Institute of Cardiovascular Research and Sports Medicine

German Sport University Cologne

Head of Institute: Prof. Dr. Wilhelm Bloch

The role of physical activity and structured exercise for physical fitness and immune function in men on androgen deprivation therapy for prostate cancer

Doctoral thesis accepted for the degree

Doktorin der Naturwissenschaft

by

Lisa Umlauff

from

Kirchheimbolanden

Cologne 2024

First reviewer:	Prof. Dr. Moritz Schumann
Second reviewer:	Prof. Dr. Jürgen Steinacker
Chair of the doctoral committee:	Prof. Dr. Mario Thevis
Thesis defended on:	12.08.2024

Affidavits following §7 section 2 No. 9 of the doctoral regulations from the German Sport University Cologne, March 30th 2020:

Hereby I declare:

The work presented in this thesis is the original work of the author except where acknowledged in the text. This material has not been submitted either in whole or in part for a degree at this or any other institution. Those parts or single sentences, which have been taken verbatim from other sources, are identified as citations.

I further declare that I complied with the actual “guidelines of qualified scientific work” of the German Sport University Cologne.

Köln, 02.05.2024

Summary

Metastatic prostate cancer is commonly treated with androgen deprivation therapy (ADT). While ADT effectively slows disease progression, it is associated with severe adverse effects, including musculoskeletal, cardiovascular and metabolic impairments, that compromise the physical fitness and function. The physical decline may be aggravated in advanced disease by the use of secondary treatments, such as androgen receptor inhibitors (ARI). Physical activity has been identified as a modifiable lifestyle factor, with benefits for physical health, prostate cancer progression and survival. These effects may be partially modulated by an anti-inflammatory immune response that is stimulated as a result of muscle activation. Structured exercise in particular is thought to promote favourable health outcomes, including fitness improvements and reductions in systemic inflammation, but studies have reported conflicting results of exercise interventions during ADT. Overall, the physiological adaptations and, particularly, the immune response to physical activity and exercise in the context of ADT are not well understood. The aim of this thesis was therefore to analyse associations of habitual physical activity with physical fitness and immune function in men treated with ADT for prostate cancer, and to investigate changes in physical fitness and immune function following a chronic, structured exercise intervention.

Two cross-sectional studies were performed using baseline data from participants of a multi-centre, randomised, controlled trial for men with advanced metastatic prostate cancer treated with ADT. Study 1 examined levels of self-reported physical activity and adherence to physical activity guidelines, as well as the association between self-reported physical activity with fitness outcomes, in a large multi-centre sample (140 participants). Study 2 expanded on this analysis by investigating levels of accelerometer-derived physical activity, determining their agreement with self-reported estimates, and analysing the association of accelerometer-derived physical activity with physical fitness and immune parameters in a German subsample (27 participants). Both studies included a between-group analysis of physical activity and fitness according to ARI use. Additionally, a longitudinal study (Study 3) of data collected at the baseline and 6-month testing visits of the trial was performed, which analysed changes in physical fitness and immune parameters in participants completing a structured exercise programme of aerobic and resistance exercise compared to the control arm (19 participants; 8 intervention, 11 control).

Habitual physical activity levels were below the recommended level according to self-reported estimates, with only 29% of participants adhering to the guidelines for aerobic physical activity, whereas accelerometer-derived physical activity estimates demonstrated substantially higher physical activity levels. The agreement between the two measurement methods was poor. Higher levels of self-reported moderate-to-vigorous physical activity (MVPA) were significantly associated with a higher maximal oxygen consumption (VO_2peak)

and a faster 400 m walk time in non-users but not in ARI users. Accelerometer-derived data confirmed the association between MVPA and walk time, but showed that VO_2peak was positively associated with light activity and not MVPA. There were no associations between strength outcomes for self-reported MVPA, although higher accelerometer-derived light activity and MVPA were linked to increased maximal strength of the lower body. Among immune parameters, higher light physical activity was associated with decreased monocyte and increased regulatory T cell proportions, while decreased sleep time was associated with increased neutrophil proportions.

After 6 months of the structured exercise intervention, maximal lower body strength increased in the intervention arm, while handgrip strength increased in both arms, with a larger effect in the intervention arm. Aerobic fitness outcomes and blood levels of immune parameters remained mostly unaltered except for an increase in lymphocyte proportions, with no differences observed between the intervention and control arm. Regarding the effects of exercise dose, higher levels of completed aerobic exercise were associated with lower natural killer cell counts in the intervention arm. Overall, the uptake of the exercise intervention varied substantially, with the highest adherence noted for resistance exercise.

The results of this thesis indicate that higher habitual physical activity and reduced sedentary behaviour are associated with improved physical fitness in men with advanced prostate cancer. Furthermore, the findings suggest a potential decrease in systemic inflammation, as demonstrated by reduced blood levels of tumour-promoting monocytes, in more active men. Treatment with ARIs may attenuate the benefits of physical activity, although the findings regarding their effects on physical activity levels and fitness outcomes are inconclusive. Because older cancer survivors spend a large share of their time performing habitual, low intensity activities that are disproportionately affected by recall bias, self-reported data may provide biased estimates and objective measurement methods may be more suited to capture this activity. Nonetheless, baseline physical activity levels, especially resistance exercise participation, were concerningly low in some participants. Interestingly, after 6 months of the structured exercise intervention, the highest adherence was recorded for the resistance exercise prescription. This indicates that men with advanced prostate cancer, despite compromised bone and muscle health, are able to perform intense resistance exercise, which is in turn associated with benefits for neuromuscular fitness. Finally, the chronic exercise programme elicited minimal changes in circulating immune parameters, and their significance for the anti-tumour immune response in prostate cancer remains to be investigated.

Zusammenfassung

Die häufigste Therapie für das metastasierte Prostatakarzinom ist die Androgendeprivations-therapie (ADT). Die ADT verlangsamt zwar wirksam den Krankheitsprogress, führt aber häufig zu unerwünschten Nebenwirkungen, wie Beeinträchtigungen von Muskeln, Knochen, Herz-Kreislauf-System und Stoffwechsel, welche die körperliche Fitness beeinträchtigen. Die Abnahme der allgemeinen Leistungsfähigkeit kann durch den Einsatz von Androgenrezeptor-Inhibitoren (ARI) verschlimmert werden. Es ist bekannt, dass körperliche Aktivität diesen negativen Effekten entgegenwirken, sowie Vorteile für die allgemeine Gesundheit und das Krebswachstum bewirken kann. Mögliche Grundlage für diese Effekte von körperlicher Aktivität sind entzündungshemmende Immunreaktionen, welche durch Muskelaktivierung stimuliert werden. Besonders strukturiertes körperliches Training ist mit positiven gesundheitlichen Effekten, wie verbesserter körperlicher Fitness und niedrigeren systemischen Entzündungswerten, assoziiert, jedoch könnten diese durch die systemische Wirkung der ADT beeinflusst werden. Es bleibt zu untersuchen, wie sich die durch körperliche Aktivität und strukturiertes Training ausgelösten physiologischen Anpassungsprozesse während einer ADT verhalten. Ziel dieser Arbeit war es daher, den Zusammenhang von alltäglicher körperlicher Aktivität mit körperlicher Fitness und Immunfunktion in Prostatakrebspatienten unter ADT zu analysieren, sowie Veränderungen von Fitness und Immunfunktion durch eine chronische, strukturierte Trainingsintervention zu untersuchen.

Basierend auf Daten der Eingangstestung einer multizentrischen, randomisierten, kontrollierten Studie für Männer mit metastasiertem Prostatakrebs unter ADT wurden zwei Querschnittsanalysen durchgeführt. Studie 1 untersuchte in einer multizentrischen Stichprobe (140 Teilnehmer) das Ausmaß subjektiver körperlicher Aktivität und die Einhaltung allgemeiner Aktivitätsvorgaben, sowie den Zusammenhang zwischen subjektiver körperlicher Aktivität und Fitness. In einer Teilstichprobe (27 Teilnehmer) wurde diese Analyse am deutschen Studienstandort in Studie 2 um die Untersuchung des Ausmaßes objektiver körperlicher Aktivität erweitert, sowie die Übereinstimmung mit subjektiv erhobener Aktivität bestimmt. Außerdem wurde der Zusammenhang von objektiver körperlicher Aktivität mit Fitness und Immunparametern analysiert, und in beiden Studien Vergleiche zwischen Teilnehmern mit und ohne ARI in Bezug auf körperliche Aktivität und Fitness durchgeführt. Zusätzlich wurde eine Längsschnittstudie (Studie 3) durchgeführt, die Veränderungen von körperlicher Fitness und Immunparametern in Teilnehmern einer 6-monatigen Trainingsintervention im Vergleich zur Kontrollgruppe untersuchte (19 Teilnehmer; 8 Intervention, 11 Kontrolle).

Die subjektive körperliche Aktivität der Stichprobe lag unterhalb der Aktivitätsvorgaben, die nur 29% der Teilnehmer einhielten, wohingegen die objektive Aktivität wesentlich höher war.

Die Übereinstimmung beider Messmethoden war gering. Es bestand ein positiver Zusammenhang zwischen subjektiver moderat-bis-anstrengender Aktivität (MVPA) und maximaler Sauerstoffaufnahme (VO_2peak), sowie einer schnelleren Gehzeit bei Männern ohne ARI, nicht aber bei ARI-Nutzern. Die Ergebnisse der objektiven Aktivitätserfassung bestätigten den Zusammenhang zwischen körperlicher Aktivität und Gehzeit, während hingegen VO_2peak nur mit leichter Aktivität assoziiert war. Bei der Maximalkraft bestand kein Zusammenhang mit subjektiver Aktivität, während objektiv gemessene leichte Aktivität und MVPA mit einer höheren Unterkörperkraft zusammenhingen. Die Immunanalyse zeigte, dass eine höhere leichte Aktivität mit einer geringeren Monozytenzahl, sowie mehr regulatorischen T-Zellen einhergingen, während eine geringere Schlafdauer mit mehr Neutrophilen zusammenhing.

Nach sechs Monaten strukturiertem Training zeigte die Interventionsgruppe eine Zunahme der Maximalkraft des Unterkörpers, wohingegen die Handgriffkraft in beiden Gruppen anstieg, allerdings mit einem größeren Effekt in der Interventionsgruppe. Keine chronischen Veränderungen wurden bei der aeroben Fitness und den Immunparametern beobachtet, mit Ausnahme eines Anstiegs des Lymphozytenanteils, welcher allerdings keine Unterschiede zwischen den Gruppen zeigte. Was den Effekt der Trainingsdosis betrifft, so war ein höheres Maß an aerobem Training mit einer niedrigeren Anzahl natürlicher Killerzellen verbunden. Insgesamt schwankte die Adhärenz der Trainingsintervention erheblich, wobei die höchste Beteiligung beim Krafttraining festgestellt wurde.

Die Ergebnisse zeigen, dass höhere körperliche Aktivität mit einer verbesserten Fitness, sowie möglichen Reduktionen in ausgewählten entzündungsfördernden Immunzellen bei Männern mit fortgeschrittenem Prostatakrebs verbunden ist. Der Einsatz von ARIs könnte die vorteilhaften Effekte von körperlicher Aktivität abschwächen, obwohl die Ergebnisse hinsichtlich ARI-abhängiger Unterschiede in Aktivitäts- und Fitnesslevel nicht eindeutig sind. Da ältere Menschen mit Krebs viel Zeit mit niedrig-intensiven Aktivitäten verbringen, können subjektive, auf Erinnerungen basierende Messmethoden die Ergebnisse verzerren, weswegen objektive Messmethoden von Vorteil sein könnten. Unabhängig von der Messmethode war das Ausgangsniveau der körperlichen Aktivität, insbesondere die Prävalenz von Krafttraining, bei einigen Teilnehmern niedrig. Im Gegensatz dazu wurde bei der strukturierten Trainingsintervention die höchste Adhärenz beim Krafttraining beobachtet. Daraus kann geschlossen werden, dass Männer mit fortgeschrittenem Prostatakrebs trotz reduzierter Knochen- und Muskelgesundheit ein intensives Krafttrainingsprogramm durchführen können, was wiederum mit Vorteilen für die neuromuskuläre Fitness verbunden ist. In Bezug auf die Immunfunktion zeigte das chronische Trainingsprogramm nur wenige Veränderungen der zirkulierenden Immunparameter, deren Bedeutung für die Immunabwehr gegen Prostatakrebs weiter untersucht werden sollte.

Table of contents

Abbreviations

1RM	one-repetition maximum
ADT	androgen deprivation therapy
ANOVA	analysis of variance
ASR	age-standardised rate
AR	androgen receptor
ARI	androgen receptor inhibitor
BMD	bone mineral density
BMI	body mass index
CD	cluster of differentiation
CI	confidence interval
CPET	cardiopulmonary exercise test
CRP	C-reactive protein
CRPC	castrate-resistant prostate cancer
CT	computed tomography
CVD	cardiovascular disease
CYP17	cytochrome P450 17-alpha hydroxysteroid dehydrogenase
DHT	5α-dihydrotestosterone
DNA	deoxyribonucleic acid
ECG	echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	ethylenediaminetetraacetic acid
ENMO	Euclidean norm minus one
FSC	forward scatter
FSH	follicle-stimulating hormone
GnRH	gonadotropin-releasing hormone
GSLTPAQ	Godin-Shephard Leisure-Time Physical Activity Questionnaire
HDI	Human Development Index
HIIT	high-intensity interval training
HPG	hypothalamic-pituitary-gonadal
HR	heart rate
HRmax	maximal heart rate
HSPC	hormone-sensitive prostate cancer
IFN-γ	interferon-γ
IL	interleukin
IL-1RA	interleukin-1 receptor antagonist
IQR	interquartile range
LH	luteinising hormone
LSI	leisure-score index

mCRPC	metastatic castrate-resistant prostate cancer
MET	metabolic equivalent of task
MHC	major histocompatibility complex
mHSPC	metastatic hormone-sensitive prostate cancer
MICT	moderate-intensity continuous training
min	minute
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MVPA	moderate-to-vigorous physical activity
NK cell	natural killer cell
NLR	neutrophil-to-lymphocyte ratio
PARP	poly(adenosine diphosphate-ribose) polymerase
PBMC	peripheral blood mononuclear cell
PBS	phosphate-buffered saline
PD-L1	programmed death-ligand 1
PET/CT	positron emission tomography/computed tomography
PLR	platelet-to-lymphocyte ratio
PLS	partial least squares
PSA	prostate-specific antigen
PSMA	prostate-specific membrane antigen
Q	quartile
RCT	randomised controlled trial
RPE	rating of perceived exertion
SD	standard deviation
SHBG	sex hormone binding globulin
SII	systemic immune-inflammation index
SSC	side scatter
Tc cell	cytotoxic T cell
TCR	T-cell receptor
TGF- β	transforming growth factor β
Th cell	T helper cell
TNF-α	tumour necrosis factor α
Treg cell	regulatory T cell
VIP	variable importance for projection
VO_2peak	peak oxygen consumption
Wmax	maximal workload

1. Introduction

The prostate is the main gland of the male reproductive system and as such, is involved in key reproductive functions like ejaculation control and sperm motility [1]. Central to prostate physiology is the androgen receptor (AR), which acts as a ligand-activated nuclear transcription factor and promotes genes that are necessary for normal prostate function and homeostasis [2]. The main ligand of the AR in prostate cells is the testosterone derivate 5α-dihydrotestosterone, which regulates prostate cell metabolism and plays a crucial role in male sexual development and function [3]. Mutations of the AR gene lead to aberrant AR signalling and overactivation of anabolic pathways, resulting in uncontrolled prostate cell growth and the development of prostate cancer [4]. Prostate cancer is the second most common malignancy in men globally and accounts for 1.4 million new cases each year [5].

The immune system plays an ambivalent role in cancer, because it employs cytotoxic effector mechanisms that antagonise tumour growth but at the same time is involved in tumour formation and progression [6]. Inflammation in the prostate can support carcinogenesis by inducing genomic damage through increased oxidative stress, stimulating rapid cell replication and promoting angiogenesis [7]. Tumours carry antigens that are recognised by the immune system as foreign and stimulate immune cells to eliminate the tumour cells, a role that is mostly executed by natural killer cells and cytotoxic T lymphocytes [6,8]. In turn, tumour cells exploit various mechanisms to suppress anti-tumour immune responses and enable immune escape, including aberrant regulation of immune cell differentiation, activation and effector function [9,10].

Although screening efforts and novel treatments have improved prostate cancer survival rates, men diagnosed with the disease are at risk of physical health declines induced by the cancer and its treatments [11-13]. Due to the androgen-dependency of prostate cancer, the mainstay treatment is androgen deprivation therapy (ADT), which blocks the synthesis or action of androgens and deprives the tumour of its main anabolic stimulus to inhibit tumour growth [14]. While these drugs significantly delay prostate cancer progression and improve overall survival, the continuous and long-term withdrawal of androgens is associated with pronounced adverse effects [15]. Because androgens regulate multiple physiological processes, men on ADT commonly experience debilitating symptoms such as muscle wasting, reduced muscle strength, increased body fat mass and fatigue [16,17]. Furthermore, ADT and secondary AR inhibitors (ARIs) for prostate cancer have been associated with hypertension, increased blood levels of glucose and lipids, poor bone health and a higher risk of cardiovascular events [18-20]. Altogether, these ADT-induced adverse effects exacerbate the decline of physical health and fitness that is typically observed in cancer.

Physical activity has been identified as a modifiable lifestyle factor that can delay disease progression, improve survival and overall health, and reduce treatment-related adverse effects in various cancer populations [21,22]. As a subset of physical activity, structured exercise in particular has been recognised as a potent stimulus that promotes favourable health outcomes, such as improvements in neuromuscular and cardiorespiratory fitness, which could counteract the adverse effects of ADT [23,24]. Therefore, the American Cancer Society encourages cancer survivors to engage in physical activity and regularly perform aerobic and resistance exercise [25]. Despite this, studies that have assessed physical activity levels and exercise participation have reported concerning results, with the majority of prostate cancer survivors demonstrating insufficient levels of physical activity [26-28]. In light of the adverse effects on physical fitness induced by androgen withdrawal, physical inactivity may be exacerbated in men with advanced prostate cancer who receive long-term ADT combined with ARIs, however, this has not been investigated yet.

The anti-tumour effects of physical activity are thought to result from increased immunosurveillance and enhanced immune function [29]. Exercise is a potent stimulus of immune responses because it induces the release of muscle-derived signalling molecules that activate immune cells and mediate exercise adaptations, such as tissue repair [30]. Repeated bouts of exercise reduce systemic inflammation while increasing immune cell regeneration, activation and migration [31]. Importantly, exercise stimulates various immune cell populations to infiltrate tumours and enhances anti-tumour cytotoxicity. Previous studies have demonstrated enhanced anti-tumour immunity following exercise in early stage prostate cancer [32], but changes in the immune function of men with advanced disease have not been investigated. Furthermore, in this highly sedentary population that is confronted with exercise-limiting factors, such as advanced age and bone metastases, increased habitual physical activity may present a viable stimulus that enhances immune function, while also promoting physical fitness improvements.

The aim of this thesis was therefore to analyse how the physical fitness and immune function of men treated with ADT for prostate cancer relates to habitual physical activity, as well as to investigate changes in physical fitness and immune function following a structured exercise intervention. This incorporated an assessment of the adherence to physical activity guidelines and the prescribed exercise intervention. Furthermore, a subgroup analysis of ARI use was performed to investigate its effects on physical activity and fitness. For the purpose of this thesis, data from participants of a multi-centre, randomised, controlled trial for men with advanced metastatic prostate cancer collected at baseline and at the 6-month testing visit was analysed.

2. Review of the literature

2.1. Prostate cancer biology and epidemiology

2.1.1. Basics of prostate function and biology

Prostate anatomy

The prostate is an accessory gland, which is part of the male reproductive system [1]. It is a round-shaped organ located in the pelvis directly below the bladder and partly surrounds the urethra. The size of the prostate typically increases as men age [33]. The prostate gland itself is surrounded by a collagenous capsule, a fascia and a neurovascular bundle [34]. Anatomically, the prostate is divided into five distinct zones and regions [4] (Figure 1). The peripheral zone makes up roughly 70% of prostate tissue. Most of the glandular structures are located within this zone, which extends to the lateral, posterior and apical boundaries of the organ [1]. The central zone surrounds the ejaculatory ducts that come from the seminal vesicles, and extends to the base of the bladder. The periurethral gland region and the transition zone are located adjacent to the central zone and partly surround the urethra. The fibromuscular region forms the anterior boundary of the prostate and consists of non-glandular tissue.

Prostate function

The prostate is composed of two distinct cellular structures: a glandular epithelium and a fibromuscular stroma [1]. The prostate epithelium is embedded in the stroma and its dominant cell types are secretory luminal cells, which produce and release a fluid that is part of the semen. In addition, the epithelium includes basal and neuroendocrine cells, which line the basement membrane between the layer of secretory cells and the stroma. Basal cells exert a supportive function for the secretory luminal cells [35], while the rarer neuroendocrine cells act as intraepithelial regulators by releasing a variety of hormones [36]. The stroma provides a microenvironment that allows for and promotes the ideal function of the prostate epithelium. It contains predominantly smooth muscle myocytes, which can contract spontaneously to prevent fluid stagnation, as well as fibroblasts, which support the prostatic ducts that enable fluid transport [4].

Prostatic fluid is drained into the urethra during ejaculation and contains several factors that are involved in ejaculation control, semen liquefaction and sperm motility [1]. Among these factors is the prostate-specific antigen (PSA), a serine protease belonging to the kallikrein family. PSA, together with other kallikreins, is activated after ejaculation and promotes semen liquefaction. This process is necessary to release the sperm so that it can travel upwards in

the female uterus towards the Fallopian tube, where fertilisation occurs. Because the prostatic fluid contains a mixture of metabolites, which trigger mechanisms that enable sperm to reach and fertilise the egg, the prostate plays a major role in male fertility.

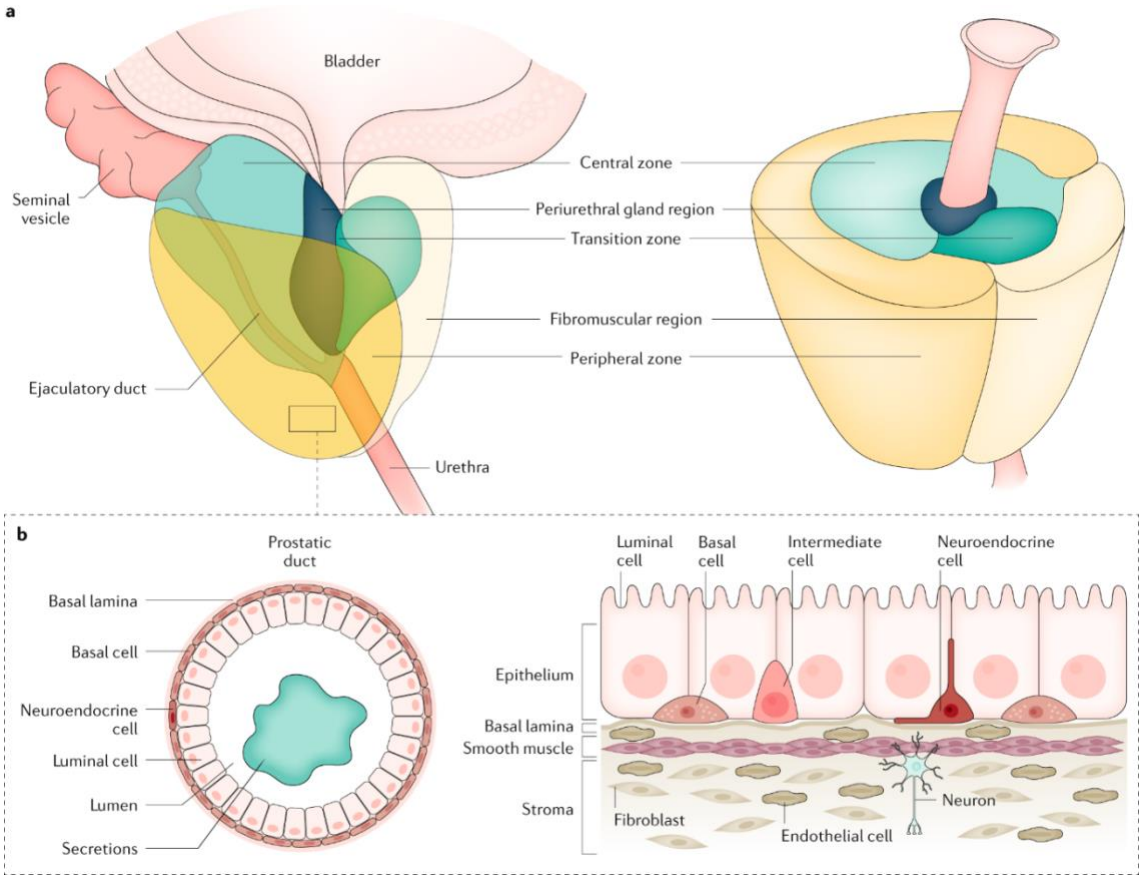


Figure 1. Anatomy and histological structure of the human prostate. (a) The prostate is located beneath the bladder and surrounds the urethra and ejaculatory ducts. Anatomically, the prostate can be divided into five distinct regions: the central zone, the periurethral gland region, the transition zone, the fibromuscular region and the peripheral zone. **(b)** Each region consists of ducts, which are composed of a single layer of epithelium surrounded by a basal lamina, embedded in a fibromuscular stroma. The prostate epithelium contains several cell types, which each play an important role for prostate function. Luminal cells produce the prostatic fluid and are supported in this by basal cells, while neuroendocrine cells have a signalling function. Intermediate cells present a phenotype intermediate between luminal and basal cells. Reproduced with permission from Rebello et al. (2021) [4].

Androgen-dependency of the prostate

The signalling processes within the prostate that ensure ejaculation control and release of the prostatic fluid are regulated by androgens [37]. Androgens are a group of sex steroid hormones that are primarily responsible for developing and regulating the reproductive organs and maintaining reproductive capacity [38]. The dominant androgens involved in male sexual development and reproductive function are testosterone and 5α-dihydrotestosterone (DHT) [3,39]. Testosterone is the most abundant androgen in adult men. Physiological serum

testosterone concentrations range from 10 to 30 nmol·L^{-1} in a 30-year old man and decline by 1 to 2% per year with ageing [3].

Testosterone can be converted via an enzymatic reaction to DHT, which is a more potent activator of the AR [39]. Androgen synthesis in men occurs primarily in the Leydig cells of the testes and is regulated by a complex signalling pathway known as the hypothalamic-pituitary-gonadal (HPG) axis [40] (Figure 2). The HPG axis consists of the hypothalamus-pituitary unit, which belongs to the brain and controls the function of the gonads, i.e. the testes, via endocrine signalling. Neurosecretory cells in the hypothalamus produce gonadotropin-releasing hormone (GnRH), which is released in a pulsatile fashion and activates hormone synthesis in the anterior pituitary gland [40]. GnRH stimulates gonadotropic cells in the anterior pituitary gland to produce and release two hormones: luteinising hormone (LH) and follicle-stimulating hormone (FSH). While both hormones are essential regulators of testicular function, only LH is involved in androgen synthesis. LH binds to the LH receptor on the surface of Leydig cells in the testes and stimulates the biosynthesis of testosterone from cholesterol via a multi-level metabolic pathway [3]. Testosterone is then released by the Leydig cells into the circulation, where it is transported to its target tissues and exerts its function as a signalling hormone [3]. Less than 2% of testosterone circulates freely in the blood, with the majority bound to plasma proteins such as sex hormone binding globulin (SHBG) or albumin [41,42]. In order to enter its target cells, testosterone has to dissociate from these plasma proteins [42]. The testosterone metabolite DHT is to a much lesser extent also found in the blood, with serum DHT concentrations only amounting to one-tenth of testosterone concentrations [39].

Testosterone is involved in the regulation of various signalling pathways [43]. In the male body, the predominant function of testosterone is the development and regulation of reproductive function, including the induction of secondary sex characteristics during puberty, stimulation and maintenance of sexual function and activation of spermatogenesis. Testosterone is also a major regulator of signalling pathways in bones, skeletal muscles, blood cells, liver, heart, vasculature and brain [43]. Testosterone inhibits bone resorption and promotes the formation or remodelling of bone tissue, stimulates muscle protein synthesis and haematopoiesis, regulates glucose metabolism and contributes to the proper function of the central nervous system by maintaining neuron viability [44-47].

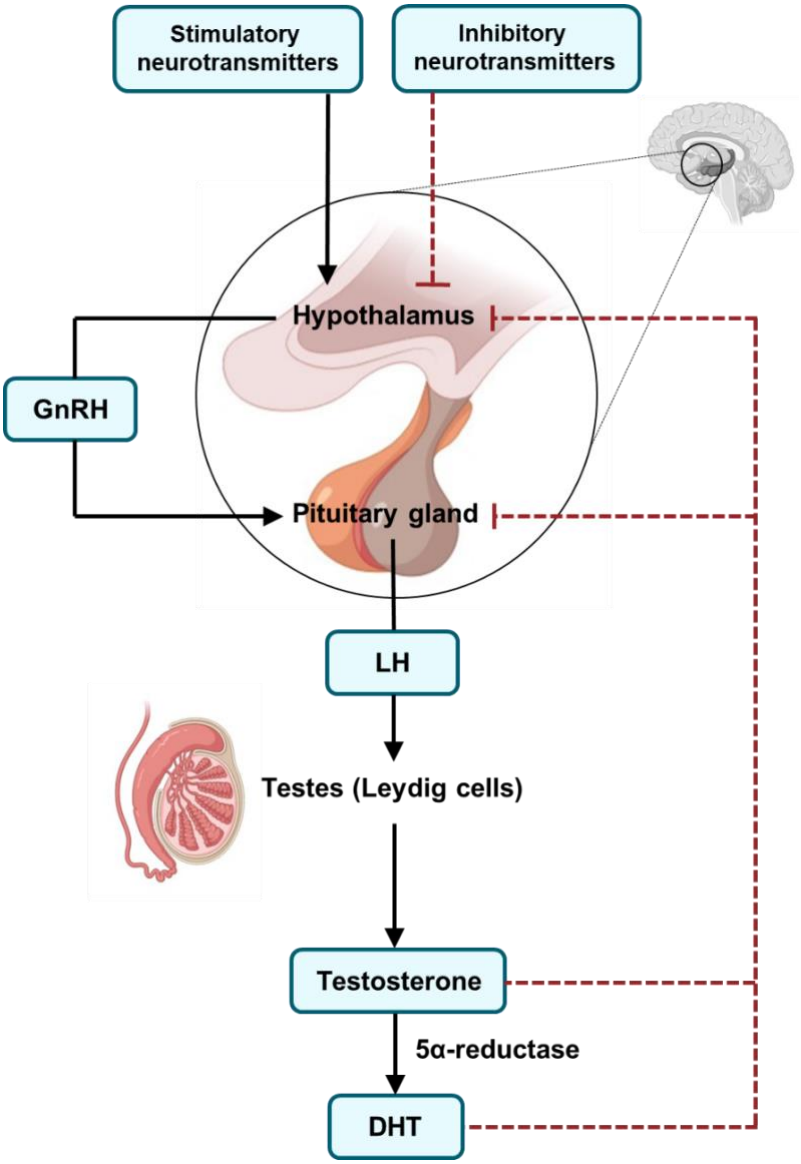


Figure 2. Regulation of the hypothalamic-pituitary-gonadal (HPG) axis and testicular androgen synthesis. The complex regulation of the HPG axis is mediated by stimulatory and inhibitory signals on neurosecretory cells in the hypothalamus. Upon activation, these cells secrete gonadotropin-releasing hormone (GnRH) to stimulate the release of luteinising hormone (LH) from cells in the anterior pituitary gland. LH binds to receptors in Leydig cells of the testes, which activates testosterone synthesis. Testosterone is either transported to target tissues directly or converted to 5α-dihydrotestosterone (DHT). The HPG axis is regulated through negative feedback by both testosterone and DHT. Adapted from Naamneh Elzenaty et al. (2022) [3].

Once androgens have reached their target cells, they exert their function by binding to their main intracellular effector, the AR [2] (Figure 3). The AR belongs to the family of steroid hormone receptors and is a nuclear receptor, which acts as a transcription factor when activated by its ligand. In the absence of a ligand, the AR remains inactive and forms a complex with heat shock proteins, which help to maintain a receptor shape that is ready for ligand binding. Within prostate cells, AR-activation mainly occurs via DHT, which is converted

from testosterone by the enzyme 5α-reductase in the cytoplasm. DHT binds to the AR with a higher affinity than testosterone [39]. The binding of DHT to the AR removes the heat shock proteins and facilitates the translocation of the ligand-activated receptor to the cell nucleus, where it dimerises and exerts its role as a transcription factor [2]. By binding to androgen response elements located in the promoter regions of its target genes, the AR dimer enables other regulatory proteins involved in transcription to attach and form the transcription machinery. This transcription machinery transcribes the genetic information into messenger ribonucleic acid (mRNA), which is then translated and assembled into the target protein. Many different genes involved in normal prostate function and homeostasis have been recognised to be regulated by androgens, most prominently the gene encoding the protein PSA [1].

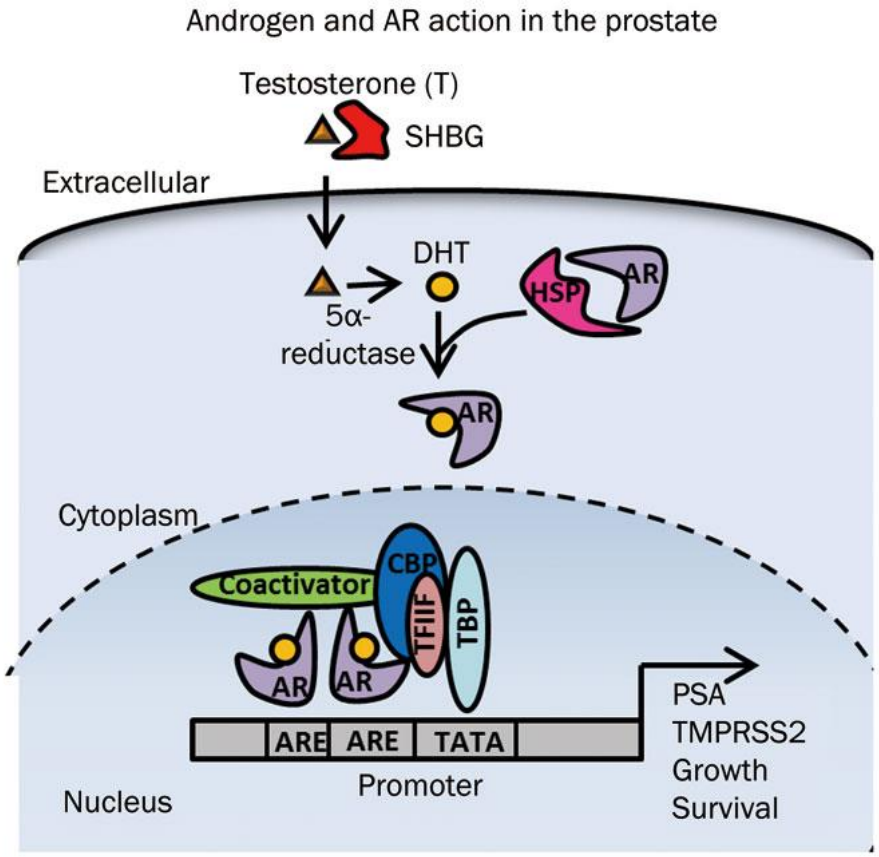


Figure 3. Androgen receptor (AR) signalling in prostate cells. Following synthesis in the testes, testosterone is transported to its target tissues while bound to sex hormone binding globulin (SHBG). Upon entry into prostate cells, testosterone is converted to 5α-dihydrotestosterone (DHT). DHT replaces the heat shock proteins (HSP) that stabilise the inactivated AR by binding to the receptor, thereby activating the translocation into the nucleus, where the AR dimerises and binds to androgen response elements (ARE) of target genes. That allows other transcription factors and coregulators to attach to form the transcription machinery, which facilitates the transcription of genes encoding the prostate specific antigen (PSA), as well as growth and survival factors. CBP: CREB-binding protein, TBP: TATA-box-binding protein, TFIIF: transcription factor IIF, TMPRSS2: transmembrane protease serine subtype 2. Reproduced under a Creative Commons licence (CC BY-NC-ND) from Tan et al. (2014) [2].

2.1.2. Carcinogenesis and pathophysiology of prostate cancer

Disease initiation

Prostate cancer occurs when cells in the prostate proliferate uncontrollably and produce abnormal prostate tissue growth. The most common type of prostate tumour, also referred to as prostate adenocarcinoma, originates from basal or luminal prostate epithelial cells, as opposed to the much rarer prostate tumours with neuroendocrine differentiation originating from neuroendocrine cells [48,49]. Cancer of any type is often caused by gene mutations in actors of growth factor signalling, which result in overactivation of anabolic pathways and the promotion of excessive cell growth [50]. In the case of the prostate, mutations associated with the development of a tumour are located in genes of the androgen metabolism and the AR signalling pathway in prostate epithelial cells. AR-mediated activation of target genes is central to prostate biology and, thus, also to prostate cancer. Currently, there are 159 known mutations of the AR gene that represent a genetic predisposition to prostate cancer [51]. Elevated AR activity due to gene mutations has been established to increase growth signals for prostate cells to the point where the rate of proliferation exceeds the rate of cell death, resulting in tissue net growth [2]. Such a transformation of the prostate epithelium is classified as prostate cancer once the proliferating cells break through the basal lamina and invade the stroma, because this step signifies the loss of structural integrity of the tissue [52] (Figure 4).

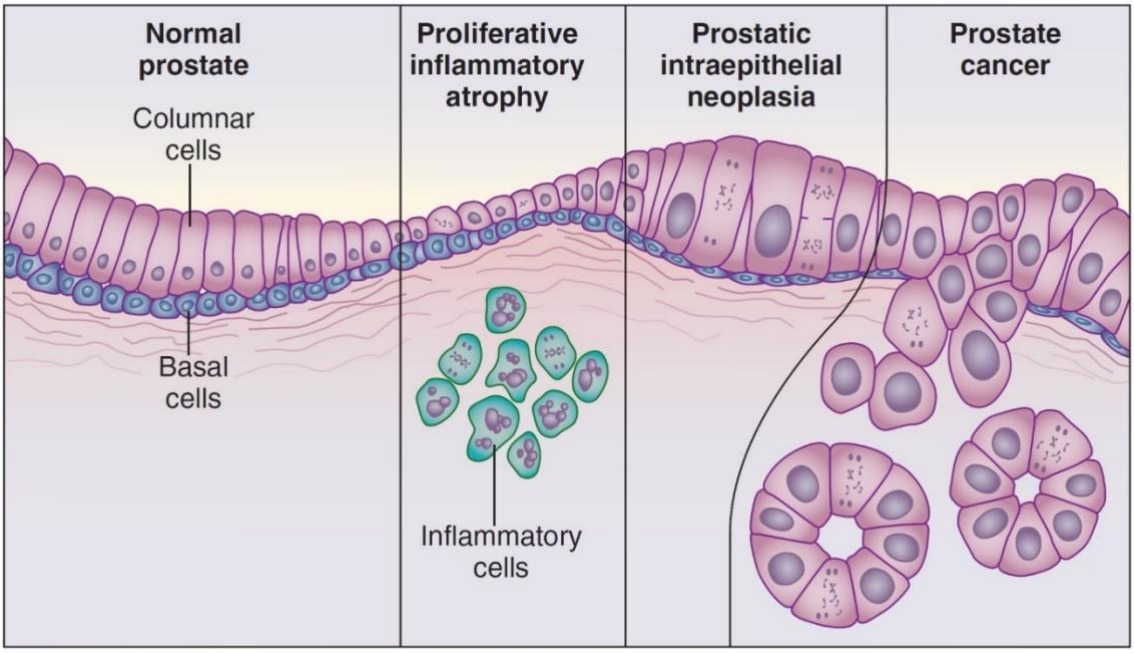


Figure 4. Stages of prostate carcinogenesis. Cellular atrophy and deoxyribonucleic acid (DNA) damage induced by endogenous and exogenous factors result in inflammation and subsequent proliferation of the prostate epithelium. Continuous proliferation and pro-inflammatory stimuli promote the accumulation of genomic changes and ultimately lead to the development of invasive adenocarcinoma of the prostate. Reproduced with permission from Nelson et al. (2020) [53].

The AR-driven reprogramming in prostate cancer also alters the activation of metabolic pathways, such as glycolysis, oxidative phosphorylation and amino acid uptake and metabolism, among others, to provide the metabolites required for increased cell proliferation [50]. As in normal prostate tissue, the metabolic pathways that fuel prostate cancer growth are mainly controlled by the AR [50]. This is supported by studies showing that the withdrawal of androgens significantly inhibits tumour growth because prostate cancer cells transition into a state of senescence when AR signalling is suppressed [54,55]. The initial reliance of prostate cancer on androgen signalling is applied clinically in the form of ADT, which deprives the tumour of its proliferation signals and thereby arrests growth and progression [4].

Metastatic disease

Prostate tumour growth is not limited to the prostate. Metastatic spread occurs when malignant cells emigrate from their tissue of origin and survive in the bloodstream, before invading other tissues to proliferate and establish cancer growth there [56]. Prostate cancer metastasis mostly affects the lymphatic system and the bones [4]. Locoregional lymph nodes and the pelvic bones are common sites of initial metastatic growth due to the proximity to the prostate, from where the metastasis can further spread to distant lymph nodes and across the entire axial skeleton as the disease progresses [4]. Other organs, such as lungs, liver or brain, are less frequently affected and metastasis in these tissues is often associated with particularly aggressive disease and poor prognosis [57].

Metastasis is a multi-step process that requires extensive transformation of the malignant cells to relocate from the primary tumour site to distant organs [56]. First, they must downregulate some of their membrane structures in order to detach from neighbouring cells and become motile [4,56]. Next, the newly motile cells perform intravasation, meaning that they penetrate the basement membrane of the prostate epithelium and enter the bloodstream. Entry into blood vessels allows these malignant cells to travel to distant sites but also poses a challenge as they are now exposed to surveillant immune cells. Several immune evasion mechanisms and an acquired resistance to programmed cell death enable the survival of cancer cells in the bloodstream [56]. To establish tumour growth at a distant site, the cancer cells need to extravasate, i.e. leave the blood vessels by transmigrating through the endothelium, and attach to native cells at the new site where they can proliferate and form a metastasis [4,56]. Notably, most cancer cells that extravasate do not immediately result in metastases, but instead enter a dormant state because they cannot proliferate without the presence of growth factor signalling, immunological stimuli or angiogenic factors [56]. Such cells are referred to as micrometastases. However, micrometastases can eventually escape from their dormant state and, provided the right environment, resume proliferation to form a

secondary site of tumour growth. While the process of metastasis is not yet fully understood on a cellular and molecular level, evidence suggests that different types of cancer cells home to different tissues. For example, more than 80% of men with metastatic prostate cancer have bone metastases, which may be facilitated by signalling molecules on the prostate cancer cell surface that attract these cancer cells to bone tissue through interaction with markers expressed on bone marrow cells [58,59].

Disease progression

Disease progression despite androgen deprivation occurs when prostate cancer cells recover their AR-mediated signalling and maintain proliferation even in the absence of androgens [60]. These androgen-independent cells develop as a result of genetic alterations, which arise from the increased selective pressure of continuous androgen deprivation that forces the tumour to adapt in order to maintain growth. Thus, AR-targeted therapies eventually fail in almost all patients when the tumour develops a resistance to the androgen withdrawal, a state that is termed castration resistance [61].

How exactly castration resistance develops remains uncertain but four potential mechanisms have been proposed to explain androgen-independence in prostate cancer [2] (Figure 5). Firstly, castration resistance might be driven by increased sensitivity of the AR to its ligands. Although ADT significantly reduces the serum levels of circulating androgens, testosterone is not completely eliminated. While the major androgen synthesising pathway via the HPG axis is downregulated by ADT, residual androgen production from the adrenal gland and intra-tumoral secretion of enzymes involved in androgen synthesis maintain a critical level of testosterone [62]. The tumour counters the scarcity of androgens by increasing AR expression in the cell to ensure androgen signalling when only few ligands are available [2]. The second explanation for castration resistance involves mutations of the AR gene, which produce alterations in the receptor that could allow other steroid hormones, like oestrogen or glucocorticoids, to bind and activate the transcriptional activity of the AR. A third potential mechanism is ligand-independent activation of the AR facilitated by mutations that make the AR immune to its natural inhibitors. Lastly, there is evidence that prostate cancer cells sometimes bypass the AR signalling pathway completely and activate the transcription of its target genes independently. Some of these bypasses involve the immune system, which reacts to proinflammatory signals released by dying prostate cancer cells with the secretion of survival-stimulating factors. It is worth noting that these four potential mechanisms of castration resistance are not mutually exclusive and it is likely that the tumour, forced by the selective pressure of androgen deprivation, adapts in more ways than one.

