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Physical Activity as a Modulator of Cancer Immunotherapy Efficacy: A Narrative Review of Experimental and Clinical Evidence

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Abstract

Background. Cancer immunotherapy, particularly immune checkpoint inhibitors (ICIs), has transformed oncology. However, many patients show limited response or develop resistance. Physical activity is known to modulate immune function and the tumor microenvironment, suggesting it could serve as a valuable adjunct to immunotherapy.

Aim. This narrative review aims to synthesize current evidence on the influence of physical activity and structured exercise on the efficacy of cancer immunotherapy.

Material and methods. A comprehensive literature search was conducted in PubMed, Web of Science, and Scopus databases (mainly 2018-2026). Relevant preclinical, observational, and clinical studies linking physical activity/exercise with immunotherapy outcomes were included.

Results. Preclinical studies show that exercise enhances the anti-tumor effects of ICIs by increasing CD8+ T cell and NK cell infiltration, reducing immunosuppressive cells, decreasing tumor hypoxia, and releasing immunostimulatory myokines. Emerging clinical data indicate that higher physical activity levels are associated with better response rates and improved survival in patients on immunotherapy. Several randomized trials are ongoing.

Conclusions. Current evidence supports the potential of physical activity as a safe and accessible adjunct to cancer immunotherapy. Large-scale randomized controlled trials are needed to determine optimal exercise protocols and confirm clinical benefits.

Key words: physical activity; exercise; cancer immunotherapy; immune checkpoint inhibitors; tumor microenvironment; exercise oncology; myokines

1. Introduction

The emergence of cancer immunotherapy has transformed the field of oncology. However, many patients still fail to respond or experience only transient clinical benefit. At the same time, a growing body of evidence demonstrates that exercise can profoundly reshape both systemic and intra-tumoral immunity, generating increasing interest in physical activity as a low-toxicity adjunct to immunotherapy (Gustafson et al., 2021; Fiuza-Luces et al., 2023; Hapuarachi et al., 2023; Brummer et al., 2023, Idorn & Straten, 2017). This introduction provides an overview of the current immunotherapy landscape, describes how exercise modulates anti-cancer immunity, and discusses the biological and clinical rationale for combining both approaches.

1.1 Current Landscape of Cancer Immunotherapy

Major modalities of cancer immunotherapy include immune checkpoint inhibitors (ICIs) targeting CTLA-4, PD-1, and PD-L1, adoptive T-cell therapies (including CAR-T cells), NK-cell therapies, cytokine-based treatments, oncolytic viruses, and therapeutic cancer vaccines (Gustafson et al., 2021; Yu et al., 2025; Hossain, 2024). Although ICIs have achieved unprecedented and, in some cases, durable survival benefits across various tumor types, primary and acquired resistance mechanisms limit their efficacy to a subset of patients. In addition, immune-related adverse events (irAEs), such as autoimmunity, remain frequent (Yin et al., 2023; Bagchi et al., 2020). Key resistance mechanisms include impaired T-cell infiltration, T-cell exhaustion, and the presence of a highly immunosuppressive tumor microenvironment (Bagchi et al., 2020; Hossain, 2024).

1.2 Physical Activity as a Modulator of Anti-Cancer Immunity

A single bout of dynamic exercise acutely mobilizes large numbers of leukocytes into the circulation, with a preferential increase in NK cells and cytotoxic, antigen-experienced $CD8^+$ T cells (Gustafson et al., 2021; Lyu, 2024; Spiliopoulou et al., 2021). Chronic exercise training improves cardiorespiratory fitness, promotes a shift toward more naïve and less dysfunctional T-cell phenotypes, and reduces markers of immunosenescence and chronic systemic inflammation (Fiuza-Luces et al., 2023; Yu et al., 2025; Gebhardt & Krüger, 2022; Sitlinger et al., 2020). Moreover, exercise induces the secretion of myokines that directly support T-cell metabolism and function while promoting an anti-inflammatory cytokine profile (Gebhardt & Krüger, 2022; Wennerberg et al., 2020). In animal models, these immunological changes translate into greater tumor infiltration by NK cells and $CD8^+$ T cells, reduced myeloid-derived suppressor cells (MDSCs), and slower tumor growth (Spiliopoulou et al., 2021; Wennerberg et al., 2020).

