125].

Exercise may also increase immunotherapy efficacy by mobilizing natural killer (NK) cells and CD8+ T cells into circulation thus enhancing IL-15/IL-15Rα signaling, promoting tumour vascular normalization and reprogramming “cold” tumours to “hot” microenvironments [126–128]. A systematic review of 8 studies with 1,172 cancer patients found consistent positive effects of exercise on immune function and treatment outcomes [129].

In LC patients, exercise programs have demonstrated improvements in cardiorespiratory fitness (CRF) expressed by VO2 peak, physical function, fatigue and quality of life, with non-significant impact on measures of cardiac remodeling [86,130,131]. Preoperative exercise specifically reduces postoperative length of stay and complications, while physical activity has long been considered by the National Comprehensive Cancer Network (NCCN) a Category 1 recommendation for cancer-related fatigue [132]. The NCCN Survivorship Guidelines recommend the **"ABCDEs" of cardiovascular wellness** for cancer survivors, which include **A**ssessment of CVD risk, **B**lood pressure management, **C**holesterol/**C**igarette cessation, **D**iet/**D**iabetes management, and **E**xercise/**E**chocardiogram [133] The NCCN NSCLC guidelines specifically recommend LC-specific exercise programs and perioperative pulmonary rehabilitation [134].

4.2. Role of Exercise in Cancer Treatment-Induced Metabolic Syndrome (CTMS)

CTMS comprises central obesity, insulin resistance, dyslipidemia, and hypertension, and is diagnosed when three or more criteria are met (increased waist circumference, low HDL-Cholesterol, elevated triglycerides ≥1.7 mmol/L, BP ≥130/85 mmHg, or fasting glucose ≥5.6 mmol/L) [135]. Exercise counteracts CTMS as documented in a 2025 umbrella review of 80 meta-analyses in which exercise significantly modulates insulin, insulin-like growth factor (IGF-1), insulin-like growth factor-binding protein-1 (IGFBP-1) and C-reactive protein (CRP) [136]. Another meta-analysis of 74 RCTs has confirmed that exercise significantly reduces insulin levels and that high-intensity aerobic exercise (Heart Rate Reserve>85%) has an effective impact on IL-6, adiponectin and IGF-1, whereas longer weekly exercise duration (>280 min/week) improve TNF-α and IL-8 [137]. Favorable results of exercise for breast cancer (BC) survivors have been documented: in a seminal RCT of 100 overweight/obese BC survivors, 16 weeks of combined aerobic and resistance exercise (3 times per week, 65–85% heart rate max) produced a significant improvement in metabolic syndrome z-score (calculated from modified z-scores of the following variables: waist circumference, systolic blood pressure, diastolic blood pressure, HDL cholesterol, triglycerides and glucose using individual participant data, US National Cholesterol Education Program Adult Treatment Panel III criteria, and standard deviations denominator of each factor in the formulas [138]), with improvements in insulin, IGF-1, leptin, and adiponectin that persisted after a 3-month follow-up [139]. Similarly, 8 weeks of HIIT in BC patients receiving anthracyclines significantly improved the metabolic syndrome z-score, HDL Cholesterol, glucose, and triglycerides and the result was independent of body composition changes [140].

LC specific data on metabolic syndrome are limited and the largest part of evidence is extrapolated from broader cancer populations [137,138,140], but we know that platinum-based chemotherapy is a recognized contributor of CTMS and that the high prevalence of smoking, obesity and sedentary behavior in LC patients further amplifies the risk of CTMS [137].

4.3. Clinical Implementation and Safety

Individuals living with cancer and cancer survivors are burdened by physical side effects of cancer and its treatment, functional and cognitive impairment, and psychological and economic