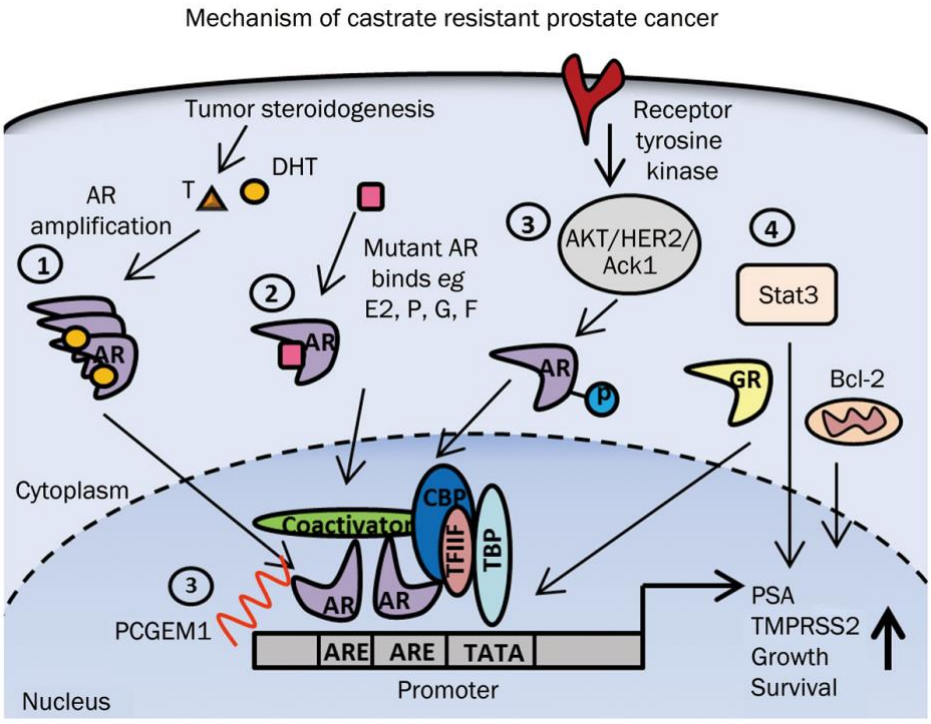


Figure 5. Mechanisms of androgen-independence in castrate-resistant prostate cancer. Four mechanisms have been proposed as drivers of castration resistance: 1) Androgen receptor (AR) amplification to increase sensitivity to residual androgen concentrations, combined with intra-tumoral steroidogenesis. 2) AR mutations resulting in promiscuous ligand binding and activation by other molecules, such as oestrogen (E2), progesterone (P), glucocorticoids (G) or the pharmacological AR antagonist flutamide (F). 3) Ligand-independent AR activation through AR mutations that prevent binding of negative regulators or facilitate binding of long non-coding RNAs (e.g. PGCEM1). 4) AR-independent mechanisms that active AR target genes via other pathways, like Stat3 signalling stimulated by pro-inflammatory factors released from infiltrating immune cells. Reproduced under a Creative Commons licence (CC BY-NC-ND) from Tan et al. (2014) [2].

2.1.3. Epidemiology of prostate cancer

Prostate cancer is the second most common cancer in men worldwide and is estimated to account for 1.4 million new cases or 7% of total new cancer diagnoses annually [5]. With an estimated 375,000 associated deaths, prostate cancer ranks fifth in the leading causes of cancer-related deaths in men globally but second in Western countries such as the United States and Germany [5,63,64]. Death rates for prostate cancer have been decreasing in many Western countries, a development that has been attributed to increased screening efforts and improved treatment options. In Germany, the most recent data show a relative 5-year survival rate for prostate cancer of 89% [64]. The high incidence paired with a higher survival rate than other cancers leads to prostate cancer now being the primary cause of years lived with cancer-related disability in developed countries [65].

Prostate cancer mostly occurs in men of older age. While the probability of developing prostate cancer for men under 50 years is 0.2%, it increases to 9.2% for men 70 years or

older in the United States [63], with similar numbers reported for Germany [64]. Current estimates of the cumulative lifetime risk show that 1 in 9 men will develop prostate cancer and 1 in 30 will die of the disease [64]. Although some of the rise in the global incidence of prostate cancer may be attributable to intensified screening efforts and overdiagnosis, the increasing life expectancy of the world's population will see the number of men living with prostate cancer increase further in the future [5].

The incidence and mortality rates of prostate cancer differ between countries but also between different population groups in a country. Recent estimates of prostate cancer incidence by region show that Northern Europe has the highest age-standardised rate (ASR) with 83 per 100,000, followed by Western Europe and Australia with 78 and 76, respectively [66]. South-Eastern Asia and South-Central Asia show a lower incidence with estimated ASRs of 14 and 6 per 100,000, respectively. Mortality of prostate cancer on the other hand was higher in the Caribbean, Middle Africa and Southern Africa, with estimated ASRs of 28, 25 and 22 per 100,000, respectively, compared to 11 and 4 in Europe and Asia. When analysing populations by their Human Development Index (HDI), the highest prostate cancer incidence ASR is present in populations with a very high HDI, which is likely a result of increased access to diagnostic screening, whereas the highest mortality ASR is present in low HDI populations suggesting an association with socioeconomic risk factors [66].

Regarding the individual risk of developing prostate cancer, there are few risk factors that are well established and many more that have been proposed to explain the epidemiology of the disease. In addition to advancing age, which has been shown to be closely linked to the occurrence of prostate cancer, the factors with sufficient evidence for a causal relationship with prostate cancer risk include family history, genetic predisposition and ethnicity [66]. A man with a family history of prostate cancer has a two-fold risk of developing prostate cancer himself and approximately 20% of men who are diagnosed have familial prostate cancer [67]. The risk increases with a higher number of affected family members, as well as with decreasing age at diagnosis of the family member. Furthermore, a first-degree family history of breast cancer has been identified as a risk factor for developing prostate cancer, which suggests a shared genetic predisposition to hormone-related cancers [68]. Germline alterations in several DNA damage repair genes, e.g. BRCA1, BRCA2 and CHEK2, as well as transcription factor genes, e.g. HOXB13, have been linked to a predisposition to prostate cancer [69]. However, hereditary cancer and genetic predisposition due to germline alterations are complex because cancer risk is also influenced by environmental factors. This also holds true for ethnicity, which has been used to explain patterns of prostate cancer risk among different populations [70]. African-American men in the United States show a higher prostate cancer incidence and mortality than White men, yet this might be related to a multitude of

factors, including inequality regarding access to screening and treatment, exposure to occupational hazards, or various risk behaviours [71]. Many additional individual or environmental factors have been proposed to influence the risk of developing or dying of prostate cancer [66,70]. These include behaviours such as smoking, physical activity and sexual activity, as well as various dietary factors and symptoms associated with metabolic disease. However, the relationship between prostate cancer risk and these factors remains controversial.

2.2. Prostate cancer management

2.2.1. Screening and diagnosis of prostate cancer

Because prostate cancer is a prevalent malignancy that is often asymptomatic in the initial stages and can be cured if detected early, many countries conduct extensive screening programmes for prostate cancer as part of routine healthcare. The standard screening method is the measurement of serum PSA levels [4]. Since PSA is a prostate-specific molecule secreted as part of the prostatic fluid into the urethra, increased blood levels may be indicative of prostatic disease. However, PSA serum elevations also occur in prostatitis, i.e. inflammation of the prostate, or low-grade tumours that present no threat to overall health or survival.

The value of population-based PSA screening for reducing the disease burden of prostate cancer has therefore been questioned as its benefits for mortality reduction are unclear and it may result in overdiagnosis and overtreatment [72,73]. Instead, experts recommend an individualised approach that considers risk factors such as age and family history [73]. This approach is employed in Germany, where healthcare providers cover the costs for men 45 years of age or older to undergo an annual digital rectal examination, but not measurement of serum PSA levels, as part of prostate cancer screening [74]. As of 2016, only 24% of eligible men utilised the offered screening, although percentages differed considerably between age groups, with the lowest participation rate among men aged 45 to 49 years [74].

Standard diagnostic procedure for detecting prostate cancer consists of a digital rectal examination of the prostate to detect any enlargement or textural changes combined with analysis of serum PSA levels [75]. Generally, serum PSA levels below 4 $ng \cdot mL^{-1}$ have been regarded as normal [76]. If either of these results are abnormal, a scan of the prostate using magnetic resonance imaging (MRI) can confirm a suspected malignancy [75]. Ultimately, a definitive cancer diagnosis is obtained through prostate biopsy and subsequent histopathological analysis of prostate tissue samples. The result for each of the tissue samples is reported separately, including the location, differentiation grade and extent of the

tumour. The Gleason classification was established to set a universal standard for the grading of prostate cancer aggressiveness and the categorisation of patients by their disease risk [77,78]. The Gleason grade quantifies how much each biopsy sample has deviated from normal prostate tissue, with the highest and the most common grade summed to obtain the Gleason score [77] (Table 1).

Table 1. The Gleason grading system for classification of prostate cancer [77].

Gleason grade		**Gleason score**	
1	Small, uniform glands	< 6	No cancer
2	More stroma between glands	6	Low-risk group
3	Distinctly infiltrative margins	7	Intermediate-risk group
4	Irregular masses of neoplastic glands	≥ 8	High-risk group
5	Poor differentiation, only occasional gland formation		

The chance for men in the low-risk group of prostate cancer to have metastases is minimal, thus, no further diagnostic procedures are required after the biopsy [75]. By contrast, it is recommended that some men with intermediate-risk and all men with high-risk tumours undergo further diagnostic assessment, such as imaging to screen for metastases. Imaging methods include bone scintigraphy, computed tomography (CT) or prostate-specific membrane antigen (PSMA) positron emission tomography (PET)/CT [79]. This allows the accurate determination of the prostate cancer stage at diagnosis and is pivotal for selecting the optimal treatment approach. The standard classification system for staging of prostate cancer is the TNM system, which describes the anatomical extent of the cancer and combines test results from several diagnostic procedures [80,81] (Table 2).

Table 2. The TNM classification of malignant tumours issued by the American Joint Committee on Cancer [81].

Primary tumour (T)	
Tx	Primary tumour cannot be assessed
T0	No evidence of primary tumour
T1	Clinically inapparent tumour not palpable or visible by imaging
T2	Tumour confined within prostate
T3	Tumour extends through the prostatic capsule
T4	Tumour invades adjacent structures (e.g. bladder, pelvic wall)

Regional lymph nodes (N)	
Nx	Regional lymph nodes were not assessed
N0	No regional lymph node metastasis
N1	Metastasis in regional lymph node(s)
Distant metastasis (M)	
Mx	Distant metastasis was not assessed
M1	Distant metastasis
M1a	Metastasis to non-regional lymph node(s)
M1b	Metastasis to bone(s)
M1c	Metastasis to other site(s) with or without bone metastasis

The combination of these diagnostic results allows the differentiation between localised, locally advanced and metastatic disease [4]. Localised prostate cancer is confined to the organ and usually remains asymptomatic, whereas this changes in advanced disease. Locally advanced prostate cancer refers to a tumour that has broken through the capsule of the prostate gland and spread to nearby organs, such as the bladder or regional lymph nodes [75]. Consequently, the symptoms of locally advanced prostate cancer depend on the affected organs, and typically include frequent urination, urinary retention, pain during urination, or haematuria (i.e. blood in the urine) [82]. The overall tumour burden typically increases further when distant metastasis occurs. At this stage, tumour growth is often associated with debilitating symptoms that are no longer limited to the urinary tract [4]. Metastasis to distant organs impairs the normal physiological function of these tissues and can result in local symptoms such as pain, pathological fractures, spinal cord compression or lymph oedema, amongst others [83,84]. The diagnosis of metastatic prostate cancer can either come after progression from an initially localised tumour or as a *de novo* diagnosis, where the tumour growth is only detected once it has already formed metastases to distant organs [4]. Metastatic cancer is generally considered incurable and men with metastatic prostate cancer have considerably lower 5-year survival rates than those with localised disease [71].

Lastly, prostate tumours are classified by their androgen-dependency. Initially, prostate cancer is androgen-dependent as characterised by effective tumour control in response to androgen withdrawal through ADT, which is classified as hormone-sensitive prostate cancer (HSPC). By contrast, a tumour that has progressed to androgen-independence as determined by disease progression despite androgen deprivation is referred to as castrate-resistant prostate cancer (CRPC). This differentiation is crucial for the selection of appropriate treatment options.

2.2.2. Overview of treatment options for prostate cancer

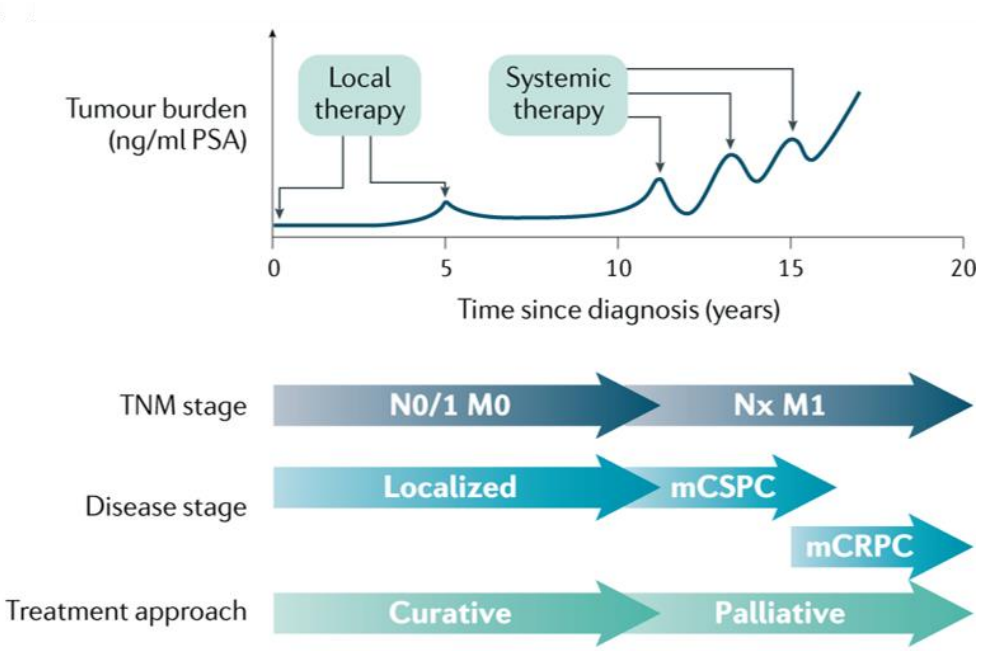


Figure 6. Overview of treatment approaches according to prostate cancer stage. Men with localised prostate cancer who do not respond to local therapy eventually progress to metastatic disease accompanied by increased prostate-specific antigen levels. Various forms of systemic therapy, such as androgen deprivation and chemotherapy, are available for the treatment of metastatic prostate cancer, although at this stage further progression from metastatic castrate-sensitive prostate cancer (mCSPC, also referred to as metastatic hormone-sensitive prostate cancer (mHSPC)) to metastatic castrate-resistant prostate cancer (mCRPC) is inevitable and the intent of the treatment switches to palliative care. Reproduced with permission from Rebello et al. (2021) [4].

The treatment course of each individual with prostate cancer depends heavily on the histopathological and molecular profile of the tumour, the clinical prostate cancer stage at diagnosis, as well as patient characteristics [4] (Figure 6). While the early disease stages of prostate cancer often present as slow-growing and indolent tumours that can be managed using surveillance and local treatment, men with advanced prostate cancer may experience rapid disease progress that requires aggressive treatment [75]. Additionally, because prostate cancer is a disease that often presents late in life, a patient-oriented treatment approach also entails a consideration of estimated life expectancy and overall health status. The androgen-dependent nature of prostate cancer was discovered more than eighty years ago [14]. Due to advances in medical research over the last decades, prostate cancer patients now have a variety of treatment options and a high long-term survival rate compared to other cancers.

Localised prostate cancer

Treatment options for localised prostate cancer include active surveillance, radical prostatectomy or radiotherapy [75]. Active surveillance refers to a predefined schedule of

regular follow-up visits, where digital rectal examination, measurement of serum PSA levels and prostate biopsy are repeated. The aim of active surveillance is to monitor the disease closely to ensure the detection of a potential progression requiring surgical or pharmacological intervention, while preventing overtreatment in men with very low-risk prostate cancer that may never progress during their lifetime. While active surveillance is designed to simply manage a slow growing tumour, radical prostatectomy and radiotherapy are pursued with curative intent in this setting [4]. Radical prostatectomy is a surgical procedure in which the entire organ is removed. A similar result is achieved by radiation applied to the prostatic area, which is comparable to prostatectomy in regards to tumour control but carries a different spectrum of adverse events [85]. While the benefit of these local treatments for men with low-risk prostate cancer remains unclear, clinical guidelines recommend them for men with intermediate or high-risk localised disease to prevent metastatic spread [75].

Although localised prostate cancer can be cured, regular monitoring after completion of local treatment is still warranted. If serum PSA levels fail to decrease or continue to rise after prostatectomy or radiation, it indicates either residual disease or biochemical recurrence [4]. Biochemical recurrence refers to a rise of serum PSA above a certain threshold, the exact value of which depends on the primary treatment, and is indicative of occult prostate cancer growth that will eventually lead to disease progression if not managed [86]. Thus, serum PSA levels should be frequently monitored even after the completion of primary treatment [75].

Metastatic hormone-sensitive prostate cancer

Because prostate cancer progression relies on the androgen signalling pathway [2,60], metastatic HSPC (mHSPC) is treated with systemic hormone ablation through treatments that directly or indirectly target the androgen-receptor interaction [87]. This therapeutic strategy was pioneered by Huggins and Hodges in the 1940s, when they demonstrated that surgical castration significantly reduced levels of prostatic acid phosphatase, a biomarker of prostate cancer [54]. Advances in medical research have led to the approval of various therapeutic agents that facilitate systemic hormone ablation, most prominently pharmacological ADT and secondary hormone therapies [2,60].

ADT encompasses several drugs that interfere with the androgen metabolism to inhibit the anabolic effects of testosterone. The aim of ADT is to maintain serum testosterone concentrations at castrate level, which has been defined as below 50 $ng \cdot dL^{-1}$ and requires continuous application of the treatment [88]. Only in cases with a low risk of progression and asymptomatic disease, may the treating clinician decide to instead administer the treatment as intermittent ADT instead [89]. Intermittent ADT means that androgen deprivation is

continued until the PSA level is very low, typically below the detection level of the laboratory tests, before treatment is suspended and only restarted once a notable PSA rise occurs. A meta-analysis of 12 clinical trials found that intermittent ADT was comparable to continuous ADT in terms of prostate-cancer specific mortality [89]. The advantage of an intermittent approach is temporary relief from testosterone withdrawal and its often debilitating adverse effects of androgen deprivation, although careful consideration is required to avoid disease progression during treatment-free intervals [87].

Men with a particularly aggressive form of prostate cancer or a high burden of metastasis, indicated by either a large number of metastases in one organ or metastasis to visceral organs, require additional treatment such as taxane-based chemotherapy or secondary hormone therapy [87]. Secondary hormone therapy includes androgen biosynthesis inhibitors and ARIs, which are administered in addition to ADT to further inhibit AR signalling pathways. The addition of either chemotherapy or secondary hormone therapy to ADT provides significant survival benefits for men with mHSPC and a high burden of metastasis [90-94]. However, toxicity increases with the addition of either of these treatments and their benefit should be carefully weighed against the involved risks, especially in older men with a poor health status [4,87].

Metastatic castrate-resistant prostate cancer

Despite advances in the treatment landscape of mHSPC, the majority of patients inevitably progresses to metastatic CRPC (mCRPC) as marked by disease progression during ADT, mostly within the first year of treatment for metastatic disease [95]. At present, mCRPC is considered to be non-curable, since there are no treatment options to meaningfully prevent further tumour growth and avert cancer-related death. While estimates vary between studies, the median overall survival of men with mCRPC is 25 to 36 months, with positive trends noticeable as new treatments become available [96-99]. Although the tumour has become androgen-independent at this stage, activation of AR signalling is thought to still promote tumour proliferation. Therefore, ADT is continued as the primary treatment in mCRPC but is usually combined with additional treatments that target AR signalling or general cancer cell growth mechanisms to improve disease control [100].

Similar to high-risk mHSPC, available treatments for mCRPC include chemotherapy and secondary hormone therapy. The taxane-based chemotherapies docetaxel and cabazitaxel have been shown to improve survival outcomes in mCRPC through their cytotoxic effects but are associated with adverse events, such as decreased blood cell concentrations and diarrhoea [4,101]. Likewise, secondary hormone therapy has been associated with prolonged overall survival in chemo-naïve men, as well as in men who already received chemotherapy

as first-line therapy [102-105]. The changing treatment landscape also presents new challenges for clinical research as drugs that were formerly only approved for men with progressive mCRPC are now routinely prescribed to men at earlier disease stages and their efficacy upon second application remains to be investigated [4].

In men who no longer respond to any of the standard treatments for mCRPC, novel agents such as poly(adenosine diphosphate-ribose) polymerase (PARP) inhibitor olaparib may slow tumour growth and defer cancer-related death [106,107]. Olaparib blocks the DNA repair enzyme PARP and induces cell death in cells with DNA repair defects, resulting in a preferential killing of malignant cells. Olaparib has been approved for use in selected patients with confirmed DNA repair gene mutations, which are estimated to occur in roughly one third of men with mCRPC, but requires genomic analysis of tumour tissue prior to treatment [4]. Additionally, patients may receive bone-targeted treatments like receptor activator of nuclear factor κB ligand inhibitor denosumab to block bone-specific signalling pathways, which are overactivated by prostate cancer and fuel the growth of bone metastases [108]. Furthermore, potential novel therapeutic agents like ^{177}lutetium-PSMA, a radionuclide targeted at the PSMA surface protein on prostate cancer cells, are undergoing clinical investigation [100].

2.2.3. Therapeutic agents targeted at androgen signalling

Antiandrogens

Antiandrogens, or first-generation ARIs, are pharmaceutically engineered AR ligands that block androgen action by competing for their binding site at the AR [2] (Figure 7). Their chemical properties allow antiandrogens to bind to the AR but not activate its effector function, making the receptor unavailable for interaction with androgens. Available antiandrogens for prostate cancer treatment include bicalutamide and flutamide. Antiandrogens are typically administered to men with locally advanced prostate cancer, either as a monotherapy or as adjuvant therapy after prostatectomy or radiotherapy, where they have been shown to delay disease progression [109,110]. However, their efficacy is limited by a substantially lower affinity to the AR compared to endogenous DHT; thus, other therapeutic agents are necessary to achieve maximum androgen blockade [111].

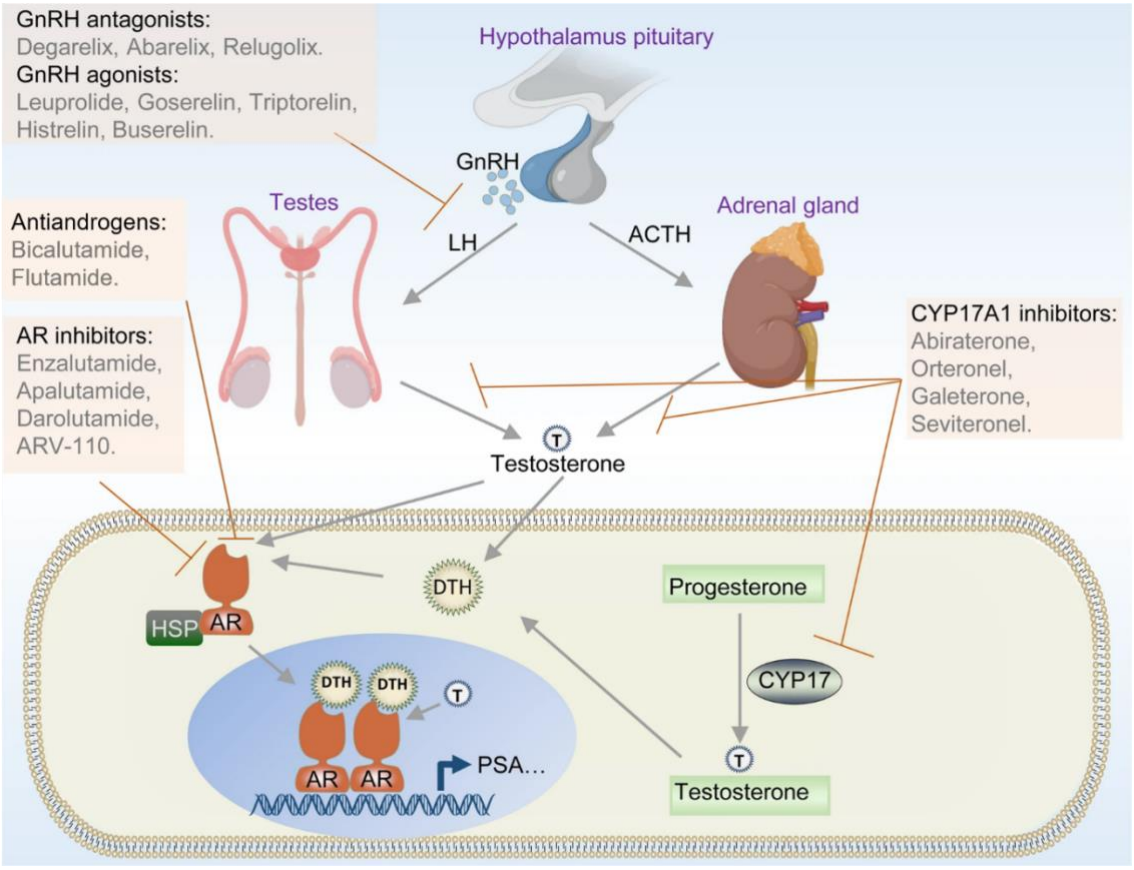


Figure 7. Therapeutic agents for prostate cancer targeted at the androgen receptor (AR) signalling pathway. Multiple drugs have been approved for the treatment of prostate cancer. These drugs block androgen action, either by inhibiting androgen synthesis via the hypothalamic-pituitary-gonadal (HPG) axis and CYP17, or by directly targeting the AR to prevent AR transcriptional activity. Modified and reproduced under a Creative Commons licence (CC BY) from He et al. (2022) [112].

Androgen deprivation therapy

In contrast to antiandrogens, ADT refers to treatments that reduce testosterone production through disruption of the HPG axis. While ADT was originally achieved via orchiectomy, i.e. surgical removal of the testicles, most patients today receive pharmacological ADT in the form of GnRH agonists or antagonists [54,113].

GnRH agonists as a therapeutic agent for prostate cancer were first approved in the 1980s and remain the standard of care for men with advanced disease today [114]. Commonly used GnRH agonists include leuprolide, goserelin and buserelin among others. Their mechanism of androgen suppression appears contradictory at first, in that GnRH agonists activate GnRH receptors in the hypothalamus, which stimulates the release of LH from the pituitary gland and leads to subsequent activation of testosterone synthesis. The initial overstimulation of the androgen synthesising pathway is, however, soon reverted into suppression of LH production, which results in the long-term reduction of testosterone serum concentration to castrate levels. Physiologically, the mechanism that leads to testosterone suppression is a

desensitisation of the pituitary gland through overactivation [115]. The HPG axis reacts to the overactivation of GnRH receptors with a negative feedback loop that downregulates the pathway in the long term. Because the initial response to GnRH agonist administration is a short-term flare of testosterone production that can have detrimental effects in men with already metastatic disease, they are often combined with antiandrogens during the first weeks of treatment until testosterone levels have subsided [114].

The same suppression of androgen synthesis can be achieved via the opposing mechanism through GnRH antagonists, which exert a direct inhibitory effect on GnRH receptors by competing with GnRH for the binding site but not activating its effector function [116]. By using GnRH antagonists instead of agonists, the initial flare of testosterone concentrations can be avoided. However, comparative analyses have shown that GnRH antagonists can increase the risk of certain adverse events, especially injection-site reactions [117]. Thus, the only regularly used GnRH antagonists was degarelix until very recently, when relugolix was also approved for use in advanced prostate cancer, first in the United States in 2020 followed by the European Union in 2022 [118,119]. Relugolix appeals to patients because it is administered orally in the form of daily tablets, as opposed to the monthly or three-monthly injections required for all other forms of pharmacological ADT.

Inhibitors of androgen synthesis or receptor

In advanced prostate cancer, ADT is combined with secondary androgen signalling inhibitors to amplify the testosterone blockade [87]. Approved drugs for secondary hormone therapy include second-generation ARIs, such as apalutamide, enzalutamide and darolutamide, and androgen biosynthesis inhibitor abiraterone [87].

Second-generation ARIs are engineered to bind to the AR with a high affinity and inhibit its translocation to the nucleus, as well as to impair the recruitment of transcription coactivators, thereby reducing AR transcriptional activity [120]. This leads to selective apoptosis of prostate cancer cells, whose metabolism relies heavily on AR activation, and causes the tumour volume to decrease [60]. Compared to first-generation ARIs such as bicalutamide, this new drug generation impairs the binding of the AR to its target genes more effectively [121]. Therefore, second-generation ARIs are typically prescribed to patients with aggressive or advanced disease [87]. Similar to mechanisms of ADT resistance, most men who initially respond to ARI treatment eventually experience disease progression when the tumour produces AR variants that lack the binding domain for ARIs [121]. At this stage, treatment with another ARI drug is often unsuccessful and treatment is switched to therapeutic agents with a different mechanism of action, such as abiraterone.

Contrary to ARIs, abiraterone blocks the synthesis of testosterone rather than its effector function. Abiraterone targets cytochrome P450 17-alpha hydroxysteroid dehydrogenase (CYP17), a pivotal enzyme involved in the conversion of cholesterol into the testosterone precursor dehydroepiandrosterone [122]. By irreversibly binding to CYP17 and inhibiting its enzymatic function, abiraterone suppresses androgen biosynthesis in the testes.

2.2.4. Adverse effects of AR-targeted prostate cancer treatments

Prostate cancer patients of any stage face a variety of adverse effects related to the tumour and its treatments. This is compounded among men with advanced prostate cancer undergoing systemic treatments that are associated with severe toxicities [20,123,124]. Androgens modulate a variety of different signalling pathways and, outside of the reproductive organs, AR-expressing cells are found in muscles, bones, fat tissue, the cardiovascular system and the immune system, amongst others [125,126]. Consequently, systemic androgen deprivation is associated with a variety of adverse effects that can cause significant morbidity and impair quality of life [20] (Figure 8).

Body composition

Changes in body composition are among the most prevalent adverse effects among men undergoing any form of androgen deprivation [20]. Androgens are a strong activator of skeletal muscle protein synthesis and skeletal muscle growth [127]. In the absence of androgen signalling, anabolic pathways in the skeletal muscle are impaired and muscle mass declines [128]. In turn, ADT is associated with significant reductions in muscle mass and a subsequent decline in muscle strength [16,129-131]. Body composition analysis of 72 men at treatment initiation and after 36 weeks of ADT showed a 2.4% reduction in whole-body lean mass, with upper limb lean mass experiencing the largest reduction with 5.6% [129]. Similarly, Smith et al. investigated the effects of GnRH agonist leuprolide and found that lean body mass decreased by 2.7% and cross-sectional muscle area of the paraspinal area decreased by 3.2% within the first year of treatment [16]. In another longitudinal study of the long-term effects of ADT in 252 men with prostate cancer, lean mass reductions accumulated over time with the overall loss greater at 36 months than at both six and twelve months [130]. Interestingly, the rate of lean mass loss in this study was highest in older men and in those who had already received ADT for at least six months prior to the start of the study.

ADT-induced changes in muscle mass are often accompanied by an increase in fat mass, which can result in the manifestation of sarcopenic obesity [132]. Reports of increased fat mass during ADT are highly consistent and appear to affect patients regardless of treatment duration and disease stage [16,133,134]. Body fat mass is estimated to increase by

approximately 9 to 14% within the first year of ADT [16,134]. Even more pronounced body composition changes were reported by Galvão et al., who observed a mean increase of 13.8% in whole-body fat mass and 20.7% in upper limb fat mass after just 36 weeks on ADT [129]. In addition to the changes in muscle and fat tissue, some patients experience gynaecomastia as an adverse effect of ADT [135]. Gynaecomastia refers to the excessive development of breast tissue and, while generally considered harmless, can be associated with breast sensitivity, pain and adverse psychological effects.

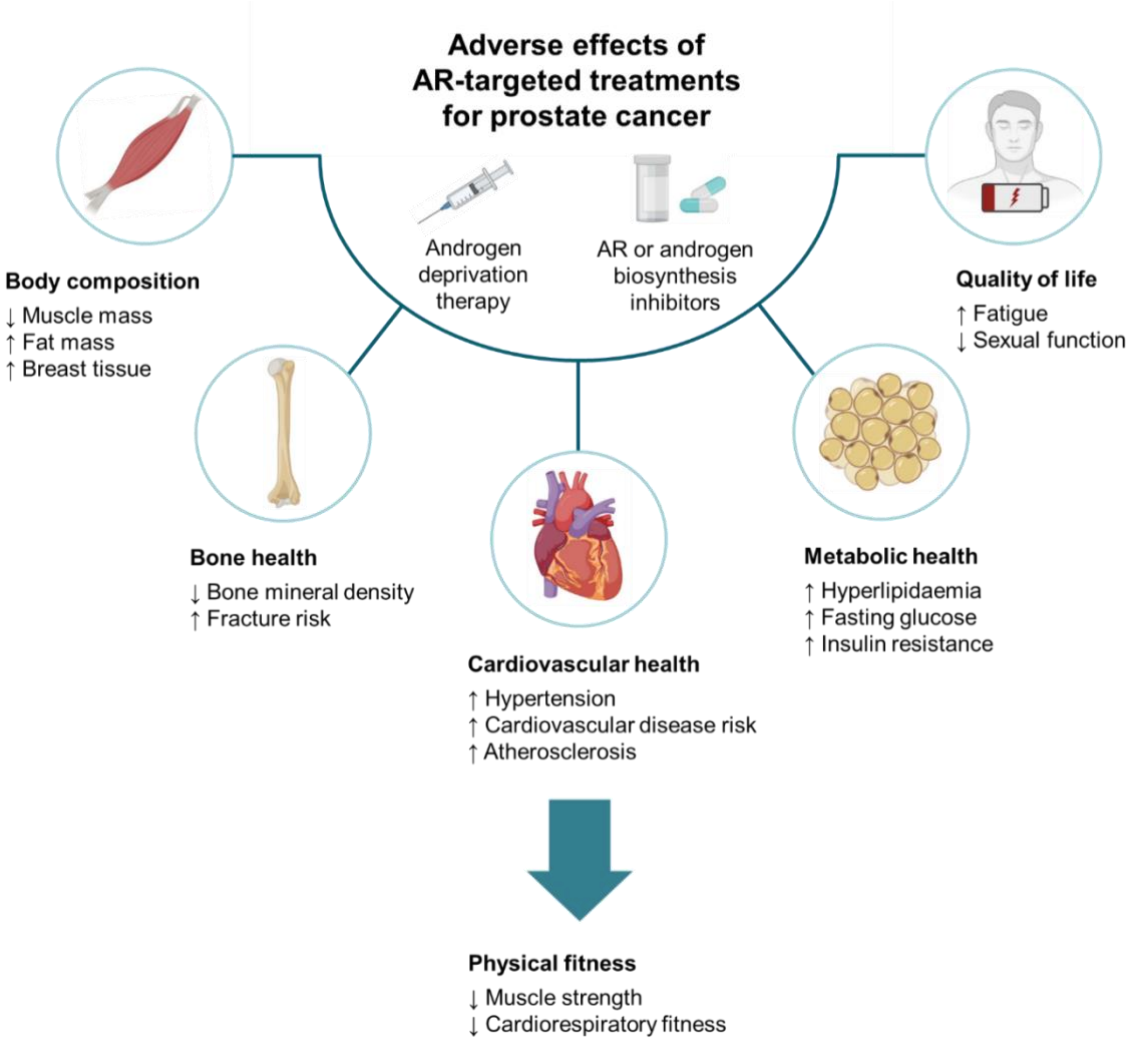


Figure 8. Adverse effects related to treatment with androgen deprivation therapy and secondary inhibitors of the androgen signalling pathway. Androgen deprivation therapy (ADT) is a key component of the treatment for advanced prostate cancer but it is associated with numerous adverse effects on musculoskeletal, cardiovascular, metabolic, cognitive and sexual health. Long-term androgen deprivation, either as monotherapy or in combination with second-generation androgen receptor (AR) inhibitors, can lead to significant impairments of physical fitness. Figure conceptualisation based on Edmunds et al. (2020) [20].

Bone health

Bone health poses a serious concern for men undergoing long-term androgen deprivation [20]. Bone mineral density (BMD) is known to decline with age as testosterone levels decrease and ADT accelerates this development [136]. Total BMD loss is estimated to amount to 5 and 10% after one and two years of ADT, respectively, which is considerably higher than the normal age-related decline of 1% per year observed in healthy older men [18,137]. This puts patients at risk of developing osteopenia or osteoporosis, which are very common side effects of ADT [11,20]. Reduced BMD is also an established risk factor for bone fractures, which in turn have been related to an increased risk of mortality in older and frail individuals [138,139]. Beebe-Dimmer et al. analysed data from 80,844 men with prostate cancer and found that ADT was associated with increased fracture risk, with the mortality risk doubling after a fracture occurred [12]. Interestingly, this study reported that fracture rates increased with a higher cumulative ADT dose, which is equivalent to a longer treatment duration.

Cardiovascular health

Cells in cardiac tissues are known to express the AR and, while the exact mechanisms have not been fully established, androgens are assumed to have a cardioprotective effect [140,141]. In this regard, there is a growing body of evidence supporting a link between androgen deprivation and increased cardiovascular toxicity [19]. Several studies have identified that ADT increases the risk of cardiovascular events, cardiovascular disease (CVD) and CVD-related mortality [13,142-144]. Some evidence suggests a particularly high risk of cardiovascular events for GnRH agonists [143,145], while others found no differences between mechanisms of androgen deprivation [144]. Not only are cardiac tissues affected by ADT-induced metabolic changes, but vascular function is too, which can lead to peripheral artery disease or venous thromboembolisms [146]. FSH depletion through downregulation of the HPG axis by GnRH agonists and antagonists has been suggested as a potential mechanism behind ADT-induced cardiovascular toxicity [147]. FSH stimulates proliferation of vascular endothelial cells and is thought to be involved in plaque formation processes [148]. The situation is aggravated because ADT also affects the immune system and induces a pro-inflammatory state, which may further contribute to the development of atherosclerosis [147].

Metabolic health

ADT has further been linked to decrements in metabolic health that can result in excess morbidity [15,20]. Several of the metabolic effects elicited by ADT overlap with the criteria for metabolic syndrome. The diagnosis of metabolic syndrome is based on five criteria, of which at least three must be present to confirm the disease: elevated serum triglycerides, elevated fasting serum glucose, decreased high-density lipoprotein, increased waist circumference,

and hypertension [149]. ADT has been consistently linked to increases in serum triglycerides, fasting serum glucose and waist circumference [15]. Unsurprisingly, the incidence of metabolic syndrome is significantly higher in men receiving long-term ADT than in prostate cancer controls [150]. While the link between ADT and blood pressure is inconsistent, several studies showed that treatment with secondary hormone therapy like abiraterone and enzalutamide significantly increases the risk of hypertension [151,152]. This further aggravates the risk of metabolic syndrome and associated morbidity in men with advanced prostate cancer. Moreover, the conditions clustered under the diagnosis of metabolic syndrome are considered risk factors for other metabolic diseases, such as diabetes, whose incidence is also expected to surge during ADT. In fact, two large population-based studies with a combined total of 110,000 men with prostate cancer provided compelling evidence of a link between treatment with GnRH agonists and an increased risk of incident diabetes [142,145].

Quality of life

Considering the prolonged overall survival of men with prostate cancer nowadays, quality of life during the years lived with the disease is of major importance. Several studies have found that ADT significantly reduces quality of life outcomes compared to prostate cancer controls [153-155]. One of the most prevalent and distressing cancer-related symptoms is fatigue, which manifests as a general tiredness that is unrelated to prior physical activity and causes major disruption to all aspects of quality of life [156]. Nelson et al. showed that cancer-related fatigue is exacerbated by ADT and that this effect may accumulate over time, as they found that fatigue scores gradually worsened at 6 and 12 months of treatment [17]. Supporting these findings are results from Rodríguez Antolin et al., who observed that fatigue was present in 74% of participants with CRPC and that higher fatigue levels were associated with worse quality of life [157]. In terms of second-generation ARIs additional to ADT, enzalutamide seemed to increase fatigue levels more than abiraterone, while men treated with apalutamide reported a similar fatigue level to those receiving a placebo [158,159].

Other common side effects with implications for quality of life include hot flushes characterised by sudden and repeated episodes of intense heat sensation, flushing and excessive sweating, which are considered by affected patients to be very discomforting [160]. While these are not directly harmful, men who experience multiple hot flushes per day report a significant impairment of daily functioning and quality of life. Another important subdomain of quality of life in the context of prostate cancer is sexual health. Given the vital role that androgens play in the male reproductive system, it is unsurprising that ADT leads to sexual dysfunction in most men [161]. Symptoms of sexual dysfunction include erectile dysfunction, loss of libido, and infertility, which are estimated to affect more than 90% of men on ADT [15].

Several studies have also linked treatment with ADT to cognitive declines, such as impairments of memory, attention and executive functions [162,163].

Physical fitness

Reduced physical fitness is a common consequence of cancer and anti-cancer treatments [164]. The conditions underlying physical fitness reductions, such as muscle wasting, are not only a consequence of cancer-induced metabolic alterations but can also be linked to anti-cancer treatments [165]. ADT, in particular, has been linked to impairments across a range of physical fitness qualities, including reductions in muscle strength, walking speed and peak aerobic performance [131,166]. Importantly, a study by Gong et al. established that patients who undergo prolonged treatment with ADT show reduced cardiorespiratory fitness and increased cardiovascular mortality [166].

For men with particularly aggressive prostate cancer or disease progression despite ADT, the addition of second-generation ARIs provides a survival advantage [167]. The use of ARIs is, however, associated with greater impairments of physical function and cognition, as well as a higher risk of falls and fractures [168-170]. The various ways in which treatments such as ADT and ARIs interfere with determinants of physical fitness present considerable barriers for physical activity and exercise participation and promote inactivity, thus aggravating the decline in physical fitness.

2.3. Role of the immune system in prostate cancer

2.3.1. Structure and function of the immune system

Basics of the immune system

The immune system is a complex and highly interactive network of various organs, cells and molecules that protects the host from various external pathogens and responds to cellular damage [171]. Generally speaking, the immune system plays a central role in fending off and clearing infection, repairing tissues and restoring tissue homeostasis, which are vital functions that ensure the integrity and health of the host. The characteristic immune response to invading pathogens and tissue injury is inflammation, a multi-step process involving numerous immune cells and signalling molecules that initiate and maintain a host response aimed at eliminating the pathogens and healing the afflicted tissue [172]. Inflammation is mediated by pro-inflammatory and anti-inflammatory signals, predominantly in the form of cytokines, whose actions antagonise each other. Consequently, the magnitude of the inflammatory response depends on the balance of either type of cytokines. Acute inflammatory responses are an effective mechanism to clear pathogens and destroy defective cells; however, chronic activation of inflammatory responses creates an

environment that promotes chronic inflammatory diseases and is conducive to carcinogenesis and tumour growth [173]. Therefore, it is essential that the immune system strikes a balance that allows the activation of defence mechanisms when needed but avoids overactivation and destruction through excessive inflammation.

A major challenge for the immune system is the need to correctly distinguish the structures it encounters into self and non-self, as well as potentially harmful and harmless [174]. The immune system is equipped with a variety of cells and soluble factors that cooperate to prevent harm by inactivating and destroying any pathogens recognised as foreign. It is of critical importance for the host's integrity to only direct destructive immune responses at foreign antigens while at the same time tolerating its own, a mechanism referred to as self-tolerance [175]. Discrimination between self and foreign structures relies on the presence of surface molecules, which are recognised by immune cells via specific receptors [174]. This mechanism of recognition also extends to virus-infected host cells and tumour cells, which allows the immune system to destroy aberrant cells to prevent further harm [176,177].

Innate and adaptive immunity

The immune response is divided into two parts that differ in the speed and specificity of their reaction: the fast-acting innate immune response, which presents the first line of defence against invading pathogens; and the long-acting adaptive immune response, which employs more specialised mechanisms to eliminate foreign antigens [171]. Importantly, while innate and adaptive immunity are often regarded as two separate defence mechanisms, an effective immune response requires both systems to function synergistically as their mechanisms complement and depend on each other [178]. It is understood that innate immune cells recognise patterns that provide information about the type of antigen and, in response, activate appropriate defence mechanisms, including cells of the adaptive immunity. Adaptive immune cells, in turn, support and enhance mechanisms of innate immunity [178].

The innate immune system includes all germ-line-encoded features of the human body that provide protection from pathogens, including physical barriers like epithelial and mucus layers, certain immune cells and soluble factors [179]. While innate immune responses act quickly, they are not specific to the pathogen. Instead, innate immune recognition relies on a limited number of receptors that recognise conserved microbial molecules [180]. One major family of receptors that enable innate immune recognition is the toll-like receptor family, which is expressed by various innate immune cells. Interaction with a toll-like receptor ligand triggers a downstream cascade of signalling molecules that stimulate the production of pro-inflammatory cytokines and chemokines to activate other immune cells [181]. Upon activation, innate immune cells respond with phagocytosis of the pathogen, the production of toxic

molecules, and the release of signalling molecules to alert and recruit further immune cells to the site of infection or tissue damage [171]. Altogether, the structure and mechanisms of the innate immunity allows a small number of immune cells to detect and respond rapidly to a variety of antigens, usually within a few hours of first contact [182]. The innate immune response is also a critical part of anti-tumour immunity, which is mediated by innate immune cells recognising tumour-associated antigens and recruiting other actors to the tumour microenvironment to eliminate neoplastic cells [8].

When innate immune mechanisms fail to eliminate infectious organisms or lack the receptors to recognise certain antigens, the actors of the adaptive immunity are recruited [179]. In contrast to the innate immune system, the actors of the adaptive immunity possess a high specificity for their target antigens [183]. Adaptive immune responses are mediated by lymphocytes [182]. Their main function lies in the initiation and execution of antigen-specific effector mechanisms to eliminate extracellular and intracellular pathogens and defective cells, such as tumour cells. Adaptive immune cells are activated by antigen-presenting cells, which express a group of proteins referred to as major histocompatibility complex (MHC) on their surfaces [182]. There are two types of MHC molecules. MHC I is found on all nucleated cells and can present intracellular peptides, such as virus fragments or tumour-specific antigens, while MHC II is only expressed by professional antigen-presenting cells, such as macrophages or dendritic cells [184]. These specialised cells process extracellular antigens and use MHC II to display their fragments to adaptive immune cells. Encounter of lymphocytes with a foreign antigen triggers rearrangement of gene elements and results in the expression of distinct antigen receptors [183]. Following this process of priming, the lymphocytes differentiate and proliferate in order to generate an effective immune response. Therefore, the maximal response of the adaptive immune system requires several days up to weeks after first antigen contact [179]. A key feature of adaptive immunity, however, is its capacity for memory, which is mediated by specialised cells that store the relevant information for each unique antigen and allow for a more rapid immune response upon subsequent encounters [185,186].