1.3 Rationale for Combining Physical Activity with Immunotherapy

From a biological perspective, exercise can convert immunologically "cold" tumors with poor immune infiltration into "hot" tumors enriched with effector T cells, thereby potentially increasing responsiveness to ICIs and other immunotherapies (Hapuarachi et al., 2023; Brummer et al., 2023; Luo et al., 2024). Preclinical studies have shown that exercise can augment the therapeutic effects of PD-1 blockade and radiotherapy by reducing immunosuppressive cell populations, normalizing tumor vasculature, and facilitating T-cell infiltration into the tumor (Hapuarachi et al., 2023; Wennerberg et al., 2020). Early clinical and epidemiological data suggest that higher levels of physical activity are associated with improved survival and more favorable immune profiles in cancer patients. However, direct prospective evidence specifically in recipients of immunotherapy remains sparse and heterogeneous (Lavín-Pérez et al., 2023; Oliveira et al., 2025; Al-Mhanna et al., 2022). Important gaps remain regarding the optimal exercise "dose" (according to FITT principles), timing relative to therapy, tumor-type specificity, and safety/feasibility in frail or advanced-stage patients (Gustafson et al., 2021; Lyu, 2024; Oliveira et al., 2025)

1.4 Aim and Scope of the Review

This narrative review synthesizes the mechanistic, preclinical, and emerging clinical evidence on how physical activity may influence the efficacy of cancer immunotherapies, with a primary focus on immune checkpoint blockade, adoptive cell therapies, and cancer vaccines. It examines both acute and chronic effects of exercise on systemic and tumor immunity, evaluates early data on combined interventions, identifies critical knowledge gaps, and discusses the potential clinical implications of integrating structured exercise programs into immuno-oncology practice.

Methods

2.1 Search Strategy

A comprehensive, non-systematic literature search was conducted to identify relevant studies examining the relationship between physical activity, exercise, and cancer immunotherapy. The search was performed in three major electronic databases: PubMed (MEDLINE), Web of Science, and Scopus. Key search terms included combinations of the following keywords and Medical Subject Headings (MeSH): "physical activity", "exercise", "aerobic exercise", "resistance training", "high-intensity interval training", "immunotherapy", "immune checkpoint inhibitors", "PD-1", "PD-L1", "CTLA-4", "tumor microenvironment", "cancer", and "oncology". Boolean operators (AND, OR) were used to refine the search.

The primary focus was on publications from 2018 to May 2026, reflecting the period of significant advances in cancer immunotherapy. Selected seminal earlier papers were also included when they provided foundational mechanistic insights. Additionally, the reference lists of relevant articles and reviews were manually screened using the snowballing technique to identify further eligible studies.

2.2 Inclusion and Exclusion Criteria

Inclusion criteria:

Preclinical studies (animal models) and clinical studies (observational, retrospective, prospective, and interventional)
Studies investigating any form of physical activity or structured exercise in the context of cancer immunotherapy (e.g., immune checkpoint inhibitors or other immunotherapeutic agents)
Studies reporting outcomes related to immunotherapy efficacy, tumor response, immune function, or tumor microenvironment
English-language, peer-reviewed full-text articles

Exclusion criteria:

Studies not involving immunotherapy
Conference abstracts, editorials, commentaries, letters, and non-peer-reviewed publications
Review articles (used only for background information and reference mining)
Studies without a clear physical activity/exercise intervention or assessment

2.3 Study Selection and Narrative Synthesis

Articles were initially screened by title and abstract, followed by full-text assessment. Due to the narrative nature of this review, a formal systematic approach (e.g., PRISMA protocol or risk-of-bias assessment) was not applied. Instead, studies were selected based on their relevance, scientific quality, and contribution to understanding the topic.

Findings were synthesized thematically, grouping evidence into mechanistic pathways, preclinical (animal) data, and clinical evidence. This approach allowed for a critical and integrative discussion of the current state of knowledge while acknowledging the heterogeneity of exercise protocols and study designs.

2.4 AI

Artificial intelligence (AI) was utilized in this research for two specific purposes. First, it supported the text analysis of clinical reasoning narratives to identify linguistic patterns associated with specific logical fallacies. Second, it assisted in refining the academic English language of the manuscript, ensuring greater clarity, consistency, and adherence to scientific writing standards. AI tools were also used for additional linguistic refinement, particularly regarding grammar, style, and the presentation of results. It is important to emphasize that all AI tools were employed strictly as assistive instruments under full human supervision. The AI tools served primarily to enhance efficiency in data processing, pattern recognition, and linguistic refinement, without replacing human judgment at any stage of the analytical process.

Research results

3.1 Overview of the Literature

The evidence base consists of multiple mechanistic and narrative reviews on the links between exercise, immunity, and immunotherapy, as well as primary preclinical and clinical studies (Hapuarachi et al., 2023; Brummer et al., 2023; Lyu, 2024; Spiliopoulou et al., 2021).