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sequelae [141] with a negative impact on social roles and on quality of life [142]. LC survivors may also have the unpleasant feeling of being stigmatized because of the perception that LC is a self-inflicted disease, and this perception is especially painful for patients who have never smoked [143]. In these patients, rehabilitation and exercise interventions have an extremely favorable role in reducing the negative impact of treatment-related symptoms and in improving quality of life [144]. A meta-analysis of RCT has documented an improved cognitive function induced by mind-body exercise (yoga, tai chi, qigong, etc.) in patients with LC [145]. The Guidelines from the American College of Chest Physicians recommend rehabilitation for a better management of persistent cough in lung cancer survivors [146] while The European Respiratory Society/European Society of Thoracic Surgery guidelines endorse rehabilitation for patients at high risk for adverse surgical outcomes [147]. ASCO Guidelines state that "Oncology providers should recommend aerobic and resistance exercise during active treatment with curative intent to mitigate side effects of cancer treatment" noting that "Exercise interventions during active treatment reduce fatigue; preserve cardiorespiratory fitness, physical functioning, and strength", in some population exercise may even improve quality of life (QoL), and reduce anxiety and depression. All these beneficial effects of exercise during treatment have low risk of adverse events. The Guidelines also recommend preoperative exercise for patients undergoing surgery for lung cancer to reduce length of hospital stay and postoperative complications (86). The improvement in cardiorespiratory fitness, muscle strength, quality of life and fatigue can be obtained also in advanced LC as outlined in a recent systematic review and meta-analysis including nine RCTs [148]. As far as physical activity in patients with advanced cancer is concerned, the NCCN Guidelines (Version 5.2026) recommend *consideration* for specific vulnerable populations such as survivors with bone loss or bone metastases [135]. Unfortunately, cancer rehabilitation is underutilized [86,149,150]. To address this care gap, in 2017, the World Health Organization (WHO) has initiated "Rehabilitation 2030" to increase global access to rehabilitation as an essential component of health care service for individuals with NCD [151], defining oncology a priority area for this program [152].

4.3. Barriers/Solutions (Training at Home, Hybrid Training

A scarce awareness of the positive effects of rehabilitation, especially in the presurgical scenario, plays a relevant role in constraining a full implementation of rehabilitation programs, followed by logistic difficulties, frailties, and digital illiteracy [153–159]. LC patients face unique barriers to exercise, including dyspnea, reduced pulmonary function, anxiety, depression, insomnia, pain and cancer-related fatigue. These barriers are even more challenging in remote and rural areas. Another issue is also gaining momentum: "financial toxicity" driven by the "chronicity" of cancer and facilitated by expensive therapies and continuous medical investigations. Financial toxicity including "intrinsic" factors (e.g. gender, age, ethnicity, and lower income), and "disease-related" factors (e.g., costs of systemic anticancer) has a significant impact not only for healthcare systems but also for the quality of life of cancer patients and their families [160–164]. As highlighted by the ESMO expert consensus statements, socioeconomic determinants play a critical role in this regard [166]. To counteract these barriers there are some innovations for neglected under-represented patients. A paper by Menezes et al. on technology-based cardiac rehabilitation therapy in women (a well-known under-represented population in cardiac rehabilitation, especially in lower-income settings), has stressed the importance of a tailored, technology-based comprehensive cardiac rehabilitation therapy to improve accessibility and has emphasized the critical role of patient preferences [165]. More specifically, in the oncological setting, a prospective study on a real-world population of 180 cancer patients undergoing oncologic treatment has documented the feasibility, the effectiveness (improvements on six-minute walking test, leg press strength, handgrip strength and flexibility tests) and the safety of a tailored exercise program [166], while a single-blind, 3-arm randomized controlled trial with an 8 week-follow up has documented an increased total physical exercise driven by a brief oncologist-delivered recommendation combined with a dedicated guidebook [167]; however, data on long-term impact of exercise are still needed. A recent cost/effectiveness evaluation of a

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multimodal prehabilitation program in 284 high-risk LC surgery has documented clinical effectiveness and economic benefit even in this vulnerable cohort of patients [168]. Technology-based, remote, at home or hybrid programs, along with increased awareness on the beneficial effects of rehabilitation, may pave the way for a widespread use of rehabilitation programs throughout the cancer journey.

4.3. Integration with Nutritional Support

The synergistic combination of exercise and tailored nutritional interventions preserve lean mass, enhances therapy response, and reduces metabolic and cardiac stress. This multimodal approach addresses both oncologic and cardiovascular outcomes [169] and it has been proven successful in LC patients [170].

4.4. Physical Activity and Trained Immunity

Physical activity has a relevant impact on immunity, modulating innate immune function and possibly influencing trained immunity through metabolic and epigenetic mechanisms. While robust evidence has documented the role of regular moderate exercise in enhancing innate immune parameters (e.g. increased activity of NK cells), improving immunosurveillance and reducing systemic inflammation [171–175], the link between physical activity and trained immunity has not been established yet in clinical trials.