Actors of the immune system

Immune responses are mediated by leukocytes, which can be further categorised into different cell types with distinct effector functions [187] (Figure 9). The different leukocyte subsets are characterised by their unique expression of surface glycoproteins termed clusters of differentiation (CD), which allows for phenotype identification through antibody staining [188]. While the morphological features and effector functions displayed by mature leukocytes differ considerably, they all derive from hematopoietic stem cells in the bone

marrow [189]. Hematopoietic stem cells are pluripotent cells, and as such, they can differentiate into most cell types of the human body [190]. In the case of immune cells, these hematopoietic stem cells produce two lineages of progenitor cells from which the different leukocyte subsets derive: myeloid and lymphoid progenitors [187]. Myeloid progenitor cells differentiate into most innate immune cells [191]. Lymphoid progenitor cells, on the other hand, give rise to T and B cell populations, which are the main effector cells of the adaptive immunity, as well as natural killer cells (NK cells), which belong to the innate immunity. Furthermore, the innate immunity also includes the complement system consisting of serum glycoproteins, which can opsonise antigens to mark them for phagocytosis and are activated in cascade sequence to amplify the response [171].

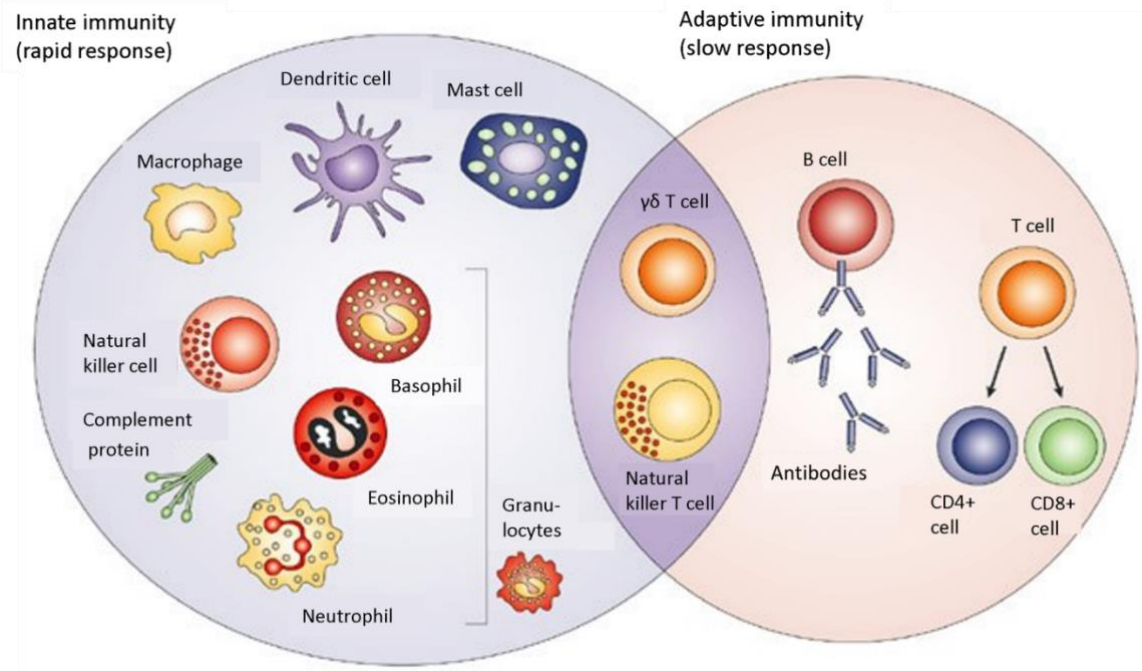


Figure 9. Actors of innate and adaptive immunity. The innate immune response is the body's fast-acting, first line of defence against pathogens. It includes immune cells like granulocytes, macrophages, dendritic cells and natural killer cells, which can recognise pathogens via common molecular surface structures, as well as soluble factors like complement proteins. Innate immune cells eventually activate the adaptive immune response, which consists of T cells, B cells and antibodies. The adaptive immune response develops slower but possesses mechanisms that allow for specific antigen recognition and formation of immunological memory, which leads to effective pathogen destruction and quicker response upon subsequent encounters of the same pathogen. Reproduced with permission from Dranoff (2004) [192].

The differentiation and activation of immune cells is regulated by soluble mediators and their corresponding cellular receptors [193]. Soluble mediators include a vast range of small secreted proteins such as cytokines, growth factors, metabolites and cell adhesion molecules, amongst others [194]. They play a major role in the interaction and communication

between cells, not only within the immune system but also as a crosstalk mechanism with other organs, as they are secreted by most cell types in the human body [195].

2.3.2. Innate immune cells and their role in the anti-tumour response

Innate immunity also represents the first line of immune defence against neoplastic cell growth, which occurs during tumour development and progression [192]. The innate anti-tumour immune response is mediated by multiple types of effector cells, including monocytes, macrophages, dendritic cells, mast cells, NK cells and granulocytes, which are further divided into neutrophils, eosinophils and basophils [182] (Figure 10).

Monocytes are a versatile cell type, whose maturation processes and functions are not yet fully understood, but they are known for their ability to differentiate into macrophages and monocyte-derived dendritic cells [196]. Macrophages and neutrophils share common features, and are thus grouped together as phagocytes [182]. Their main function is phagocytosis, a process during which antigens are engulfed and subsequently destroyed by the immune cells [182]. Macrophages are among the first cells present at the site of tissue damage, where they identify and process tumour antigens before quickly releasing cytokines to recruit more immune cells [174]. Among these cytokines are granulocyte and granulocyte-macrophage colony stimulating factors, which promote the differentiation of neutrophils in the bone marrow [171]. Neutrophils are then released into the blood, thus causing a substantial increase in circulating leukocytes, also referred to as neutrophil leucocytosis, which is a characteristic feature during the early stages of the innate immune response. A combination of signals, involving pro-inflammatory cytokines, chemoattractants and cell adhesion molecules, then stimulates neutrophils to home to the site of inflammation, where they execute their effector function. In addition to their ability to phagocytose tumour antigens, macrophages also occupy an important messenger function [182]. They process phagocytosed tumour particles and present the foreign antigens to lymphocytes to involve the adaptive immune response, a role they share with dendritic cells [197].

Mast cells and basophils are instrumental during the initial phase of the immune response because they store large quantities of soluble mediators, such as histamine, cytokines and enzymes, that they release upon activation to initiate a pro-inflammatory response and engage other cells [198]. In a similar manner, eosinophils contain granules filled with enzymes and cytokines, which they release upon encountering pathogens that are too large for phagocytosis [199]. Evidence suggests that eosinophils perform targeted degranulation in close proximity to the tumour to elicit cytotoxic effects [200].

A major role in the innate anti-tumour immunity is occupied by NK cells, which can destroy malignant cells through the release of perforins and granzymes that cause the targeted cells to enter into apoptosis [8,201]. In addition to their cytotoxic function, NK cells also produce and release cytokines such as interferon-γ (IFN-γ) to modulate adaptive immune responses [202]. NK cells are mostly found circulating in the blood, where they account for approximately 5 to 10% of peripheral blood mononuclear cells (PBMCs) [201]. As cells of the innate immune system, NK cells do not express specific receptors for target antigen recognition; instead, they rely on other actors such as dendritic cells for activation of the anti-tumour response. NK cell activity is regulated by a balance of signals from activating and inhibitory receptors, a safety mechanism that prevents the destruction of healthy cells. Once the activating receptors dominate, NK cells exert their killing function, which in the context of cancer is directed either against circulating tumour cells in the blood or primary tumour cells in the tissue. Morphologically, human NK cells are characterised by the expression of the surface marker CD56 and can be further divided based on the cell surface density of that marker into $CD56^{bright}$ and $CD56^{dim}$ subsets, each with distinct phenotypic properties [203]. $CD56^{bright}$ NK cells exhibit a high level of cytotoxicity, while $CD56^{dim}$ NK cells exert a predominantly regulatory function. Recently, another NK cell subset has been identified that exhibits an immunological memory function, a feature previously thought to be exclusive to adaptive immune cells, thus underlining the diversity in NK cell function [201].

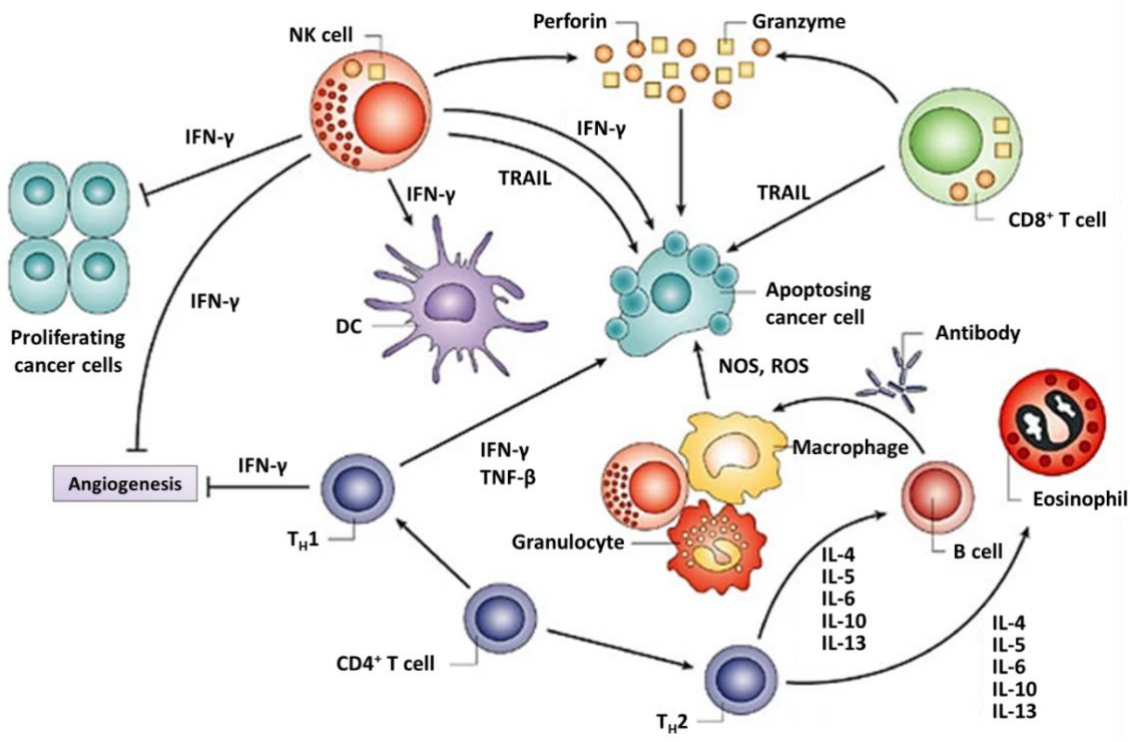


Figure 10. Defence mechanisms of innate immune cells and their interaction with adaptive immunity in the anti-tumour immune response. Innate immune cells are equipped with various effector mechanisms that can inhibit tumour cell growth. Natural killer

(NK) cells induce tumour cell apoptosis through secretion of perforin and granzymes or the stimulation of apoptosis-inducing ligands via specialised surface receptors. NK cells also secrete interferon-γ (IFN-γ) to inhibit tumour angiogenesis and support antigen presentation by dendritic cells (DC) to activate adaptive immune cells. Macrophages produce nitric oxide (NOS) and reactive oxygen species (ROS) to induce tumour cell lysis. Reproduced with permission from Dranoff (2004) [192].

2.3.3. Adaptive immune cells and their role in the anti-tumour response

The adaptive anti-tumour immune response is largely activated by innate immune cells, when their effector mechanisms are ineffective in defence against neoplastic cells [204]. The hallmarks of adaptive immunity are antigen-specific defence mechanisms for effective clearing and the development of an immunological memory that allows a quicker response upon subsequent encounter with the same antigen [182]. Adaptive immunity is mediated by two types of lymphocytes, which are named T cells and B cells according to the tissue of their maturation. The precursor of both cell types originates in the bone marrow from hematopoietic stem cells and either migrates to the thymus to mature into T cells or remains in the bone marrow to mature into B cells [191].

T cells

T cells play a key role in the cell-mediated immunity [182]. T cells are equipped with a surface-bound T-cell receptor (TCR), which can bind to antigenic peptides presented on MHC molecules by various types of antigen-presenting cells [183]. Each mature T cell expresses a unique TCR that binds to one specific foreign antigen. To ensure protection against the variety of existing threats, the human immune system requires an equally large variety of T cells with discrete TCRs [187]. The wide range of TCRs is generated during T cell maturation through somatic recombination of gene segments, from which the TCR is assembled [183]. This is the most remarkable feature of adaptive immunity, because the random rearrangement of gene segments paired with purposeful gene alterations produces an enormous repertoire of TCR that is large enough to cover the variability among antigens [171]. Before they are released from the thymus into circulation, T cell precursors must pass negative selection, where their affinity to self-peptides, i.e. peptides that are commonly expressed by the host, is tested [183]. This selection process is critical, as it ensures self-tolerance through the elimination of autoreactive T cell precursors. As part of the development in the thymus, T cell precursors also differentiate into one of two main subclasses: either $CD8^+$ cells known as cytotoxic T cells (Tc cells) or $CD4^+$ cells known as T helper (Th cells) cells [205]. Although both T cell subclasses share the same progenitors, once activated they develop into effector cells with highly specialised phenotypes. The process of differentiation and phenotype development is strictly regulated by signalling

involving various cytokines, chemokines, transcription factors and metabolic signals, and T cell lineages are regarded to be fixed and mutually exclusive [206].

After passing the developmental checkpoints, naïve T cells are released from the thymus into the bloodstream, where they circulate in search for their antigen. Naïve T cells are activated upon contact with antigen-presenting cells that display the unique antigen to which their TCR binds specifically, provided that required co-stimulatory signals are present [182]. Their chance of encountering an antigen-presenting cell is increased by their high level of mobility. Naïve T cells constantly circulate in the blood and lymphatic system and accumulate in lymph nodes, where large numbers of immune cells are present. Contact with tumour-associated antigens is mediated by professional antigen-presenting cells that collect these antigens in the primary tumour tissue and migrate to the lymph nodes or reside in lymphatic organs and take up soluble antigens for presentation [207]. Activated through antigen contact, T cells enter a state of proliferation and clonal expansion that can produce up to one thousand progeny of each cell [171]. The activated T cells then are stimulated by chemotactic factors released from tumour cells to home to the tumour microenvironment, where they fulfil their effector function [208].

The main role of Tc cells is the elimination of infected or neoplastic cells, which they exert by releasing soluble factors that induce apoptosis of their targets (Figure 11). Tc cells create pores in the target cell membrane either through the use of mechanical force or the release of granulysin and perforin [209,210]. Cytotoxic enzymes secreted by Tc cells can pass through these pores into the cytoplasm of the target cells and induce cell death. Additionally, Tc cells express the transmembrane protein Fas ligand, which binds to Fas receptors on target cells and induces alternative cell death mechanisms, such as the enzymatic fragmentation of target cell DNA [211]. This process of killing target cells occurs in a matter of minutes and individual Tc cells are capable of simultaneously killing multiple target cells [212]. Because of their cytotoxic abilities, Tc cells are powerful effectors in the anti-tumour immune response [213]. Tc cell recognition of tumour cells occurs via neoantigens, which are newly formed antigens generated by tumour cells as part of tumour-specific alterations to the cell genome and metabolism [214]. Neoantigens interact with the TCR and are recognised as non-self, which triggers an anti-tumour immune response to eliminate the neoplastic cells.

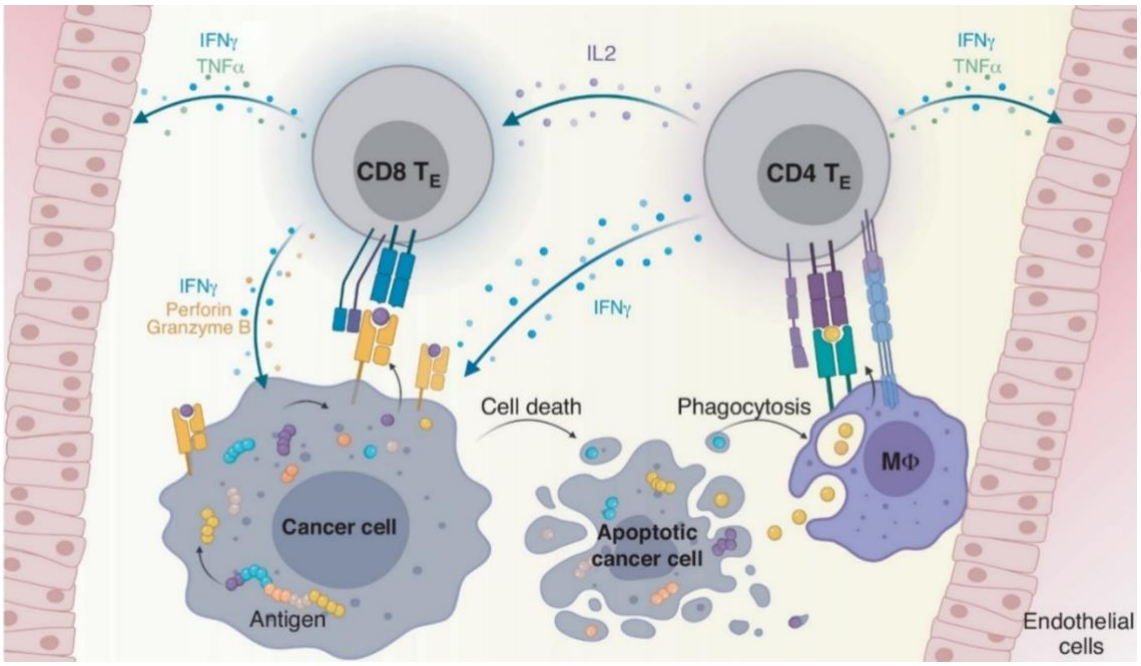


Figure 11. Interaction of CD4⁺ and CD8⁺ T cells in the anti-tumour immune response. $CD8^+$ T cells recognise tumour neoantigens presented on major histocompatibility complex (MHC) I molecules and respond with mechanical efforts and the release of perforins and granzymes to induce target cell death. $CD4^+$ T cells recognise their target through cross-presentation of tumour antigens by macrophages (MΦ) and respond with cytokine release for additional activation of $CD8^+$ T cells. Cytokines released by both cell types also alter the tumour microenvironment and surrounding tissue to facilitate tumour cell killing, for example through destruction of blood vessels. Particles of apoptotic tumour cells are phagocytosed by MΦ and tumour antigens are presented to $CD4^+$ T cells to amplify the response. Reproduced under a Creative Commons licence (CC BY NC ND) from Poncette et al. (2022) [215].

While Th cells do not display the same level of cytotoxicity as Tc cells, they further differentiate into various subsets with specific effector functions that make them important coordinators of the anti-tumour immune response [187]. The differentiation into these effector populations is largely controlled by cytokine signalling and depends on the type of antigen exposure, which allows for tailored immune responses to different antigens [187]. Several Th cell subsets have been identified in the tumour microenvironment, including Th1, Th2, Th17 and regulatory T cells (Treg cells) [216] (Figure 12). Th cell subsets are characterised by the specific cytokines that they release to mediate their effector functions.

The best described Th cell subsets are Th1 and Th2, which are induced by innate immune cells secreting interleukin-12 (IL-12) and IFN-γ for Th1 differentiation and IL-4 for Th2 differentiation [217]. Th1 cells mainly produce IFN-γ, which activates macrophages, NK cells and Tc cells to enhance intracellular killing of microbes and cytotoxicity against infected or neoplastic cells. Th1-derived cytokines also stimulate B cells to produce opsonising antibodies that mark target cells for phagocytosis [182]. Important for the anti-tumour response is the ability of Th1-derived IFN-γ to indirectly inhibit tumour growth by suppressing

angiogenesis and promoting blood vessel regression that leads to starvation of the tumour [218]. Th2 cells release a variety of cytokines, such as IL-4, IL-5 and IL-13, that activate eosinophils and macrophages, but also self-induce Th2 cell differentiation in situ to provoke a strong inflammatory response [182]. Th2-mediated immune responses play a critical role in wound healing and tissue regeneration, two processes that generally involve the stimulation of cell proliferation, and are therefore thought to stimulate tumour cell growth rather than inhibit it [219]. While Th1 and Th2 cells work together in the coordination of an immune response, the nature of their responses is diverging and therefore, one cell type will eventually dominate [183].

Less is known about the roles of Th17 cells, which are characterised by the secretion of the pro-inflammatory cytokine IL-17. Differentiation of Th17 cells occurs upon exposure to combinations of IL-1, IL-6 and transforming growth factor β (TGF-β). Secretion of IL-17 is essential for the defence against extracellular pathogens but is also involved in the pathogenesis of several autoimmune and inflammatory diseases due to its pro-inflammatory properties [220].

Once the identified threat in the form of invading pathogens or neoplastic cells is successfully eliminated, it is important that the immune response is resolved to avoid tissue damage caused by excessive inflammation [182]. The resolution of immune responses is in part thought to be mediated by Treg cells, which secrete the inhibitory cytokines IL-10 and TGF-β to suppress inflammatory processes [221]. Most T cells die and are cleared by phagocytes once the immune response has been resolved, with the exception of a few cells that are retained as memory cells to allow a more rapid immune response upon subsequent contact with the same antigen [182]. While several Th cell subsets display effector functions that can destroy tumour cells, Th-derived cytokines can also contribute to immunosuppression in the tumour microenvironment and enhance immune tolerance and tumour growth, which makes their role in cancer immunity controversial [215].

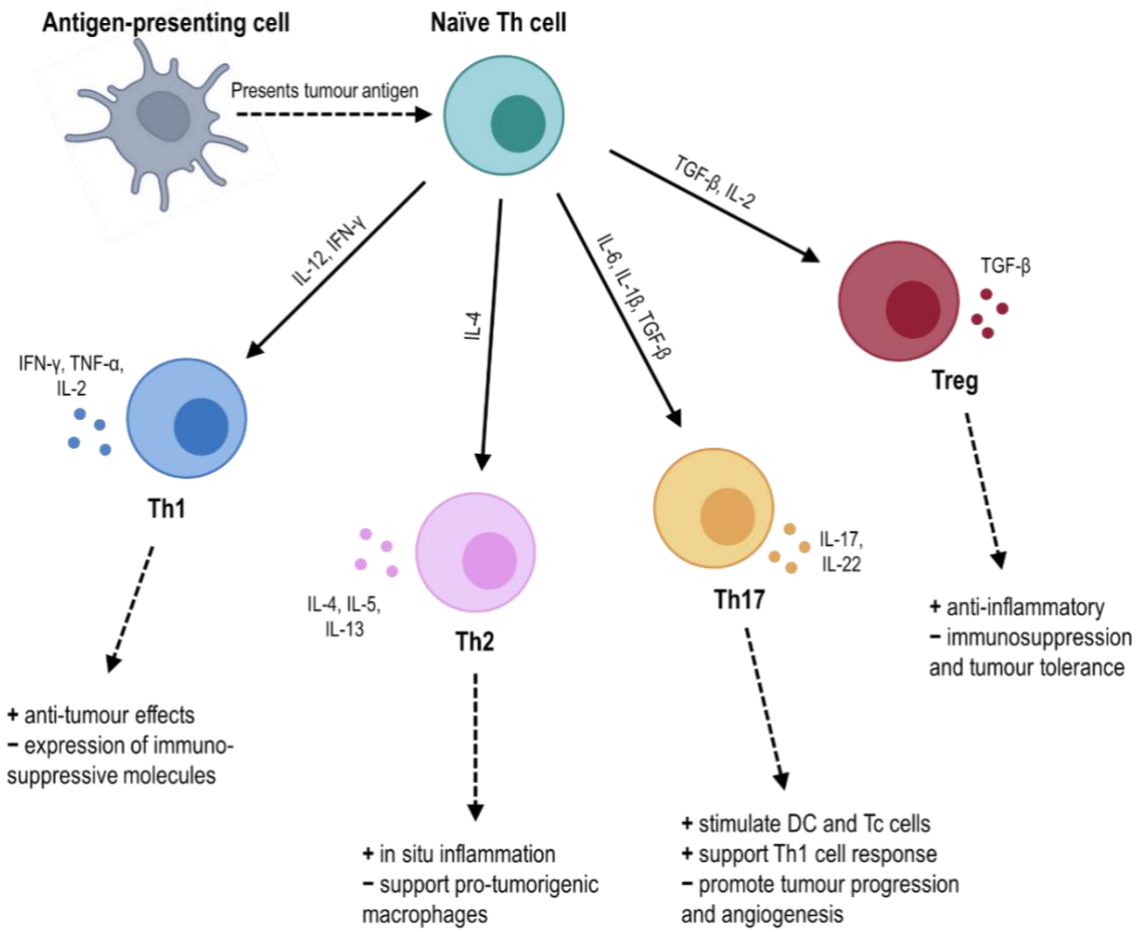


Figure 12. Characteristics of T helper cell (Th cell) subsets and their effects on tumour cells. Upon activation through antigen presentation, naïve Th cells differentiate into distinct subsets in a process controlled by cytokine signalling. Each subset mediates specific effector functions through the production and release of cytokines. Some of the mechanisms stimulated by Th-derived cytokines promote anti-tumour immunity (favourable, +), while others contribute to immune evasion and enhance tumour growth (unfavourable, −). DC: dendritic cells, IFN-γ: interferon-γ, IL: interleukin, Tc cell: cytotoxic T cell, TGF-β: transforming growth factor β, TNF-α: tumour necrosis factor α, Treg cell: regulatory T cell. Figure conceptualisation based on Speiser et al. (2023) [216].

B cells

The B cell immune response relies on the release of antibodies and is therefore also referred to as antibody-mediated or humoral immunity [182]. Contrary to T cells, B cells remain in the bone marrow for maturation, only migrating to other tissues as mature cells. B cells are characterised by the expression of unique antigen-binding receptors on their surface, which are assembled in a similar gene recombination process as the TCR in T cells [187]. This maturation process occurs under the direction of cytokines released by primed T cells, which makes the B cell response partly dependent on T cells [183]. Structurally, the B cell receptor is a membrane-bound immunoglobulin with two identical antigen binding sites that allow the B

cell to bind antigens directly, a process that does not require the involvement of antigen-presenting cells [222,223].

Naïve B cells predominantly reside in lymphoid organs, with only a small percentage circulating in the bloodstream [224]. B cell activation is initiated upon antigen recognition via the B cell receptor, which activates a signalling cascade that stimulates B cells to proliferate and differentiate into either plasma cells or memory B cells [182]. Plasma cells produce and release large amounts of clonal antibodies that neutralise antigens by marking them for destruction by other immune cells [186]. While plasma cells are short-lived and undergo apoptosis when the inflammation ceases, memory B cells have a longer lifespan and can be activated much quicker upon subsequent encounters with the same antigen.

B cells produce five major antibody classes (IgA, IgD, IgE, IgG and IgM) that differ in their ability to recognise and neutralise antigens, thus, each antigen provokes a unique antibody response [225]. B cells are also known to infiltrate tumours and produce tumour-specific antibodies that recognise and react against tumour-associated antigens [226]. The presence of B cells in the tumour microenvironment supports the efforts of the T cell-mediated anti-tumour immunity by marking tumour cells for cytotoxic effector cells or initiating complement-dependent cytotoxicity [227].

2.3.4. The immune system in prostate cancer pathophysiology

Similar to tissue injury, tumours trigger an inflammatory response initiated by the innate immune system and completed by tumour-antigen specific defence mechanisms of the adaptive immunity [228]. Various immune cells infiltrate the tumour microenvironment and release molecular mediators, including cytokines, chemokines and transforming growth factors, to amplify the immune response and induce tumour cell cytotoxicity. However, many signalling molecules can have ambivalent effects, and whether the immune response restricts or supports tumour survival depends on the balance of effector cells and mediators. While the initial inflammatory immune response inhibits tumour growth, chronic inflammation has been implicated as a driver of carcinogenesis and tumour progression [173]. Moreover, tumours manipulate their immediate environment through the release of immunosuppressive signalling molecules and modulate immune responses to evade immune surveillance. Prostate cancer in particular is understood to employ a complex network of cellular and molecular mechanisms that induce extensive immunosuppression in the tumour microenvironment, which leads to poor success rates of immunotherapy compared to other solid tumours [229].

Inflammation-induced prostate carcinogenesis

While inflammation serves as a physiological defence mechanism, increased inflammation in prostate tissue has been associated with a higher risk for prostate cancer development [230,231]. Prostatic inflammation can be caused by multiple factors, including microbial infections, urine reflux, chemical irritation or dietary factors [232-236]. Any of these factors can trigger a pro-inflammatory immune response, during which infested or damaged cells are cleared and proliferative signals are required to complete tissue repair [7]. The remodelling of prostate tissue in response to pro-inflammatory stimuli promotes structural and epigenetic changes that can ultimately result in uncontrolled proliferation of prostate cells and initiate tumour growth [237]. The causative relationship between inflammation and malignant prostate tissue changes was first shown in mice, where injection of *Escherichia coli* bacteria into the prostate resulted in the development of reactive hyperplasia induced by chronic inflammation [238]. In line with these findings, human genome analyses discovered mutations in inflammation-related genes, such as immune cell receptors and immune-modulating enzymes, among families with an increased risk of hereditary prostate cancer [239,240].

Inflammatory processes are not only involved in tumour initiation but are also vital to sustain the transformation and promote tumour progression and treatment resistance [241,242]. A chronically pro-inflammatory tumour microenvironment stimulates tumour growth via several mechanisms. The inflammatory response enhances the release of free radicals, such as reactive oxygen and nitrogen species, as well as cytokines that cause tissue injury, which triggers compensatory epithelial proliferation [7]. Mass release of these highly reactive compounds also induces DNA damages through genome destabilisation and promotes gene mutations, which are a hallmark of cancer.

Continued recruitment of certain immune cell types and alteration of their effector function by the tumour sustains the pro-inflammatory tumour microenvironment that is conducive to tumour growth [173]. Immune cell migration during cancer and its implication for tumour aggressiveness is complex. Some cell types have been identified as drivers of tumorigenesis, and their presence in the tumour microenvironment is associated with poorer outcomes [243]. Tumour-associated macrophages release signalling molecules that suppress immune responses targeted at killing tumour cells and stimulate tumour growth by promoting angiogenesis [244]. Tumour-associated macrophages also promote cell migration and secrete proteases that destabilise the basement membrane of the prostate epithelium, which is thought to facilitate metastasis formation [244,245]. Signalling by tumour cells also mobilises large numbers of neutrophils that fulfil a similar role to macrophages in the tumour microenvironment, by enhancing proliferation and supporting tumour cell invasion [246]. The

maintenance of an immunosuppressive tumour microenvironment is aided by cancer-associated fibroblasts, which release a range of signals that stimulate the pro-tumour polarisation of macrophages and recruit neutrophils, whilst suppressing NK cell activation and Tc cell infiltration to avoid cytotoxicity [247].

Because immune cell recruitment and activation are largely mediated by cytokines and chemokines, the tumour microenvironment is characterised by distinct release patterns of pro-inflammatory signalling molecules from tumour cells, surrounding stroma cells and tumour-associated immune cells [173]. Increased blood levels of IL-6 and its soluble receptor have been associated with biochemical prostate cancer progression and bone metastases [248]. IL-6 activates three major signalling pathways that promote angiogenesis and enhance anti-apoptotic and proliferative processes [249]. Therefore, IL-6 is thought to act as an important survival signal in prostate cancer cells and presents a target of interest for anti-cancer therapies [250]. IL-6 and other pro-inflammatory cytokines, such as IL-1β and IL-8, are produced by tumour cells, cancer-associated fibroblasts and various immune cells [173]. By contrast, expression of IFN-γ, which is an important mediator of the T cell response and promotes anti-tumour effects, is often reduced in cancer [251]. Overall, tumours manipulate the recruitment and functional differentiation of immune cells through continued release of pro-inflammatory and immunosuppressive signals to create a tumour microenvironment that fosters tumour survival and growth.

Immune escape strategies of prostate cancer

While prostate cancer derives from healthy epithelial prostate cells, the originating tumour cells are not invisible to the immune system. Tumour cells carry antigens that are recognised by innate immune cells such as NK cells that can kill target cells, as well as macrophages and dendritic cells that present the antigens to T lymphocytes and activate Tc cell-mediated cytotoxicity [6]. Apoptotic cancer cells release more tumour-associated antigens, which alert and activate further immune cells and intensify the anti-tumour immune response [252]. This positive feedback loop would allow the immune system to rapidly and efficiently eliminate cancer cells. However, prostate cancer employs multiple immune escape strategies that inhibit the anti-tumour immune response and protect tumour cells from detection and destruction by the immune system [253].

A large-scale analysis of the expression of immune-related genes in prostate cancer tissue found that in 90% of samples expression levels of genes responsible for antigen processing and presentation, immune cell recruitment and activation were low [10]. The failure to upregulate these genes results in immunologic ignorance, where the foreign antigen is not recognised by the immune system. Furthermore, half of the tumours in this study also

expressed decoy molecules, such as programmed death-ligand 1 (PD-L1), that bind to surface receptors of Tc cells and weaken their cytotoxic activity. Expression of PD-L1 on tumour cells has been associated with reduced metastasis-free survival in men with locally advanced prostate cancer at the time of prostatectomy [254]. One of the predominant cell types implicated in the immune escape by prostate cancer are the anti-inflammatory Tregs [255]. Tregs inhibit Th and Tc cell activity to avoid excessive inflammation and enhanced Treg activation is a major suppressor of anti-tumour immune responses. In fact, prospective studies of prostate tissue samples have linked the presence of higher numbers of Tregs to increased prostate cancer risk and aggressiveness [256,257].

Among the innate immune cells, NK cells are the main effector cells responsible for killing tumour cells [201]. Because NK cells are required to act fast and do not possess adaptive receptors to recognise their target, they rely on the balance between activating and inhibitory signals released from other innate immune cells to exert their killing function. Tumours have been shown to express tumour-derived molecules like prostaglandin E2, adenosine and programmed cell death ligand 1, which inhibit NK cell activation and function [258-260]. Moreover, tumours are known to further evade the immune response by remodelling their actin cytoskeleton to protect themselves from cytotoxicity [261]. These findings originate from studies of various cancers and, while it remains uncertain which of these immune escape mechanisms are characteristic for prostate cancer, as the first line of defence against tumours NK cells are certainly a desired target of tumour-induced alterations.

2.3.5. Influence of prostate cancer treatments on the immune function

Cancer treatments interact with the immune system, either deliberately by enhancing anti-tumour immune responses or inadvertently through cytotoxic effects that affect tumour cells and host cells in equal measure. Chemotherapy is a widely used cancer treatment that has proven effective in reducing tumour progression in many types of cancer [262]. The effectiveness of chemotherapy derives from its cytotoxic properties that primarily target rapidly proliferating cells, such as tumour cells, but can also have deleterious effects on healthy cells, such as immune cells. Immune suppression, most commonly in the form of leukopenia or thrombocytopenia, is therefore a frequent adverse effect associated with chemotherapy [263]. Some chemotherapeutic agents can induce apoptosis of T cells or NK cells or impair the maturation of dendritic cells, all of which are crucial for the recognition and elimination of tumour cells [264]. Furthermore, chemotherapy may not only suppress immune cell populations but also disrupt communication pathways among immune cells, which compromises the coordinated efforts within the complex network of immune actors and can result in immune dysregulation [264]. Analysis of 421 men treated with first-line docetaxel for

mCRPC found that 47% experienced a severe adverse event during the treatment, 11% developed febrile neutropenia (i.e. fever during severe neutropenia), which indicates an infection during a state of immunosuppression and is considered life-threatening, and 41% required hospital admission during treatment [265]. Similar cytotoxic effects can occur following radiotherapy, which induces tumour cell apoptosis that leads to the release of tumour antigens and a subsequent immune response but can also negatively affect immune cells in the surrounding tissue [266].

While not inherently cytotoxic, androgen deprivation may also influence the immune response, although the direction of that interaction is less clear. Many different immune cells are known to express the AR, including neutrophils, monocytes, macrophages, mast cells and T lymphocytes, as well as hematopoietic stem cells and both lineages of progenitor cells [267,268]. Testosterone-mediated activation of the AR in immune cells is generally considered to induce immunosuppressive effects by decreasing T cell numbers and activity, reducing antibody production and stimulating anti-inflammatory signalling pathways [269]. Androgen signalling supresses the production of pro-inflammatory cytokines like tumour necrosis factor α (TNFα) and IL-1β and, instead, promotes the release of anti-inflammatory cytokines, such as IL-10 [270]. Some of the androgen-dependent mechanisms benefit the tumour and promote its progression, while others enhance tumour-specific immune responses [271] (Figure 13). Evidence for the effects of androgen deprivation on circulating immune cells and their corresponding soluble mediators is limited and often inconclusive [269]. Some studies observed an impaired Tc cell response to stimulation during ADT, whereas others demonstrated that androgen-axis blockade may increase T cell infiltration within the prostate and enhance Tc cell-driven anti-tumour immune responses [272-274]. Altogether, a better understanding of immune function in men with prostate cancer undergoing androgen deprivation is desirable.

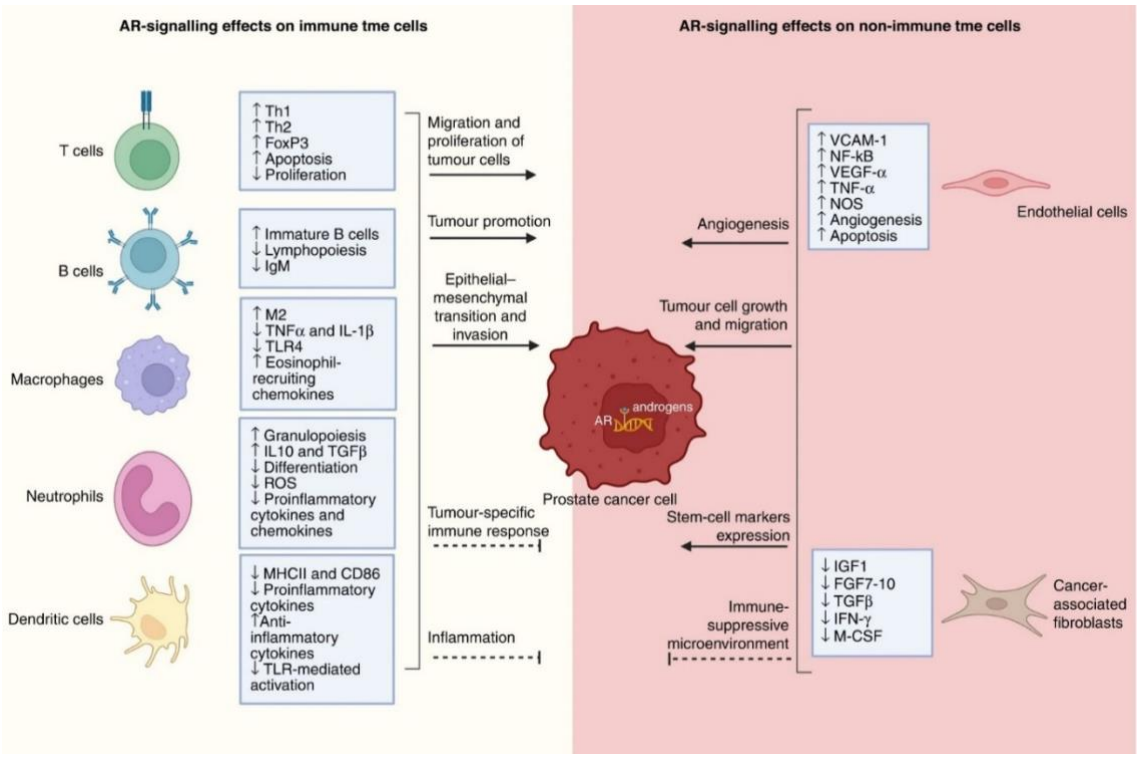


Figure 13. The effects of androgen signalling on immune and non-immune cells in the tumour microenvironment (TME) of prostate cancer. The abundance of androgen receptor (AR) expression by cells in the TME makes androgens important modulators of anti-tumour immunity. Androgen signalling promotes tumour progression by inhibiting T helper (Th) cell activation, decreasing antibody production by B cells and activating tumorigenic M2-polarised macrophages. However, androgen signalling also suppresses pro-inflammatory cytokine production and, in turn, stimulates the release of some anti-inflammatory mediators by cells in the TME, which promotes anti-tumour immunity. Solid black arrows represent stimulating actions, truncated dotted black lines represent inhibitory actions. Reproduced with permission from Conteduca et al. (2023) [271].

2.3.6. Cellular markers of immune responses in prostate cancer

The role of the immune system in cancer is ambivalent because it holds effector mechanisms that can exert anti-tumour immunity, though certain immune cells have also been implicated as drivers of tumorigenesis [253]. Therefore, the quantification and characterisation of immune cells and their effector function has become a focus of cancer research. Tumour-induced changes of the immune response not only affect the immediate tumour microenvironment but also result in systemic changes, which is indicated by altered differentiation, mobilisation and function of immune cells [173]. The immune system comprises a complex network of effector cells, whose function is highly dependent on their location and the presence of signalling molecules [187]. Nevertheless, characterisation of immune cell populations in peripheral blood has been shown to reflect immunological changes in cancer [275]. In individuals with breast cancer, lymphocyte and Treg concentrations in the peripheral blood negatively correlated with tumour size [276].

Ratios of certain cell types can provide additional information concerning the balance of the immune response. Frequently used cell ratios include the Th1/Th2 ratio and Treg/Th17 ratio. Both Th1 and Th2 are activated upon antigen contact as part of adaptive immunity, yet environmental and genetic factors decide which Th cell type will dominate the immune response [277]. Th1-dominated immune responses are generally considered pro-inflammatory and Th1-derived cytokines activate Tc cells, NK cells and macrophages, which are important effectors of the anti-tumour response. Conversely, Th2-specific cytokines are known to antagonise inflammation by inhibiting Th1 immune responses [278]. A reduced Th1/Th2 ratio has been associated with poor prognosis in cervical, colorectal and breast cancer [279-281]. The Th17/Treg ratio represents a similar balance between pro and anti-inflammatory stimuli. Th17 cells release cytokines that stimulate Tc cell cytotoxicity, whereas Tregs are known to suppress anti-tumour immune responses. Despite evidence for Th17/Treg imbalance in other chronic immune disorders, such as asthma, the role of this cell ratio as a potential marker for the immune milieu in cancer remains to be investigated [282].

Chronic inflammation is considered a hallmark of cancer and several immune cell-based markers have been proposed in the scientific literature to quantify systemic inflammation [173]. The most commonly used markers are the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII), which is obtained by multiplying the NLR with the number of platelets [283-285] (Figure 14). Platelets, also known as thrombocytes, are small cells without a nucleus that originate from the same hematopoietic lineage as other immune cells [286]. Their most characteristic function is thrombus formation through cell adhesion and clotting in response to vascular injury to prevent blood loss. Additionally, they have lately gained recognition for their involvement in immunity as they express the same class of receptors that recognise pathogen-associated patterns as other innate immune cells. The advantage of these indices is that their calculation only requires few blood values that are typically collected as part of routine care. Multiple studies have suggested these indices as prognostic markers to predict survival, disease progression and treatment outcomes across a variety of cancers, including prostate cancer [287-290]. A higher SII, which is indicative of a greater level of inflammation, has been associated with poorer overall survival in mCRPC, as well as being linked to a higher Gleason score and poorer recurrence-free survival in non-metastatic prostate cancer [290]. Similarly, an elevated NLR has been shown to predict poorer overall survival and recurrence-free survival in men with advanced prostate cancer [291].

As the main effector cells of innate anti-tumour immunity, NK cells are of particular interest in the context of cancer [8]. NK cells levels in the peripheral blood, however, do not necessarily reflect NK cell-mediated cytotoxicity because their effector function depends on a variety of

factors, including cytokines, surface receptors and ligands. Similar to the already described ratios of T lymphocytes, the balance between the NK subsets $CD56^{dim}$ and $CD56^{bright}$ is considered to reflect NK cell cytotoxicity due to the diverging effector functions of both subsets [203]. In fact, an increased $CD56^{dim}/CD56^{bright}$ ratio was associated with improved disease-free survival and a lower relapse rate in children with haematological malignancies [292].