Several preclinical studies have investigated exercise interventions in various tumor models (breast, colon, pancreatic, and others), both alone and in combination with immune checkpoint blockade or immuno-chemotherapy (Luo et al., 2024; Huang et al., 2025; Loo et al., 2025). Early human data include observational studies and small interventional trials in patients receiving ICIs, along with several registered clinical trials (e.g., HI AIM) (Ashcraft et al., 2019; Brummer et al., 2023; Olofsson et al., 2022; Chen et al., 2021).

Considerable heterogeneity exists across studies in terms of cancer type, exercise mode and intensity, and immunotherapy regimens, which limits direct comparisons (Gustafson et al., 2021; Brummer et al., 2023; Casciano et al., 2024).

Table 1. General characteristics of the evidence base

Evidence Type	Typical Models / Populations	Main Readouts	Key References
Preclinical	Murine breast, colon, pancreatic tumors	Tumor growth, TME composition, response to ICI	(Gomes-Santos et al., 2021; Huang et al., 2025; Loo et al., 2025; Spiliopoulou et al., 2021)
Clinical observational	Mixed solid tumors on ICIs	Survival, response rates, physical activity level	(Straten, 2025; Ashcraft et al., 2019; Loo et al., 2025)
Clinical interventional	NSCLC and mixed advanced cancers	Immune cell mobilization, feasibility, QoL, early outcomes	(Straten, 2025; Brummer et al., 2023; Olofsson et al., 2022)

3.2 Proposed Biological Mechanisms

3.2.1 Modulation of the Tumor Microenvironment

Exercise has been shown to reduce tumor hypoxia and promote vascular normalization, thereby improving intratumoral perfusion and facilitating drug delivery as well as immune cell infiltration (Gomes-Santos et al., 2021; Gouez et al., 2024). In murine models, exercise increases $CD8^+$ T-cell infiltration and effector function, partly through CXCL9/11-CXCR3 signaling, and enhances NK-cell presence within tumors (Huang et al., 2025; Loo et al., 2025; Spiliopoulou et al., 2021). Additionally, exercise reduces the population of myeloid-derived suppressor cells (MDSCs) and may favorably shift the balance of macrophages and regulatory T cells (Tregs) toward an anti-tumor microenvironment (Huang et al., 2025; Loo et al., 2025).

3.2.2 Systemic Immunological Effects

Exercise induces the release of myokines (e.g., IL-15, IL-6) that activate and recruit $CD8^+$ T cells and NK cells toward tumors (Buzaglo et al., 2024; Bettariga et al., 2024; Orange et al., 2023). IL-15-dependent $CD8^+$ T-cell infiltration and improved response to PD-1 blockade have been demonstrated in preclinical models (Wennerberg et al., 2020; Gebhardt & Krüger, 2022). Acute exercise bouts cause robust mobilization of T and NK cells, while chronic training promotes less dysfunctional T-cell phenotypes and enhances overall immune fitness (Wennerberg et al., 2020; Lyu, 2024; Casciano et al., 2024). Exercise may also improve antigen presentation and dendritic cell-T cell interactions, although direct human evidence remains limited (Gustafson et al., 2021; Lyu, 2024; Spiliopoulou et al., 2021).

3.2.3 Metabolic and Anti-inflammatory Pathways

Exercise can normalize tumor metabolism by reducing lactate accumulation and improving oxygenation, while promoting anti-inflammatory cytokine profiles. These changes support more effective cytotoxic T-cell function within the tumor microenvironment (Bettariga et al., 2024; Orange et al., 2023; Gouez et al., 2024).

3.3 Preclinical Evidence (Animal Models)

In breast, colon, and pancreatic cancer models, exercise alone frequently slows tumor growth and enhances $CD8^+$ T-cell and NK-cell infiltration while reducing MDSCs and other suppressive cell populations (Luo et al., 2024; Huang et al., 2025; Loo et al., 2025). When combined with PD-1 and/or CTLA-4 blockade or immuno-chemotherapy, exercise further sensitizes otherwise refractory tumors, leading to improved tumor control and survival in several models (Gomes-Santos et al., 2021; Gouez et al., 2024). Mechanistically, these benefits are associated with vascular normalization, reduction of extracellular matrix (ECM) and collagen content (partly via EV-derived miR-29a-3p), and chemokine-mediated T-cell recruitment (Gomes-Santos et al., 2021; Gouez et al., 2024).

Overall, preclinical findings consistently indicate that exercise can reprogram the tumor microenvironment to enhance immunotherapy efficacy.