5. Integrative Approaches and Clinical Evidence

5.1. Multimodal Interventions

The NCCN and AHA recommend a multidisciplinary team including cardio-oncologists, exercise oncology specialists, registered dietitians (especially specialists in Oncology Nutrition) and behavioral health professionals to address the multifaceted needs of cancer patients [134 170). Evidence indicates that combined nutrition and exercise programs improve functional capacity, reduce systemic inflammation, mitigate cancer therapy-induced metabolic syndrome [176] and enhance therapy response while reducing CV risk. Prehabilitation, defined by Silver and Baima as "*a process of cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identify impairment and provide interventions that promotes physical and psychological health to reduce the incidence and/or the severity of future impairment* "[177] has been proved to be more effective than rehabilitation in a randomized controlled trial of 77 patients with colorectal cancer; at 8 weeks after surgery, a significantly higher proportion of patients in the prehabilitation group were at or above baseline walking capacity (on average 23 m above baseline in their 6-min walking capacity versus a decline of 22 m in the rehabilitation group, $p < 0.05$) [178]. Prehabilitation may also increase cardiovascular reserve during subsequent cancer therapy [179]. A meta-analysis of 11 studies on prehabilitation in LC patients concluded that moderate to intense preoperative exercise has beneficial effects on aerobic capacity, physical fitness, and quality of life in this vulnerable patient population [180]. A more recent study has compared postoperative outcomes in LC patients with respiratory disease, predicted length of stay and neoadjuvant therapy enrolled in a multimodal prehabilitation program versus control (147 matched pairs per group). The control group showed significantly higher rates of overall and major complications whereas patients who underwent multimodal prehabilitation had a significantly lower Comprehensive Complication Index and a reduced intensive care unit admission rate [158].

5.2. The Multifaceted Network of Gut Microbiota

The gut microbiota (GM) is a sophisticated ecosystem and a crucial player in physiological homeostasis and systemic health [181]. GM includes bacteria, fungi, viruses and other organisms,

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and, along with its metabolites, has a pivotal role in many cross-organ networks giving rise to different axes that regulate myocardial health such as the gut-brain-heart, gut-heart-muscle, gut-liver-heart and gut-lung-heart axes [182]. The gut-heart-muscle axis, a complex multidirectional network between the GM, cardiac muscle and skeletal muscle physiology, may lead to HF, muscle decline, and metabolic diseases [183–185]. GM and its metabolites activate fibroblasts, but they also have an immunomodulating and anti-inflammatory role. The intestinal wall harbors gut-associated lymphoid tissue and residual macrophages and stimulates dendritic cells, increasing the secretion of IgA and the production of antibacterial protein [186]. GM and microbial metabolism are involved in the development of cardiometabolic disease [187]; moreover, GM has a bidirectional and dynamic interaction with its host's immune system [188] and with tumor immune microenvironment, influencing the effectiveness of immunotherapy [189] and the immune-related adverse events [190]. A recent study with a small number of patients (19) has found that ICI treatment seems to be more effective in patients with more indigenous bifidobacteria [191]; the prevalence of *Bifidobacterium* in ICI treatment responders compared to non-responders had been previously documented [192,193], thus implying that the antitumor efficacy may be enhanced by *Bifidobacterium.* Another intriguing issue is the role of GM in activating myofibroblast and inducing fibrosis. This effect is intermingled in a complex network of neuromodulation where sympathetic hyperactivity enhances peripheral inflammation and subsequent fibrosis whereas cholinergic stimulation seems to have an anti-inflammatory and anti-fibrotic effect [194].

Nutrition has a significant bidirectional relationship with GM; while diet modulates gut microbial composition and function, gut metabolites obtained by dietary substrates affect glucose and lipid metabolism, vascular tome and immune signaling [195,196]. A high- fiber diet increases the diversity of the gut microbiome, the amount of short-chain fatty acids (SCFA) and of hydrogen sulfide (H2S); SCFA exert anti-inflammatory effects through G-protein-coupled receptors, eventually reducing hypertension and fibrosis [197,198]. MD, for instance, enhances the growth of beneficial bacteria whose metabolites, including SCFA decrease pro-inflammatory microbial species and reduce metabolic dysfunction. All these effects strengthen gut barrier integrity, reducing intestinal permeability and activation of systemic inflammatory pathways [199,200]. On the other end, Western diets may induce a reduction of microbial variety of genus and phyla, leading to dysbiosis, dysfunction of barrier permeability and irregular stimulation of immune cells; all these derangements increase the risk of chronic diseases [201]. Moreover, obesity is frequently associated to a leaky gut that enhances adipose tissue inflammation [27].