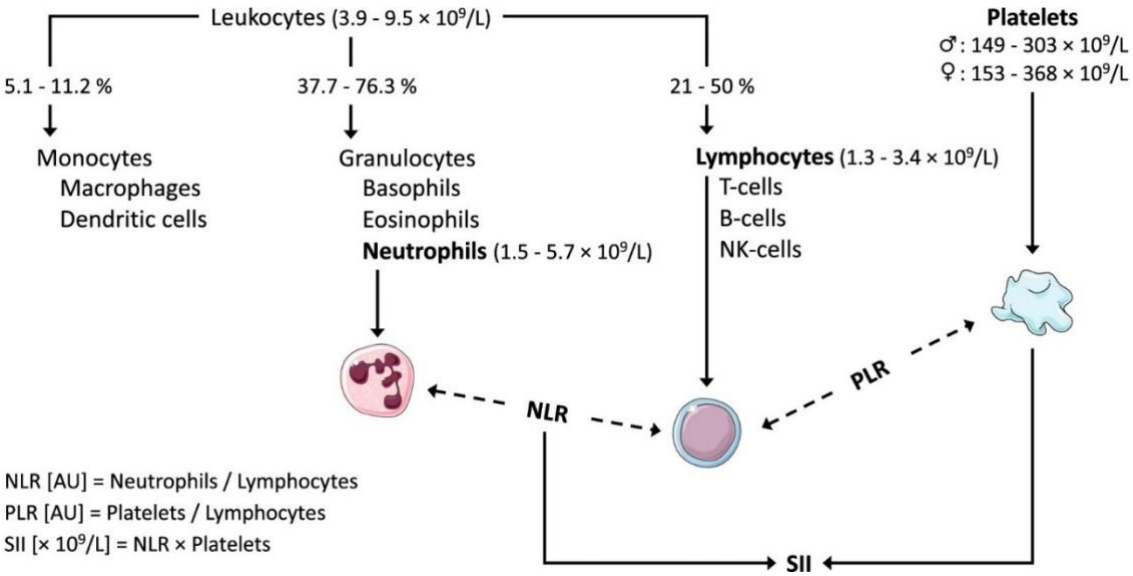


Figure 14. Cellular immune inflammation indices. Calculating the ratios of different immune cell populations can provide insight on the overall immune balance. Established inflammation indices that have been associated with clinical outcomes in cancer include the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII). Higher values for any of the three indices represent greater levels of inflammation. Reproduced under a Creative Commons licence (CC BY) from Walzik et al. (2021) [293].

2.4. Physical activity and exercise in prostate cancer

2.4.1. Recommendations for physical activity and exercise during cancer

Epidemiological studies provide accumulating evidence for modifiable lifestyle factors, such as physical activity and exercise behaviour, as important mediators of health and survival following a cancer diagnosis [22]. Though often used interchangeably, physical activity and exercise are two distinct concepts. The term physical activity refers to any movements produced by the muscles that result in energy expenditure [294]. Exercise is a subset of physical activity and describes planned, structured and purposeful activities that aim to maintain or enhance physical fitness [294]. Higher physical activity levels and exercise participation post cancer diagnosis are thought to promote favourable outcomes, including longer overall and disease-free survival, quality of life improvements, better physical function and reduced side effects of anti-cancer

treatments. Consequently, several organisations have issued public health recommendations for the minimum levels of physical activity and exercise that offer significant health benefits for different groups of individuals, including cancer survivors [25,295] (Table 3).

Generally, these guidelines present strong evidence for the association between physical activity and cancer risk and survival for a variety of cancer types, especially for post-diagnosis physical activity, and conclude that health professionals should promote physical activity as an integral component of cancer care [296]. They also highlight the understanding that more physical activity is generally considered favourable but that benefits diminish at high levels of physical activity. The latter is also the rationale for stating an upper limit of 300 minutes per week, although this number is considered conditional as benefits may still occur above this level [295]. Furthermore, they state that the benefits of physical activity outweigh potential risks for people living with chronic conditions, including cancer, provided that they have no contraindications to exercise.

Table 3. Physical activity and exercise recommendations issued by public health organisations or clinical experts.

American Cancer Society (Rock et al., 2022) [25]
• During and immediately after cancer treatment physical activity provides benefits for quality of life and treatment-related side effects. • After completion of cancer treatment being physically active improves survival and other health outcomes. • Cancer survivors should regularly engage in physical activity with consideration of cancer type, overall health, treatments and symptoms to avoid obesity and maintain or increase muscle mass. • **Aerobic physical activity:** 150 to 300 min moderate intensity or 75 to 150 min vigorous intensity physical activity per week. • **Resistance exercise:** Participation in muscle-strengthening activities on two or more days per week.
World Health Organization (Bull et al., 2020) [295]
• Across all populations, any amount of physical activity is favourable over inactivity. The amount of time spent sedentary should be limited to avoid adverse health effects. • Habitual physical activity is generally safe and can be adopted by inactive individuals without seeking medical clearance, provided that intensity and duration are increased gradually. • **Aerobic physical activity:** 150 to 300 min moderate intensity or 75 to 150 min vigorous intensity or an equivalent combination of moderate-to-vigorous physical activity (for adults 18 to 64 years). • **Resistance exercise:** Participation in muscle-strengthening activities at moderate or greater intensity on two or more days per week (for adults 18 to 64 years). • Engaging in a wide range of physical activities, including aerobic, strength and balance exercise, can improve various aspects of physical function and prevent osteoporosis for older adults (65 years and above).

International Multidisciplinary Roundtable (Campbell et al., 2019) [297]
• Effective exercise programmes should have a duration of 8 to 12 weeks at minimum. • Cancer survivors are encouraged to engage in regular exercise throughout the cancer care continuum. • **Aerobic exercise:** Moderate intensity aerobic exercise at least three times per week, with a minimum session duration of 30 min. • **Resistance exercise:** Two or more sessions per week, including at least two sets with 8 to 15 repetitions per exercise. Exercises should be performed at loads of 60% of the one-repetition maximum or above.

After initially approaching the topic of exercise with apprehension due to fear of adverse events, oncologists are nowadays encouraged to recommend cancer survivors to participate in exercise if their physical condition allows [21,298]. Several clinical trials have established that exercise is generally safe and acceptable before, during and after cancer treatment for individuals of all cancer types or stages, including those with advanced disease receiving palliative care [299-301]. Most studies to date have shown benefits of exercise when the exercise programme was professionally supervised and included at least three sessions per week of moderate or high intensity, although the reported efficacy of interventions varies [302,303]. An overview of frequently used categories of physical activity intensity and corresponding activities is presented in Table 4. Furthermore, studies have demonstrated that patients benefit from structured exercise programmes that include resistance exercise to counteract cancer-related muscle dysfunction and from prescriptions that are tailored to their individual needs [303].

Table 4. Categories of physical activity intensity including objective and subjective measures. Adapted from Norton et al. (2010) [304] and Bull et al. (2020) [295].

Intensity	Objective measures	Subjective measures	Description
Sedentary	< 1.6 METs < 40% HR_{max} < 20% VO_2max	RPE: < 1	Activities that involve sitting, reclining or lying with little additional movement and a low energy requirement. E.g. desk-based office work, driving a car
Light	1.6 to < 3 METs 40% to < 55% HR_{max} 20% to < 40% VO_2max	RPE: 1 − 3	Activities that do not cause a substantial increase in heart rate or breathing rate. E.g. slow walking, bathing

Intensity	Objective measures	Subjective measures	Description
Moderate	3 to < 6 METs 55% to < 70% HR_{max} 40% to < 60% VO_2max	RPE: 4 − 6	Activities that allow maintaining a conversation uninterrupted but cause a noticeable increase in heart rate and breathing rate. E.g. brisk walking, gardening
Vigorous	> 6 METs > 70% HR_{max} > 60% VO_2max	RPE: > 6	Activities that do not allow maintaining a conversation uninterrupted and cause a substantial increase in heart rate and breathing rate. E.g. running, swimming

Notes: RPE refers to ratings from 0 to 10 on a 10-point Likert scale.

Abbreviations: HR_{max}; maximal heart rate; MET: metabolic equivalent of task; RPE: rating of perceived exertion; VO_2max: maximal oxygen consumption.

Short-term exercise restrictions may apply after major surgery or during immunocompromising treatments but the general consensus is that most cancer survivors are able to exercise [25]. This specifically includes individuals with bone metastasis, for whom exercise is considered safe, provided a risk assessment is performed and the exercise programme is prescribed by a professional to limit the risk of skeletal complications [305]. Recommendations from a recent expert consensus on exercise for people with bone metastases included that greater emphasis should be placed on proper technique and controlled movement and that the location and presentation of bone lesions warrants consideration [305]. While in the past, regions with bone metastasis were avoided completely [306], recent studies have concluded that exercises with load on affected bone regions are tolerable and may even improve bone health [307,308]. Similar recommendations apply to people with advanced, incurable cancer, who should undergo risk assessment prior to exercise initiation to identify unmanaged medical conditions that could require adaptation of the exercise prescription [300]. All in all, the current expert consensus is that all cancer survivors benefit from physical activity and exercise throughout the cancer care continuum and are highly encouraged to perform such activities, albeit with some adaptations required to ensure safety and increase tolerance [21].

2.4.2. Physical activity and exercise participation among men with prostate cancer

Despite recommendations by public health organisations that cancer survivors should engage in physical activity and exercise, studies have shown that many individuals with various cancer entities are highly sedentary and fail to meet the recommended activity levels [309-312]. Coletta et al. analysed the adherence of cancer survivors to the physical activity guidelines from the American Cancer Society and found that 23% met the aerobic guidelines (≥ 150 minutes moderate-to-vigorous physical activity (MVPA) per week), 15% met the resistance guidelines (resistance exercise ≥ 2 times per week) and only 10% met both [312]. Comparably low physical activity and exercise participation has been reported for men with prostate cancer [26,313,314].

Physical activity assessments in men undergoing prostatectomy for localised prostate cancer by Smith et al. showed that 11% met the aerobic guidelines prior to prostatectomy [26]. Activity levels were even lower post-surgery, with 9% and 6% attaining the required aerobic physical activity volume at the 6 and 12-month follow-up, respectively. Santa Mina et al. also assessed physical activity in men scheduled for prostatectomy, and in contrasting results found that 46% of participants met aerobic guidelines prior to surgery [313]. Similar estimates were reported for cancer survivors with bone metastases by Guinan et al., with 48% of participants meeting aerobic guidelines; however, this sample included both prostate and breast cancer survivors [314]. None of these studies reported adherence to resistance guidelines. One of the few studies that evaluated habitual resistance exercise participation in men with prostate cancer is an analysis of self-reported physical activity and exercise behaviour in a large cohort of male health professionals in the United States [315]. The 2,705 men diagnosed with prostate cancer in this cohort spent on average 4.5 metabolic equivalent of task (MET)-hours per week performing weightlifting or exercises using weight machines, which corresponded to 4.3% of their total active time. Previous intervention studies have also reported that the adherence of men with prostate cancer to prescribed exercise programmes depends on the delivery mode, intervention duration, as well as participants' age and behavioural characteristics [316-318].

In addition to the proportion of cancer survivors meeting the guidelines, physical activity patterns including sedentary behaviour have gained interest among researchers because they could provide more insight on the relationship between activity and health [319]. Trinh et al. reported that men treated with ADT were highly sedentary, with 72% (equivalent to 9 hours per day) of their waking time spent in sedentary behaviour [27]. Consequently, their weekly physical activity fell below the recommended level, with participants accumulating on average 17 minutes of MVPA per day. Even lower estimates of physical activity have been reported by Lynch et al., who measured activity levels among a cohort of prostate cancer

survivors with various disease stages and found that only 1% of waking time (equivalent to 6 minutes per day) was spent in MVPA [320]. In contrast, results by Gaskin et al. showed that participants engaged in 38 minutes MVPA per day, however, the sample consisted of men who had already completed active treatment (i.e. surgery, radiotherapy or both, with or without additional ADT) [321]. Altogether, evidence suggests that the proportion of prostate cancer survivors meeting the minimum recommended level of physical activity is concerningly low, especially among men with advanced disease. Despite strong recommendations by public health organisations, it remains unclear to which extent men with prostate cancer engage in targeted exercise, specifically muscle-strengthening activities.

2.4.3. Methodological considerations for the assessment of physical activity and exercise adherence

Assessment of physical activity

The assessment of guideline adherence requires quantification of individual physical activity levels. Daily habitual physical activity includes the sum of all bodily movements that result in energy expenditure performed within the 24 hours of one day [322]. Physical activity levels can be characterised by assessing the duration, intensity and frequency of physical activity bouts throughout the day, as well as the type of activity [323]. Any assessment method should ideally provide as much information as possible on these four physical activity dimensions while also considering day-to-day variations. There are multiple tools available for physical activity estimation, though they vary in their level of precision and information provided. Hence, the selection warrants careful consideration of the research question and study population [322].

Traditionally, physical activity has been estimated using self-reported measures, such as questionnaires and activity diaries [322]. While they are easy to use for most respondents and involve minimal costs, the accuracy of self-reported measures is limited by subjective reporting, social desirability and recall biases, which may lead to systematic over or underestimation of physical activity. Importantly, self-reported measures have shown particularly poor accuracy for measuring light intensity physical activity, which includes the majority of walking and routine household tasks, and thus presents a large share of daily activity [324]. Furthermore, self-reporting of physical activity requires a high level of cognitive processing that can present a barrier for some respondents, such as individuals with cognitive or memory deficits caused by older age or cancer treatments [325].

Technological advancements have produced wearable motion sensors such as the accelerometer, which provides detailed information on the movement direction, duration and intensity of the user by measuring the changes in acceleration in up to three dimensions [323]. This technology captures bodily movement as amplitudes and frequencies of acceleration in

one or several planes and is based on the assumption that all accelerations of a body are produced by muscle force and, thus, relate to energy expenditure [326]. Accelerometers allow the collection of large quantities of detailed movement data, which then needs to be processed into step counts or physical activity estimates at different intensities. Their use has shown good reliability in free-living settings, which is of particular interest because it provides information on habitual activity behaviour [323]. Consequently, accelerometers are considered the current standard of physical activity assessment [322]. However, even accelerometer-derived activity assessments can vary considerably between studies. Accelerometers can be placed on various locations of the body, yet most studies to date had used hip-worn devices until wrist-worn devices emerged in recent years [323]. Advantages of wrist-worn accelerometers include the capability to capture upper body movements, their unobtrusive placement that allows devices to be worn during sleep, and an overall increased user compliance. However, they also require adapted algorithms for data analysis and limit comparability between studies [327].

Several studies have investigated the agreement between subjective and objective physical activity in individuals with cancer and found vast discrepancies [26,328,329]. Smith et al. observed considerable differences between methods among men with localised prostate cancer, with 73% and 11% meeting physical activity recommendations according to questionnaire and accelerometer data, respectively [26]. Supporting these findings, results from a large analysis of 1,348 cancer survivors also demonstrated that the assessment method significantly influenced the evaluation of meeting physical activity guidelines, as well as the relationship between physical activity estimates and health outcomes [311].

Assessment of exercise adherence

The recognition of exercise benefits for cancer survivors has led to an increase in exercise intervention research in oncology; however, reporting of the prescriptions remains inadequate, thus limiting the reproducibility and interpretability of results [330]. Therefore, researchers have called for universal reporting standards for exercise intervention trials that provide detailed information on the planned exercise dose, as well as permit quantification of the completed exercise dose to calculate adherence measures and gain insight on the tolerability of exercise programmes [331]. Because exercise programmes for cancer survivors require frequent individualisation of exercise selection and dose to accommodate patients who experience fatigue, pain, nausea or other adverse effects of cancer and anti-cancer treatments, traditional metrics of adherence, such as loss to follow-up or session attendance, have limited utility in this setting [331]. Therefore, detailed descriptions of prescribed and

completed training volume including number of sets and repetitions and, if available, load for both aerobic and resistance training should be provided [331,332].

2.5. Benefits of physical activity and exercise for health outcomes in prostate cancer

2.5.1. Benefits of physical activity and exercise for prostate cancer outcomes

Physical activity-mediated effects on prostate cancer outcomes

Physical activity has been linked to improved mortality in individuals diagnosed with cancer [333,334]. Specific to prostate cancer, higher levels of physical activity have been associated with reduced overall and cancer-specific mortality in men with localised or advanced disease, with survival benefits evident for physical activity of both vigorous and non-vigorous intensity [28,315,335,336]. Additionally, a lower risk of disease progression has been observed in physically active men with prostate cancer compared to inactive peers [337,338].

Furthermore, clinical evidence suggests that regular physical activity improves cancer-related health outcomes and reduces morbidity. Among a sample of prostate cancer survivors of various disease stages, an increase in MVPA of less than one hour per day was associated with clinically important reductions of cancer-related fatigue [321]. Similarly, cancer survivors with bone metastases who spent more time in MVPA reported a higher quality of life and physical functioning, as well as lower pain scores, though the sample was not exclusive to men with prostate cancer [314]. Interestingly, an analysis of physical activity patterns by Trinh et al. found that sedentary bouts of ≥ 30 minutes were inversely associated with health-related quality of life, whereas a higher number of breaks in sedentary activity was related to improved physical well-being [27].

Exercise-mediated effects on prostate cancer outcomes

Because the nature of these studies is largely observational there is limited evidence regarding the survival benefits of structured exercise. Preclinical data suggests that exercise reduces tumour growth in rodents, including prostate cancer progression in a specific transgenic mouse model [339,340]. Similarly, exercise-conditioned serum from healthy males inhibited prostate cancer cell growth *in vitro* [341]. Moreover, a randomised controlled trial (RCT) by Kong et al. showed that a high-intensity interval training (HIIT) intervention for men on active surveillance for prostate cancer inhibited prostate cancer cell growth *in vitro* [342]. As for clinical data, aerobic exercise interventions for cancer patients undergoing cytotoxic chemotherapy were associated with reduced toxicity, which may result in higher chemotherapy completion rates and improve treatment outcomes [299]. Numerous studies have investigated exercise as a non-pharmaceutical strategy to counteract the adverse

effects of androgen deprivation and found largely positive effects, such as improvements in metabolic markers, quality of life and fatigue [343]. When it comes specifically to survival and disease-related benefits of exercise for men with prostate cancer, data is scarce and exercise oncologists call for intervention studies to investigate these outcomes [344].

2.5.2. Effects of physical activity and exercise on physical fitness in prostate cancer

Distinction of physical fitness from activity

Reduced physical fitness is a common consequence of cancer and anti-cancer treatments [164]. Cancer survivors are often caught in a vicious cycle where low physical fitness aggravates adverse symptoms, such as fatigue, and contributes to inactivity [345]. The lack of regular physical activity and exercise, in turn, promotes muscular dysfunction and weight gain that result in progressive physical deconditioning and functional decline. Reduced physical fitness is associated with worse anti-cancer treatment tolerability, decreased independence and higher all-cause mortality [346-350].

Physical fitness as a concept differs from physical activity, although the two are often interlinked. Physical fitness comprises a set of attributes related to the individual's ability to perform activities of daily living and engage in physical activity [351]. Two core components of physical fitness are neuromuscular and cardiorespiratory fitness. Neuromuscular fitness describes the ability to generate muscle force, which is primarily determined by muscle strength and flexibility [352]. Cardiorespiratory fitness describes the ability of the circulatory and respiratory systems to supply oxygen during sustained physical activity [353]. There is also considerable overlap between physical fitness and physical function (or functioning), with the latter describing the ability to complete basic tasks required for independent living as well as to perform more complex activities [354].

Physical activity-mediated effects on physical fitness

Regular physical activity and exercise can promote physical fitness by increasing muscle mass, cardiovascular health and overall physical function in healthy adults, including elderly populations, and cancer survivors [297,300,314,355-359]. Evidence for a similar relationship in prostate cancer is provided by Faithfull et al., who observed that lower levels of physical activity were associated with poorer cardiopulmonary fitness in older men with prostate cancer [360]. Furthermore, Lynch et al. found that higher levels of MVPA were inversely associated with waist circumference as a surrogate marker for body composition in a self-identified sample of prostate cancer survivors [320]. In support of a link between habitual physical activity and body composition is a study by Philipps et al., who assessed self-reported physical activity in a sample of 1,917 men with non-metastatic prostate cancer and

found that men with the highest activity levels had a lower body mass index (BMI) than those with the lowest activity levels [361]. Other than these few studies, investigations of the role of habitual physical activity for physical fitness outcomes in men with prostate cancer are scarce and analyses of physical activity benefits are often conflated with structured exercise interventions [362].

Exercise-mediated effects on physical fitness

Numerous studies have investigated the potential of exercise interventions to improve physical fitness, particularly outcomes like body composition and muscle strength that are known to be severely affected by androgen deprivation [23,24,363]. A meta-analysis by Ussing et al. pooled results from 968 men on ADT and found that supervised exercise interventions significantly increased muscle strength [24]. Most interventions combined aerobic and resistance exercise, although some prescribed resistance exercise only, with durations ranging from 3 to 12 months. A subgroup analysis for effects on muscle strength by training intensity of only resistance exercise interventions showed a significantly larger increase in muscle strength for high intensity compared to moderate intensity [24]. In support of the results is a meta-analysis by Chen et al., who found that supervised exercise interventions of combined aerobic and resistance training increased upper and lower body muscle strength in men on ADT [363].

Chen at al. also analysed changes in lean mass and, interestingly, results across all seven included RCTs showed consistently that exercise did not lead to lean mass gains [363]. By contrast, a review of isolated progressive resistance exercise interventions for men on ADT found consistent increases in lean mass [23]. Additional analysis of skeletal muscle biopsies in one of the included studies showed a significant increase in total muscle fibre cross-sectional area following four months of resistance training compared to the control group, whose cross-sectional area decreased [364]. Altogether, it can be concluded that muscle strength during ADT can be improved through structured exercise, with the largest effects to be expected for isolated resistance exercise at high intensities, while lean mass appears to remain unaltered unless a targeted resistance exercise stimulus is provided.

In addition to neuromuscular fitness, evidence also suggests favourable effects of structured exercise on measures of cardiorespiratory fitness, such as performance in maximal and submaximal fitness tests. A meta-analysis of supervised exercise interventions for men on ADT reported significant improvements in peak oxygen consumption (VO_2peak) and walking speed in favour of the intervention group [24]. Similarly, another meta-analysis of exercise interventions that combined direct measures (e.g. VO_2peak) and indirect fitness estimates from submaximal tests (e.g. 400 metre walk test) in men with any prostate cancer stage

found a positive effect in favour of the intervention group [365]. The study further stratified the interventions into aerobic exercise, resistance exercise and combined interventions and showed that the largest benefits for cardiovascular fitness were associated with aerobic exercise. Even though supervision of exercise provides benefits, there are inherited barriers to participation that can be reduced in a non-supervised setting. Van Blarigan et al. investigated the effects of a 4-month walking intervention for men with early stage prostate cancer that was conducted in a home-based setting and observed a significant VO_2peak improvement in the intervention group [366].

Exercise is understood to further contribute to cardiorespiratory fitness improvements through favourable effects on body fat mass [365,367]. A pooled analysis of exercise intervention RCTs for men with prostate cancer reported a significant reduction of whole-body fat mass in favour of the interventions, regardless of the exercise modality [365]. Other studies found no significant reductions but rather observed a maintenance as opposed to fat mass gains, which arguably still underline the importance of exercise during treatment with ADT [367]. In addition to improvements in cardiorespiratory fitness, exercise has also been shown to prevent treatment-induced declines when administered simultaneously as supportive therapy. Harrison et al. compared changes in physical fitness among 26 men initiating ADT plus enzalutamide for non-metastatic prostate cancer either with or without a supervised exercise intervention of combined aerobic and resistance exercise [368]. After 16 weeks, VO_2peak values of the usual care group had decreased to a greater extent than in the intervention group.

2.5.3. Effects of physical activity and exercise on immune responses in prostate cancer

Mechanisms of immune regulation by physical activity and exercise

The skeletal muscle possesses endocrine properties, which becomes evident during exercise when it releases signalling molecules into the circulation [30]. Muscle-derived signalling molecules include mainly proteins, such as cytokines, but also lipids, nucleic acids and metabolites like lactate, and are collectively referred to as myokines [29]. Several myokines can modulate the immune system, which explains the observation of characteristic immune responses during and after exercise bouts. The initial immune response to exercise is characterised by mobilisation of large numbers of lymphocytes, mainly NK cells and $CD8^+$ T cells, which enhances immunosurveillance [29,369]. Additionally, anti-inflammatory myokines are released, resulting in an initial reduction in systemic inflammation. The extent of lymphocyte mobilisation and myokine release is proportional to the intensity and duration of the exercise stimulus [370]. During recovery shortly after exercise, blood levels of lymphocytes decrease as cells migrate into tissues, such as skeletal muscles or lungs, to exert their roles

in immune defence and tissue repair. This transient lymphopenia peaks approximately one to two hours post exercise bout and usually resolves within 24 hours, with circulating numbers of immune cells returning to baseline [29].

The release of myokines through repeated bouts of exercise is an important stimulus for maintaining healthy effector cell populations and an anti-inflammatory milieu [29]. Thus, a physically active lifestyle is considered to have a protective effect against chronic inflammation-induced diseases [31]. The inhibition of inflammation through exercise is in part mediated by the release of IL-6 from skeletal muscle in response to muscle contractions [371]. This increase in circulating levels of IL-6 during exercise is transient, with a return to resting levels within one hour after exercise cessation. The magnitude of the IL-6 response depends on exercise duration and intensity, with longer, more intense exercise stimuli eliciting a greater IL-6 release. The rise in IL-6 concentrations during exercise promotes a subsequent release of the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1RA), which downregulate T cell activation and production of pro-inflammatory cytokines [372]. Additionally, exercise-induced IL-6 has been shown to stimulate acute NK cell mobilisation to the bloodstream, as well as instigate their migration to tumours [373,374]. Interestingly, chronic effects of regular exercise include a decrease in peripheral IL-6 and C-reactive protein (CRP) concentrations, which is associated with reduced systemic inflammation, and highlights that the effects of immune responses are highly context-dependent [375].

Muscle activity also increases sympathoadrenal activity in an intensity-dependent manner and stimulates the adrenal gland to release cortisol and adrenaline immediately after the onset of exercise [31]. Increased levels of circulating cortisol and adrenaline, in turn, are known to suppress inflammation by downregulating the expression of pro-inflammatory cytokines, such as TNFα, by immune cells. Moreover, regular exercise is associated with increased Treg cell numbers in the peripheral blood, which may further suppress inflammatory responses [31]. Even though the specific modulations of the complex network of immune cells and mediators by exercise are not fully understood, there is mounting evidence that exercise can reduce inflammation and improve outcomes in highly inflammatory diseases, such as cancer [375].

Physical activity and exercise-related effects on immune markers in prostate cancer

Anti-tumorigenic effects of physical activity may be the result of improved anti-cancer immunity through increased immunosurveillance, preferential mobilisation and activation of effector cells, and immune cell infiltration of the tumour microenvironment [29,375]. Following an exercise stimulus, various tissues and organs release signalling molecules to restore homeostasis and regulate physiological adaptation processes that increase activation and

migration of immune cells and promote tumour perfusion [375] (Figure 15). In fact, several studies have shown a significant increase in the proportion of the highly cytotoxic CD56^{dim} NK cell subset in the blood following an acute bout of aerobic exercise in men with prostate cancer both with and without ADT [32,376,377]. Furthermore, acute exercise also improved NK cell cytotoxicity, as indicated by increased target cell lysis after co-incubation with PBMCs *in vitro* [32,376]. Acute exercise also provoked a rise in circulating Th and Tc cell concentrations in men on ADT [378].

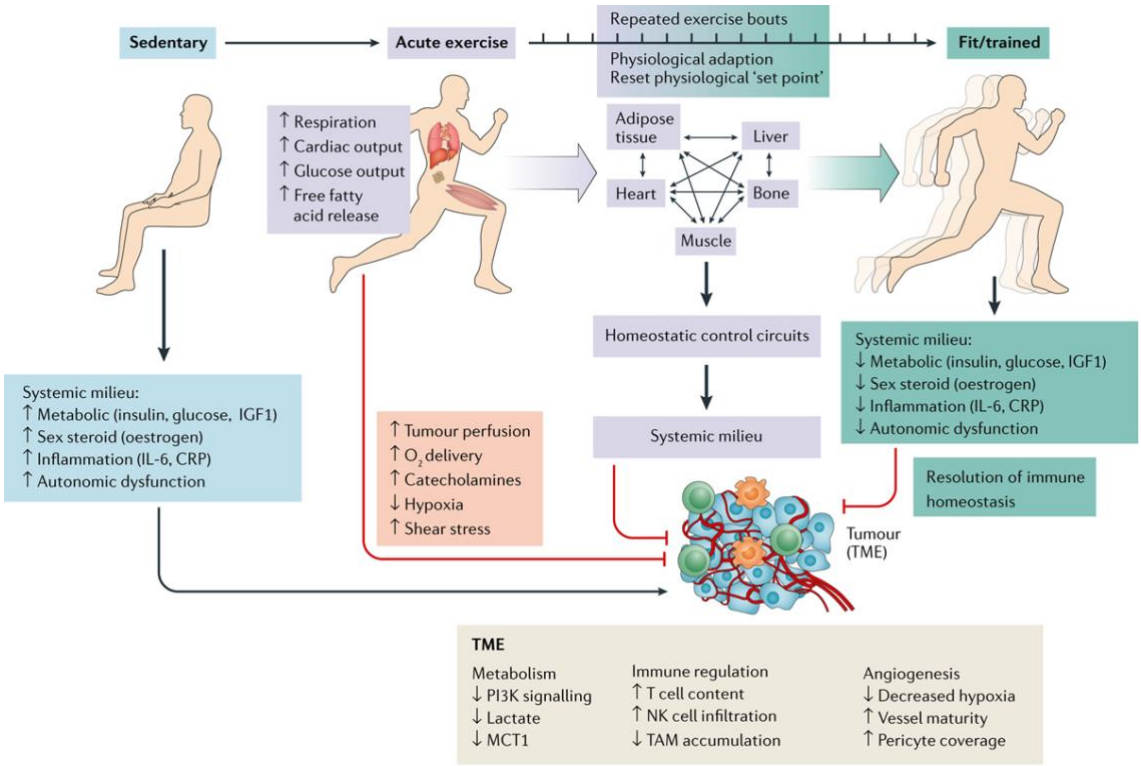


Figure 15. Systemic effects of exercise and exercise-dependent regulation of the immune response in the tumour microenvironment. Sedentary behaviour is associated with circulating markers that are characteristic for a pro-inflammatory environment and promote tumour growth. Acute exercise stimulates the release of signalling molecules, such as cytokines, that activate homeostatic control circuits and mediate systemic effects. Repeated exposure to exercise promotes physiological adaptation and alters the systemic milieu through changes in metabolite and cytokine levels, amongst others, which can stimulate immune cell populations in the tumour microenvironment and improve the anti-tumour immune response. Reproduced with permission from Koelwyn et al. (2017) [375].

Reports of chronic exercise-induced effects on the immune system in cancer vary. For example, a 20-week resistance training intervention did not alter immune cell concentrations or plasma levels of IL-6, IL-1RA, TNFα or CRP in men with prostate cancer [379]. By contrast, a 6-month combined aerobic and resistance training intervention significantly altered myokine serum levels in men on ADT for mCRPC [380]. Interestingly, in this study treatment of tumour cells with serum from the intervention group reduced cell growth compared to the control group, indicating enhanced anti-tumour activity induced by exercise. Supporting this

argument is a study that reported reduced numbers of Treg cells and myeloid-derived suppressor cells in men with localised prostate cancer after a six-week yoga intervention [381]. Both of these cell populations act as suppressors of immune responses and are upregulated by tumours as an immune escape mechanism, thus, exercise-induced reduction in cell concentrations may promote anti-tumour effects. While the promotion of an anti-inflammatory milieu is considered the key to exercise-induced benefits in cancer, studies of changes in inflammatory indices, such as the SII, in the context of exercise oncology are rare. The only existing study to date analysed the effects of combined moderate intensity aerobic exercise and strength exercise among childhood cancer survivors and observed a significant decrease in the SII following the intervention [382].

Most studies investigating the effects of physical activity on the immune system in cancer include a structured exercise intervention. However, based on findings from healthy populations, it is well understood that a high level of habitual physical activity also benefits the immune system, especially in older adults [383]. Regular participation in physical activity among older adults is associated with improved NK cell and neutrophil function, increased T cell proliferation, reduced systemic inflammation and fewer signs of immunosenescence (i.e. increasing immune dysfunction with advancing age) [384-386]. Immunosenescence, which is usually accompanied by a chronic inflammatory state, has in fact been implicated as a driver of cancer [387]. Therefore, there is a push for prospective studies to examine the relationship between physical activity and immune responses in individuals with cancer [388]. In summary, current evidence suggests that the complex interplay between muscle activity and the immune system shapes the positive association of a physically active lifestyle with beneficial health outcomes in cancer.

3. Aim of the thesis

Management of metastatic prostate cancer revolves around treatment with ADT, which significantly improves survival but is associated with severe adverse effects that negatively impact physical health and quality of life. The continuous testosterone withdrawal induced by ADT evokes characteristic changes in body composition, including accelerated loss of muscle mass and strength, reduced bone mineral density and increases in body fat mass. These changes are often accompanied by reduced physical fitness and increased inactivity, despite recommendations from leading public health organisations that cancer survivors should engage in regular physical activity and structured exercise. Sedentary behaviour and lack of exercise also affect the immune system, because signalling molecules released by muscles in response to exercise are known to decrease systemic inflammation, as well as increase immunosurveillance and immune cell infiltration in the tumour microenvironment. Consequently, exercise is recognised by clinicians for its role in reducing cancer risk and disease progression, which is presumably mediated by enhanced anti-tumorigenic immune responses. Men with prostate cancer, in particular, can benefit from exercise as a means to counteract the adverse effects of ADT and improve physical fitness, which in turn may increase habitual physical activity to the recommended level. However, the link between physical activity, exercise and physical fitness in the context of androgen deprivation for prostate cancer and their association with immune function remains to be investigated. The picture is further complicated by the use of ARIs, which are commonly administered as secondary treatments in addition to ADT. While ARIs improve disease control in men with advanced prostate cancer, they may also aggravate the decline in physical function.

Two cross-sectional studies and one longitudinal study using data from participants in the INTERVAL-GAP4 trial were conducted for this thesis. INTERVAL-GAP4 is a multi-centre RCT investigating the effects of a two-year structured exercise intervention consisting of intense aerobic and resistance exercise on survival, disease progression, and various health and exercise outcomes in men with advanced prostate cancer undergoing ADT. In addition to the procedures detailed in the original study protocol that were performed across all sites, a substudy including measurements of immune cell populations and accelerometer-derived physical activity was added at the German study site. The studies in this thesis combined data from both the INTERVAL-GAP4 study and the additional German substudy. Study 1 analysed levels of self-reported physical activity and their associations with physical fitness at baseline in the multicentre study sample and investigated differences between ARI users and non-users. Study 2 examined levels of objectively measured physical activity using accelerometers and analysed differences between ARI users and non-users, as well as the agreement between accelerometer-derived and self-reported physical activity. Furthermore, Study 2 analysed the associations of accelerometer-derived physical activity with physical

fitness, circulating immune cell concentrations and specific immune markers at baseline in the German study sample. Lastly, Study 3 analysed the adherence to a 6-month structured intense exercise intervention, as well as associated changes in physical fitness and immune parameters compared to the control arm.

Based on these three studies, the specific aims of this thesis were defined as follows:

Aim 1: To examine the self-reported physical activity and adherence to physical activity guidelines of men with advanced prostate cancer, as well as to investigate differences between ARI users and non-users (Study 1)

Aim 2: To analyse the association of self-reported physical activity with physical fitness in men with advanced prostate cancer, as well as to investigate differences between ARI users and non-users (Study 1)

Aim 3: To examine the accelerometer-derived physical activity, including differences between ARI users and non-users, of men with advanced prostate cancer and to investigate the agreement between accelerometer-derived and self-reported physical activity estimates (Study 2)

Aim 4: To analyse the association of accelerometer-derived physical activity with physical fitness, as well as immune cells and inflammation markers in the peripheral blood of men with advanced prostate cancer (Study 2)

Aim 5: To analyse the adherence to a 6-month structured exercise intervention and investigate its effects on physical fitness, as well as immune cells and inflammation markers in the peripheral blood of men with advanced prostate cancer (Study 3)

4. Methods

4.1. Participants

4.1.1. Recruitment

The data analysed in the studies conducted for this thesis was collected in participants of the INTERVAL-GAP4 trial. INTERVAL-GAP4 is a multi-centre, randomised, controlled, phase 3 trial for men diagnosed with advanced metastatic prostate cancer in seven countries across Europe, North America and Australia. Participants were recruited at 15 sites: German Sport University, Cologne, Germany; Edith Cowan University, Perth, Australia; Queensland University of Technology, Brisbane, Australia; Victoria University, Melbourne, Australia; University of Alberta, Edmonton, Canada; Cedars Sinai, Los Angeles, CA, United States; Oregon Health and Science University, Portland, OR, United States; University of Colorado, Denver, CO, United States; Fred Hutchinson Cancer Centre, Seattle, WA, United States; University of California San Francisco, San Francisco, CA, United States; Erasmus Medical Centre, Rotterdam, Netherlands; University of Glasgow, Glasgow, United Kingdom; Queens University, Belfast, Ireland; University of Surrey, Guildford, United Kingdom; and King's College, London, United Kingdom. Recruitment commenced in April 2016 and stopped in February 2023 with various sites joining the INTERVAL-GAP4 trial later or terminating recruitment earlier.

The INTERVAL-GAP4 study protocol has been published previously [389]. However, inclusion criteria were later amended to accommodate changes in clinical practice that occurred during the trial. A detailed summary of inclusion and exclusion criteria is presented in Table 5. Briefly, men were considered eligible if they had histologically documented adenocarcinoma of the prostate with systemic metastatic disease and confirmed castrate levels of testosterone (< 50 $ng \cdot dL^{-1}$) due to orchiectomy or treatment with a GnRH agonist or antagonist. In regards to the prostate cancer stage at enrolment, men with mCRPC or mHSPC, who matched the criteria for high-risk or high-volume disease, were eligible. Eligible secondary treatments for prostate cancer included secondary hormone therapies abiraterone, enzalutamide, apalutamide, or first-line chemotherapy with docetaxel or cabacitaxel. Men were excluded if they showed signs indicating uncontrolled disease progression, exacerbating pain, physical impairment or frailty, or met any other criteria that would impede exercise performance or make participation in intense aerobic and resistance exercise unsafe. Furthermore, participants were required to travel to the designated facilities for exercise testing visits, be proficient in the local language of the study site and provide written clearance by the treating oncologist to participate in exercise testing and training. Due to the nature of the exercise intervention trial, men were also excluded if they regularly

participated in vigorous aerobic exercise for more than one hour or structured resistance exercise more than once per week. However, there were no restrictions on habitual physical activity of any intensity level.

Table 5. Detailed inclusion and exclusion criteria of the INTERVAL-GAP4 trial.

Inclusion criteria	Exclusion criteria

• Histologically documented adenocarcinoma of the prostate
• Distant metastasis (bones, visceral organs, non-regional lymph nodes)
• Castrate levels of testosterone (< 50 ng·dL^{-1}) due to orchiectomy or continuous treatment with a GnRH agonist or antagonist
• mCRPC or mHSPC high-risk/high-volume disease
  • **mCRPC:** disease progression despite castrate levels of testosterone as marked by metastatic disease progression (> 20% diameter increase of measurable lesions or appearance of new lesions attributable to prostate cancer on bone scan, CT/MRI or PSMA PET/CT) or PSA progression (serial rise in PSA serum concentration on at least two occasions measured at minimum one week apart and only for absolute PSA values ≥ 2 ng·mL^{-1})
  • **mHSPC**: no disease progression during ADT and meeting criteria for **high-risk disease** (meeting at least two of the following: Gleason score ≥ 8; presence of ≥ 3 lesions on bone scan; visceral metastasis) or **high-volume disease** (visceral metastasis or ≥ 4 bone metastases with at least one located outside of the pelvis and vertebral column) or both
• Written medical clearance by the treating oncologist for participation in exercise testing and training
• Proficiency in local language of the study site
• Willingness to travel to the designated facilities for exercise testing visits
	• Disease progression after first-line chemotherapy and subsequent treatment with either secondary hormone therapy or second-line chemotherapy prior to/at the time of enrolment
	• Halabi prognostic risk score 'high'
	• ECOG performance status ≥ 2
	• Brain metastasis
	• Small cell prostate carcinoma
	• Spinal cord compromise or instrumentation that would impede exercise performance
	• Moderate or severe bone pain according to the Common Terminology Criteria for Adverse Events by the National Cancer Institute
	• Uncontrolled hypertension (BP ≥ 160/90)
	• Congestive heart failure, recent serious cardiovascular events, uncontrolled cardiac disease or symptoms of cardiac disease including chest pain or palpitations
	• Peripheral neuropathy grade 3 or higher
	• Currently active secondary cancer
	• Mental illness that would prevent informed consent
	• Regular participation in vigorous aerobic exercise (> 60 min per week) or structured resistance exercise (> 1 session per week)

Abbreviations: ADT: androgen deprivation therapy; BP: blood pressure; CT: computed tomography; ECOG: Eastern Cooperative Oncology Group; GnRH: gonadotropin-releasing hormone; mCRPC: metastatic castrate-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; min: minute; MRI: magnetic resonance imaging; PET: positron emission tomography; PSA: prostate-specific antigen; PSMA: prostate-specific membrane antigen.

4.1.2. Ethics approval

The INTERVAL-GAP4 trial (ClinicalTrials.gov: NCT02730338) as well as the additional substudy at the German study site (German Clinical Trials Register: DRKS00010310) were prospectively registered and approved by the respective research ethics boards of all participating institutions. While the research questions of the studies performed for this thesis were formulated retrospectively, all data was collected as part of approved study procedures. Each participant received a detailed participant information package and was offered a personal meeting, during which the study procedures were explained and questions were answered by trained study personnel. The participant information package at the German site also included separate information about the substudy. Written informed consent was obtained from all participants prior to inclusion. All study procedures were performed in accordance with the Declaration of Helsinki.

4.1.3. Cross-sectional multi-centre study (Study 1)

Study 1 included pooled data collected at baseline from participants at all global sites. The CONSORT diagram with detailed reasons for exclusion of participants is shown in Figure 16. Some assessments of physical fitness were performed after randomisation but before intervention delivery, thus, allocation was included in the CONSORT chart. Briefly, a total of 232 men with prostate cancer were screened for eligibility. Eighty-three men were excluded with 113 exclusion reasons recorded since more than one exclusion reason may have been identified in some cases. Consequently, 149 participants were determined as eligible. Four participants did not did not complete baseline testing and five participants were excluded due to missing outcome data, resulting in a total of 140 participants included in the analysis.

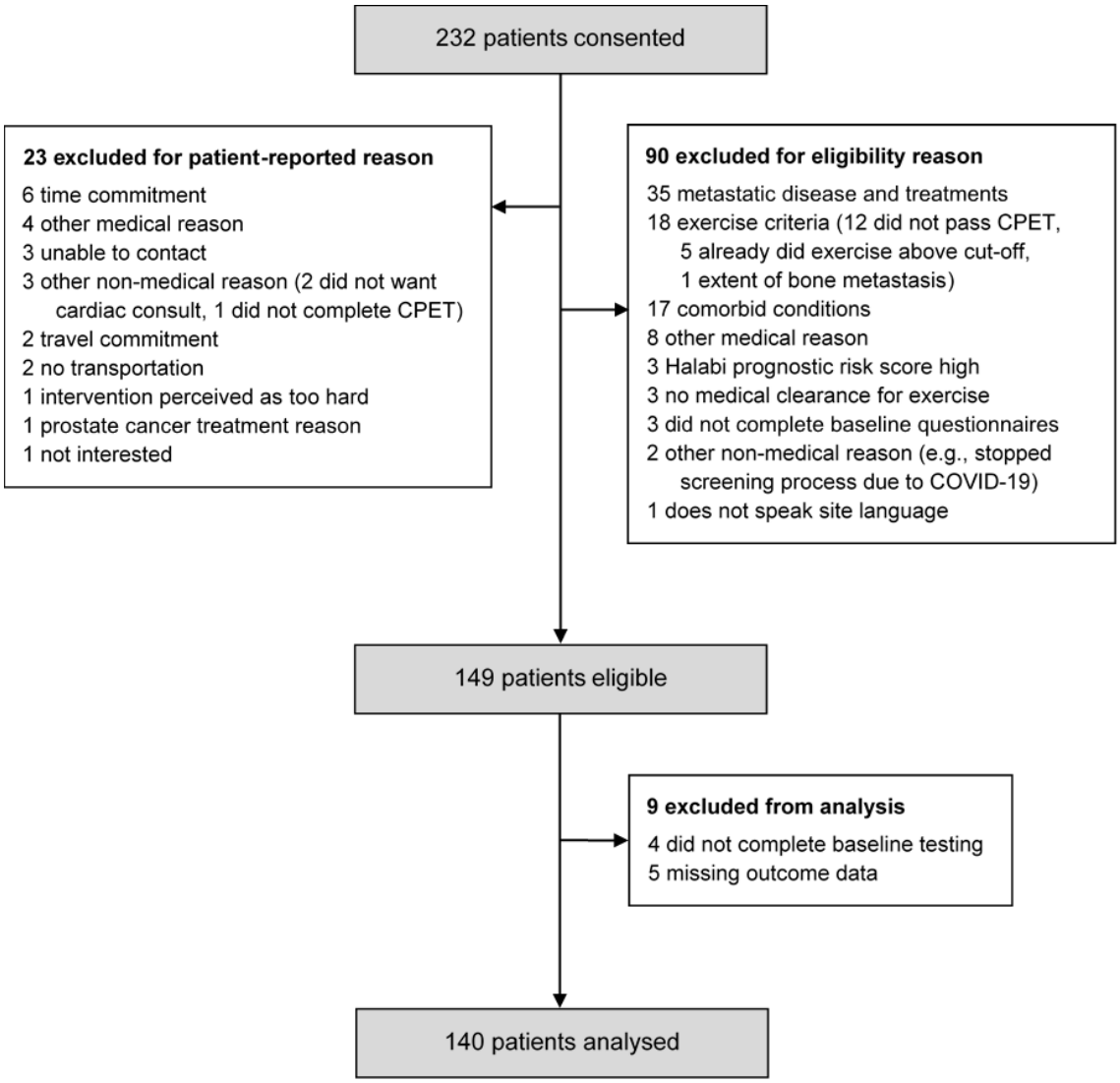


Figure 16. CONSORT diagram of participants in the cross-sectional, multi-centre study (Study 1). Exclusion prior to randomisation may have been due to more than one reason. Study 1 included data collected at baseline. CPET: cardiopulmonary exercise test.