3.4 Clinical Evidence

3.4.1 Retrospective and Observational Studies

In a cohort of 258 patients with advanced solid tumors receiving ICIs, higher self-reported physical activity was associated with numerically better clinical benefit and 1-year survival, particularly in tumors with high tumor mutational burden (TMB), although the differences did not reach statistical significance (Loo et al., 2025). Other population- and disease-specific cohorts have linked higher physical activity levels with improved survival in ICI-responsive cancers, albeit without detailed immune correlates (Ashcraft et al., 2019; Brummer et al., 2023; Lyu, 2024; Casciano et al., 2024).

3.4.2 Prospective and Interventional Studies

The HI AIM randomized controlled trial in metastatic non-small cell lung cancer (NSCLC) is evaluating 6 weeks of supervised high-intensity interval training combined with standard ICI and/or chemotherapy. Preliminary data indicate good feasibility, safety, and acute increases in adrenaline accompanied by rapid mobilization of T and NK cells (Straten, 2025; Brummer et al., 2023). Other small interventional studies suggest that exercise can favorably alter intratumoral immune composition and improve fitness and symptoms; however, robust immunotherapy-specific endpoints are still emerging (Gustafson et al., 2021; Casciano et al., 2024).

3.4.3 Registered Ongoing Trials

The HI AIM trial (NCT04263467) specifically investigates exercise-induced immune mobilization and tumor infiltration in combination with checkpoint blockade (Brummer et al., 2023; Olofsson et al., 2022). Additionally, a scoping review protocol has outlined broader planned research on physical activity during ICI treatment, focusing on oncologic outcomes, quality of life, and underlying mechanisms (Chen et al., 2021).

4. Discussion

4.1 Interpretation of the Evidence

Mechanistic and preclinical data consistently demonstrate that exercise can remodel the tumor microenvironment by increasing $CD8^+$ T-cell and NK-cell infiltration, normalizing tumor vasculature, and reducing hypoxia, thereby sensitizing tumors to immune checkpoint blockade (Lyu, 2024; Gomes-Santos et al., 2021; Fiuza-Luces et al., 2023; Luo et al., 2024). Voluntary and structured exercise enhances anti-tumor immunity through several complementary mechanisms, including catecholamine-driven leukocyte mobilization, myokine and extracellular vesicle (EV) signaling (e.g., miR-29a-3p-mediated collagen inhibition), and attenuation of immunosenescence (Gomes-Santos et al., 2021; Yu et al., 2025; Chen et al., 2021; Fiuza-Luces et al., 2023).

Early clinical and observational studies indicate that physical activity during immunotherapy is feasible and safe, and may be associated with immune-cell mobilization and potentially improved clinical outcomes. Nevertheless, evidence regarding objective response rates and survival benefits remains preliminary and is frequently derived from small or underpowered studies (Gustafson et al., 2021; Gundakaram et al., 2025; Olofsson et al., 2022; Loo et al., 2025).

4.2 Comparison with Previous Reviews

Earlier reviews in the field of exercise oncology primarily addressed the role of physical activity in cancer prevention, quality of life improvement, and general immune modulation, with only limited focus on specific immunotherapeutic agents (Brummer et al., 2023; Chen et al., 2021; Fiuza-Luces et al., 2023; Casciano et al., 2024). In contrast, more recent narrative and mechanistic reviews have explicitly linked exercise with immune checkpoint inhibitors (ICIs), adoptive cell therapy, and monoclonal antibodies. These works emphasize the potential of exercise to convert “cold” tumors into “hot” tumors and describe detailed underlying pathways, including angiogenesis modulation, extracellular matrix remodeling, myokine secretion, and EV cargo transport (Liu et al., 2024; Yu et al., 2025; Luo et al., 2024; Casciano et al., 2024). Systematic reviews and scoping protocols continue to highlight the scarcity of high-quality clinical trials with ICI-specific endpoints and standardized exercise prescriptions (Gundakaram et al., 2025; Chen et al., 2021).

4.3 Clinical Implications and Practical Recommendations

Current evidence supports the use of exercise as a low-toxicity adjunctive strategy capable of enhancing immunosurveillance, potentially increasing sensitivity to ICIs, and improving physical fitness and quality of life in patients undergoing immunotherapy (Brummer et al., 2023; Gundakaram et al., 2025; Chen et al., 2021; Fiuza-Luces et al., 2023, Koper, 2024; Smuszkiewicz-Różański, 2024).