Physical exercise, too, positively modulate the GM, increasing anti-inflammatory metabolites such as SCFA, which support cardiac and skeletal muscle metabolism and reduce systemic inflammation [202]. Exercise can significantly modify the genes of most Bacteroides and Clostridium species involved in the synthesis of SCFA. In prediabetic subjects without drug treatment, GM increases its ability to produce SCFA after exercise [203]. Sample analysis of marathon runners showed a post-race increase in SCFA [204]. Given the great impact of GM on inflammation and immunity, it is mandatory to develop an effective strategy in LC patients to maintain a healthy gut microenvironment, particularly before and during ICI treatment, even when antibiotics are used.

5.3. Personalized Lifestyle Interventions

Precision nutrition and exercise programs tailored to metabolic, genetic, and microbiomic profiles maximize efficacy and adherence. CV monitoring should be integrated to identify subclinical cardiotoxicity early. Digital tools can support ongoing assessment and adaptation of interventions.

6. Future Perspectives

As LC survival improves, CVD emerges as a major competing risk. Therapy-induced cardiotoxicity, allostatic load [205–207], metabolic stress, and financial toxicity [165] may limit adherence to lifestyle interventions and reduce their effectiveness. Future research should focus on longitudinal studies evaluating integrated nutrition and exercise programs, incorporating

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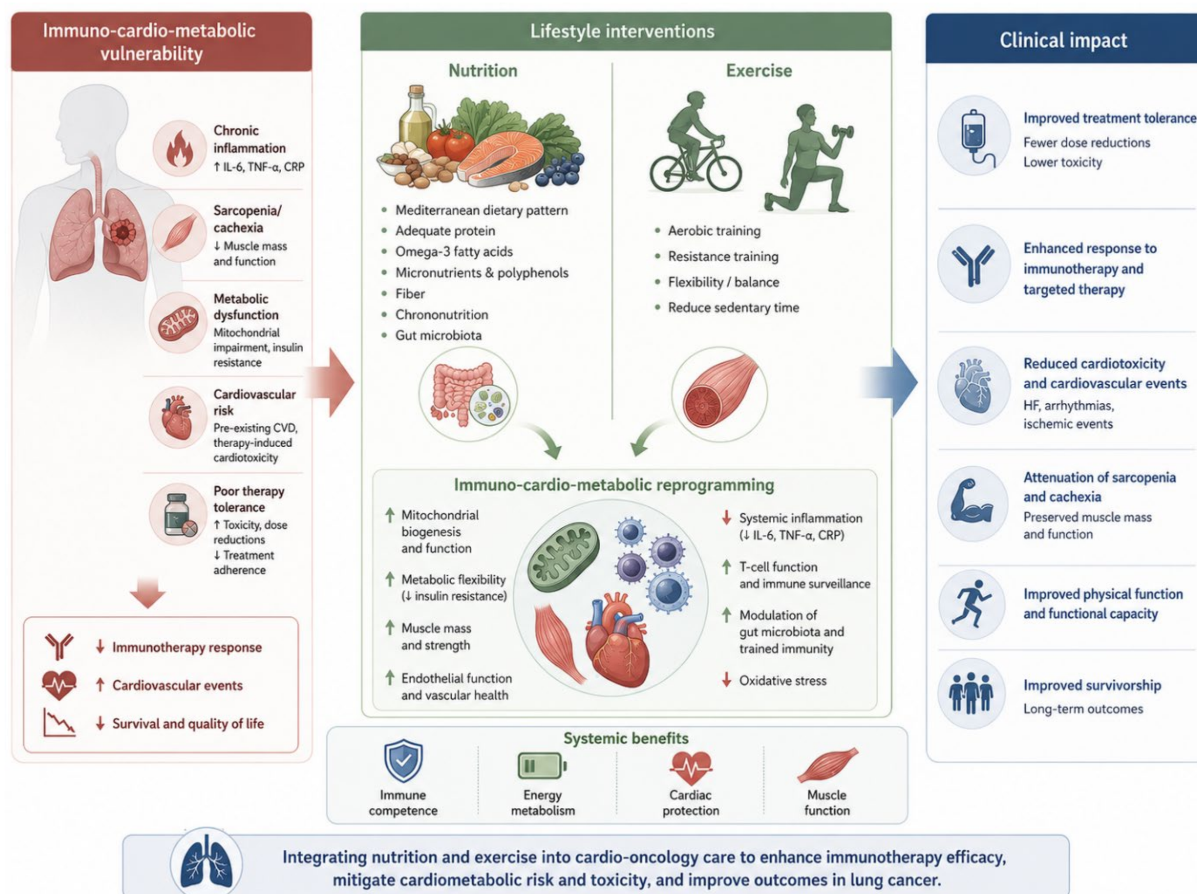
cardiovascular endpoints alongside oncologic outcomes. Microbiota composition may become a useful predictor of response to immunotherapy and may be modulated [208]. Personalized approaches using biomarkers of metabolism, inflammation and cardiac function, combined with digital health monitoring, may optimize effectiveness while mitigating financial and logistical barriers. Emerging modulators of vascular inflammation and remodelling such as Chemerin Receptor 23 (ChemR23) may be therapeutically targeted in atherosclerosis and CVD [209,210]. New technology-based, remote, at home or hybrid programs should increase rehabilitation programs throughout the cancer journey [134], in line with the project of the WHO [152].