4.1.4. Cross-sectional single-centre study (Study 2)

Study 2 included data collected at baseline from participants at the German study site only. The CONSORT diagram with detailed reasons for exclusion of participants is shown in Figure 17. Some assessments of physical fitness were performed after randomisation; thus, allocation was included in the CONSORT chart of Study 2 but all procedures were completed prior to the intervention start. Briefly, a total of 50 men with prostate cancer were screened for eligibility at the German Sport University in Cologne, Germany. Sixteen men were excluded, with 21 exclusion reasons recorded since more than one exclusion reason may have been identified in some cases. Consequently, 34 participants were randomised with 16 allocated to the intervention arm and 18 allocated to the control arm. Three participants were excluded from Study 2 due to missing accelerometer data, 2 participants due to missing immune cell data and 2 participants due to abnormal blood counts related to medical treatment for neutropenia at baseline, resulting in a total of 27 participants included in the analysis.

4.1.5. Longitudinal single-centre study (Study 3)

Study 3 was a longitudinal study of data collected at baseline and at the 6-month testing visits and included participants from the German study site only. The CONSORT diagram with detailed reasons for exclusion or discontinuation of participants is shown in Figure 17. Of the 34 randomised participants, 16 were allocated to the intervention arm and 18 to the control arm. A total of 4 participants (2 intervention, 2 control) were excluded from Study 3 due to missing baseline data, of which 2 participants had missing immune cell data and 2 participants had abnormal blood counts related to medical treatment for neutropenia. Additionally, 11 participants were excluded from Study 3 because of missing 6-month testing data. Of these, 2 participants (1 intervention, 1 control) died during the study period, 6 participants (3 intervention, 3 control) did not complete the testing visit at 6 months and 3 participants (2 intervention, 1 control) had missing immune cell data, resulting in a total of 19 participants (8 intervention, 11 control) included in the analysis.

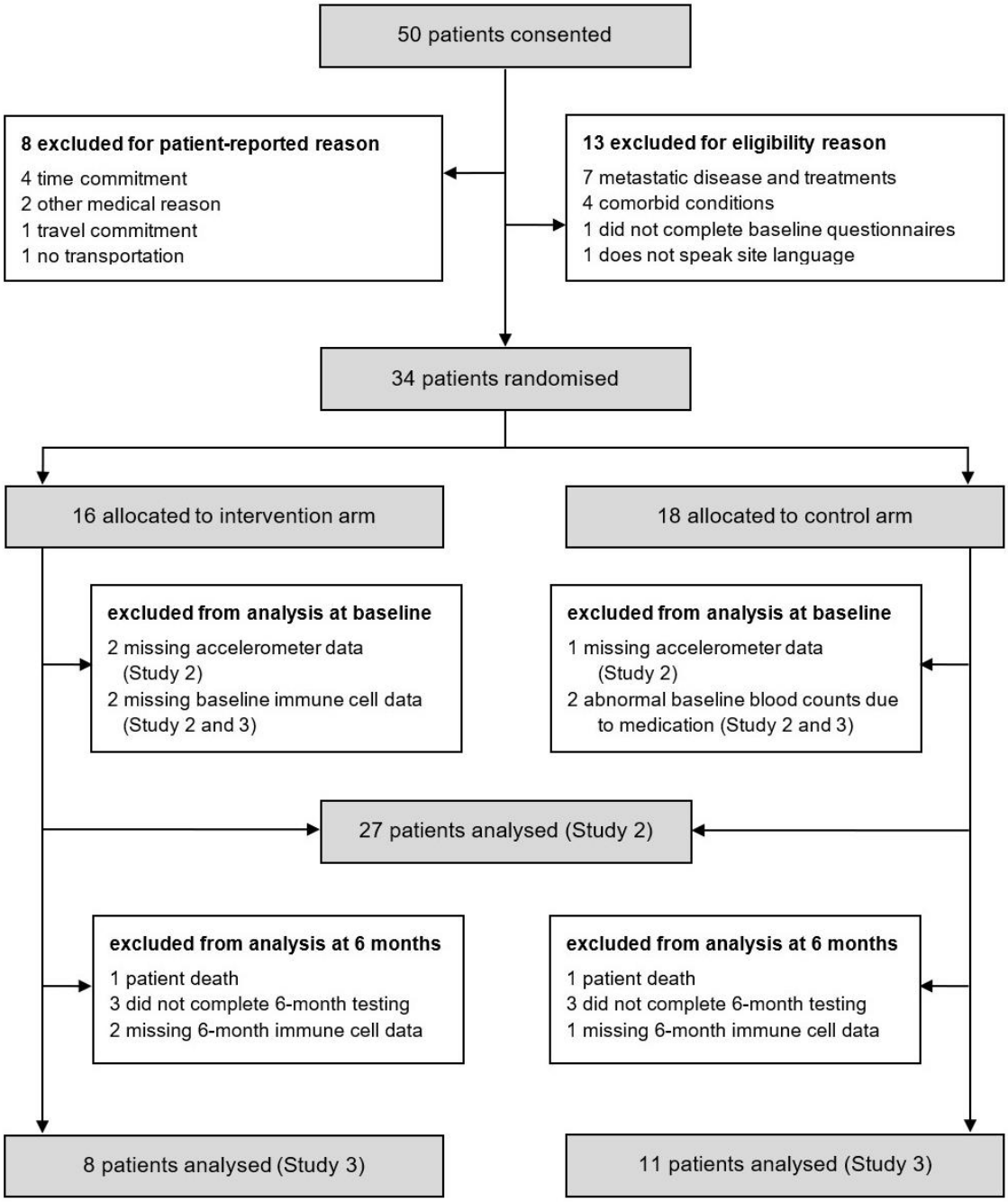


Figure 17. CONSORT diagram of participants at the German study site included in the cross-sectional (Study 2) and longitudinal (Study 3) single-centre studies. Exclusion prior to randomisation may have been due to more than one reason. Study 2 included data collected at baseline. Of the 34 randomised participants, 3 participants were excluded from Study 2 due to missing accelerometer data and 4 participants due to missing immune cell data or abnormal blood counts at baseline. 15 participants were excluded from Study 3 due to discontinuation before the 6-month visit, missing immune cell data or abnormal blood counts at baseline or 6 months.

4.2. Experimental design

The experimental design of both cross-sectional studies (Study 1 and 2) and the longitudinal study (Study 3) is shown in Figure 18. Study 1 analysed baseline levels of self-reported physical activity and their association with physical fitness outcomes using data from participants across all sites of the multi-centre trial. For Study 2, baseline data from participants at the German study site was analysed to assess levels of accelerometer-derived physical activity and determine the agreement with self-reported physical activity, as well as the association with physical fitness outcomes. Secondly, this study also analysed the association of physical activity with circulating levels of immune cells and immune cell-derived inflammation markers at baseline. Study 3 comprised of a longitudinal analysis to investigate the effects of a 6-month structured exercise intervention on peripheral blood levels of immune cells and immune cell-derived inflammation markers in participants at the German study site.

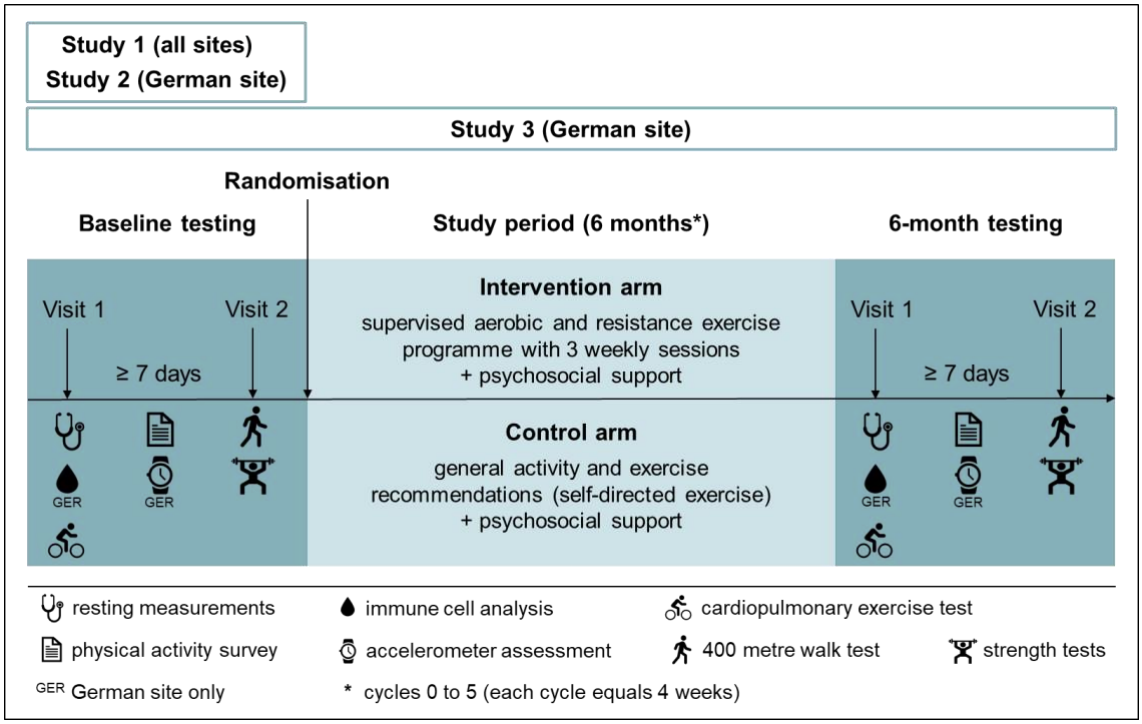


Figure 18. Experimental design of the two cross-sectional studies (Study 1 and 2) and one longitudinal study (Study 3). Baseline measures were collected at two testing visits, with resting measurements, blood sampling for immune cell analysis (German site only) and the cardiopulmonary exercise test performed at visit 1 and 400 metre walk test and maximal strength tests performed at visit 2. Visits were separated by at least 7 days, during which physical activity assessments (self-reported survey, additionally accelerometer at the German site only) were conducted. Eligible participants were randomly allocated to either the intervention arm, which received a supervised aerobic and resistance exercise programme, or the control arm. All baseline testing procedures were repeated at the 6-month testing.

Data collection procedures at baseline and after 6 months were identical across all study sites. These included two separate testing visits performed within seven days of each other, with the exception of the University of California San Francisco that completed the testing during a single day (1 participant). The first visit included resting measurements, blood sampling and the cardiopulmonary exercise test (CPET), while 400 metre walk time and maximal strength were assessed at the second visit. Participants were told to refrain from intense exercise in the 48 hours prior to each visit. In addition to anthropometric measurements, procedures conducted at rest included blood pressure measurement, lung function test, resting echocardiogram (ECG) recording and blood draw for a complete blood count to verify absolute neutrophil and platelet count eligibility criteria. These procedures were required for participants to receive clearance by a medical professional to perform the CPET. Participants were told to refrain from intense exercise in the 48 hours prior to each visit. For the assessment of self-reported physical activity, participants were asked to complete a digital version of the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) prior to visit 2. Accelerometer-derived physical activity was assessed using a wrist-worn ActiGraph device during the seven days between visit one and two. To assess immune parameters, blood sampling was performed on the morning of the first exercise visit and samples were immediately processed and cryopreserved until immune cell analysis.

After completion of baseline procedures, eligible participants were randomised in a 1:1 ratio to intervention or control arm with stratification by treatment status at the time of enrolment. Treatment status was determined based on participants' medical history and converted into a binary variable with participants considered either low risk (defined as one of these four groups: 1) mCRPC and treatment naïve; 2) mCRPC and stable on abiraterone, enzalutamide or apalutamide; 3) mHSPC high-risk disease; 4) mHSPC high-volume disease) or high risk (defined as one of these three groups: 1) mCRPC with PSA progression while on abiraterone, enzalutamide or apalutamide; 2) mCRPC treated with docetaxel, cabazitaxel, or other first line chemotherapy; 3) mCRPC with progression following chemotherapy and now responding or stable on abiraterone, enzalutamide or apalutamide with an estimated life expectancy of at least one year). Randomisation was performed through the Research Electronic Data Capture (REDCap) software platform [390] in random blocks of two, four or six. Due to the nature of the intervention, participants, study staff and investigators could not be blinded to the randomisation outcome.

Participants allocated to the intervention arm received a supervised exercise intervention consisting of intense aerobic and resistance exercise. The periodised, progressive exercise programme included three weekly exercise sessions: two combined HIIT and strength training and one included moderate-intensity continuous training (MICT). The exercise

intervention was paired with behavioural support in the form of regular text messages to promote adherence. Participants allocated to the control arm were provided with print information about physical activity recommendations and exercise benefits but did not receive individualised exercise programmes. Both arms were also provided with psychosocial support in the form of monthly newsletters about topics such as physical activity, exercise and diet.

4.3. Measurements

4.3.1. Resting measurements

Prior to physical assessments, participants completed a standard medical check-up and anthropometric measurements to record baseline clinical information and assess eligibility for study participation. The standard medical check-up included blood pressure measurement taken both in a seated and supine position, spirometry to assess lung function (Geratherm Respiratory GmbH, Bad Kissingen, Germany) and a resting ECG recording (Fukuda Denshi, Tokyo, Japan) that was performed in a supine position. Anthropometric measurements included weight and height measured using a scale and a wall-mounted stadiometer (seca, Hamburg, Germany).

4.3.2. Physical activity

Self-reported physical activity (Study 1 and 2)

Self-reported physical activity was assessed using a modified version of the GSLTPAQ [391], which is considered a standard tool for cancer populations [392]. The self-administered questionnaire consists of three items to assess the number of times the participant engaged in light, moderate and strenuous physical activity bouts of at least 15 minutes duration in the past seven days. The questionnaire provided examples of aerobic activities for each intensity level. The GSLTPAQ was modified by adding one item to record the frequency and duration of any resistance exercise. Participants at non-native English-speaking sites received a translated version of the GSLTPAQ in the local language. Weekly MVPA in minutes was calculated as [MVPA = 2 x (frequency of vigorous physical activity x duration of vigorous physical activity) + (frequency of moderate physical activity x duration of moderate physical activity)] [393]. Participants who reported at least 150 minutes of weekly MVPA met the aerobic MVPA guidelines [393]. The leisure score index (LSI) as a measure specific to the GSLTPAQ was also reported. The LSI is calculated as [LSI = (9 x frequency of vigorous physical activity) + (5 x frequency of moderate physical activity) + (3 x frequency of light physical activity)] [394]. Previous studies have established cut-points to determine the physical activity status of participants based on the LSI, with a LSI ≥ 24 considered active and a LSI < 24 considered insufficiently active [395].

Accelerometer-based physical activity analysis (Study 2)

To measure free-living physical activity objectively, participants were asked to wear the ActiGraph GT9X Link triaxial accelerometer (ActiGraph, Pensacola, FL, United States) on their non-dominant wrist for seven consecutive days except during showering or other water-based activities. Accelerometers were given to participants in person, along with instructions on how to wear the device properly. The device was programmed to not display any information on the digital screen to ensure that participants did not receive feedback about their physical activity. Accelerations were recorded at a frequency of 100 Hz. Only days with a minimum of 16 hours wear time were included in the analysis and participants had to record at least four complete days, including three weekdays and one weekend day, for the measurement to be considered valid [396,397]. Raw accelerometer data were downloaded via the ActiLife v.6.13.4 software (ActiGraph, Pensacola, FL, United States) as '.gt3x' files and subsequently processed using R version 4.2.2 [398], RStudio [399] and the GGIR package version 2.8-2 [396]. Auto-calibration of raw acceleration to the local gravity was performed as recommended by GGIR [400]. The Euclidean norm minus one (ENMO) of the raw acceleration was calculated over five-second epochs. Non-wear time was determined by assessing the standard deviation (SD) and value range within 60-minute windows centred at 15-minute intervals, with an interval considered non-wear time for any SD below 13 m*g* or value range below 50 m*g* for at least two of the three axes [401]. Periods of non-wear time were then imputed. Sleep periods were detected using an automated algorithm [402].

Two different sets of ENMO cut-points validated for the ActiGraph device worn at the non-dominant wrist were applied to classify physical activity intensity, because specific cut-points validated in older men with cancer are lacking. The cut-points by Hildebrand et al. [403,404], which were validated in a sample of the general adult population (21 to 61 years), classified physical activity intensities as: sedentary behaviour (< 45 m*g*), light physical activity (45 to 99 m*g*), moderate physical activity (100 to 430 m*g*), vigorous physical activity (> 430 m*g*) and MVPA (≥ 100 m*g*). To account for the older age and chronic disease status of the study population, the second selected set of cut-points was that by Migueles et al. [405], which was validated in older adults (≥ 70 years) and classified physical activity intensities as: sedentary behaviour (< 18 m*g*), light physical activity (18 to 60 m*g*) and MVPA (> 60 m*g*). Physical activity estimates were calculated using both total minutes at each intensity and after applying requirements of minimal bout length for sedentary behaviour (≥ 30 minute bouts with at least 90% of the bout above the cut-point), light physical activity and MVPA (≥ 10 minute bouts with at least 80% of the bout above the cut-point for both) as is commonly done in physical activity research [406].

4.3.3. Physical fitness

Cardiopulmonary exercise test (all studies)

A medically supervised, symptom-limited CPET with 12-lead ECG recording and respiratory gas exchange analysis was performed on a stationary cycle ergometer to assess aerobic fitness. After a 4-minute warm up without resistance, participants cycled for one minute at an initial load of 20 Watts (W) and each minute thereafter the load increased by either 10 W or 15 W, depending on the estimated fitness of the participant as determined by the supervising exercise physiologist. The CPET was stopped when the participant reached volitional exhaustion, defined as a rating of perceived exhaustion (RPE) ≥ 9 on the 10-point Borg scale, or when the cadence dropped below 50 revolutions per minute. Maximal workload (W_{max}) during the incremental test was recorded as the last completed increment and divided by bodyweight to obtain the relative W_{max}. Maximal heart rate (HR_{max}) was measured using a chest strap heart rate monitor to verify that participants performed the test to the maximum, which was assumed when the measured HR_{max} was no more than 10 beats per minute below the age-predicted HR_{max} (i.e. 220 − age). Respiratory gas exchange was measured continuously breath by breath during the CPET and averaged over 30-second intervals to obtain the VO_2peak, which was defined as the highest VO_2 value for any given 30-second interval.

400 metre walk test (all studies)

Functional performance was assessed in a 400 metre walk test, which was performed as ten laps of 40 metres. After one warm-up round, participants were instructed to walk 400 metres as fast as possible without running. Time to completion and RPE on the 10-point Borg scale at the end of the test were recorded.

Maximal strength tests (all studies)

Maximal strength was determined as the one-repetition maximum (1RM) of leg press, chest press, leg extension and seated row. Based on review of the most recent imaging results regarding the location and presentation of bone metastases for each participant, an exercise specialist determined whether these exercises were considered safe and those determined to be unsafe were excluded. The warm-up for each exercise consisted of six repetitions at 60% of the estimated 1RM and three repetitions at 80% of the estimated 1RM with two minutes rest between sets. The 1RM was then determined as the maximal weight that a participant was able to complete the exercise with using correct technique. Participants had a maximum of five attempts to reach the 1RM for each exercise with two minutes rest between attempts. Maximal handgrip strength of the dominant hand was assessed in a seated position using a handgrip dynamometer. Participants were instructed to set their elbow at 90° flexion while keeping a neutral wrist position and rest the lower arm against their

upper thigh. Each participant performed three attempts with 30 seconds rest between attempts and the highest value was recorded.

4.3.4. Blood sample collection and processing

Blood collection and PBMC isolation (all studies)

Blood collection was performed on the morning of the first exercise testing visit between 7 and 10 a.m. when participants were in a fasted state. Venous blood was collected from the antecubital vein into two ethylenediaminetetraacetic acid (EDTA)-coated containers, one for a complete blood count and one for PBMC isolation, and one heparin-coated container (both BD, Franklin Lakes, NJ, United States) for analysis of serum concentrations of testosterone and PSA in an external laboratory. A complete blood count was performed immediately after blood collection using an automated cell counter (Sysmex XN-350, Kobe, Japan) as it was required for medical clearance for exercise participation. Complete blood counts were also used to calculate the inflammation markers NLR, PLR and SII. To isolate PBMCs, the other EDTA blood sample was diluted with phosphate-buffered saline (PBS) (gibco, Thermo Fisher Scientific, Waltham, MA, United States) to a final volume of 25 mL and carefully layered on top of 20 mL of lymphocyte separation medium (PromoCell, Heidelberg, Germany) in a 50 mL conical tube. After centrifugation at 300 g for 30 minutes without brake, the PBMC-containing layer was collected and transferred to another 50 mL conical tube, diluted with PBS to a final volume of 30 mL and centrifuged at 300 g for 10 minutes. The supernatant was discarded and the pellet was resuspended in 2 mL Recovery™ Cell Culture Freezing Medium (gibco, Thermo Fisher Scientific, Waltham, MA, United States). Four aliquots of 500 µL each were transferred to cryogenic vials and stored at −80°C using a cell camper for controlled freezing, before transfer to −150°C the next day and storage until analysis.

Flow cytometry-based immune cell analysis (Study 2 and 3)

Immune cell analysis was performed by labelling PBMCs with monoclonal antibodies against surface antigens and quantifying immune cell populations using flow cytometry. PBMC samples were thawed by briefly transferring them into a 37°C water bath until only a small amount of ice remained. The content of each vial was then transferred to a conical tube containing 10 mL AutoMACS Running Buffer (Miltenyi Biotec, Bergisch Gladbach, Germany) pre-warmed to 37°C for washing. After centrifugation at 300 g for 10 minutes the supernatant was discarded and the pellet was resuspended in 10 mL warm AutoMACS Running Buffer and centrifuged at 200 g for 10 minutes for a second washing step. Again, the supernatant was discarded and the pellet was resuspended in 200 µL AutoMACS Running Buffer. 10 µL of each sample were diluted at a 1:10 ratio with MACSQuant Running Buffer (Miltenyi Biotec, Bergisch Gladbach, Germany) for automated cell counting using the MACSQuant10 (Miltenyi

Biotec, Bergisch Gladbach, Germany). Based on the cell count two suspensions containing 5×10^5 cells with a total volume of 100 µL each was prepared for antibody labelling.

For labelling, two panels with the following antibodies were used: panel 1 included anti-CD3 VioBlue (REA613), anti-CD4 APC (REA623), anti-CD25 VioBright 515 (REA570), anti-CD127 PE (REA614), anti-CD16 VioGreen (REA423) and anti-CD56 PE-Vio770 (REA196); panel 2 included anti-CD3 VioBlue (REA613), anti-CD4 APC-Vio770 (REA623), anti-CD194 PE-Vio770 (REA279), anti-CCR6 APC (REA190), anti-CCR10 PE (REA326), anti-CD183 VioBrightFITC (REA232) and anti-CD19 VioGreen (REA675) (all Miltenyi Biotec, Bergisch Gladbach, Germany). Propidium iodide (PI) for differentiation between live and dead cells was added to each sample immediately prior to measuring. Both cell suspensions, one for each panel, were incubated with 2 µL of each antibody for 30 minutes at room temperature protected from light. 10 µL Tandem Signal Enhancer (Miltenyi Biotec, Bergisch Gladbach, Germany) were added to each sample prior to staining. After incubation, cells were washed by adding 1 mL AutoMACS Running Buffer followed by centrifugation at 300 g for 10 minutes. The supernatant was discarded, cells were resuspended in 150 µL MACSQuant Running Buffer and transferred onto a 96-well plate (VWR International, Radnor, PA, United States) for analysis.

Cell analysis was performed using the MACSQuant10. Both a calibration (MACSQuant calibration beads, Miltenyi Biotec, Bergisch Gladbach, Germany) and a compensation (MACS Comp Bead Kit, anti-REA, Miltenyi Biotec, Bergisch Gladbach, Germany) procedure were performed according to the manufacturer's instructions prior to measuring samples. Following measurements, cell populations were analysed using the MACSQuantify software (Miltenyi Biotec, Bergisch Gladbach, Germany). First, live cells were identified as PI-negative cells, then single cells were gated on the forward scatter (FSC)-A and FSC-H plot and from those lymphocytes were gated using FSC and side scatter (SSC). Then the following cell populations were gated using panel 1: T cells ($CD3^+$), Th cells ($CD3^+CD4^+$), Tc cells ($CD3^+CD4^-$), Treg cells ($CD4^+CD25^+CD127^{low}$), NK cells ($CD3^-CD56^+$) and NK subpopulations $CD56^{dim}$ ($CD56^+CD16^{+/-}$) and $CD56^{bright}$ ($CD56^{++}CD16^-$) (Figure 19). Panel 2 was used to identify Th cell subpopulations (Th1, Th2, Th17) according to the strategy proposed by Mahnke et al. [407], and also gate B cells (Figure 20). Control conditions included isotype controls to detect unspecific binding and fluorescence minus one controls to determine gates for positive populations.

Immune cell populations were analysed using both absolute counts and relative proportions. Proportions of all cell populations were calculated relative to total lymphocytes and, in addition, proportions of NK subpopulations ($CD56^{dim}$ and $CD56^{bright}$) were calculated relative to total NK cells, proportions of Th and Tc cells were calculated relative to total T cells and

proportions of Th subpopulations (Th1, Th2, Th17 and Treg cells) were calculated relative to total Th cells.

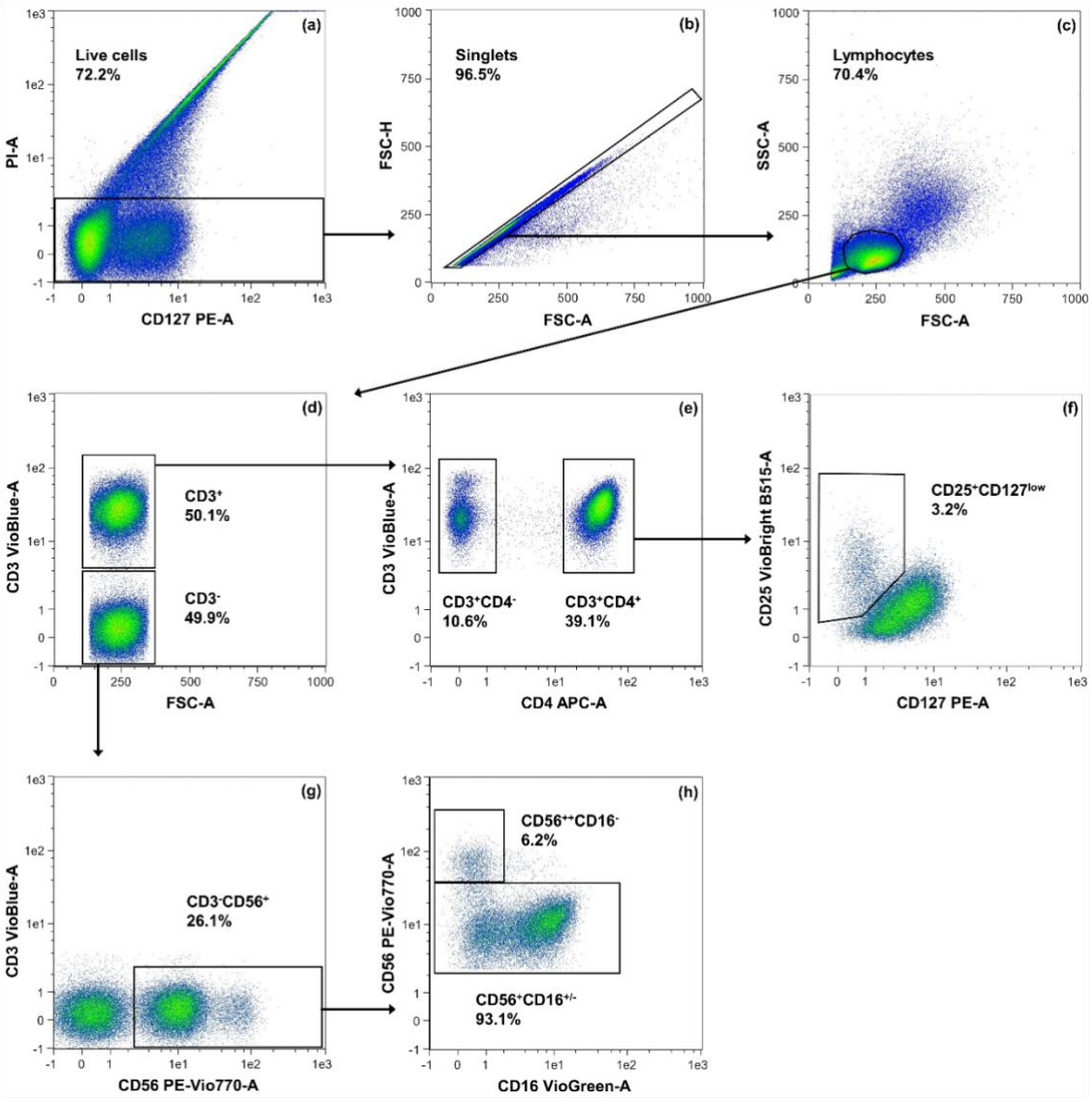


Figure 19. Gating strategy for the identification of lymphocyte subpopulations. (a) Live cells were identified via propidium iodide (PI) staining and **(b)** singlets were distinguished from forward scatter area (FSC-A) and height (FSC-H). **(c)** Lymphocytes were gated by size and granularity from FSC-A and side scatter area (SSC-A), from which T cells were identified as $CD3^+$ **(d)**. **(e)** Tc cells ($CD3^+CD4^-$) and Th cells ($CD3^+CD4^+$) were gated from the $CD3^+$ subpopulation and the latter were used to identify Treg cells ($CD25^+CD127^{low}$) **(f)**. **(g)** NK cells ($CD3^-CD56^+$) were gated from the $CD3^-$ subpopulation and further differentiated into NK subpopulations $CD56^{dim}$ ($CD56^+CD16^{-/+}$) and $CD56^{bright}$ ($CD56^{++}CD16^-$) **(h)**. Percentages in the graphs indicate the proportion of total cells in (a), proportion of live cells in (b), proportion of singlets in (c), proportions of lymphocytes in (d) to (g) and proportions of NK cells in (h). CD: cluster of differentiation; NK: natural killer cell; Tc: cytotoxic T cell; Th: T helper cell; Treg: regulatory T cell.

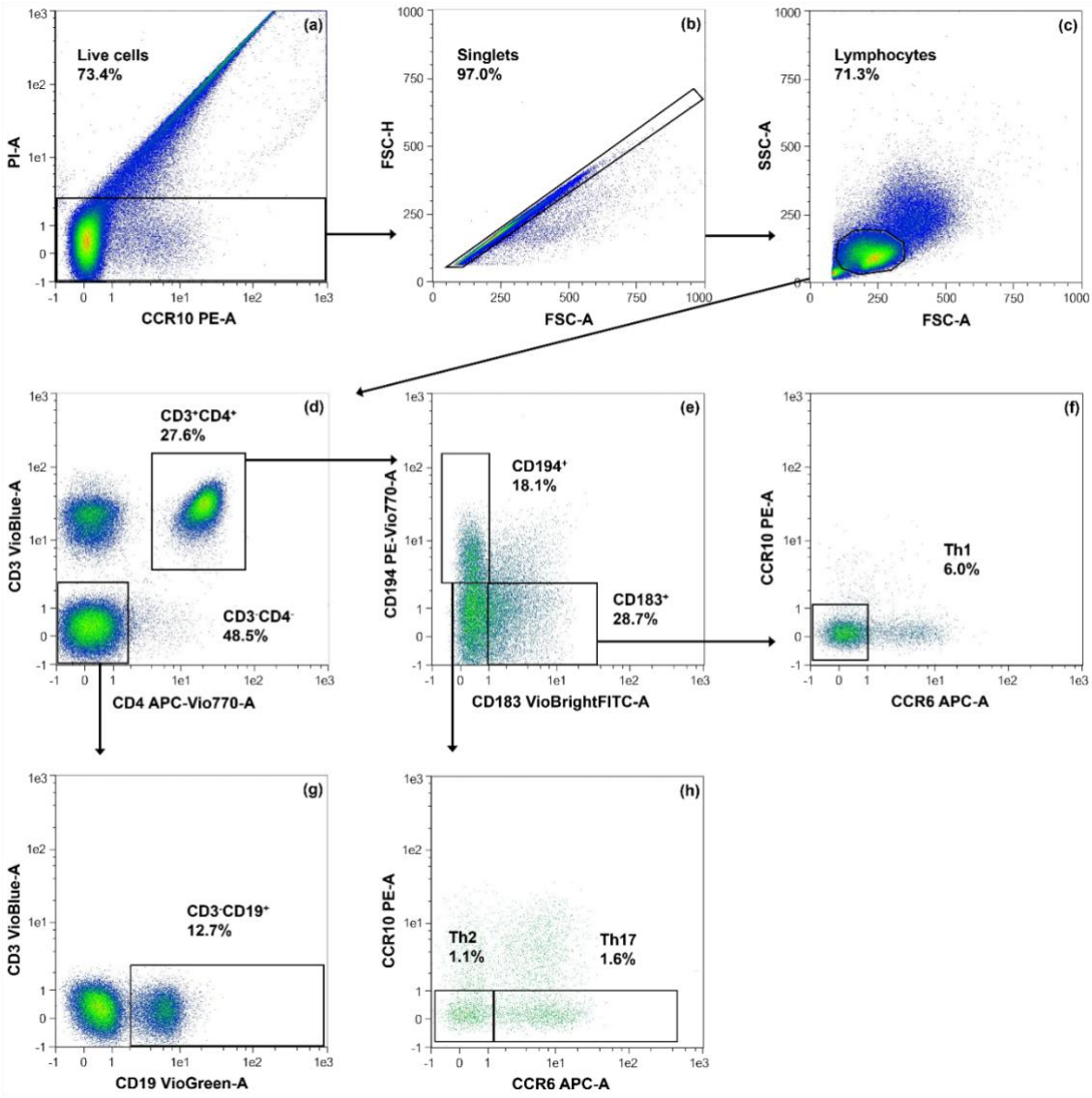


Figure 20. Gating strategy for the identification of T helper (Th) cell subpopulations. **(a)** Live cells were identified via propidium iodide (PI) staining and **(b)** singlets were distinguished from forward scatter area (FSC-A) and height (FSC-H). **(c)** Lymphocytes were gated by size and granularity from FSC-A and side scatter area (SSC-A), from which a $CD3^-CD4^-$ subpopulation and Th cells ($CD3^+CD4^+$) were identified **(d)**. **(g)** The $CD3^-CD4^-$ subpopulation was used to gate B cells ($CD3^-CD19^+$), while Th cells were further differentiated into $CD183^+$ and $CD194^+$ cells **(e)**. **(f)** $CD183^+$ cells were used to gate Th1 cells ($CD183^+CCR10^-CCR6^-$). **(h)** $CD194^+$ cells were used to gate Th2 cells ($CD194^+CCR10^-CCR6^-$) and Th17 cells ($CD194^+CCR10^-CCR6^+$). Percentages in the graphs indicate the proportion of total cells in (a), proportion of live cells in (b), proportion of singlets in (c), proportions of lymphocytes in (d) to (h). CD: cluster of differentiation.

4.4. Intervention design

4.4.1. Exercise prescription

Participants allocated to the intervention arm received a 6-month structured exercise intervention, consisting of 6 cycles á 4 weeks each. The exercise prescription combined aerobic and strength training in a periodised, progressive programme that was tailored to the individual needs of each participant based on the physical fitness assessments performed at baseline and subsequent testing visits. Additional to the exercise prescription, participants in the intervention arm were provided with behavioural support in the form of regular text messages to their mobile phones to encourage programme adherence. A detailed description of the exercise prescription for all six cycles (cycle 0 to 5) is presented in Table 6.

Briefly, participants exercised three times per week with sessions 1 and 3 comprised of aerobic exercise in the form of HIIT followed by resistance exercise, whereas session 2 comprised of MICT. During the first cycle (cycle 0) participants were familiarised with the programme and the individual exercises and incrementally built towards the training load that was then maintained throughout the subsequent five cycles (cycles 1 to 5) with a deload week included every fourth week to improve recovery. Two types of HIIT, either 30 s interval length followed by 90 s active recovery or 60 s interval length followed by 120 s active recovery, were employed and alternated weekly with longer intervals prescribed for weeks 1 and 3 and shorter intervals prescribed for weeks 2 and 4 of each cycle. The MICT in session 2 was structured as two longer efforts of 5 to 15 minutes duration, with 2 minutes rest between efforts if needed, during cycles 0 to 4 and increased to one continuous effort of 30 minutes duration by cycle 5. Participants could choose from available aerobic exercise machines, including cycle ergometer, cross-trainer or treadmill.

The resistance exercise prescription included six exercises, three each for the lower and upper body, that were selected individually by an exercise physiologist under consideration of the participant's fitness, physical capacities and metastatic sites. Because bone health is a priority in this population, the latest scan results of each participant were reviewed by a specialist prior to resistance exercise selection and exercises targeting skeletal regions with increased fracture risk were prohibited. Potential resistance exercises included leg extension, leg curl, leg press, calf raises and back squat or sit-to-stand exercise for the lower body and chest press, seated row, lat pulldown, biceps curls and triceps extension for the upper body. Exercises were performed using modern resistance machines except for back squat and sit-to-stand exercise, which were performed using bodyweight only or dumbbells for additional resistance. Participants who completed the intervention during the COVID-19 pandemic received home-based alternative exercises using dumbbells or resistance bands during times when access to the exercise facilities was restricted. The prescribed resistance training volume ranged from 1 to 4 sets of 6 to 12 repetitions per exercise, which were

selected to promote neuromuscular adaptations but avoid maximal weight to minimise the injury risk.

The exercise intervention employed an autoregulation approach that allowed participants to lower the exercise intensity when feeling fatigued or unwell and increase the exercise intensity when feeling motivated and energetic. Autoregulation was achieved through the use of target RPE on a 10-point Borg scale to determine aerobic exercise intensity, while resistance exercise intensity was regulated via repetition maximum, i.e. participants were asked to choose the maximal weight that they could perform the required number of sets and repetitions with. This approach also allowed adjustments of the exercise intensity as the participants' strength increased throughout the intervention, as well as reductions to accommodate times of decreased exercise capacity.

The original study protocol intended most sessions during the first six cycles to be supervised by exercise specialists with gradual transition to self-managed exercise during the later stages of the trial. However, because regular travel to the exercise clinic presented a barrier to participation, a remote training option was introduced. Participants who trained remotely completed several sessions on site during cycle 0, where they were familiarised with the training protocol and individual exercise selection, and then performed most subsequent sessions independently at external exercise facilities. Moreover, participants were allowed to complete MICT sessions outdoors using appropriate modes of exercise, e.g. jogging, brisk walking or cycling. Remotely training participants were asked to come on site once per cycle for a supervised session to review the exercises and adapt the exercise selection if needed.

All participants were provided with Polar Unite fitness trackers (Polar, Kempele, Finland) for HR monitoring during aerobic exercise and were asked to record HR_{max} and HR_{avg} for aerobic exercise only. Records also included the completed number of repetitions and achieved RPE for aerobic exercise and completed number of sets and repetitions, as well as weight used for each resistance exercise. Overall training intensity was recorded as session RPE at the end of each training session. Training sessions that were missed for reasons unrelated to health, e.g. vacation or conflicting appointments, were rescheduled or combined with other training sessions if possible.

Table 6. Aerobic and resistance exercise prescription for cycles 0 to 5 of the supervised, periodised, progressive exercise intervention.

Period	Aerobic exercise	Resistance exercise
Cycle 0		
Week 1		
Session 1	3 × 30 s at RPE 5, 90 s active recovery	1 set × 8 rep
Session 2	10 min at RPE 4	
Session 3	3 × 30 s at RPE 5, 90 s active recovery	1 set × 12 rep
Week 2		
Session 1	4 × 30 s at RPE 6, 90 s active recovery	1 sets × 8 rep
Session 2	10 min at RPE 4	
Session 3	4 × 30 s at RPE 6, 90 s active recovery	1 sets × 12 rep
Week 3		
Session 1	3 × 30 s at RPE 5, 90 s active recovery	1 set × 8 rep
Session 2	10 min at RPE 4	
Session 3	3 × 30 s at RPE 5, 90 s active recovery	1 set × 12 rep
Week 4		
Session 1	3 × 30 s at RPE 5, 90 s active recovery	1 set × 8 rep
Session 2	10 min at RPE 4	
Session 3	3 × 30 s at RPE 5, 90 s active recovery	1 set × 12 rep
Cycles 1 to 5		
Week 1		
Session 1	6 × 60 s at RPE 8, 120 s active recovery	4 sets × 8 rep
Session 2	10 to 30 min* at RPE 5	
Session 3	6 × 60 s at RPE 8, 120 s active recovery	4 sets × 12 rep
Week 2		
Session 1	6 × 30 s at RPE 9, 90 s active recovery	4 sets × 6 rep
Session 2	10 to 30 min* at RPE 6	
Session 3	6 × 30 s at RPE 9, 90 s active recovery	4 sets × 10 rep
Week 3		
Session 1	6 × 60 s at RPE 8, 120 s active recovery	3 sets × 8 rep
Session 2	10 to 30 min* at RPE 5	
Session 3	6 × 60 s at RPE 8, 120 s active recovery	3 sets × 12 rep
Week 4 (deload)		
Session 1	4 × 30 s at RPE 6, 90 s active recovery	2 sets × 6 rep
Session 2	10 to 30 min* at RPE 4	
Session 3	4 × 30 s at RPE 6, 90 s active recovery	2 sets × 10 rep

Notes: The resistance exercise prescription included six exercises per session, three each for upper and lower body. Exercise intensity was determined via an autoregulation approach using RPE on a 10-point Borg scale for aerobic exercise and repetition maximum for resistance exercise. * Aerobic exercise duration of session 2: 10 min in cycle 1 weeks 1−2, 20 min in cycle 1 weeks 3−4, 30 min in cycles 2−5.

Abbreviations: min: minutes; rep: repetitions; RPE: rating of perceived exertion; s: seconds.

4.4.2. Adherence and intensity outcomes

Exercise adherence was analysed according to the approaches proposed by Nilsen et al. and Fairman et al. for aerobic and resistance exercise, respectively [331,332]. MICT dose was calculated as cumulative MICT duration and HIIT dose was calculated as cumulative time exercising at high intensity by multiplying the number of work intervals with the work interval duration. For the statistical analysis, MICT and HIIT dose were combined into total aerobic exercise dose by summing up both values with HIIT dose multiplied by a factor of two. This approach was chosen based on the American Cancer Society guidelines, which equate 75 minutes of vigorous intensity physical activity with 150 minutes at a moderate intensity [25]. Resistance exercise dose was calculated as the cumulative number of repetitions by multiplying the numbers of exercises, sets and repetitions. MICT, HIIT and resistance exercise adherence were determined separately as the completed dose relative to the prescribed dose for each exercise modality. The prescribed number of resistance exercises was six, with additional exercises considered if they were adequately recorded and participants adhered to the prescribed training mode of sets and repetitions. Additionally, mean values of RPE, HR_{max} and HR_{avg} were reported as measures of aerobic exercise intensity. Furthermore, total completed sessions as a traditional exercise dose metric were reported for each exercise modality to facilitate comparison with previous studies. All descriptive variables of exercise intervention adherence, dose and intensity were calculated for the same 24-week period (cycle 0 to 5) for all participants. By contrast, the total aerobic and resistance exercise doses for each participant that were used as confounders in the statistical analysis included all exercise sessions recorded between the intervention start and the individual 6-month testing visit, which occurred during cycles 6 or 7.

4.4.3. Psychosocial support

All participants received psychosocial support in the form of digital newsletters that provided educational content on topics identified as relevant to men with advanced prostate cancer. Newsletter topics included physical activity, nutrition, general health-promoting behaviours, management of side effects related to cancer or its treatments, mental health, and sexual intimacy, amongst others.

4.4.4. Control arm

The control arm in the INTERVAL-GAP4 trial was also referred to as the self-directed exercise arm. Participants allocated to this arm were provided with print information about physical activity recommendations for cancer survivors and suggestions on how to pursue a self-directed exercise programme, as well as the identical psychosocial support newsletters. Importantly, the control arm was not instructed to refrain from exercise as this would be

unethical considering the evidence for exercise-induced benefits during cancer. Unlike the intervention arm, however, they did not receive a structured, individualised exercise programme and were not offered supervised training at the study site.

4.5. Statistical analyses

Statistical analyses were performed using R Version 4.3.0 (R Core Team, Vienna, Austria) [398] unless specified otherwise. Descriptive statistics included demographic and clinical participant characteristics and were calculated as mean with SD for continuous variables and n with relative proportion for categorical variables. Statistical significance was defined as $p < 0.05$.

Study 1

Quantile regression analysis was used to examine the associations of physical fitness outcomes, i.e. relative VO_2peak, relative W_{max}, 400 metre walk time, relative 1RM of leg extension, leg press, chest press and seated row, and handgrip strength (dependent variables), with MVPA (independent variable) at the 25th, 50th and 75th percentiles of the dependent variables. Quantile regression allows the distinction of associations between the independent and dependent variables at different parts of the distribution of the dependent variables while analysing the entire sample, which results in improved statistical power [408]. In contrast to linear regression, the quantile regression coefficient β represents the change in the value at each modelled percentile, as opposed to the mean, of the dependent variable. For the subgroup analysis of ARI use, separate quantile regression models were calculated for ARI users and non-users with the exception of all strength outcomes but leg extension, because the number of participants with complete data was insufficient for a subgroup analysis. All models were adjusted for the same selection of covariates considered to be potential confounders based on previous studies of physical activity among individuals with cancer [27,409]. Covariates used for model adjustment included age, BMI, time since diagnosis, time on ADT and prostate cancer stage at enrolment (mHSPC or mCRPC). Time on ADT was defined as the time since the current ADT was started and does not include previous treatments with ADT if interrupted before starting the current treatment. Additionally, a between-group analysis of ARI users and non-users was performed in IBM SPSS Statistics for Windows (Version 29.0, IBM Corp., Armonk, NY, United States) using a Mann-Whitney-U test for continuous variables after non-normal distribution was detected using the Shapiro-Wilk test and visually by inspecting Q-Q plots. Distribution of each variable was assessed per group and results were presented as median for similarly distributed variables and mean rank (M_{rank}) for dissimilarly distributed variables. The Pearson's chi-square test was used to determine differences between ARI users and non-users for dichotomous variables. Participants with missing data for physical activity or fitness variables were excluded from

the analyses with the exception of the strength assessments, which were only completed by a subsample of participants. Missing data for any of the covariates was replaced using a random forest model as is commonly used in epidemiological research due to its superiority to other imputation methods [410].