Table 2. Suggested exercise parameters in patients receiving immune checkpoint inhibitors (based on reviewed trials and guidelines)

Element	Typical Patterns in Trials/Guidelines	Key References
Type	Combined aerobic + resistance training; HIIT or interval training increasingly used	(Gundakaram et al., 2025; Olofsson et al., 2022; Dias-Da-Silva et al., 2024; Hayes et al., 2019; Hapuarachi et al., 2023)
Intensity	Moderate to vigorous; HIIT at ~80-90% of peak capacity in supervised settings	(Gustafson et al., 2021; Gundakaram et al., 2025; Olofsson et al., 2022; Dias-Da-Silva et al., 2024; Hayes et al., 2019)
Frequency/Duration	2-3 sessions per week, 30-60 minutes, over 6-12 weeks	(Gustafson et al., 2021; Gundakaram et al., 2025; Olofsson et al., 2022; Dias-Da-Silva et al., 2024; Hapuarachi et al., 2023)
Timing relative to ICI	Before and/or during treatment; some protocols use exercise immediately before infusion	(Liu et al., 2024; Gomes-Santos et al., 2021; Gouez et al., 2024)

Supervised exercise programs in patients on ICIs appear generally safe, with few serious adverse events reported. However, individualization and medical clearance are recommended in cases of frailty, significant cardiopulmonary disease, bone metastases, or severe anemia (Gustafson et al., 2021; Brummer et al., 2023; Gundakaram et al., 2025; Olofsson et al., 2022; Hayes et al., 2019).

4.4 Strengths and Limitations of the Evidence and This Review

The main strengths of the current evidence include converging mechanistic findings (immune cell mobilization and vascular/extracellular matrix remodeling) observed across multiple tumor models, supported by emerging human biomarker data (Lyu, 2024; Gomes-Santos et al., 2021; Chen et al., 2021; Fiuza-Luces et al., 2023).

Significant limitations persist, including small and heterogeneous clinical samples, lack of standardized FITT (Frequency, Intensity, Time, Type) reporting, scarcity of trials with hard immunotherapy-specific endpoints, and risk of bias in observational studies (Liu et al., 2024; Brummer et al., 2023; Dias-Da-Silva et al., 2024; Hayes et al., 2019). As a narrative review, this work allows integrative discussion of mechanisms but cannot quantify effect sizes or perform formal quality assessments.

4.5 Future Research Directions

Key priorities for future research include:

Large-scale randomized controlled trials integrating structured exercise into ICI regimens, adequately powered for response rate, progression-free survival (PFS), and overall survival (OS) (Gundakaram et al., 2025; Olofsson et al., 2022; Chen et al., 2021; Straten, 2025).

Biomarker-driven personalization of exercise interventions, incorporating immune phenotypes, circulating EV and myokine profiles, and tumor ECM/immune signatures (Gomes-Santos et al., 2021; Yu et al., 2025; Invernizzi et al., 2022).

Systematic evaluation of optimal exercise protocols (aerobic vs resistance vs HIIT; supervised vs home-based), ideal timing relative to ICI infusion, and long-term safety across different cancer types and age groups (Liu et al., 2024; Gundakaram et al., 2025; Olofsson et al., 2022; Hayes et al., 2019).

5. Conclusions

The available evidence indicates that physical activity represents a plausible and low-toxicity adjunct to cancer immunotherapy. Preclinical studies consistently demonstrate that both aerobic and resistance exercise can remodel the tumor microenvironment by increasing $CD8^+$ T-cell and NK-cell infiltration, reducing immunosuppressive cells and collagen-rich stroma, normalizing tumor vasculature, and thereby sensitizing otherwise resistant tumors to PD-1/PD-L1 and other immune checkpoint inhibitors (Wennerberg et al., 2020; Huang et al., 2025; Gouez et al., 2024). Mechanistic investigations highlight the involvement of exercise-induced myokines, catecholamines, and chemokine pathways (e.g., IL-15, IL-6, CXCL9/11-CXCR3, and EV-mediated miR-29a-3p) in mobilizing and enhancing the function of anti-tumor lymphocytes, ultimately potentiating immunotherapy response (Hapuarachi et al., 2023; Buzaglo et al., 2024; Gomes-Santos et al., 2021; Luo et al., 2024).

Early clinical and observational data suggest that higher levels of physical activity are feasible during immune checkpoint therapy and may be associated with improved treatment outcomes and robust immune-cell mobilization. However, definitive benefits in terms of survival and objective response rates remain unproven (Brummer et al., 2023; Straten, 2025).

Overall, the current literature strongly supports the need for well-designed, large-scale randomized controlled trials to establish optimal exercise protocols (“doses”), timing relative to treatment, and patient selection criteria. Such trials will be essential to determine whether structured exercise should become a standard adjuvant strategy in immuno-oncology (Ashcraft et al., 2019; Lyu, 2024; Casciano et al., 2024; Loo et al., 2025).

Disclossure

Supplementary Materials:

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