7. Conclusions

Malnutrition, sarcopenia, systemic inflammation, cancer therapy-induced metabolic syndrome and elevated CV risk compromise treatment response and survival in LC patients. CVD remains a leading cause of death in cancer survivors, and metabolic syndrome is a key modifiable driver of that risk. GM is gaining momentum for its role in the delicate balance between microbes and the host immune system, given the fact that dysregulation of this equilibrium leads to chronic low-grade inflammation through an uncontrolled immune activation [211]. Non-pharmacological interventions such as tailored nutrition and structured exercise improve metabolic balance, preserve cardiac and skeletal muscle function, enhance therapy tolerance, and reduce the likelihood of CV events competing with oncologic outcomes. Integration of these interventions into standard care, with attention to metabolic, cardiovascular, and socioeconomic factors, represents a critical step toward personalized, cardio-metabolically oriented supportive care, improving both survival and quality of life in LC patients. Counseling on CVD risk factors and the ABCDEs principles of CVD risk assessment where Diet and Exercise play a relevant role must be implemented to reduce the CVD burden on cancer survivorship, as stated by the NCCN Guidelines Version 5.2026 [135].

The **graphical abstract** (Figure 1) summarizes the crucial points where non-pharmacological interventions (diet, exercise) intersect with immune-cardio-metabolic pathways.



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Abbreviations

The following abbreviations are used in this manuscript.

AECs; airborne environmental contaminants
ALK/ROS1: anaplastic lymphoma kinase/c-ros oncogene 1
AHA: American Heart Association
BAT: brown adipose tissue
BC: breast cancer
BIA: bioimpedance analysis
BP Blood Pressure
BRAF/MEK V-Raf murine sarcoma viral oncogene homolog B/ mitogen-activated extracellular signal-regulated kinase
ChemR23 Chemerin Receptor 23
CKM cardiovascular-kidney-metabolic
CONUT Controlling Nutritional Status
CRF cardiorespiratory fitness
CRP C-reactive protein
CT computed tomography
CTGF connective tissue growth factor
CTMS Cancer treatment-induced metabolic syndrome
CV cardiovascular
CVD cardiovascular disease
DASH Dietary Approaches to Stop Hypertension
DEXA dual-energy X-ray absorptiometry
EC endothelial cells
FGF fibroblast growth factor
GM gut microbiota
HDL high density lipoprotein
HF heart failure
H2S hydrogen sulfide
hs-CRP high-sensitivity C-reactive protein
ICIs immune checkpoint inhibitors
IL Interleukin
IGF Insulin-like growth factor
IGFBP Insulin-like growth factor-binding protein
irAEs immune-related adverse events
LC Lung cancer
LDL loe-density lipoprotein
LRR [leucine-rich repeat]-containing
MD Mediterranean diet

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MMP matrix metalloproteinase
mtDNA mitochondrial DNA
MUST Malnutrition Universal Screening Tool
NCCN National Comprehensive Cancer Network
NK natural killer
NLRP3 NOD [nucleotide oligomerization domain]-containing, LRR [leucine-rich repeat]-containing, and PYD [pyrin domain]-containing protein3
NRS-2002 Nutritional risk score (screening)-2002
PDGF platelet derived growth factor
PG-SGA Patient-Generated Subjective Global Assessment
RCTs randomized controlled trials (RCTs)
RET Rearranged during Transfection
SCFA short-chain fatty acids
SDOH social determinants of health
TGF-b transforming growth factor beta
TRE time restricted eating
VEGF vascular endothelial growth factor
WAT white adipose tissue

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