Study 2

Raw ActiGraph data was processed into four distinct time-use behaviours (sedentary behaviour, light physical activity, MVPA and sleep) and summarised as cumulative time spent in each of these across the 24-hour activity cycle of one day. Two distinct sets of time-use behaviour variables were generated using ENMO cut-points by Hildebrand et al. ($ActiGraph_H$) and Migueles et al. ($ActiGraph_M$). For physical activity and fitness outcomes, a between-group analysis of ARI users and non-users was performed using the Mann-Whitney-U test after non-normal distribution was detected using the Shapiro-Wilk test and visually by inspecting Q-Q plots. Agreement between either $ActiGraph_H$ or $ActiGraph_M$ with self-reported physical activity estimates obtained by the GSLTPAQ was analysed using Bland-Altman analysis and linear regression. Bland-Altman analysis was performed by calculating the bias (mean difference of both methods) and the 95% limits of agreement (bias ± 1.96 × SD). Linear regression analyses were performed to determine the association of light physical activity and MVPA measured by the GSLTPAQ (dependent variable) with those derived from $ActiGraph_H$ or $ActiGraph_M$ (independent variable).

By definition, time-use behaviour variables are co-dependent as the sum of all variables always equals 24 hours. To account for the inherent multicollinearity between explanatory variables, analysis of the association between time at different physical activity intensities and physical fitness was conducted using a partial least squares (PLS) regression approach as recommended [406]. First, time-use behaviour variables were standardised to a sum of 1. Covariates used for model adjustment included age, BMI, time since diagnosis, time on ADT and prostate cancer stage at enrolment (mHSPC or mCRPC). Then, leave-one-out crossvalidation was performed to select the optimal number of components using the first local minimum of the root mean square error of crossvalidation as selection criterion. Variable selection was based on variable importance for projection (VIP) scores and only variables with a VIP ≥ 1 were included as predictors in the final model to improve model performance. Alpha levels, t-values and 95% confidence intervals (CIs) of regression coefficients for predictors in the final model were inferred using the Jack-Knifing method. For interpretation of the coefficient of determination (R^2), cut-off values by Chin were applied as follows: < 0.19 very weak association, 0.19 to < 0.33 weak association, 0.33 to < 0.67 moderate association, ≥ 0.67 substantial association [411]. PLS analysis was performed using the mdatools package version 0.14.1 [412].

Study 3

Firstly, data was checked for outliers using quartiles (Q) and the interquartile range (IQR) and extreme outliers were defined as data points above Q3 + 3 × IQR or below Q1 − 3 × IQR. All analyses were computed with and without including extreme outliers and as there were no differences in the levels of statistical significance, extreme outliers were included in the reported results. Normal distribution was assessed using the Shapiro-Wilk test and visually by inspecting Q-Q plots. The Levene test was used to assess homogeneity of variance and Box's M test to assess homogeneity of covariance. Baseline differences in continuous variables were analysed using the independent t-test and, alternatively, Welch's t-test for variables with unequal variances, while Pearson's chi-square test was used to determine differences in dichotomous variables. A two-way mixed analysis of variance (ANOVA) and pairwise t-tests with Bonferroni correction for post hoc comparisons were performed to analyse the intervention effect on changes in immune cells and inflammation markers (time × arm). Effect sizes for main effects were reported as partial eta squared (η^2) and interpreted as follows: $\eta^2 = 0.01$ indicates a small effect, $\eta^2 = 0.06$ indicates a medium effect and $\eta^2 = 0.14$ indicates a large effect [413]. Effect sizes for post hoc comparisons were reported as Cohen's d and interpreted as follows: d = 0.2 indicates a small effect, d = 0.5 indicates a medium effect and d = 0.8 indicates a large effect [414]. ANOVA was performed using the rstatix package version 0.7.2 [415].

For participants in the intervention arm, multiple linear regression was performed to analyse the association of changes in physical fitness and immune parameters with completed exercise dose and sessions. Absolute deltas (Δ = 6-month − baseline values) of physical fitness variables, immune cells and inflammation markers (dependent variables) were modelled with total aerobic exercise dose, total resistance exercise dose and baseline values (independent variables) for associations with completed exercise dose and number of total exercise sessions and baseline values (independent variables) for associations with completed exercise sessions.

5. Results

5.1. Cross-sectional multi-centre study (Study 1)

5.1.1. Participant characteristics

Demographic and clinical characteristics of the participants are presented in Table 7. Briefly, participants were on average 69 ± 8 years of age, had a BMI of 29.2 ± 4.7 $m \cdot kg^{-2}$ and had been diagnosed with prostate cancer for 69 ± 66 months. Thirty-eight (27%) and 102 (73%) participants had mHSPC and mCRPC at the time of enrolment, respectively. The mean treatment time with ADT was 37 ± 42 months and 59 (42%) participants received second-generation ARIs in addition to ADT.

Table 7. Demographic and clinical characteristics of participants included in Study 1.

	All participants (n = 140) Mean ± SD or n (%)
Demographic characteristics	
Age, years	69 ± 8
Height, m	1.75 ± 0.08
Weight, kg	89.2 ± 16.3
BMI, $m \cdot kg^{-2}$	29.2 ± 4.7
Employment status, n	
Retired	96 (69)
Full-time	19 (14)
Part-time	16 (11)
Volunteer work	1 (1)
Unemployed	3 (2)
Unable to work	4 (3)
Unknown	1 (1)
Smoking status, n	
Non-smoker	60 (43)
Active smoker	11 (8)
Previous smoker	68 (49)
Unknown	1 (1)
Clinical characteristics	
Time since diagnosis, months	69 ± 66
Time on ADT, months	37 ± 42
Testosterone, $ng \cdot dL^{-1}$	11.4 ± 9.6
PSA, $ng \cdot mL^{-1}$	6.6 ± 13.9
Disease stage, n	
mHSPC	38 (27)
mCRPC	102 (73)

	All participants (n = 140)
	Mean ± SD or n (%)
Metastases, n	
Bones	113 (81)
Lymph nodes	83 (59)
Lung	6 (4)
Liver	4 (3)
Other	5 (4)
ARI use, n	
Yes	59 (42)
Apalutamide	12 (8)
Enzalutamide	47 (33)
No	81 (58)
ECOG performance status, n	
0	101 (72)
1	39 (28)
Bone pain, n	
No pain	110 (79)
Mild pain	30 (21)

Abbreviations: ADT: androgen deprivation therapy; ARI: androgen receptor inhibitor; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; mCRPC: metastatic castrate-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; SD: standard deviation.

5.1.2. Self-reported physical activity and guideline adherence

Participants self-reported engaging in light physical activity and MVPA for an average of 111 ± 216 and 128 ± 181 minutes per week, respectively, as well as performing resistance exercise on 0.7 ± 1.4 days per week (Table 8). Sixty-two (44%) participants self-reported engaging in no MVPA. Forty-one (29%) participants met the aerobic physical activity guidelines for cancer survivors by achieving at least 150 minutes of MVPA per week. Only twenty-eight (20%) participants self-reported engaging in resistance exercise.

Table 8. Baseline physical activity and physical fitness estimates of participants included in Study 1.

	All participants (n = 140)
	Mean ± SD or n (%)
Physical activity (modified GSLTPAQ)	
Light physical activity, min·week^{-1}	111 ± 216
Moderate physical activity, min·week^{-1}	84 ± 135
Vigorous physical activity, min·week^{-1}	22 ± 49
Moderate-to-vigorous physical activity (MVPA), min·week^{-1}	128 ± 181
Resistance exercise, days·week^{-1}	0.7 ± 1.4

	All participants (n = 140)
	Mean ± SD or n (%)
Leisure score index (LSI), a.u.	21 ± 19
Meeting aerobic physical activity guidelines	
Meeting MVPA guidelines (≥ 150 min·week^{-1}), n (%)	41 (29)
Not meeting MVPA guidelines (< 150 min·week^{-1}), n (%)	99 (71)
Meeting LSI guidelines (≥ 24), n (%)	46 (33)
Not meeting LSI guidelines (< 24), n (%)	94 (67)
Physical fitness	
Relative VO_2peak, ml·min^{-1}·kg^{-1}	20.3 ± 6.1
Maximal workload W_{max}, W	131.4 ± 43.7
Relative W_{max}, W·kg^{-1}	1.5 ± 0.5
400 metre walk time, s	285.3 ± 82.8
Relative leg extension 1RM, kg·kg^{-1} [a]	0.7 ± 0.3
Relative leg press 1RM, kg·kg^{-1} [b]	1.2 ± 0.3
Relative chest press 1RM, kg·kg^{-1} [c]	0.5 ± 0.2
Relative seated row 1RM, kg·kg^{-1} [d]	0.7 ± 0.2
Handgrip strength, kg [e]	39.6 ± 9.5

Abbreviations: 1RM: one-repetition maximum; a.u.: arbitrary unit; GSLTPAQ: Godin-Shephard Leisure-Time Physical Activity Questionnaire; SD: standard deviation; VO_2peak: peak oxygen consumption; W_{max}: maximal workload.

[a] Participants with relative leg extension 1RM data: n = 115.

[b] Participants with relative leg press 1RM data: n = 49.

[c] Participants with relative chest press 1RM data: n = 51.

[d] Participants with relative seated row 1RM data: n = 48.

[e] Participants with handgrip strength data: n = 57.

5.1.3. Associations of self-reported MVPA with physical fitness

Adjusted quantile regression estimates of MVPA at the 25th, 50th and 75th percentiles of the physical fitness outcomes are presented in Table 9. MVPA was positively associated with relative VO_2peak at the 25th percentile (β = 0.009, p = .020) and 75th percentile (β = 0.011, p = .001), as well as relative W_{max} at the 25th percentile (β = 0.001, p = .003), 50th percentile (β = 0.001, p = .009) and 75th percentile (β = 0.001, p = .004). MVPA was inversely associated with 400 metre walk time at the 75th percentile (β = –0.071, p = .023) but not at the 25th or 50th percentiles (p > .05). There were no statistically significant associations between MVPA and any of the strength outcomes at the 25th, 50th or 75th percentiles (p > .05).

Table 9. Adjusted quantile regression estimates of moderate-to-vigorous physical activity at the 25th, 50th and 75th percentiles of physical fitness outcomes of all participants included in Study 1 (n = 140), as well as separated into ARI users (n = 59) and non-users (n = 81).

Physical activity (min*week^{-1})	**p25** β (95% CI)	**p50** β (95% CI)	**p75** β (95% CI)
MVPA	**Relative VO_2peak**		
All participants	0.009 (0.003, 0.014) *	0.007 (0.004, 0.016)	0.011 (0.005, 0.018) ***
ARI users	0.008 (–0.004, 0.010)	0.006 (0.003, 0.021)	0.011 (0.003, 0.029)
Non-users	0.014 (0.003, 0.018) **	0.013 (0.002, 0.017) *	0.008 (0.007, 0.027)
MVPA	**Relative W_{max}**		
All participants	0.001 (0.000, 0.001) **	0.001 (0.001, 0.002) **	0.001 (0.000, 0.002) **
ARI users	0.001 (–0.000, 0.002) *	0.001 (0.000, 0.001)	0.001 (0.000, 0.002)
Non-users	0.001 (0.000, 0.001)	0.001 (0.000, 0.002)	0.001 (0.000, 0.002) *
MVPA	**400 metre walk time**		
All participants	–0.043 (–0.163, –0.024)	–0.060 (–0.089, –0.017)	–0.071 (–0.120, –0.022) *
ARI users	–0.047 (–0.180, 0.002)	–0.048 (–0.110, 0.003)	–0.068 (–0.111, 0.007)
Non-users	–0.142 (–0.177, –0.010) **	–0.080 (–0.190, 0.036)	–0.073 (–0.180, 0.044)
MVPA	**Relative leg extension 1RM** [a]		
All participants	0.000 (–0.000, 0.000)	0.000 (–0.000, 0.000)	0.000 (–0.000, 0.000)
ARI users	0.000 (–0.000, 0.001)	0.000 (–0.000, 0.001)	0.000 (0.000, 0.001)
Non-users	–0.000 (–0.001, 0.000)	0.000 (–0.000, 0.001)	0.000 (–0.000, 0.001)
MVPA	**Relative leg press 1RM** [b]		
All participants	0.000 (–0.003, 0.001)	0.000 (–0.001, 0.001)	–0.000 (–0.001, 0.001)
ARI users	NA	NA	NA
Non-users	NA	NA	NA

Physical activity (min*week^{-1})	**p25** β (95% CI)	**p50** β (95% CI)	**p75** β (95% CI)
MVPA	**Relative chest press 1RM** [c]		
All participants	0.000 (–0.001, 0.000)	0.000 (–0.000, 0.001)	0.001 (–0.000, 0.002)
ARI users	NA	NA	NA
Non-users	NA	NA	NA
MVPA	**Relative seated row 1RM** [d]		
All participants	–0.000 (–0.002, 0.000)	–0.000 (–0.000, 0.000)	0.000 (–0.000, 0.001)
ARI users	NA	NA	NA
Non-users	NA	NA	NA
MVPA	**Handgrip strength** [e]		
All participants	0.010 (–0.011, 0.030)	0.012 (–0.003, 0.023)	0.015 (–0.007, 0.036)
ARI users	NA	NA	NA
Non-users	NA	NA	NA

All models were adjusted for age, body mass index, prostate cancer stage, time since diagnosis, and time on androgen deprivation therapy.

Abbreviations: β: unstandardised regression coefficient; ARI: androgen receptor inhibitor; CI: confidence interval; MVPA: moderate-to-vigorous physical activity; NA: not available; VO_2peak: peak oxygen consumption; W_{max}: maximal workload.

[a] Participants with relative leg extension 1RM data: all participants, n = 115; ARI users, n = 44; non-users, n = 71.

[b] Participants with relative leg press 1RM data: all participants, n = 49; ARI users, n = 18; non-users, n = 31.

[c] Participants with relative chest press 1RM data: all participants, n = 51; ARI users, n = 21; non-users, n = 30.

[d] Participants with relative seated row 1RM data: all participants, n = 48; ARI users, n = 21; non-users, n = 27.

[e] Participants with handgrip strength data: all participants, n = 57; ARI users, n = 24, non-users, n = 33.

* $p \leq .05$, ** $p \leq .01$, *** $p \leq .001$.

5.1.4. Analysis of self-reported MVPA and physical fitness according to ARI use

MVPA was significantly higher in ARI users (M_{rank}: 80.2) than non-users (M_{rank}: 63.5), U = 1819.5, Z = −2.518, p = .012. There was no significant difference between ARI users and non-users for any of the physical fitness outcomes (p > .05) (Table 10). In ARI users, MVPA was positively associated with relative W_{max} at the 25th percentile (β = 0.001, p = .046) but not at the 50th or 75th percentiles (p > .05) (Table 6). ARI users showed no statistically significant associations between MVPA and relative VO_2peak or 400 metre walk time (p > .05). In non-users, MVPA was positively associated with relative VO_2peak at the 25th percentile (β = 0.014, p = .008) and 50th percentile (β = 0.013, p = .014) but not at the 75th percentile (p > .05). Non-users also showed a significant association of MVPA with relative W_{max} at the 75th percentile (β = 0.001, p = .041) and 400 metre walk time at the 25th percentile (β = −0.142, p = .010). Neither group showed a significant association of MVPA with relative leg extension 1RM at the 25th, 50th or 75th percentiles (p > .05).

Table 10. Participant characteristics, physical activity and physical fitness of ARI users and non-users included in Study 1.

	ARI users (n = 59)	**Non-users (n = 81)**	
	Mean ± SD or n (%)	Mean ± SD or n (%)	p-value
Participant characteristics			
Age, years	70 ± 8	69 ± 9	.710
BMI, m·kg^{-2}	28.7 ± 4.1	29.7 ± 5.0	.272
Time since diagnosis, months	69 ± 59	68 ± 72	.386
Time on ADT, months	36 ± 43	37 ± 41	.884
Physical activity			
Moderate physical activity, min·week^{-1}	116 ± 154	61 ± 116	.012
Vigorous physical activity, min·week^{-1}	30 ± 61	17 ± 37	.558
Moderate-to-vigorous physical activity (MVPA), min·week^{-1}	176 ± 207	94 ± 151	.012
Meeting MVPA guidelines			.011
Yes (MVPA ≥ 150 min·week^{-1})	24 (41)	17 (21)	
No (MVPA < 150 min·week^{-1})	35 (59)	64 (79)	
Physical fitness			
Relative VO_2peak, ml·min^{-1}·kg^{-1}	20.5 ± 6.0	20.1 ± 6.2	.841
Relative W_{max}, W·kg^{-1}	1.6 ± 0.6	1.5 ± 0.5	.469
400 metre walk time, s	277.6 ± 55.9	290.8 ± 97.9	.854
Relative leg extension 1RM, kg·kg^{-1} [a]	0.7 ± 0.2	0.7 ± 0.3	.950
Relative leg press 1RM, kg·kg^{-1} [b]	1.2 ± 0.3	1.2 ± 0.3	.494
Relative chest press 1RM, kg·kg^{-1} [c]	0.6 ± 0.2	0.5 ± 0.2	.151

	ARI users (n = 59)	Non-users (n = 81)	
	Mean ± SD or n (%)	Mean ± SD or n (%)	p-value
Relative seated row 1RM, kg·kg^{-1} [d]	0.7 ± 0.2	0.8 ± 0.2	.194
Handgrip strength, kg [e]	39.9 ± 9.7	39.3 ± 9.5	.728

Abbreviations: 1RM: one-repetition maximum; ADT: androgen deprivation therapy; ARI: androgen receptor inhibitor; BMI: body mass index; MVPA: moderate-to-vigorous physical activity; SD: standard deviation; VO_2peak: peak oxygen consumption; W_{max}: maximal workload.

[a] Participants with relative leg extension 1RM data: all, n = 115; ARI users, n = 44; non-users, n = 71.

[b] Participants with relative leg press 1RM data: all, n = 49; ARI users, n = 18; non-users, n = 31.

[c] Participants with relative chest press 1RM data: all, n = 51; ARI users, n = 21; non-users, n = 30.

[d] Participants with relative seated row 1RM data: all, n = 48; ARI users, n = 21; non-users, n = 27.

[e] Participants with handgrip strength data: all, n = 57; ARI users, n = 24, non-users, n = 33.

5.2. Cross-sectional single-centre study (Study 2)

5.2.1. Participant characteristics

Demographic and clinical characteristics and baseline physical fitness of the participants are presented in Table 11. Participants of the cross-sectional single-centre study were on average 65 ± 9 years of age and had a BMI of 26.0 ± 2.8 m·kg^{-2}. Furthermore, 59% of participants had mHSPC, 96% had confirmed bone metastases and the majority received secondary hormone therapy in addition to ADT.

Table 11. Demographic and clinical characteristics and baseline physical fitness of participants included in Study 2.

	All participants (n = 27)
	Mean ± SD or n (%)
Demographic characteristics	
Age, years	65 ± 9
Height, m	1.78 ± 0.07
Weight, kg	83.1 ± 10.4
BMI, m·kg^{-2}	26.0 ± 2.8
Employment status, n	
Retired	13 (48)
Full-time	7 (26)
Part-time	5 (19)
Unemployed	1 (4)
Unable to work	1 (4)
Smoking status, n	
Non-smoker	13 (48)
Active smoker	4 (15)
Previous smoker	10 (37)

	All participants (n = 27)
	Mean ± SD or n (%)
Clinical characteristics	
Time since diagnosis, months	38 ± 46
Time on ADT, months	11 ± 9
Testosterone, $ng \cdot dL^{-1}$	14.8 ± 8.0
PSA, $ng \cdot mL^{-1}$	9.4 ± 19.3
Disease stage, n	
mHSPC	16 (59)
mCRPC	11 (41)
Metastases, n	
Bones	26 (96)
Lymph nodes	18 (67)
Visceral organs (e.g. lung)	4 (15)
Secondary prostate cancer treatment, n	
Hormone therapy	20 (74)
ARI (apalutamide or enzalutamide)	13 (48)
Other (abiraterone)	7 (26)
None	7 (26)
ECOG performance status, n	
0	22 (81)
1	5 (19)
Bone pain, n	
No pain	21 (78)
Mild pain	6 (22)
Physical fitness	
Relative VO_2peak, $ml \cdot min^{-1} \cdot kg^{-1}$	26.1 ± 5.7
400 metre walk time, s	250.2 ± 44.0
Relative leg extension 1RM, $kg \cdot kg^{-1}$	0.9 ± 0.2
Handgrip strength, kg [a]	44.9 ± 7.6

Abbreviations: 1RM: one-repetition maximum; ADT: androgen deprivation therapy; ARI: androgen receptor inhibitor; BMI: body mass index; ECOG: Eastern Cooperative Oncology Group; mCRPC: metastatic castrate-resistant prostate cancer; mHSPC: metastatic hormone-sensitive prostate cancer; PSA: prostate-specific antigen; SD: standard deviation; VO_2peak: peak oxygen consumption.

[a] Participants with handgrip strength data: n = 24.

5.2.2. Accelerometer-derived and self-reported physical activity

The mean number of valid days included in accelerometer-derived data analysis was 6.5 days (range: 6 to 8), which was divided into 4.5 weekdays (range: 4 to 6) and two weekend days consistently for all participants. Mean daily physical activity estimated from accelerometer-derived and self-reported data is presented in Table 12. Figure 21 shows mean and participant-level proportions of different physical activity intensities across the 24-hour activity cycle separately for each set of cut-points applied to accelerometer-derived

data. Of these 24 hours, participants spent on average 33% sleeping and 47% in sedentary behaviour, 15% in light physical activity and 6% in MVPA according to ActiGraph$_H$, compared to 31% in sedentary behaviour, 22% in light physical activity and 14% in MVPA according to ActiGraph$_M$.

Table 12. Mean daily physical activity estimated from accelerometer-derived and self-reported data of participants included in Study 2.

	All participants (n = 27) Mean ± SD
Accelerometer-derived physical activity (ActiGraph)	
Raw acceleration, m*g*	26.6 ± 9.4
Sleep, h·day^{-1}	7.9 ± 0.9
Cut-points by Hildebrand et al. (ActiGraph$_H$)	
Sedentary behaviour, h·day^{-1}	11.2 ± 1.7
Sedentary behaviour (30 min bouts), h·day^{-1}	6.2 ± 3.6
Light physical activity, h·day^{-1}	3.6 ± 1.6
Light physical activity (10 min bouts), h·day^{-1}	0.5 ± 0.8
MVPA, min·day^{-1}	80 ± 44
MVPA (10 min bouts), min·day^{-1}	17 ± 16
Cut-points by Migueles et al. (ActiGraph$_M$)	
Sedentary behaviour, h·day^{-1}	7.5 ± 1.9
Sedentary behaviour (30 min bouts), h·day^{-1}	1.3 ± 1.3
Light physical activity, h·day^{-1}	5.2 ± 1.0
Light physical activity (10 min bouts), h·day^{-1}	0.8 ± 0.6
MVPA, min·day^{-1}	204 ± 93
MVPA (10 min bouts), min·day^{-1}	56 ± 44
Self-reported physical activity (modified GSLTPAQ) [a]	
Light physical activity, h·day^{-1}	0.3 ± 0.3
MVPA, min·day^{-1}	32 ± 28

Abbreviations: a.u.: arbitrary unit; GSLTPAQ: Godin-Shephard Leisure-Time Physical Activity Questionnaire; h: hours; m*g*: milligravity; min: minutes; MVPA: moderate-to-vigorous physical activity; SD: standard deviation.

[a] Participants with self-reported physical activity data: n = 25.

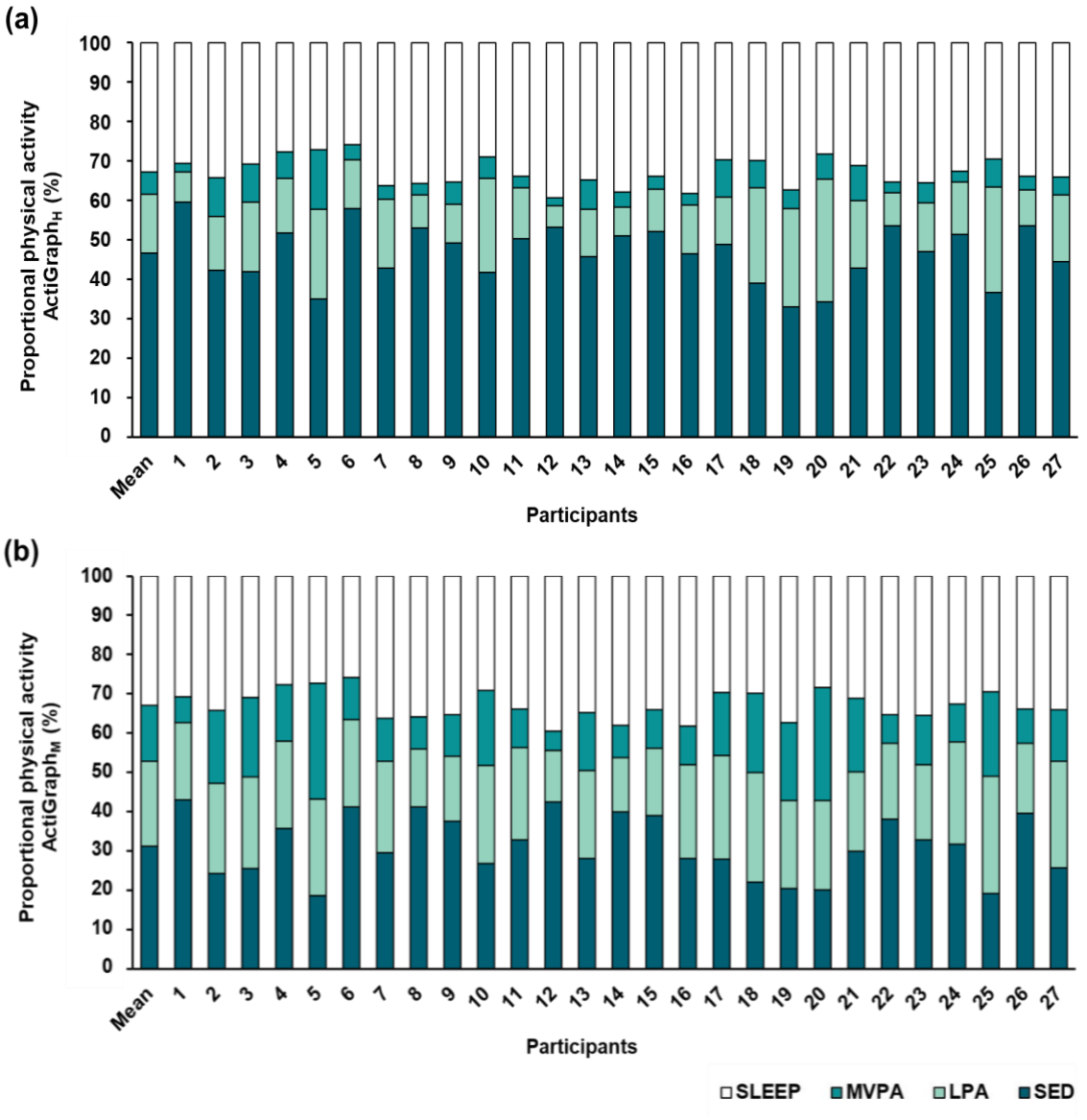


Figure 21. Individual participant data on accelerometer-derived physical activity proportions across the 24-hour activity cycle, including sedentary behaviour (SED), light (LPA) and moderate-to-vigorous physical activity (MVPA) and sleep (SLEEP). Translation of activity counts into physical activity intensity was performed using cut-points by **(a)** Hildebrand et al. [403,404] (adults aged 21 to 61 years) and **(b)** Migueles et al. [405] (older adults ≥ 70 years). Physical activity proportions were calculated using total time spent at each intensity.

5.2.3. Analysis of physical activity and physical fitness according to ARI use

There were no significant differences between ARI users and non-users for any of the participant characteristics, physical activity or physical fitness ($p > .05$) (Table 13).

Table 13. Participant characteristics, physical activity and physical fitness of ARI users and non-users included in Study 2.

	ARI users (n = 13)	**Non-users (n = 14)**	
	Mean ± SD	Mean ± SD	p-value
Participant characteristics			
Age, years	66 ± 8	65 ± 10	.961
BMI, $m \cdot kg^{-2}$	26.0 ± 2.7	26.1 ± 3.0	.846
Time since diagnosis, months	46 ± 57	29 ± 34	.680
Time on ADT, months	9 ± 7	13 ± 10	.188
Accelerometer-derived physical activity (ActiGraph)			
Raw acceleration, m*g*	25.0 ± 9.4	28.0 ± 9.6	.583
Sleep, $h \cdot day^{-1}$	8.2 ± 0.8	7.7 ± 0.9	.220
Cut-points by Hildebrand et al. ($ActiGraph_H$)			
Sedentary behaviour, $h \cdot day^{-1}$	11.1 ± 1.5	11.2 ± 2.0	.943
Sedentary behaviour (30 min bouts), $h \cdot day^{-1}$	5.8 ± 3.6	6.6 ± 3.7	.583
Light physical activity, $h \cdot day^{-1}$	3.6 ± 1.7	3.6 ± 1.6	.905
Light physical activity (10 min bouts), $h \cdot day^{-1}$	0.5 ± 1.0	0.4 ± 0.7	.729
MVPA, $min \cdot day^{-1}$	65 ± 30	93 ± 52	.141
MVPA (10 min bouts), $min \cdot day^{-1}$	18 ± 19	16 ± 13	.981
Cut-points by Migueles et al. ($ActiGraph_M$)			
Sedentary behaviour, $h \cdot day^{-1}$	7.5 ± 1.7	7.4 ± 2.1	.830
Sedentary behaviour (30 min bouts), $h \cdot day^{-1}$	1.4 ± 1.4	1.3 ± 1.2	.733
Light physical activity, $h \cdot day^{-1}$	5.2 ± 1.1	5.3 ± 0.9	.943
Light physical activity (10 min bouts), $h \cdot day^{-1}$	0.7 ± 0.7	0.8 ± 0.5	.720
MVPA, $min \cdot day^{-1}$	186 ± 92	220 ± 95	.402
MVPA (10 min bouts), $min \cdot day^{-1}$	56 ± 52	57 ± 38	.550
Self-reported physical activity (modified GSLTPAQ) [a]			
Light physical activity, $h \cdot day^{-1}$	0.3 ± 0.3	0.2 ± 0.3	.486
MVPA, $min \cdot day^{-1}$	38 ± 31	26 ± 24	.310
Physical fitness			
Relative VO_2peak, $ml \cdot min^{-1} \cdot kg^{-1}$	26.1 ± 6.5	26.1 ± 5.1	.903
400 metre walk time, s	259.5 ± 47.1	241.6 ± 40.7	.280
Relative leg extension 1RM, $kg \cdot kg^{-1}$	0.9 ± 0.1	1.0 ± 0.2	.452
Handgrip strength, kg [b]	46.6 ± 7.4	42.8 ± 7.7	.257

Abbreviations: 1RM: one-repetition maximum; ADT: androgen deprivation therapy; ARI: androgen receptor inhibitor; BMI: body mass index; GSLTPAQ: Godin-Shephard Leisure-Time Physical Activity Questionnaire; h: hours; kg: kilograms; m: metres; m*g*: milligravity; min: minutes; MVPA: moderate-to-vigorous physical activity; s: seconds; SD: standard deviation; VO_2peak: peak oxygen consumption.

[a] Participants with self-reported physical activity data: all, n = 25; ARI users, n = 13; non-users, n = 12.

[b] Participants with handgrip strength data: all, n = 24; ARI users, n = 13; non-users, n = 11.

5.2.4. Agreement between accelerometer-derived and self-reported physical activity

For the Bland-Altman analysis, accelerometer-derived physical activity estimates by $ActiGraph_H$ and $ActiGraph_M$ were compared against self-reported physical activity measured by the GSLTPAQ. For daily light physical activity, the mean bias was −202.9 min (upper limit: 0.8 min, lower limit: −406.5 min) for $ActiGraph_H$ and −297.4 min (upper limit: −156.1 min, lower limit: −438.8 min) for $ActiGraph_M$ (Figure 22 a and c). When using minimal requirements of 10 min bouts for light physical activity, the mean bias was reduced to −14.2 min (SD: 58.7 min, upper limit: 100.9 min, lower limit: −129.2 min) for $ActiGraph_H$ and −32.7 min (SD: 47.6 min, upper limit: 60.7 min, lower limit: −126.1 min) for $ActiGraph_M$ (Supplemental Figure 1 a and c). For MVPA, the mean bias was −46.1 min (upper limit: 54.2 min, lower limit: −146.5 min) for $ActiGraph_H$ and −171.0 min (upper limit: 29.0 min, lower limit: −370.9 min) for $ActiGraph_M$ (Figure 22 b and d). When using minimal requirements of 10 min bouts for MVPA, the mean bias was reduced to 15.3 min (SD: 28.0 min, upper limit: 70.2 min, lower limit: −39.5 min) for $ActiGraph_H$ and −22.3 min (SD: 52.3 min, upper limit: 80.2 min, lower limit: −124.8 min) for $ActiGraph_M$ (Supplemental Figure 1 b and d).

Linear regression analysis showed no significant association between light physical activity measured by the GSLTPAQ and either $ActiGraph_H$ ($F(1, 23) = 0.24$, $p = .63$, adjusted $R^2 = 0$) or $ActiGraph_M$ ($F(1, 23) = 2.61$, $p = .12$, adjusted $R^2 = .06$). Similarly, MVPA measured by the GSLTPAQ was not significantly associated with MVPA by $ActiGraph_H$ ($F(1, 23) = 0.03$, $p = .87$, adjusted $R^2 = 0$) or $ActiGraph_M$ ($F(1, 23) = 0.23$, $p = .64$, adjusted $R^2 = 0$). Likewise, no significant association was found when using minimal requirements of 10 minute-bouts for light physical activity ($ActiGraph_H$: $F(1, 23) = 0.93$, $p = .35$, adjusted $R^2 = 0$; $ActiGraph_M$: $F(1, 23) = 3.59$, $p = .07$, adjusted $R^2 = .10$) or MVPA ($ActiGraph_H$: $F(1, 23) = 2.05$, $p = .17$, adjusted $R^2 = 0.04$; $ActiGraph_M$: $F(1, 23) = 0.04$, $p = .85$, adjusted $R^2 = 0$).

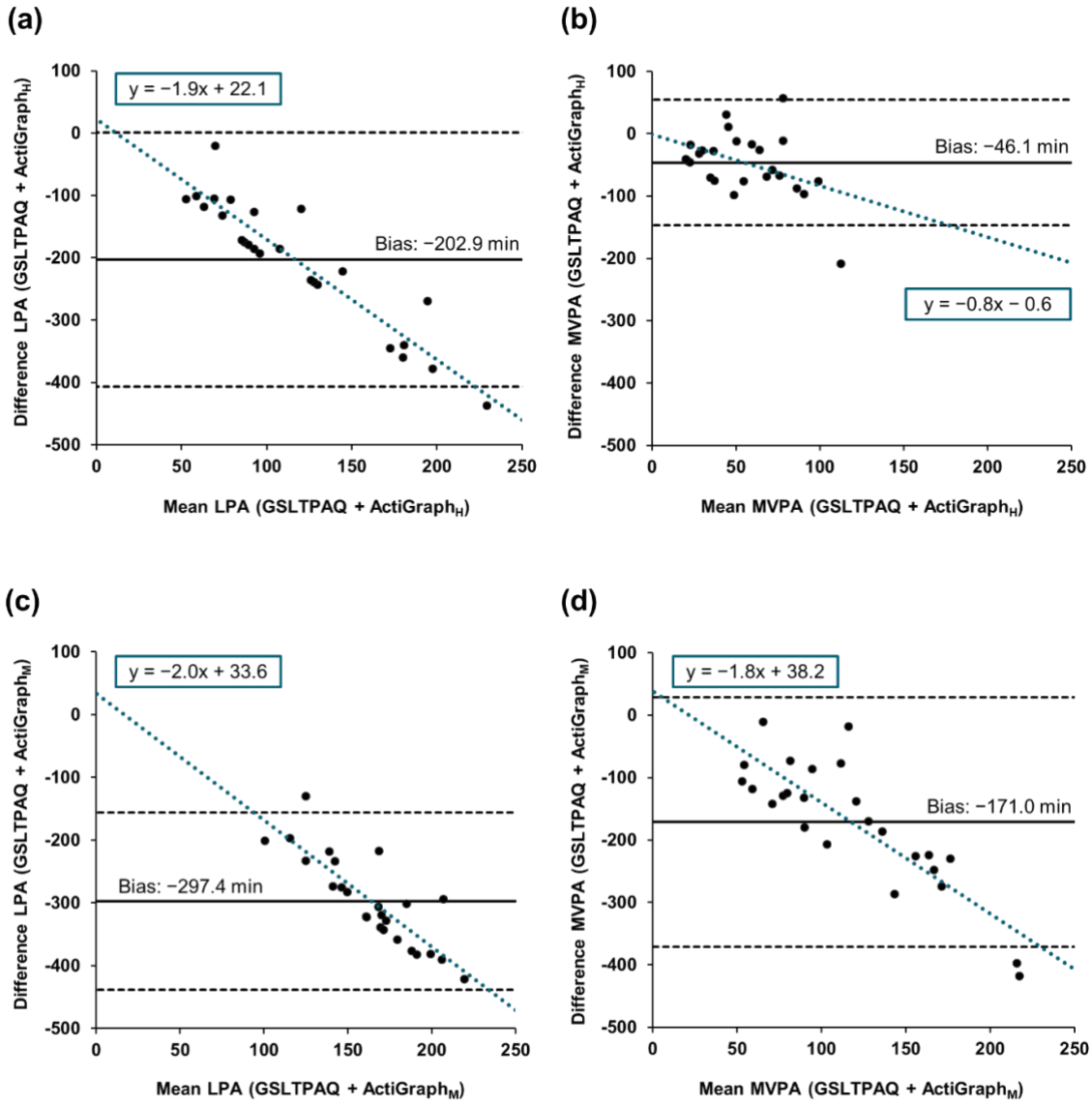


Figure 22. Bland-Altman plots showing the agreement between daily accelerometer-derived and self-reported physical activity. Agreement of **(a)** light physical activity (LPA) estimates from the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) and ActiGraph$_H$, **(b)** moderate-to-vigorous physical activity (MVPA) estimates from the GSLTPAQ and ActiGraph$_H$, **(c)** LPA estimates from the GSLTPAQ and ActiGraph$_M$ and **(d)** LPA estimates from the GSLTPAQ and ActiGraph$_M$. The unit of measurement for physical activity depicted in all plots is minutes (min). Dashed lines in black represent the upper and lower limits of agreement. Dotted lines in blue represent regression lines and blue boxes include regression line equations.

5.2.5. Associations of accelerometer-derived physical activity with physical fitness

PLS regression models were calculated to analyse the association between physical fitness outcomes and daily physical activity estimates by $ActiGraph_H$ and $ActiGraph_M$. A detailed description of the PLS regression results is presented in Table 14. For VO_2peak, significant predictors were time spent in sleep (β = −0.18, p = .004) and time since diagnosis (β = −0.14, p = .046) in the $ActiGraph_H$ model and time spent in sedentary behaviour (β = −0.11, p = .044), light physical activity (β = 0.15, p = .026) and sleep (β = −0.14, p = .010) in the $ActiGraph_M$ model. Significant predictors of 400 m walk time were identical in both models and included time spent in MVPA ($ActiGraph_H$: β = −0.28, p < .001; $ActiGraph_M$: β = −0.23, p < .001) and sleep ($ActiGraph_H$: β = 0.26, p < .001; $ActiGraph_M$: β = 0.28, p < .001), age ($ActiGraph_H$: β = 0.19, p < .001; $ActiGraph_M$: β = 0.20, p < .001) and time since diagnosis ($ActiGraph_H$: β = 0.18, p = .034; $ActiGraph_M$: β = 0.19, p = .035). Significant predictors of leg extension 1RM were time spent in sedentary behaviour (β = −0.24, p = .006) and light physical activity (β = 0.22, p = .010) in the $ActiGraph_H$ model and time spent in sedentary behaviour (β = −0.22, p = .017) and MVPA (β = 0.19, p = .009) in the $ActiGraph_M$ model. For handgrip strength, none of the physical activity variables were identified as important predictors and were thus excluded from the models. Among the confounders, handgrip strength showed a significant association with age (β = −0.41, p = .010).

Table 14. Partial least squares regression results on the association between accelerometer-derived physical activity and physical fitness.

Model information	**Model statistics**				
	R^2	Regression coeff. β	95% CI	t-value	p-value
VO_2peak ~ $ActiGraph_H$					
Model	.21				
Light physical activity		0.13	−0.01, 0.28	1.93	.065
MVPA		0.18	−0.01, 0.37	1.99	.057
Sleep		−0.18	−0.30, −0.06	−3.14	**.004**
Time since diagnosis		−0.14	−0.28, −0.00	−2.10	**.046**
VO_2peak ~ $ActiGraph_M$					
Model	.18				
Sedentary behaviour		−0.11	−0.22, −0.00	−2.11	**.044**
Light physical activity		0.15	0.02, 0.29	2.37	**.026**
MVPA		0.11	−0.00, 0.22	2.03	.053
Sleep		−0.14	−0.24, −0.04	−2.80	**.010**
400 metre walk time ~ $ActiGraph_H$					
Model	.46				
MVPA		−0.28	−0.39, −0.18	−5.60	**< .001**
Sleep		0.26	0.14, 0.38	4.49	**< .001**

Model information	Model statistics				
	R^2	Regression coeff. β	95% CI	t-value	p-value
Age		0.19	0.10, 0.28	4.37	**< .001**
Time since diagnosis		0.18	0.02, 0.35	2.24	**.034**
400 metre walk time ~ $ActiGraph_M$					
Model	.41				
MVPA		−0.23	−0.34, −0.12	−4.40	**< .001**
Sleep		0.28	0.13, 0.42	4.00	**< .001**
Age		0.20	0.10, 0.31	3.98	**< .001**
Time since diagnosis		0.19	0.01, 0.37	2.22	**.035**
Leg extension 1RM ~ $ActiGraph_H$					
Model	.26				
Sedentary behaviour		−0.24	−0.41, −0.08	−2.96	**.006**
Light physical activity		0.22	0.06, 0.39	2.79	**.010**
Prostate cancer stage		−0.14	−0.32, 0.04	−1.62	.116
Leg extension 1RM ~ $ActiGraph_M$					
Model	.21				
Sedentary behaviour		−0.22	−0.40, −0.04	−2.55	**.017**
MVPA		0.19	0.05, 0.33	2.81	**.009**
Prostate cancer stage		−0.15	−0.35, 0.05	−1.56	.132
Handgrip strength [a] ~ $ActiGraph_{H/M}$ [b]					
Model	.31				
Age		−0.41	−0.71, −0.10	−2.79	**.010**
BMI		0.17	−0.02, 0.36	1.85	.077
Prostate cancer stage		0.19	−0.03, 0.40	1.77	.090

Notes: Variables used for prediction models included physical activity estimates (sedentary behaviour, light physical activity, MVPA, sleep) and covariates (age, BMI, prostate cancer stage, time on ADT, time since diagnosis). Final models only included variables identified as important predictors by a variable importance for projection (VIP) score ≥ 1.

Abbreviations: β: regression coefficient; 1RM: one-repetition maximum; ADT: androgen deprivation therapy; BMI: body mass index; CI: confidence interval; MVPA: moderate-to-vigorous physical activity; VO_2peak: peak oxygen consumption.

[a] Participants with handgrip strength data: n = 24.

[b] None of the physical activity variables were considered important predictors (VIP score < 1) and consequently excluded, resulting in identical models for $ActiGraph_H$ and $ActiGraph_M$.

5.2.6. Analysis of immune cells and inflammation markers

Mean values of immune cells and inflammation markers of participants at baseline are presented in Table 15.

Table 15. Immune cells and inflammation markers of participants at baseline.

	All participants (n = 27) Mean ± SD
Immune cells	
Platelets, $10^3 \cdot \mu L^{-1}$	220.2 ± 44.9
Leukocytes, $10^3 \cdot \mu L^{-1}$	5.98 ± 1.81
Neutrophils, $10^3 \cdot \mu L^{-1}$	3.43 ± 1.25
Monocytes, $10^3 \cdot \mu L^{-1}$	0.60 ± 0.31
Lymphocytes, $10^3 \cdot \mu L^{-1}$	1.73 ± 0.75
NK cells, % lymphocytes	18.6 ± 9.8
NK^{dim} cells, % NK	95.9 ± 2.8
NK^{bright} cells, % NK	3.0 ± 2.1
B cells, % lymphocytes	10.7 ± 7.5
T cells, % lymphocytes	63.7 ± 11.2
Tc cells, % lymphocytes	24.9 ± 9.9
Th cells, % lymphocytes	38.3 ± 9.8
Th1 cells, % lymphocytes	4.11 ± 2.0
Th2 cells, % lymphocytes	2.32 ± 1.35
Th17 cells, % lymphocytes	1.47 ± 0.70
Treg cells, % lymphocytes	3.36 ± 1.33
Inflammation markers	
Neutrophil-to-lymphocyte ratio (NLR)	2.19 ± 0.95
Platelet-to-lymphocyte ratio (PLR)	147.1 ± 61.9
Systemic immune-inflammation index (SII)	471.2 ± 194.0
NK^{dim}/NK^{bright} ratio	60.5 ± 56.2
Th1/Th2 ratio	2.50 ± 2.42
Th17/Treg ratio	0.47 ± 0.22

Abbreviations: NK cell: natural killer cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SD: standard deviation; SII: systemic immune-inflammation index; Tc cell: cytotoxic T cell; Th cell: T helper cell; Treg cell: regulatory T cell.

5.2.7. Associations of physical activity with immune parameters

PLS regression models were calculated to analyse the association of immune cells and cell-derived inflammation markers with daily physical activity estimates by $ActiGraph_H$ and $ActiGraph_M$. For brevity, only model results with a $R^2 \geq 0.33$ indicating a moderate association are reported here for single immune cell analyses, whereas model results of inflammation markers are reported regardless of the model fit. A detailed description of the PLS regression results is presented in Supplemental Table 1.

Absolute proportions of monocytes were predicted by time spent in light physical activity from $ActiGraph_H$ (β = −0.19, p = .024) and age (β = 0.25, p = .039), with the model explaining 38% in the variance of the dependent variable. For physical activity estimates by $ActiGraph_M$, absolute proportions of monocytes were predicted by time spent in sedentary behaviour (β = 0.18, p = .020), with the model explaining 38% in the variance of the dependent variable. Treg cell proportions of total lymphocytes were predicted by time spent in light physical activity (β = 0.23, p < .001) and sedentary behaviour from $ActiGraph_H$ (β = −0.21, p = .006) and age (β = −0.27, p = .014), with the model explaining 34% in the variance of the dependent variable. For either method of physical activity estimation, relative proportions of neutrophils were predicted by time spent in sleep ($ActiGraph_H$: β = −0.19, p = .005; $ActiGraph_M$: β = −0.23, p = .007), age ($ActiGraph_H$: β = −0.26, p = .008; $ActiGraph_M$: β = −0.31, p = .008) and prostate cancer stage ($ActiGraph_H$: β = 0.22, p = .002; $ActiGraph_M$: β = 0.26, p = .004), but none of the physical activity variables, with the $ActiGraph_H$ and $ActiGraph_M$ models explaining 41% and 43% of the variance of the dependent variable, respectively.

Significant predictors of NLR were age ($ActiGraph_H$: β = −0.23, p = .028; $ActiGraph_M$: β = −0.25, p = .024) and prostate cancer stage ($ActiGraph_H$: β = 0.20, p = .038; $ActiGraph_M$: β = 0.22, p = .045), but none of the physical activity variables, with R^2 indicating a weak association ($ActiGraph_H$: R^2 = 0.32; $ActiGraph_M$: R^2 = 0.21). Similarly, age ($ActiGraph_H$: β = −0.23, p = .011; $ActiGraph_M$: β = −0.24, p = .019) and prostate cancer stage ($ActiGraph_H$: β = 0.19, p = .041), but none of the physical activity variables, were identified as significant predictors of SII, with R^2 indicating a weak association ($ActiGraph_H$: R^2 = 0.32; $ActiGraph_M$: R^2 = 0.25). $ActiGraph_H$ and $ActiGraph_M$ models for Th1/Th2 ratio and NK^{dim}/NK^{bright} ratio were identical and did not include any physical activity variables. Significant predictors of Th1/Th2 ratio were time spent in sleep (β = 0.17, p = .008) and prostate cancer stage (β = −0.19, p = .009), with R^2 = 0.23 indicating a weak association. Significant predictors of NK^{dim}/NK^{bright} ratio were age (β = 0.45, p < .001) and prostate cancer stage (β = −0.25, p = .008), with R^2 = 0.34 indicating a moderate association. None of the variables were significant predictors of PLR or Th17/Treg ratio (p > .05).

5.3. Longitudinal single-centre study (Study 3)

5.3.1. Participant characteristics and immune parameters at baseline

Demographic and clinical participant characteristics, as well as physical fitness outcomes are presented in Table 16. There were no differences in participant characteristics or physical fitness outcomes between participants in the intervention and control arm (p > .05). Baseline levels of immune cells and inflammation markers are presented in Table 17. Levels of individual immune cells and inflammation markers were comparable between both arms at baseline (p > .05).

Table 16. Demographic and clinical characteristics and physical fitness of participants in the intervention and control arm at baseline.

	All participants (n = 19)	**Intervention arm (n = 8)**	**Control arm (n = 11)**	
	Mean ± SD or n	Mean ± SD or n	Mean ± SD or n	p-value
Demographic characteristics				
Age, years	66 ± 8	66 ± 5	65 ± 10	.837
Height, m	1.78 ± 0.07	1.80 ± 0.09	1.78 ± 0.05	.621
Weight, kg	83.2 ± 10.6	84.7 ± 7.9	82.1 ± 12.4	.612
BMI, $m \cdot kg^{-2}$	26.1 ± 2.8	26.3 ± 2.3	25.9 ± 3.3	.754
Clinical characteristics				
Time since diagnosis, months	46 ± 47	60 ± 53	36 ± 42	.287
Time on ADT, months	12 ± 9	14 ± 11	10 ± 6	.312
Testosterone, $ng \cdot dL^{-1}$	13.8 ± 10.4	12.0 ± 10.9	15.2 ± 10.4	.527
PSA, $ng \cdot mL^{-1}$	5.3 ± 10.8	0.4 ± 1.1	8.9 ± 13.3	.091
Disease stage, n				.352
mHSPC	11	6	5	
mCRPC	8	2	6	
Physical fitness				
Relative VO_2peak, $ml \cdot min^{-1} \cdot kg^{-1}$	26.8 ± 5.2	26.2 ± 3.9	27.2 ± 6.1	.671
400 metre walk time, s	243.1 ± 40.2	242.3 ± 41.4	243.7 ± 41.3	.940
Relative leg extension 1RM, $kg \cdot kg^{-1}$	1.0 ± 0.2	1.0 ± 0.3	0.9 ± 0.2	.411
Handgrip strength, kg [a]	45.4 ± 6.8	44.1 ± 5.6	46.3 ± 7.8	.539

Abbreviations: 1RM: one-repetition maximum; ADT: androgen deprivation therapy; BMI: body mass index; SD: standard deviation; VO_2peak: peak oxygen consumption.

[a] Participants with handgrip strength data: all, n = 17; intervention arm, n = 7; control arm, n = 10.

Table 17. Immune cells and inflammation markers of participants in the intervention and control arm at baseline.

	All participants (n = 19)	**Intervention arm (n = 8)**	**Control arm (n = 11)**	
	Mean ± SD	Mean ± SD	Mean ± SD	p-value
Immune cells				
Platelets, $10^3 \cdot \mu L^{-1}$	217.0 ± 36.9	222.8 ± 42.7	212.8 ± 33.6	.578
Leukocytes, $10^3 \cdot \mu L^{-1}$	5.94 ± 1.98	5.71 ± 1.67	6.11 ± 2.24	.677
Neutrophils, $10^3 \cdot \mu L^{-1}$	3.47 ± 1.37	3.12 ± 0.96	3.73 ± 1.60	.356
Monocytes, $10^3 \cdot \mu L^{-1}$	0.53 ± 0.17	0.54 ± 0.20	0.52 ± 0.16	.843
Lymphocytes, $10^3 \cdot \mu L^{-1}$	1.68 ± 0.73	1.72 ± 0.80	1.65 ± 0.72	.836
NK cells, % lymphocytes	17.3 ± 8.9	18.1 ± 9.0	16.7 ± 9.3	.733

	All participants (n = 19)	Intervention arm (n = 8)	Control arm (n = 11)	
	Mean ± SD	Mean ± SD	Mean ± SD	p-value
NK^{dim} cells, % NK	95.7 ± 2.6	96.0 ± 3.2	95.6 ± 2.2	.751
NK^{bright} cells, % NK	3.1 ± 1.9	2.7 ± 2.1	3.5 ± 1.8	.416
B cells, % lymphocytes	13.1 ± 7.6	12.5 ± 8.8	13.5 ± 6.9	.776
T cells, % lymphocytes	63.9 ± 10.4	63.2 ± 11.0	64.4 ± 10.5	.817
Tc cells, % lymphocytes	24.3 ± 10.2	23.7 ± 9.8	24.8 ± 10.9	.825
Th cells, % lymphocytes	39.1 ± 8.0	39.0 ± 6.8	39.1 ± 9.1	.980
Th1 cells, % lymphocytes	4.2 ± 2.1	5.1 ± 2.1	3.5 ± 1.8	.097
Th2 cells, % lymphocytes	2.8 ± 1.4	2.6 ± 0.9	2.9 ± 1.7	.657
Th17 cells, % lymphocytes	1.7 ± 0.7	1.7 ± 0.6	1.6 ± 0.8	.795
Treg cells, % lymphocytes	3.6 ± 1.2	3.9 ± 1.4	3.5 ± 1.1	.499
Inflammation markers				
Neutrophil-to-lymphocyte ratio (NLR)	2.29 ± 1.02	2.03 ± 0.73	2.48 ± 1.18	.363
Platelet-to-lymphocyte ratio (PLR)	153.2 ± 67.6	154.2 ± 68.8	152.6 ± 70.1	.962
Systemic immune-inflammation index (SII)	486.0 ± 201.6	446.6 ± 166.5	514.6 ± 227.2	.484
NK^{dim}/NK^{bright} ratio	53.7 ± 53.9	63.8 ± 58.4	46.3 ± 51.9	.502
Th1/Th2 ratio	1.88 ± 1.39	2.33 ± 1.59	1.56 ± 1.19	.240
Th17/Treg ratio	0.49 ± 0.26	0.45 ± 0.09	0.52 ± 0.33	.569

Abbreviations: NK: natural killer cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SD: standard deviation; SII: systemic immune-inflammation index; T: T cell; Tc: cytotoxic T cell; Th: T helper cell; Treg: regulatory T cell.

5.3.2. Exercise intervention dose and adherence

The mean completed exercise intervention dose, adherence and intensity during cycles 0 to 5 of participants in the intervention arm are displayed in Table 17. On average, participants in the intervention arm completed 54% of the MICT aerobic exercise, 66% of the HIIT aerobic exercise and 85% of the resistance exercise prescription. This adherence rate corresponded to an average of 312 minutes of MICT aerobic exercise, 112 minutes of HIIT aerobic exercise and 6,297 total repetitions of resistance exercise completed during the 6-month intervention. The average completed exercise dose per week amounted to 13 minutes of MICT aerobic exercise, 5 minutes of HIIT aerobic

exercise and 262 total repetitions of resistance exercise. Weekly prescribed and completed aerobic and resistance exercise dose are shown in Figure 23.

Table 18. Completed exercise intervention adherence, dose and intensity during intervention cycles 0 to 5.

	Intervention arm (n = 8) Mean (range)
Aerobic exercise	
MICT adherence, %	54 (0 − 114)
MICT dose, min	312 (0 − 660)
MICT total sessions, n	12 (0 − 21)
MICT RPE, a.u.	5.7 (4.7 − 7.0)
MICT HRmax, bpm	140 (130 − 152)
MICT HRavg, bpm	119 (114 − 133)
HIIT adherence, %	66 (43 − 98)
HIIT dose (number of work intervals × duration), min	112 (73 − 165)
HIIT total work intervals, n	158 (127 − 213)
HIIT total sessions, n	33 (28 − 39)
HIIT RPE, a.u.	6.3 (2.0 − 10.0)
HIIT HRmax, bpm	132 (123 − 138)
HIIT HRavg, bpm	112 (102 − 117)
Resistance exercise	
Resistance exercise adherence, %	85 (51 − 138)
Resistance exercise dose (exercises × sets × repetitions), n	6,297 (3,754 − 10,203)
Resistance exercise total sessions, n	35 (28 − 39)

Note: All dose variables were calculated as the mean cumulative dose for cycles 0 to 5. Adherence was calculated as the mean completed dose compared to the prescribed dose for cycles 0 to 5. Intensity variables were calculated as the mean value per session for each participant.

Abbreviations: a.u.: arbitrary unit; bpm: beats per minute; HIIT: high-intensity interval training; HRavg: average heart rate; MICT: moderate-intensity continuous training; min: minute; RPE: rating of perceived exertion.

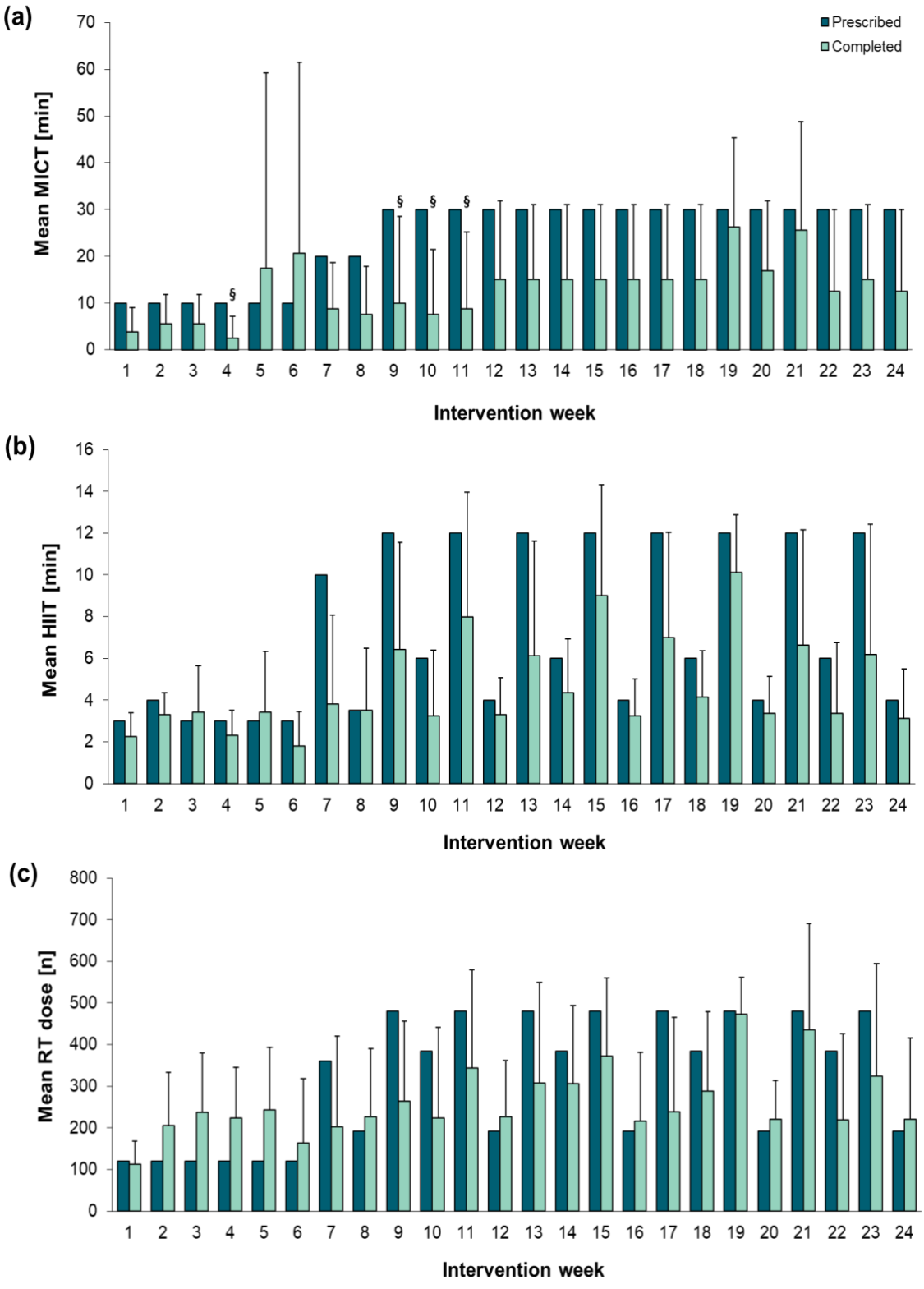


Figure 23. Weekly prescribed and completed aerobic and resistance exercise dose during cycles 0 to 5. (a) Total minutes of moderate-intensity continuous training (MICT) aerobic exercise, **(b)** total dose of high-intensity interval training (HIIT) aerobic exercise (number of repetitions × work interval duration), **(c)** total resistance exercise dose (number of exercises × sets × repetitions). Prescribed training data (blue bars) are presented as absolute values and completed training data (light green bars) as mean and standard deviation. §: only n = 2 participants completed training that week. min: minutes.

5.3.3. Changes in physical fitness

Differences between intervention and control arm

There was a significant interaction (time × arm) for relative leg extension 1RM, $F(1, 14) = 6.45$, $p = .024$, partial $\eta^2 = .32$ (Figure 24). Post hoc comparisons with Bonferroni correction showed no significant main effect for time in either arm ($p > .05$). Handgrip strength showed no significant interaction ($p > .05$) but a significant main effect for time, $F(1, 12) = 9.15$, $p = .011$, partial $\eta^2 = .43$. Handgrip strength increased from baseline (mean: 45.4 kg, SD: 6.8 kg) to the 6-month testing (mean: 47.2 kg, SD: 6.6 kg) across all participants. Post hoc comparisons showed no statistically significant time effect for handgrip strength in either arm but effect sizes indicated a large effect in the intervention arm ($d = 0.86$, $p = .127$) and a negligible effect in the control arm ($d = 0.05$, $p = .920$). Relative VO_2peak and 400 metre walk time remained statistically unaltered at the 6-month testing ($p > .05$). Absolute pre and post values of physical fitness are presented in Supplemental Table 2.

Associations of changes in physical fitness with completed exercise volume

Multiple linear regression analysis of participants in the intervention arm showed no significant associations between physical fitness changes and completed exercise dose, which was included as separate variables for total aerobic and resistance exercise, or number of completed exercise sessions ($p > .05$).

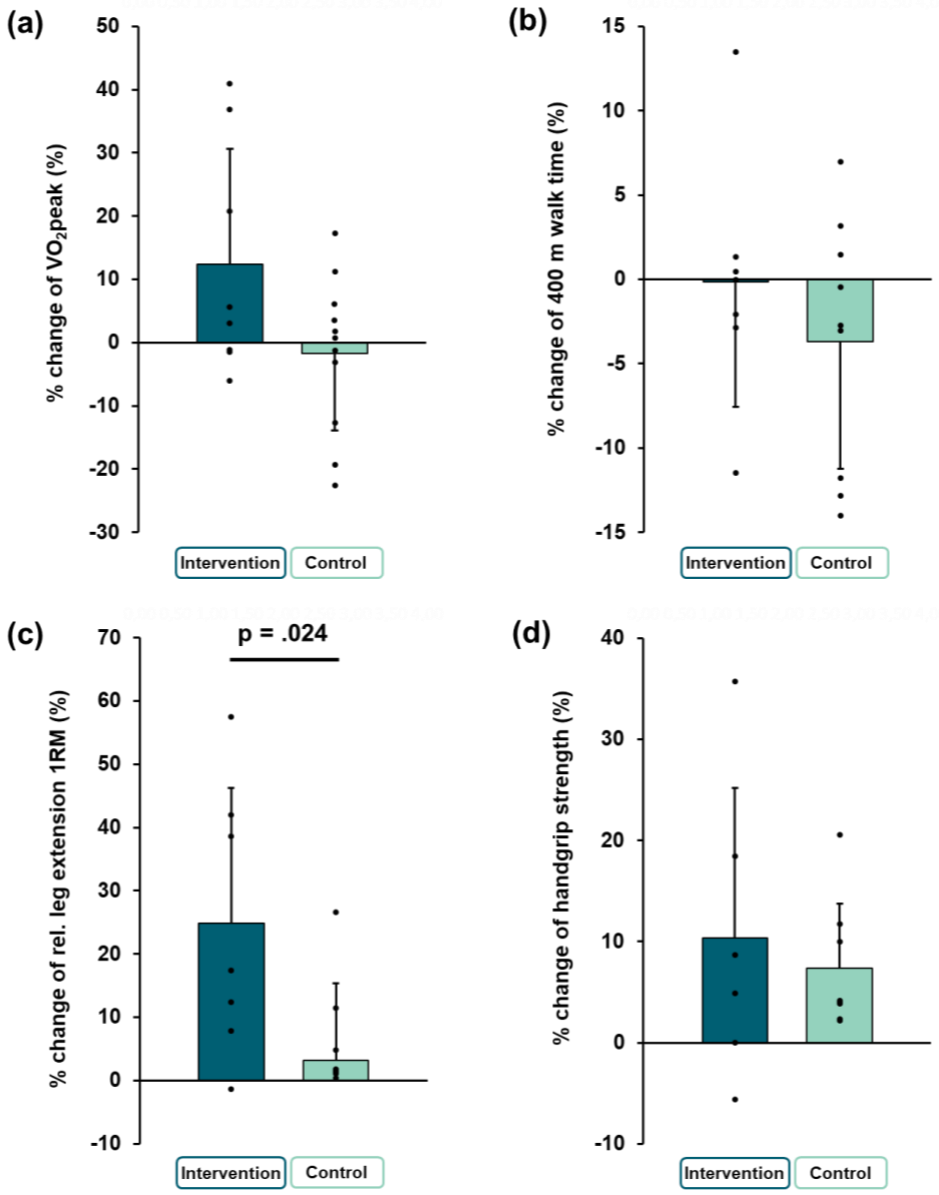


Figure 24. Percent change of physical fitness among participants in the intervention and control arm from baseline to the 6-month exercise testing visit. (a) Relative peak oxygen consumption (VO_2peak), **(b)** 400 metre walk time, **(c)** relative leg extension one-repetition maximum (1RM) and **(d)** handgrip strength. Data are presented as mean and standard deviation of the intervention (blue bars) and control arm (light green bars), as well as individual participant data (black dots). Horizontal lines with p-values indicate significant between-group differences in the change from baseline to 6-month exercise testing visit. For reasons of simplicity, significant main effects are not shown in the figure.

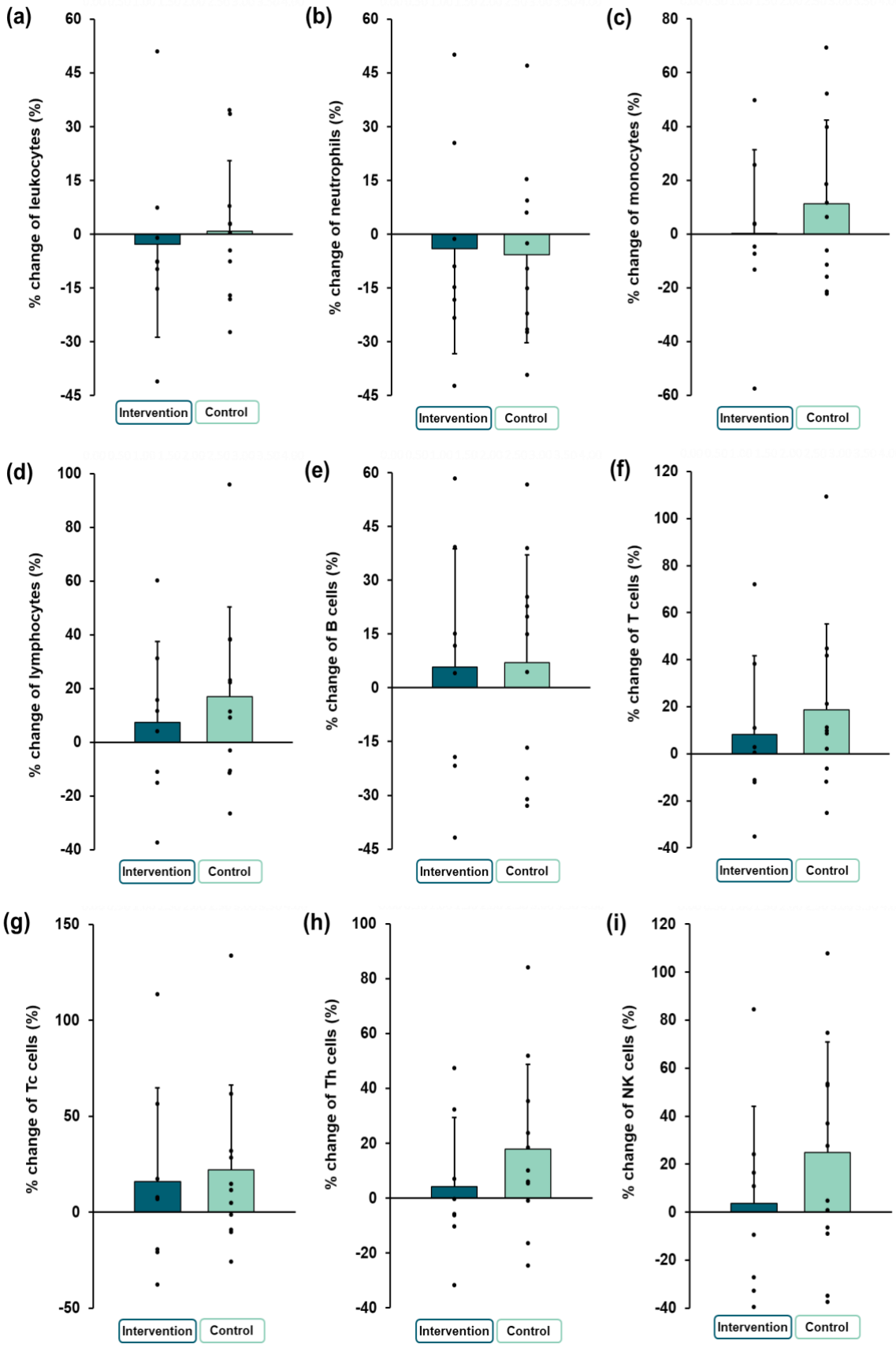
5.3.4. Changes in immune cells and inflammation markers

Differences between intervention and control arm

A two-way mixed ANOVA showed no statistically significant interaction (time × arm) for any of the immune cells or inflammation markers ($p > .05$). There was a significant main effect for time for the lymphocyte proportion of total cells, $F(1, 17) = 8.46$, $p = .010$, partial $\eta^2 = .33$. The lymphocyte proportion increased from baseline (mean: 28.0%, SD: 7.1%) to the 6-month testing (mean: 31.3%, SD: 7.5%) across all participants. There were no significant changes in absolute counts or relative proportions of any other immune cells from baseline to the 6-month testing ($p > .05$). Percent changes of immune cells and inflammation markers for participants in the intervention and control arm are displayed in Figures 25 and 26. Absolute pre and post values of immune cells and inflammation markers are presented in Supplemental Table 2.

Associations of immune parameter changes with completed exercise volume

For completed exercise dose, a statistically significant model was observed for absolute counts of NK cells, with the model explaining 80% of the variance in absolute change of NK cell counts post intervention, $F(3, 4) = 10.55$, $p = .023$, adjusted $R^2 = .80$. Total completed aerobic exercise was a significant predictor of absolute change of NK cell counts ($\beta = -0.0003$, $p = .034$), whereas resistance exercise was not ($p > .05$). Completed exercise dose did not explain changes in any of the other immune parameters ($p > .05$). Similarly, number of completed exercise sessions was not associated with changes in immune parameters ($p > .05$).


(a)
% change of leukocytes (%)
60
45
30
15
0
-15
-30
-45
Intervention
Control
(b)
% change of neutrophils (%)
60
45
30
15
0
-15
-30
-45
Intervention
Control
(c)
% change of monocytes (%)
80
60
40
20
0
-20
-40
-60
Intervention
Control
(d)
% change of lymphocytes (%)
100
80
60
40
20
0
-20
-40
Intervention
Control
(e)
% change of B cells (%)
60
45
30
15
0
-15
-30
-45
Intervention
Control
(f)
% change of T cells (%)
120
100
80
60
40
20
0
-20
-40
Intervention
Control
(g)
% change of Tc cells (%)
150
100
50
0
-50
Intervention
Control
(h)
% change of Th cells (%)
100
80
60
40
20
0
-20
-40
Intervention
Control
(i)
% change of NK cells (%)
120
100
80
60
40
20
0
-20
-40
Intervention
Control

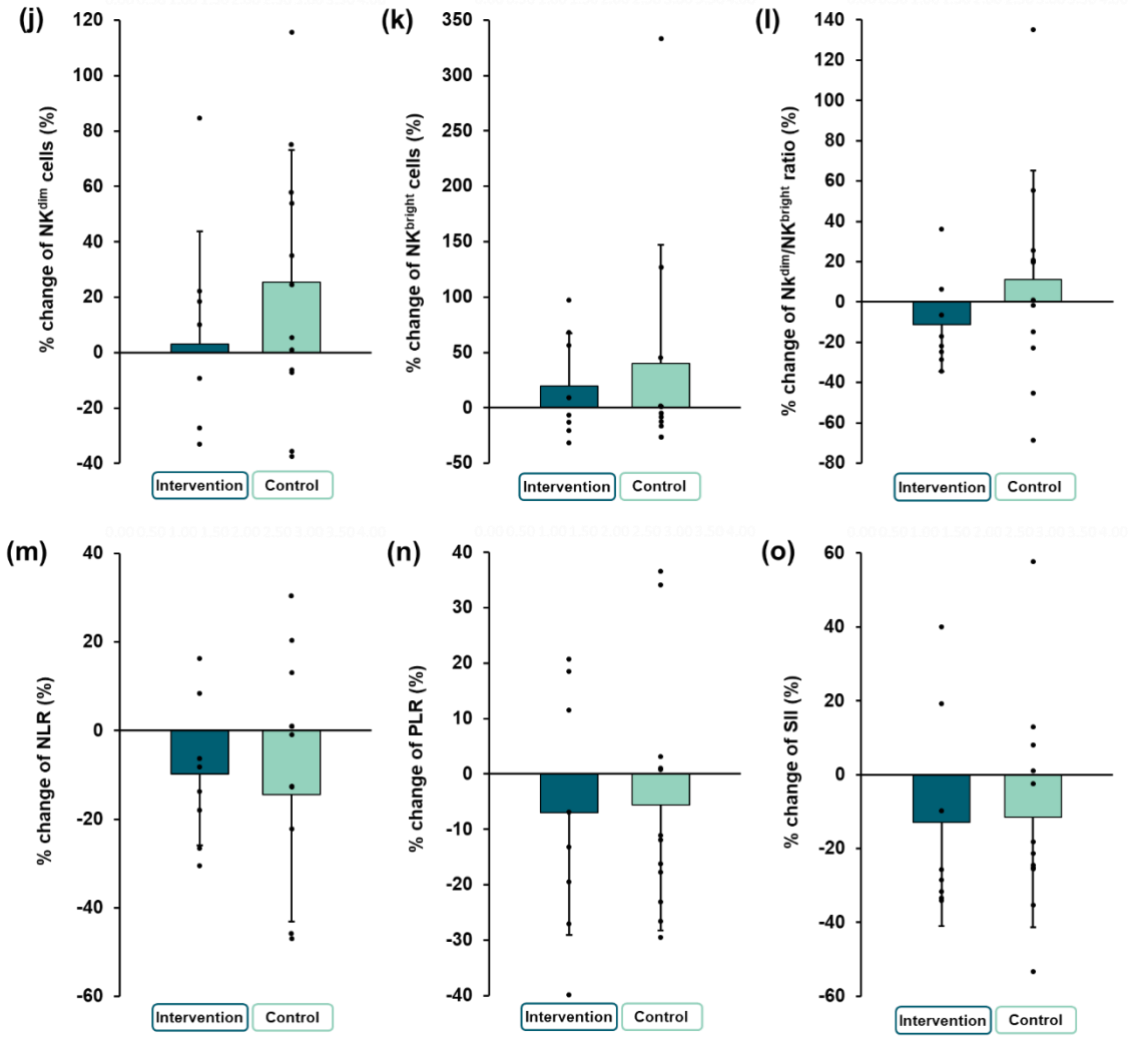


Figure 25. Percent change of immune cells and inflammation markers among participants in the intervention and control arm from baseline to 6-month exercise testing visit. Absolute counts of **(a)** leukocytes, **(b)** neutrophils, **(c)** monocytes, **(d)** lymphocytes, **(e)** B cells, **(f)** T cells, **(g)** cytotoxic T (Tc) cells, **(h)** T helper (Th) cells, **(i)** natural killer (NK) cells, **(j)** NK^{dim} cells, **(k)** NK^{bright} cells and **(l)** NK^{dim}/NK^{bright} ratio, **(m)** neutrophil-to-lymphocyte ratio (NLR), **(n)** platelet-to-lymphocyte ratio (PLR) and **(o)** systemic immune-inflammation index (SII). Data are presented as mean and standard deviation of the intervention (blue bars) and control arm (light green bars), as well as individual participant data (black dots).

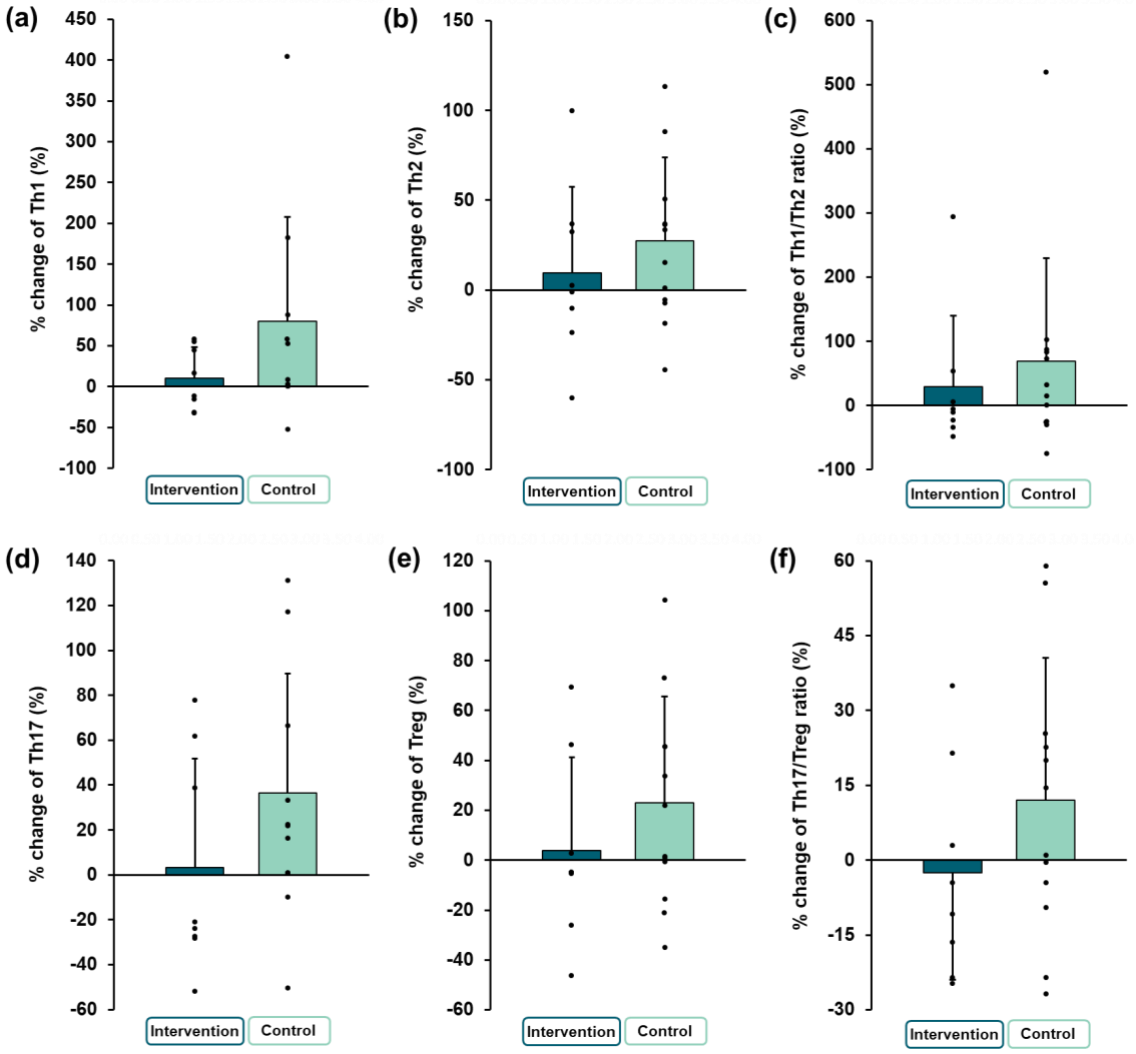


Figure 26. Percent change of Th subpopulations among participants in the intervention and control arm from baseline to 6-month exercise testing visit. Absolute counts of **(a)** Th1 cells, **(b)** Th2 cells, **(c)** Th1/Th2 ratio, **(d)** Th17 cells, **(e)** regulatory T cells (Treg) and **(f)** Th17/Treg ratio. Th: T helper cell. Data are presented as mean and standard deviation of the intervention (blue bars) and control arm (light green bars), as well as individual participant data (black dots).

6. Discussion

The objective of this thesis was to analyse the relationship of habitual physical activity with physical fitness and immune function in men treated with ADT for prostate cancer, as well as to investigate changes in physical fitness and immune function following a chronic, structured exercise intervention. For this purpose, data from participants of a multi-centre, randomised, controlled trial for men with advanced metastatic prostate cancer collected at baseline and at the 6-month testing visit were analysed. Firstly, a cross-sectional analysis was conducted of baseline self-reported physical activity, including the evaluation of physical activity guideline adherence, and its association with physical fitness in participants at all global sites of the multicentre trial. Participants were then grouped by secondary prostate cancer treatment into ARI users and non-users to investigate potential reductions in physical activity and fitness related to maximal androgen blockade. Secondly, levels of accelerometer-derived physical activity were examined in the German subsample for an analysis of their agreement with self-reported physical activity, as well as the association with physical fitness and immune parameters. Additionally, differences in physical activity and physical fitness between ARI users and non-users were analysed in the German subsample. Lastly, the adherence to a 6-month structured exercise intervention of combined aerobic and resistance exercise was evaluated and associated changes in physical fitness and immune parameters were analysed.

6.1. Habitual physical activity

6.1.1. Baseline physical activity and guideline adherence

In advanced prostate cancer, the ability to engage in physical activity is complicated by the use of treatments such as ADT and ARIs that inhibit testosterone signalling [416,417]. Study 1 assessed the weekly habitual physical activity at baseline to determine if participants achieved the level of physical activity recommended by current guidelines for cancer survivors. It should be noted that while the eligibility criteria required participants' physical activity to be both below a cut-off of 60 minutes vigorous aerobic exercise and performing no more than one structured resistance exercise session per week, no limits were placed on habitual physical activity.

MVPA is a widely used measure of physical activity and as such, it facilitates comparison with studies that assessed physical activity using varying methods. Calculating MVPA based on the GSLTPAQ estimates of moderate and vigorous physical activity also allowed quantification of the proportion of participants that met the physical activity guidelines set out by the American Cancer Society. As per these guidelines, cancer survivors should each week

aim to accumulate 150 to 300 minutes moderate intensity or 75 to 150 minutes vigorous intensity physical activity and, additionally, perform muscle-strengthening activities on at least two days [25]. In this study, self-reported levels of MVPA were lower than the recommended level, with participants reporting an average of 128 minutes MVPA per week. Other studies that used the GSLTPAQ for physical activity assessment observed higher physical activity levels when there was no pre-set exclusion criterion for maximal weekly activity. In a mixed sample of breast, prostate and colorectal cancer survivors, participants reported an average of 202 minutes MVPA per week [311]. Their average age of the sample was, however, five years younger compared to the present study and most of the participants were female. In support of the argument of lower physical activity levels when limits are enforced is a study by Papadopoulos et al., which showed that men on ADT participating in an RCT with similar eligibility criteria accumulated only 68 minutes of self-reported weekly MVPA [418]. However, it is worth highlighting that levels of MVPA among participants in the present study were driven mostly by moderate intensity physical activity and, with an average of only 22 minutes per week, vigorous physical activity was well below the cut-off.

The results of Study 1 showed that only 29% of participants achieved the minimum recommended level of 150 minutes MVPA per week according to self-reported physical activity. The finding that only a minority of cancer survivors meets the physical activity target is consistent with results from other studies in individuals with lymphoma [309], breast cancer [419] and localised prostate cancer [420], which did not specify excluding participants above a certain physical activity threshold. A markedly higher level of physical activity was reported by Santa Mina et al. in men with prostate cancer prior to prostatectomy, who found that 46% met the guidelines, although their participants were at an early disease stage and on average 9 years younger [313]. By contrast, Ozdemir et al. found that only 21% of newly diagnosed prostate cancer patients were sufficiently active [421].

A subgroup analysis by secondary prostate cancer treatment revealed higher self-reported MVPA and a larger proportion of participants meeting the aerobic activity guidelines among participants receiving ARIs in addition to ADT. This result is contrary to previous studies that found that men treated with ARIs for mCRPC have lower functional performance in tasks against gravity, such as the timed-up-and-go test, than men with mHSPC on ADT monotherapy [169]. Interestingly, these differences persist despite a similar duration of androgen withdrawal [169]. However, this comparison may be conflated by the more advanced disease stage among ARI users, as cancer progression is often accompanied by functional decline [422,423]. In the present study, the proportion of men with mCRPC was equal between ARI users and non-users. ARI use was, however, defined by the treatments that were administered at the time of enrolment and did not consider previous treatment cycles, despite

potentially long-lasting effects. Furthermore, other common cancer treatments like chemotherapy are also known to influence physical activity [333]. Nonetheless, it can be concluded from the present study that ARI use does not hinder physical activity in men with advanced prostate cancer.

Caution should be applied when interpreting these results because self-reported physical activity may provide a biased estimate of guideline compliance. A study of men with localised prostate cancer found that an astounding 73% of participants met the physical activity guidelines according to self-reported MVPA compared to only 11% according to accelerometer-derived MVPA [26]. The present study performed additional accelerometer measurements for participants in the German subsample to examine the agreement between both methods. Because consensus regarding the analysis of accelerometer-derived data is lacking, two distinct sets of cut-points were used to obtain time shares spent at each physical activity intensity. The accelerometer-derived estimates from both sets of cut-points showed substantially higher levels of light physical activity and MVPA than the self-reported levels. Likewise, other studies that compared both measurement methods found considerable underreporting of MVPA levels, as shown in results from a mixed sample of prostate and breast cancer survivors [328], as well as men on ADT [418]. Reporting bias and false classification of physical activity intensities are recognised issues that limit the interpretability of self-reported data, especially in older populations that experience a decline in cognitive function [424]. This may be aggravated in the present sample, as cancer-related adverse effects are usually more pronounced at advanced disease stages and systemic treatments like ADT and chemotherapy are associated with cognitive impairments [162,425]. For example, older individuals with cancer are expected to spend a large share of their time in light physical activity; however, 42% of participants in the multi-centre study reported not engaging in any activity of this intensity. This suggests that capturing activities at lower intensities, which comprise a large proportion of the daily activity cycle, may require objective measurement methods; yet in the absence of cognitive assessments, it is difficult to draw further conclusions.

Despite a marked discrepancy of absolute physical activity estimates from accelerometer versus physical activity recall, Sloane et al. observed a significant positive correlation between both methods [328]. This is in contrast to the present study, where a comprehensive analysis using both Bland-Altman and regression analysis showed virtually no agreement between self-reported and accelerometer-derived physical light physical activity and MVPA, regardless of the cut-points implemented.

Furthermore, while statistical analysis of the agreement between $ActiGraph_H$ and $ActiGraph_M$ lay outside the main scope, it became apparent that both methods produced vastly different

physical activity estimates. This can be attributed to the fact that ActiGraph devices placed at the wrist were used in this study, as opposed to the traditional placement at the hip, to capture upper body movements and improve compliance. The dilemma with switching to wrist-worn devices is that previously established cut points for categorisation of physical activity intensities were developed for hip-worn devices and thus are not suited for processing wrist acceleration data [426]. Due to the relatively recent uptake of wrist-worn accelerometers, fewer studies of cut-point investigation or validation exist. The two sets of cut-points used in this study were selected to reflect the age range of the study sample [403,405]. As expected, $ActiGraph_H$, which was validated in adults ≤ 61 years, produced considerably lower estimates of light physical activity and MVPA and, in turn, higher estimates of sedentary behaviour than $ActiGraph_M$, which was validated in older adults ≥ 70 years.

Further controversy exists regarding the use of minimal bout lengths to filter activities of a short duration [427], as the effectiveness of shorter bouts to improve physical health outcomes has been questioned. Despite this, the latest guidelines by the World Health Organization urge the removal of such requirements and argue that the total time in each activity should count towards the weekly volume [295]. In fact, a recent analysis by Jakicic et al. supports this argument by demonstrating that physical activity of any bout duration is associated with improved health outcomes, including lower mortality [428]. In general, this highlights the fact that there is little consensus regarding best practices for data collection and processing of accelerometer data, which leads to inconsistent estimates of physical activity between studies [429]. Experts call for standardised data processing methods and improved transparency to increase the clinical applicability of accelerometers [430].

The large discrepancy between absolute values of self-reported and accelerometer-derived physical activity, as well as the lack of consensus for the data analysis of what are presumably objective physical activity measurements, puts the reliability of estimated proportions of individuals meeting physical activity targets in question. Nonetheless, this study showed that at least some men with advanced prostate cancer seem to be insufficiently active. Even though evidence clearly demonstrates the benefits of regular physical activity for survival, overall health and well-being during and immediately after cancer treatment, inactivity remains an issue during prostate cancer survivorship that needs addressing.

6.1.2. Association of physical activity with physical fitness

Physical activity is regarded as an important modifiable risk factor in the context of overall health [431], with higher physical activity over the life course associated with well-documented benefits, including reduced risk for cancer, cardiovascular disease, depression and overall mortality [350,432-434]. Similarly, increased physical fitness has also been linked to a better

overall health status in various populations [435,436], including individuals living with cancer [437], and has consequently been recognised as a powerful marker of health [346,351]. To investigate a potential link between self-reported physical activity and fitness, their association was analysed in Study 1 in a large multi-centre sample of men with advanced prostate cancer.

Based on results from quantile regression analysis, higher self-reported weekly MVPA demonstrated a significant association with improved VO_2peak at the lowest and highest percentile. Unstandardised beta coefficients from the adjusted models translated to a VO_2peak improvement of 0.5 $ml \cdot min^{-1} \cdot kg^{-1}$ at the 25th percentile and 0.7 $ml \cdot min^{-1} \cdot kg^{-1}$ at the 75th percentile for every additional hour of MVPA per week. A minimal clinically important difference for VO_2peak improvements of 2.5 $ml \cdot min^{-1} \cdot kg^{-1}$ has been suggested previously [438], which would require 33 to 40 minutes of additional MVPA per day according to this model. These results are consistent with previous studies that observed a lower VO_2peak among less active prostate cancer survivors, as well as higher post-treatment cardiorespiratory fitness among women who accumulated more MVPA during breast cancer treatment [360,439].

To further elucidate the relationship between physical activity patterns and fitness in men on ADT, Study 2 included accelerometer measurements of seven-day habitual physical activity in a smaller subsample that were processed into time shares at different intensities across the 24-hour activity cycle. In contrast to self-reported MVPA in Study 1, accelerometer-derived MVPA was not associated with VO_2peak. Instead, significant predictors of increased VO_2peak included reduced sleep time and shorter time since diagnosis for $ActiGraph_H$, and reduced sleep and sedentary time, as well as greater time spent in light physical activity for $ActiGraph_M$. While physical activity at moderate to vigorous intensities is generally considered to provide the greatest health benefits, and is thus the focus of physical activity recommendations, increasing the daily time spent in light intensity activities has also been associated with improved physical function [440]. This may be a viable alternative for individuals who are unable to maintain sufficient levels of MVPA, particularly those of older age with chronic conditions.

The negative association between VO_2peak and sleep time seems contradictory at first, because adequate sleep duration is generally considered to be a key component of overall good health [441]. However, in the context of advanced cancer increased sleep duration may be an indicator of underlying adverse health conditions. In fact, sleep disturbances affect up to 80% of cancer patients and can include insomnia, difficulty initiating sleep, and excessive daytime sleepiness caused by severe cancer-related fatigue [442]. Cancer-related fatigue refers to persistent physical or mental tiredness combined with a general lack of energy that is provoked by cancer or its treatments and is disproportionate to exertion and sleep [443]. ADT and other prostate cancer treatments are associated with substantial increases in fatigue

levels and a higher prevalence of sleep disorders [444-446]. Patients who experience higher fatigue and poorer sleep quality may attempt to counterbalance the tiredness through longer sleep durations or periods of daytime sleep. This is consistent with activity patterns observed by Mondal et al., who found that men on ADT slept significantly longer and reported a poorer sleep quality than ADT-naïve men, as well as reports of lower sleep quality associated with higher-risk prostate cancer [447,448]. Increased cancer-related fatigue, in turn, has been linked to reduced cardiorespiratory fitness, which may provide some context for the association between sleep time and VO_2peak observed in this study [449,450].

An association between habitual MVPA and walking performance has previously been reported in ovarian cancer survivors [451]. Moreover, Demark-Wahnefried et al. [452] observed that older cancer survivors that exercised regularly at moderate or vigorous intensities, exhibited significantly higher physical function scores. Increased physical function may translate into improved walk test performance, which can be considered as a viable assessment tool for physical function [453]. These studies support the inverse association between self-reported MVPA and 400 metre walk time in Study 1, meaning that men with higher levels of MVPA recorded a faster walk time. Interestingly, this association was only present for men in the highest percentile of walk time, i.e. the slowest walking speed, which suggests a potential plateau of the benefit of habitual physical activity for improvements in walking performance. Higher accelerometer-derived MVPA was also linked to a faster walk time in Study 2, underlining the results of self-reported data.

In contrast to the observed benefits of physical activity for aerobic performance, higher self-reported MVPA did not relate to improved handgrip strength in Study 1, which was further confirmed by the analysis of accelerometer data. These results are in line with a study in head and neck cancer survivors, which found that active participants did not differ from inactive participants in their handgrip strength [310]. Kenkhuis et al., on the other hand, showed that higher MVPA was linked to better handgrip strength in colorectal cancer survivors [454]. Interestingly, regression analysis of accelerometer-derived physical activity levels in Study 2 identified age as the best predictor of handgrip strength, strongly indicating a decrease in strength with older age. Declines in handgrip strength with age are well documented and considered to be indicative of the loss of overall muscle strength and increasing frailty that occurs during ageing [455]. While age as a predictor of handgrip strength may be unsurprising, it is interesting that time on ADT was not significantly associated with strength, despite a previously reported link between treatment time and the rate of muscle mass loss [130]. However, this study by Smith et al. also showed that the rate of muscle mass loss was greatest for men with the shortest time on ADT, whereas the average treatment time with ADT at the time of enrolment was 37 and 11 months in Study 1 and Study 2, respectively.

Therefore, it can be concluded that in a fairly homogenous population of men with advanced prostate cancer, who have been treated with ADT and additional therapies for extended periods, treatment time does not serve as an indicator of fitness outcomes.

Similar to handgrip strength, self-reported MVPA also showed no association with maximal lower body strength, as measured by leg extension 1RM. The analysis of accelerometer-derived data provided a contradicting result, with improved lower body strength linked to reduced sedentary time and higher light physical activity or MVPA, depending on the cut-points. These findings highlight the importance of not only increasing activity, but also limiting sedentary behaviour to avoid adverse health effects, as is strongly recommended in the latest physical activity guidelines [295]. In fact, decreasing sedentary behaviour among prostate cancer survivors has previously been associated with positive effects on physical functioning and quality of life [27,321]. These results also reinforce that accelerometer-based assessment, which includes the entire spectrum of movement, provides inherent benefits for understanding the relationship of physical activity with fitness and health. In a population that engages in very little targeted resistance exercise, as demonstrated by only 20% of participants reporting regularly performing resistance exercise, the risk of ADT-related muscle wasting is tremendous. Therefore, decreasing sedentary behaviour may provide benefits.

Additionally, a subgroup analysis was performed to determine whether the relationship between self-reported MVPA and fitness differed between participants receiving second-generation ARIs in addition to ADT and those receiving ADT as a monotherapy or with other secondary treatments. The results showed that the positive association between MVPA and VO_2peak only persisted in non-users but not in ARI users. Similarly, higher MVPA was only linked to a faster walk time in non-users. Despite this, significantly higher levels of self-reported MVPA among ARI users did not translate into improved physical fitness. Between-group analysis of accelerometer-derived physical activity in the German subsample did not confirm the observation of higher MVPA among ARI users and also found no differences in self-reported physical activity and fitness, suggesting no aggravated decline in physical function with ARI use. It is important to note that the German subsample differed from the multi-centre sample in several participant characteristics, showing a lower age and BMI, as well as a shorter time since diagnosis and treatment start with ADT.

ARIs were originally approved for advanced prostate cancer but are more and more frequently utilised at earlier disease stages to enhance disease control and improve survival [416]. Despite the increasing use of ARIs, conclusive results on their toxicities for neuromuscular and cardiorespiratory health are lacking. A large meta-analysis demonstrated that ARI use may impair lower limb muscle function, which resulted in a significantly

increased risk of falls and fractures [168]. While this cannot be concluded from the present study, the observation of differing relationships between self-reported physical activity and fitness in the large sample suggests that ARIs, which directly interfere with the androgen receptor and elicit an even stronger androgen blockade than ADT alone, may blunt physical activity benefits for cardiorespiratory and walking fitness. In light of the inconclusive results between the two samples of men at potentially different points in the prostate cancer care continuum, further studies are needed to understand the effects of ARIs on physical activity and function.

6.1.3. Association of physical activity with immune function

Physical activity is associated with beneficial modulations of various signalling pathways, including inflammatory immune responses [456], as demonstrated by a shift towards more anti-inflammatory leukocyte subsets through physical activity and a lower risk of developing chronic inflammatory diseases in physically active individuals [31,457]. To expand on the current knowledge regarding inflammation in the context of ADT, a comprehensive analysis of immune cells and inflammation markers in the peripheral blood of men with advanced prostate cancer was performed and the results were combined with those of the accelerometer-derived physical activity data analysis. Results from the cross-sectional analysis in Study 2 suggest a moderate association between daily physical activity and circulating levels of monocytes, neutrophils and Treg cells, but not with any of the other immune parameters.

Monocytes are vital for the maintenance of tissue homeostasis by both initiating and resolving host immune responses, and have also been identified as important regulators of tumour development and progression [458]. Primary tumours and distant metastasis appear to recruit monocytes and their presence in the tumour microenvironment is associated with amplified pro-inflammatory signalling and immunosuppression [459,460]. Conversely, monocyte subsets have also been shown to prevent metastatic spread and promote tumour cytotoxicity, indicating a dual role of these cells in cancer. Importantly, Hayashi et al. have shown that the absolute monocyte count in the peripheral blood reflects tumour infiltration of tumour-supporting monocyte subsets and serves as a predictive marker of cancer outcomes [461]. In prostate cancer, increased peripheral blood monocyte counts are predictive of reduced overall and cancer-specific survival, as well as worse progression-free survival after ADT [462-464].

As demonstrated in Study 2, higher absolute monocyte counts were also linked to decreased levels of light physical activity and increased sedentary time. Little is known about the effects of physical activity on this immune cell population in healthy individuals, let alone in chronic

inflammatory diseases like cancer. Wadley et al. reported that higher levels of MVPA reduced migration of a pro-inflammatory monocyte subset from the blood into the tissue of healthy and obese men, which underlines the anti-inflammatory properties of physical activity [465]. Furthermore, Timmerman et al. reported higher levels of a pro-inflammatory monocyte subtype in physically inactive individuals and, importantly, observed a marked reduction in monocyte concentrations through structured exercise [466]. While the specific actions of monocytes are still unclear, increased blood counts appear to mostly support tumour growth, which would suggest that the association observed in Study 2 underpins the anti-tumour effects of physical activity. Most anti-tumour effects of monocytes, on the other hand, have so far only been shown *in vitro* and their translation into the *in vivo* immune defence against prostate cancer warrants further investigation [458]. Given the divergent roles of various monocyte subsets in cancer, further studies that characterise these subsets are needed to gain insight into peripheral blood counts of pro and anti-tumoral monocytes and their effects on tumour progression following physical activity.

As key regulators of immune responses, monocytes in the tumour microenvironment release signalling molecules to recruit other immune cells, including Treg cells [467]. Through chemokine ligands they stimulate the migration of Treg cells into the tumour, leading to the secretion of Treg-derived cytokines that subsequently direct the differentiation of tumour-supporting macrophages, which results in a positive feedback loop perpetuated by both cell types [468,469]. In contrast to the negative association between physical activity and monocyte counts, Study 2 highlighted that higher levels of light physical activity and less sedentary time were related to increased lymphocyte proportions of Treg cells.

Preclinical and clinical evidence has consistently shown that Treg cells highly infiltrate tumours and direct the formation of an immunosuppressive environment to promote tumour immune escape in many cancers [470-473]. Despite widely accepted benefits of physical activity for cancer outcomes, findings on the response of circulating proportions of Treg cells to increased habitual physical activity are inconclusive [474]. Cross-sectional studies in humans have observed reduced blood levels of Treg cells in participants with higher self-reported physical activity [386], but no differences among participants with higher objectively measured physical activity compared to inactive individuals [475]. Without further investigation of tumour-infiltrating cell populations, it is therefore difficult to interpret the observed increase in circulating Treg cell proportions as being either beneficial, due to reductions in systemic inflammation, or disadvantageous, due to downregulation of anti-tumour immunity.

Similarly, there is conflicting evidence regarding the role of neutrophils as mediators of immune responses in cancer, although most findings point to tumour-supporting rather than inhibitory effects of neutrophils [246,476]. In Study 2, an increased NLR was associated with a

lower age and a higher prostate cancer stage ($ActiGraph_H$: $R^2 = 0.32$, $ActiGraph_M$: $R^2 = 0.21$, both weak associations) but was unrelated to any physical activity variables. Interestingly, the negative relationship between NLR and age contradicts the dynamic observed in previous studies, which reported a steady increase with age in healthy individuals [293]. However, this association might be influenced by prostate cancer aggressiveness as an underlying factor. Prostate cancer prevalence is highest among older men, and a younger age at diagnosis of advanced stage disease is associated with more aggressive disease [477]. Because all men included in the present thesis had advanced, metastatic prostate cancer, younger participants likely presented with a more aggressive tumour and a higher risk for disease progression, which in turn has been linked to increased NLR values [478].

Generally, mean values of NLR, PLR and SII at baseline were higher than previously reported reference values [293], although these markers are known to vary considerably between patients. Furthermore, observing individual long-term trends may be more informative than using cut-off points [246]. While fluctuations in blood levels of immune cells are characteristic for the immune response to acute exercise, their relationship to habitual physical activity behaviour remains largely unclear. This is supported by the absence of associations of NLR, PLR, SII, NK^{dim}/NK^{bright} ratio and Th17/Treg ratio with time-use variables in Study 2, although several markers, including neutrophils, Treg cells and Th1/Th2 ratio, were associated with sleep time. Increased levels of inflammatory markers, such as total leukocytes, neutrophils, NLR and SII, have previously been linked to a higher prevalence of sleep disturbances [479]. Though without the assessment of sleep quality, it is difficult to draw conclusions from these findings.

6.2. Chronic, structured exercise

6.2.1. Exercise intervention adherence

Structured exercise has gained increased recognition by oncologists due to its potential to inhibit disease progression and counterbalance cancer-induced and treatment-related toxicities, such as muscle wasting, systemic inflammation and fatigue [343,480,481]. While positive health effects are known to increase with a longer duration of the exercise intervention, thereby highlighting the importance of long-term adherence, previous exercise studies have reported varying levels of adherence among prostate cancer survivors [316].

Exercise intervention adherence in the longitudinal Study 3 amounted to 54% completed MICT dose, 66% completed HIIT dose and 85% completed resistance exercise dose. These differences between exercise modalities may be explained by the fact that participants were more likely to perform MICT sessions unsupervised to reduce travel time. Other studies that included both supervised and unsupervised exercise sessions also found that supervision

was associated with increased adherence [482]. Furthermore, most intervention studies in exercise oncology employ traditional metrics to quantify intervention adherence, such as session completion or attrition rates, which provide limited insight into the actual exercise tolerability. This has been demonstrated by Nilsen et al., who analysed the tolerability of a six-month aerobic exercise intervention for men with prostate cancer and found that 96% of participants required a dose reduction in at least one exercise session [331]. To account for this consideration, exercise adherence in this thesis was quantified by calculating the proportion of completed versus prescribed dose.

An analysis of exercise adherence split by week provided further novel insight into adherence patterns across a 6-month periodised exercise intervention for men with advanced prostate cancer. Adherence rates of HIIT and resistance exercise were highest in deload weeks, showing that participants at times did not reduce their exercise load as prescribed, and lowest in weeks with a high prescribed load. Periodisation, where the training programme is structured to attain a sufficient stimulus to elicit adaptive responses while avoiding overtraining and fatigue through unloading phases, is a commonly applied approach in strength training across athletic and non-athletic populations [483,484]. Periodisation increases the effectiveness of resistance training programmes as indicated by improved muscle strength compared to non-periodised training [485]. On the other hand, it can be argued that a reduction of the exercise load may not be required in cases where the prescribed exercise dose during high load weeks is not achieved.

In general, the tolerability of the exercise intervention was good because of dose modifications and the use of autoregulation, which allowed participants to adapt exercise intensities individually to their daily form. The ability to exercise was, however, drastically impaired in cases of disease progression, thus highlighting the necessity of exercise specialist supervision for intense training programmes in individuals with advanced cancer. In a population that engaged in very few muscle-strengthening activities at baseline, the overall uptake of the exercise intervention, particularly resistance exercise, is encouraging and emphasises an unmet need for specialised exercise oncology programmes.

6.2.2. Exercise-induced changes in physical fitness

Although the ability of exercise to stimulate muscle hypertrophy during androgen deprivation remains unclear, studies have consistently shown that exercise interventions can improve muscle strength in men on ADT [24,363]. In this regard, there was a significant interaction effect for maximal lower body strength in Study 3, with a large effect size indicating a greater increase of the leg extension 1RM in the intervention arm from baseline to the 6-month testing visit. Analysis of handgrip strength also revealed a large effect size for improvements from

baseline in the intervention arm, while the control arm showed a smaller increase. These findings are consistent with a previous meta-analysis that demonstrated the effectiveness of combined interventions that include both aerobic and resistance exercise in increasing muscle strength [24]. Such observations of improved strength outcomes as a result of structured exercise are of clinical relevance for men on ADT, who commonly experience impairments in muscle function that put them at a higher risk of falls and fractures [168]. Furthermore, performance decrements induced by ADT may be difficult to recover even if androgen deprivation is stopped [155]. Particularly for men with advanced disease, who usually undergo long-term androgen withdrawal, timely interventions to prevent excess morbidity are needed.

Cardiorespiratory fitness improvements in prostate cancer survivors have been reported for several exercise modalities [24,486,487]. Ussing et al. investigated the effects of supervised exercise interventions on aerobic fitness and walking performance, in the form of either aerobic or resistance exercise as a monotherapy or in combination [24]. Based on pooled data from 406 men on ADT, they concluded that supervised exercise resulted in a mean improvement in VO_2peak of 1.76 $ml \cdot kg^{-1} \cdot min^{-1}$, which corresponded to a clinically relevant improvement of 8% across the intervention periods that ranged from 3 to 12 months. They also reported improvements in favour of the intervention group for walking performance, as indicated by a mean reduction of 23 seconds in a 400 metre walk test [24]. Importantly, grouping the interventions by exercise type demonstrated that aerobic exercise provided the largest benefits for cardiovascular fitness [24]. This may serve as the basis for an explanation of why there was no significant improvement in VO_2peak or walk time in Study 3.

The present study demonstrated large variations in exercise adherence, particularly for MICT, with the total completed exercise dose ranging from 0 to 660 minutes of aerobic exercise at moderate intensity throughout the 6-month trial. Even though HIIT is considered the superior exercise modality for improving cardiorespiratory fitness, mainly due to greater adaptations of the cardiovascular system despite a shorter total training time, both MICT and HIIT are known to provide benefits [488,489]. In fact, multiple studies have found both exercise modalities to be comparable in their ability to improve VO_2peak and other health outcomes among individuals with chronic conditions, such as diabetes or cancer [489-491]. Regardless, performing an additional weekly exercise session of MICT would certainly increase the cumulative effect on aerobic performance. Although analysis of changes in physical fitness by exercise dose did not show significant associations, which was likely affected by insufficient statistical power due to a small sample size, large differences in the adherence to the aerobic exercise programme may have attenuated the intervention effect on cardiorespiratory fitness.

Overall, the 6-month exercise intervention showed the greatest benefits for strength improvements, while adaptations in aerobic performance were limited by the heterogeneous uptake of the prescribed programme. Importantly, the results demonstrate that a structured programme of intense exercise is a safe form of supportive therapy and may improve physical fitness outcomes in men with advanced prostate cancer. There is a particularly strong rationale for the inclusion of resistance exercise, which provides not only an important physiological stimulus for the preservation of muscle mass, but has also shown promising feasibility as indicated by high overall adherence of participants to the resistance training programme.

6.2.3. Exercise-induced changes in immune function

The 6-month structured exercise intervention did not provoke chronic changes in circulating levels of immune cells and immune cell-derived inflammation markers compared to the control arm. It has been demonstrated repeatedly that moderate-to-intense exercise can enhance immunosurveillance and reduce systemic inflammation, which is of particular relevance for individuals with chronic conditions characterised by inflammation, including cancer [29,369]. The mechanical and metabolic stimulus provided by an acute exercise bout releases a network of cytokines and elicits a systemic response that influences the maturation, migration and effector function of immune cells [375,376]. Nonetheless, it remains unclear whether exercise chronically increases absolute numbers of immune cells or alters the balance of immune cell populations with opposing functions in the bloodstream.

Similar studies in cancer populations have yielded varying results regarding the immune response to chronic bouts of exercise. In line with the observation of unchanged immune cell levels is a study by Djurhuus et al., who reported that preoperative HIIT training did not alter proportions of tumour-infiltrating NK cells compared to the control arm in prostatectomy samples from men with localised prostate cancer, although the transferability to circulating NK cell concentrations remains unclear [492]. Interestingly, a 16-week exercise intervention for breast cancer survivors did not change absolute neutrophil counts but improved their effector function as seen by increased phagocytosis [493]. Analysis of an Australian subsample of the INTERVAL-GAP4 trial found an increase in serum myokine levels in the intervention arm at 6 months paired with reduced cell growth in target cells treated with exercise-conditioned serum [380]. Furthermore, eight weeks of progressive resistance training significantly reduced serum concentrations of IL-6 and TNFα, two cytokines with pro-inflammatory properties, thereby potentially mediating a shift of the immune response towards a less inflammatory state [494]. However, changes in soluble mediators do not necessarily result in altered immune cell concentrations; instead they may only affect cell function rather than maturation or

migration. Because immune cells were not assessed in these two studies, it is difficult to draw conclusions in this regard.

Immune cell analysis revealed a significant time effect for lymphocyte proportions, which increased from baseline to the 6-month testing in both arms, but no significant changes were observed in the lymphocyte-derived markers NLR, PLR and SII. Lower levels of NLR, either resulting from neutrophil reductions or lymphocyte increases, have repeatedly been linked to an improved prognosis in men with advanced prostate cancer [495]. The increase in lymphocyte proportions would therefore suggest a beneficial development; however, the immune response comprises a complex network of multiple actors, and further investigations are needed to understand how these changes affect the immune function in men with prostate cancer. The changes in lymphocyte proportions also appear to be independent of the structured exercise intervention, which may be explained by the fact that participants in the control arm received information that extends beyond the classical usual care condition, including self-directed exercise recommendations and psychosocial support. Furthermore, it can be assumed that men volunteering to participate in this two-year exercise intervention trial were greatly motivated to exercise and may have independently increased their physical activity throughout the study period.

Among participants in the intervention arm, higher levels of total aerobic exercise were associated with lower absolute NK cell counts in the blood. NK cells are a vital part of the anti-tumour immune defence and have therefore been proposed as one of the dominant cell types to mediate exercise-induced benefits in cancer [201,496]. However, their response to chronic exercise stimuli is controversial, with previous findings showing increase, reduction or no change in peripheral NK cell counts [497]. This is further elucidated by a meta-analysis by Rumpf et al. reporting increased NK cell cytotoxic activity after acute exercise, which returned to baseline within two hours of recovery and, importantly, occurred independently from changes in the NK cell count [498]. Overall, further investigations beyond the analysis of peripheral blood counts are necessary to better understand the role of NK cells in the exercise-induced regulation of the anti-tumour immune response.

Exercise intensity may mediate the relationship between training and immune responses, with higher intensities generally assumed to provoke stronger immune responses. Clifford et al. compared the effects of high-intensity (60 to 70% HR reserve) and low-intensity (30 to 40% HR reserve) cycling exercise after two weeks and found that only high-intensity exercise was associated with a decrease in CXCL12, a chemoattractant involved in neutrophil recruitment and subsequent activation of immune responses [499]. In the present study, aerobic exercise intensity was prescribed as a subjective measure using the RPE scale with the aim that all participants would achieve the same relative intensity under consideration of

their respective health status. While this allowed participants to adjust their exercise programme independently, given that most participants had limited experience with intense exercise, the approach may have resulted in a lower absolute exercise intensity than originally intended. Quantification of the cumulative exercise load through HR measurements or resistance for aerobic exercise may provide further insight into the effects of structured exercise on immune responses.

6.3. Methodological strengths and limitations

The results presented in this thesis should be interpreted within the context of important strengths and limitations. Due to the specific physiological changes and resulting side effects associated with ADT, homogeneity of the study sample in terms of androgen blockade is critical for studies of prostate cancer. While other studies often included patients at various prostate cancer stages and treatments or combined different cancer entities for a larger sample size, the INTERVAL-GAP4 trial exclusively recruited men with advanced prostate cancer undergoing continuous treatment with ADT. The additional consideration of ARI use in the analysis of physical activity and fitness data in Study 1 provides valuable and novel information that is highly relevant in the context of current treatment guidelines for advanced prostate cancer. On the other hand, the strict eligibility criteria that were enforced to ensure a homogenous sample limited the number of eligible men and contributed to a modest sample size. Older men with advanced, incurable cancer can be a challenging population to enrol in exercise intervention trials. Nevertheless, it is worth noting that low attrition paired with a high uptake of the intervention, in particular at the German study site, are promising signs for future exercise trials.

Self-reported surveys and accelerometers as objective measuring devices are commonly used to assess habitual physical activity and both are characterised by inherent benefits and limitations, which can result in biased estimates. The comparison of both measurement methods in the German subsample in Study 2 expands on the analysis in Study 1 by providing further insight into the relationship between physical activity and fitness in men with prostate cancer. Furthermore, the comprehensive analysis of accelerometer-derived data also highlights the dilemma of using wrist-worn accelerometers in the absence of appropriate, validated data processing standards. Both the processing of accelerometer data into time-use behaviours and the subsequent statistical analysis, which applied PLS regression models to account for collinearity in the data, were performed in line with the latest scientific literature [406]. While this certainly is a strength of the present study, it limits the comparability with previous studies that have applied different analytical approaches to obtain physical activity estimates and to analyse their association with health outcomes in cancer.

Physical fitness as a central outcome of the exercise intervention trial was assessed using gold standard methods, such as respiratory gas exchange for VO_2peak and 1RM tests for maximal strength. However, due to the multicentre nature of Study 1, different devices or weight machines were used at different sites, which may have introduced a systematic measurement bias. Due to the small number of participants at some sites, controlling for this variable in the statistical analysis was not feasible. No minimal physical fitness requirements were set in the eligibility criteria; however, participants had to be able to complete the study procedures, which required a moderate level of physical function. Therefore, the sample included individuals who were both motivated and able to participate in a long-term exercise intervention trial, which may not be representative of all men with advanced prostate cancer. Finally, the use of quantile regression analysis in Study 1 provided the advantage of allowing an examination of the association between MVPA as a physical activity estimate and different levels of physical fitness, without compromising the statistical power.

The challenge of exercise programmes for individuals with bone metastases is the selection of appropriate, safe exercises, particularly when including resistance training. To maximise adaptations, ensure programme variation and increase motivation and adherence, exercises were selected individually for each participant under careful consideration of their limitations and needs. This was founded in the understanding that prescribing an identical, predetermined, long-term exercise programme to all participants, regardless of their capacities, is unrealistic in a population with advanced cancer. Furthermore, exercise intensity was determined via autoregulation, which allowed participants each session to choose the additional load for strength and aerobic exercises, in relation to their maximal exercise capacity. This approach was selected to ensure a comparable relative exercise intensity for all participants, even in periods of decreased exercise capacity due to high levels of fatigue or other adverse effects. The variations in completed exercises and exercise intensity among participants could have limited the intervention efficacy and may explain the variance in physical fitness and immune changes seen in Study 3. For example, some participants used additional weights for strength exercises and high resistance for aerobic cycling, while others completed exercises with bodyweight only and low resistance.

The comparability is further limited by the two delivery modes, either fully supervised or partially supervised, whereby the majority of sessions were performed at a remote gym or at home. Although the remote training option increased the feasibility of the exercise intervention during the COVID-19 pandemic, it may have negatively impacted the study results because supervised interventions are generally associated with greater adherence and superior effects [500-502]. Additionally, restricted access to study facilities during the COVID-19 pandemic also forced some testing windows for the 6-month visit to be extended, which resulted in some participants completing the measurements up to two months after the

scheduled date. It is worth noting that participants in the intervention arm continued their exercise programme during that time and all sessions were recorded. The small number of participants in the intervention arm of Study 3 did not allow for these variations to be accounted for in the statistical analysis. Instead, a detailed analysis of the completed exercise dose was performed, which included all sessions up until the testing visit. This analysis expanded beyond traditional adherence metrics, and is thus considered a strength of this study.

The analysis of immune parameters in Study 2 and Study 3 was comprehensive and included several Th cell subpopulations, as well as two subtypes of NK cells with distinct phenotypes. Nevertheless, it should be acknowledged that the immune cell analysis was performed using venous blood samples and did not include assays of cellular function. Only a small proportion of immune cells is found in the bloodstream and, even though immune cell dynamics in the peripheral blood have been shown to reflect changes in the tumour microenvironment, the two are not necessarily synonymous [503-505]. Moreover, the ability of immune cells to fulfil their effector function is not only characterised by absolute numbers or proportions, but also signalling molecules and other regulating factors [506,507]. Therefore, further analyses of the cytotoxic capacity of immune cells against a target cell line are required to establish whether structured exercise improves the anti-tumour immune response. Lastly, it is important to consider that the interpretation of changes in immune function in men with advanced cancer is often complicated by multiple comorbidities and additional treatments.

6.4. Outlook

This thesis highlights methodological challenges associated with assessing physical activity in a free-living setting, which is a crucial component of investigations of baseline physical activity levels and changes following interventions. Although leading health organisations have established clear physical activity targets based on evidence for associated health benefits, the physical activity estimates, even those derived from objective measurement methods, include substantial variations. While technological advancements enable the collection, storage and processing of large quantities of movement data, the utilisation of these technologies in medical research could be expanded further. For example, validation studies of physical activity cut-points across a range of different populations and universal data analysis standards present two important steps towards improving physical activity assessments.

Exercise oncology research has provided sufficient evidence for exercise as a safe and effective form of adjuvant therapy for individuals with cancer, thus, research focus has shifted to understanding the mechanisms behind this association. Exercise-induced physiological adaptations are thought to counteract the immunological disturbances caused by the tumour,

thereby strengthening the ability of the host defence to initiate an effective anti-tumour immune response. Consequently, several clinical trials that investigate the influence of exercise programmes on the immune function in various cancer types have been registered in recent years, including survivors of lung cancer [508], breast cancer [509], melanoma (NCT06298734), colorectal cancer (NCT05579340), as well as lymphoma and leukaemia (NCT05876923).

While surveys among oncologists have shown a generally positive attitude towards recommending exercise for individuals with cancer, there is still a lack of adequate and accessible exercise programmes [510,511]. As highlighted by the studies presented in this thesis, uptake of an intense, individualised exercise intervention of combined aerobic and resistance exercise was satisfactory among prostate cancer survivors with low physical activity and exercise participation at baseline. Together with further analyses of the feasibility and cost-effectiveness of the INTERVAL-GAP4 exercise intervention, as well as its potential long-term benefits for disease progression, overall health and fitness outcomes, these results can be used to improve the delivery of exercise programmes for this population.

7. Conclusion

The aim of the present thesis was to analyse associations of habitual physical activity with physical fitness and immune function in men with advanced prostate cancer, as well as investigate changes in physical fitness and immune function following a 6-month structured exercise intervention. Additionally, the adherence to physical activity guidelines and the prescribed exercise programme was assessed, and a subgroup analysis of ARI use was performed to investigate its effects on physical activity and fitness. For this purpose, two cross-sectional studies and one longitudinal study of men treated with ADT for metastatic prostate cancer were conducted. The specific aims and results can be summarised as follows:

Aim 1: Cross-sectional analysis of self-reported physical activity and adherence to activity guidelines, including differences between ARI users and non-users.

Self-reported physical activity in Study 1 was below the recommended level, with participants accumulating an average of 128 minutes MVPA per week, which was mostly driven by moderate intensity activity. Only 29% reported an adequate physical activity level that was in line with the current guidelines. The results may be limited by selection bias because men with high levels of vigorous aerobic exercise or structured resistance exercise were excluded. Self-reported MVPA was higher in ARI users than non-users, which contradicts previous findings of ARI-induced physical impairments.

Aim 2: Cross-sectional analysis of associations between self-reported MVPA and physical fitness, including differences between ARI users and non-users

Higher levels of self-reported MVPA were significantly associated with a higher VO_2peak and a faster walk time in non-users but not ARI users, while no associations with strength outcomes were observed in either group in Study 1. This suggests that engaging in habitual physical activity of aerobic nature may benefit aerobic fitness outcomes in men on ADT, whereas treatment with ARI may attenuate the benefits of physical activity. However, self-reporting of physical activity may have resulted in biased estimates that limit the interpretability of the results.

Aim 3: Cross-sectional analysis of accelerometer-derived physical activity, including differences between ARI users and non-users, and the agreement with self-reported physical activity

Accelerometer-derived data indicated substantially higher physical activity levels than participants had self-reported. There were no differences in accelerometer-derived physical activity levels of ARI users and non-users. Comparison of accelerometer-derived and self-reported data revealed virtually no agreement for estimates of light physical activity and MVPA. Because older cancer survivors spend a large share of their time performing habitual, low intensity activities that are disproportionately affected by recall bias, objective methods may be more suited to capture their activity.

Aim 4: Cross-sectional analysis of associations of accelerometer-derived physical activity with physical fitness and circulating immune parameters

Accelerometer-derived data confirmed that higher MVPA was related to a faster walk time. There was a positive association of light activity but not MVPA with VO_2peak, as well as of higher light activity or MVPA with maximal lower body strength. Among the immune parameters, only monocytes and Treg cells showed moderate associations with physical activity in Study 2, while most others appeared to be unrelated to physical activity levels. The observed link between higher light physical activity and decreased monocyte proportions supports the anti-tumour effects of habitual physical activity, whereas the association with increased Treg cells proportions remains inconclusive given the diverging roles of Treg cells in cancer. Furthermore, decreased sleep time was associated with higher proportions of inflammatory neutrophils. Whether this supports previous findings of a link between sleep disturbances and systemic inflammation remains to be investigated.

Aim 5: Longitudinal analysis of the adherence to a 6-month exercise intervention and associated effects on physical fitness and circulating immune parameters

Large variations in the uptake of the exercise intervention were observed in Study 3, with the highest adherence for resistance exercise. Consequently, aerobic fitness outcomes remained unaltered, whereas maximal lower body strength increased in the intervention arm and handgrip strength increased in both arms, with a larger effect in the intervention arm. There were no differences between the intervention and control arm in chronic changes of circulating immune parameters. Levels of immune cell and inflammation markers remained mostly unaltered except for lymphocyte proportions, which showed an increase at 6 months. Higher levels of aerobic exercise were associated with lower NK

cell counts; however, the significance of this finding for the anti-tumour immune response remains unclear.

In conclusion, the results of this thesis show that both habitual physical activity and structured exercise provide some measurable benefits for the physical fitness and immune function of men treated with ADT for prostate cancer. Interestingly, ARIs may alter the physiological response to physical activity, and should be further investigated given their frequent application. While structured exercise did not lead to the hypothesised reduction in systemic inflammation markers, potentially due to a suboptimal exercise stimulus, the results show that regular, intense exercise is possible for men with advanced prostate cancer and does not adversely affect immune parameters in the blood. Further investigations of the immune function, particularly functional assessments of immune cell populations like Tc cells and NK cells with known tumour-killing effects, are required to explore the immune-modulating properties of physical activity and exercise in the context of prostate cancer.

Acknowledgements

This work was only made possible thanks to the support of wonderful people who steered me in the right direction, lent a hand on countless occasions, picked me up when times got tough and celebrated my wins with me. I truly could not imagine completing this journey without each and every one of you.

Firstly, I want to thank my supervisor, **Prof. Dr. Moritz Schumann**, for taking a chance on me, challenging me to grow as a researcher and patiently guiding me through the process of completing this dissertation. Looking back, I am amazed to see how your research group and our working relationship have evolved over the past five years. From you, I have learnt how to manage demanding projects, develop and implement my own research ideas, supervise a team of my own, and so much more. I am confident that my time in your group will always hold a special place in my heart and I have you to thank for giving me this opportunity. Secondly, I want to thank the head of the Department for Cardiovascular Research and Sports Medicine, **Prof. Dr. Wilhelm Bloch**, for providing a great environment for junior researchers to learn and develop laboratory skills, as well as for sharing his knowledge (and his fantastic wine) with us. I appreciate that you were always happy to take time out of your day to talk about my project. Furthermore, I am thankful for the **Movember Foundation** for providing the financial support to fund this research, as well as the **INTERVAL-GAP4 leaders and additional study staff** for their efforts in coordinating the trial and collecting, monitoring and providing data.

A massive thank you to my wonderful colleagues: **Hannah Notbohm**, you have become a good friend whose incredible resourcefulness and sense of adventure I admire – I would probably still be writing this thesis if it were not for your encouragement and support; **Boris Dragutinovic**, you were my favourite desk neighbour and the reason for many laughs during and outside of office hours – I will miss our coffee breaks dearly, that's for sure; **Joshua Feuerbacher** and **Mats Jacobs**, working with the two of you allowed me to witness pure comedy on some days and a firework of ideas and thoughtful discussions on others, and I cherished both; **Nils Freitag**, as the first group member and the original GAP4 project coordinator I relied on your guidance a lot during those initial years; and **Tong Zhao**, as the latest addition you have embraced our group with your openness and curiosity. I also want to thank **Anke Schmitz** for being a great colleague, a dear friend to laugh with and a shoulder to cry on when needed. I feel very lucky to have shared this journey with all of you.

The GAP4 project would not have been possible without the efforts of **Lars Heinrich**, whose calm presence and technical knowledge were invaluable, and **Christina Lautner**, who despite only joining a year ago made a lasting impression with her dedication and the many great moments that we shared. In addition, I want to thank all the students who have contributed to the project over the years: **Pia, Yuheng, Paula, Laura, Svenja, Theresa,**

Johanna, Lisa, Niklas, Anna, Nele, Katja, Isabella and **Frederik.** Thank you also to the technicians **Anika Voß, Ute Laudenbach** and **Mojgan Ghilav** for assisting in all lab-related matters, and doctors **Jonas Zacher, Lena Riemer** and **Julia Fritz** for providing medical support.

There is a saying that you should stay close to people who feel like sunshine and I am thankful to have people in my life for whom this holds true. **Katharina Sanner**, we have shared many incredible moments, from footy tournaments in Edinburgh to spontaneous road trips to the beach – I am so grateful for our friendship; **Christina Streib**, we have been friends since we were little and those long walks through our hometown where we talk about anything and everything will never get old. I enjoyed my time as a PhD student a lot more because I got to share it with **Janika Bolz**, who may be one of the most enthusiastic people on this planet and never fails to make me laugh, and **Elisabeth Habersatter**, who was a great help particularly during my long days in the lab. Huge thanks also to everyone at the **Rheinland Lions Australian Football Club** who have become a big part of my life over the past years. Particularly, I want to thank all the amazing Lionesses: you are the most special bunch of women and continue to impress me with your hard work and dedication on and off the field.

As with all things in my life, accomplishing this milestone was made a lot easier thanks to my amazing family. To **my parents**, you were the ones who sparked my interest for science and provided me with the supportive environment I needed to arrive at the starting line of the PhD in the first place. Thank you for always encouraging me to follow my dreams, no matter how far away from you in the world they take me, and for making sure that I know I always have a home to return to. To my brother **Frederik**, although you are the little one, you already inspire me so much with your curiosity and wit. Thank you for always being my cheerleader; your belief in me is invaluable. To my sister **Laura**, you are the person I call when I need to talk. You have taught me how to make the friendship bracelets, take the moment and taste it [because] you've got no reason to be afraid… and for that I am incredibly grateful.

Above all, I want to thank my partner in crime, **Ian McNamara**, who never ceases to amaze me with his positivity, confidence and love. Thank you for the countless coffees you made me while I was writing, for patiently answering all my questions about R and for carefully proofreading many chapters of this thesis. You have kept me calm through many storms and reassured me again and again that I can achieve the goals that I set out for myself, especially in those moments when I was not quite sure myself. I am grateful for your unwavering support and beyond excited for our next adventure.

Cologne, April 2024
Lisa Umlauff

References

1. Verze P, Cai T, Lorenzetti S. The role of the prostate in male fertility, health and disease. Nat Rev Urol. 2016;13(7):379-86. doi: 10.1038/nrurol.2016.89.
2. Tan MHE, Li J, Xu HE, Melcher K, Yong E-l. Androgen receptor: structure, role in prostate cancer and drug discovery. Acta Pharmacol Sin. 2014;36(1):3-23. doi: 10.1038/aps.2014.18.
3. Naamneh Elzenaty R, du Toit T, Fluck CE. Basics of androgen synthesis and action. Best Pract Res Clin Endocrinol Metab. 2022;36(4):101665. doi: 10.1016/j.beem.2022.101665.
4. Rebello RJ, Oing C, Knudsen KE, Loeb S, Johnson DC, Reiter RE, et al. Prostate cancer. Nat Rev Dis Primers. 2021;7(1):9. doi: 10.1038/s41572-020-00243-0.
5. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-49. doi: 10.3322/caac.21660.
6. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1-10. doi: 10.1016/j.immuni.2013.07.012.
7. de Bono JS, Guo C, Gurel B, De Marzo AM, Sfanos KS, Mani RS, et al. Prostate carcinogenesis: inflammatory storms. Nat Rev Cancer. 2020;20(8):455-69. doi: 10.1038/s41568-020-0267-9.
8. Chiossone L, Dumas PY, Vienne M, Vivier E. Natural killer cells and other innate lymphoid cells in cancer. Nat Rev Immunol. 2018;18(11):671-88. doi: 10.1038/s41577-018-0061-z.
9. Philip M, Schietinger A. CD8+ T cell differentiation and dysfunction in cancer. Nat Rev Immunol. 2022;22(4):209-23. doi: 10.1038/s41577-021-00574-3.
10. Bou-Dargham MJ, Sha L, Sang QA, Zhang J. Immune landscape of human prostate cancer: immune evasion mechanisms and biomarkers for personalized immunotherapy. BMC Cancer. 2020;20(1):572. doi: 10.1186/s12885-020-07058-y.
11. Bargiota A, Oeconomou A, Zachos I, Samarinas ML, Pisters L, Tzortzis V. Adverse effects of androgen deprivation therapy in patients with prostate cancer: Focus on muscle and bone health. J BUON. 2020;25(3):1286-94.
12. Beebe-Dimmer JL, Cetin K, Shahinian V, Morgenstern H, Yee C, Schwartz KL, et al. Timing of androgen deprivation therapy use and fracture risk among elderly men with prostate cancer in the United States. Pharmacoepidemiol Drug Saf. 2012;21(1):70-8. doi: 10.1002/pds.2258.
13. Bosco C, Bosnyak Z, Malmberg A, Adolfsson J, Keating NL, Van Hemelrijck M. Quantifying observational evidence for risk of fatal and nonfatal cardiovascular disease following androgen deprivation therapy for prostate cancer: a meta-analysis. Eur Urol. 2015;68(3):386-96. doi: 10.1016/j.eururo.2014.11.039.
14. Huggins C, Stevens RE, Hodges CV. Studies on prostatic cancer: II. The effects of castration on advanced carcinoma of the prostate gland. Archives of Surgery. 1941;43(2):209-23. doi: 10.1001/archsurg.1941.01210140043004.
15. Nguyen PL, Alibhai SM, Basaria S, D'Amico AV, Kantoff PW, Keating NL, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. Eur Urol. 2015;67(5):825-36. doi: 10.1016/j.eururo.2014.07.010.
16. Smith MR, Finkelstein JS, McGovern FJ, Zietman AL, Fallon MA, Schoenfeld DA, et al. Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab. 2002;87(2):599-603.
17. Nelson AM, Gonzalez BD, Jim HS, Cessna JM, Sutton SK, Small BJ, et al. Characteristics and predictors of fatigue among men receiving androgen deprivation therapy for prostate cancer: a controlled comparison. Support Care Cancer. 2016;24(10):4159-66. doi: 10.1007/s00520-016-3241-z.

18. Preston DM, Torréns JI, Harding P, Howard RS, Duncan WE, McLeod DG. Androgen deprivation in men with prostate cancer is associated with an increased rate of bone loss. Prostate Cancer and Prostatic Dis. 2002;5(4):304-10. doi: 10.1038/sj.pcan.4500599.

19. Muniyan S, Xi L, Datta K, Das A, Teply BA, Batra SK, et al. Cardiovascular risks and toxicity - The Achilles heel of androgen deprivation therapy in prostate cancer patients. Biochim Biophys Acta Rev Cancer. 2020;1874(1):188383. doi: 10.1016/j.bbcan.2020.188383.

20. Edmunds K, Tuffaha H, Galvao DA, Scuffham P, Newton RU. Incidence of the adverse effects of androgen deprivation therapy for prostate cancer: a systematic literature review. Support Care Cancer. 2020;28(5):2079-93. doi: 10.1007/s00520-019-05255-5.

21. Maddocks M. Physical activity and exercise training in cancer patients. Clin Nutr ESPEN. 2020;40:1-6. doi: 10.1016/j.clnesp.2020.09.027.

22. McTiernan A, Friedenreich CM, Katzmarzyk PT, Powell KE, Macko R, Buchner D, et al. Physical Activity in Cancer Prevention and Survival: A Systematic Review. Med Sci Sports Exerc. 2019;51(6):1252-61. doi: 10.1249/MSS.0000000000001937.

23. Lam T, Birzniece V, McLean M, Gurney H, Hayden A, Cheema BS. The Adverse Effects of Androgen Deprivation Therapy in Prostate Cancer and the Benefits and Potential Anti-oncogenic Mechanisms of Progressive Resistance Training. Sports Med Open. 2020;6(1):13. doi: 10.1186/s40798-020-0242-8.

24. Ussing A, Mikkelsen MK, Villumsen BR, Wejlgaard J, Bistrup PE, Birkefoss K, et al. Supervised exercise therapy compared with no exercise therapy to reverse debilitating effects of androgen deprivation therapy in patients with prostate cancer: a systematic review and meta-analysis. Prostate Cancer Prostatic Dis. 2022;25(3):491-506. doi: 10.1038/s41391-021-00450-0.

25. Rock CL, Thomson CA, Sullivan KR, Howe CL, Kushi LH, Caan BJ, et al. American Cancer Society nutrition and physical activity guideline for cancer survivors. CA Cancer J Clin. 2022;72(3):230-62. doi: 10.3322/caac.21719.

26. Smith L, Lee JA, Mun J, Pakpahan R, Imm KR, Izadi S, et al. Levels and patterns of self-reported and objectively-measured free-living physical activity among prostate cancer survivors: A prospective cohort study. Cancer. 2019;125(5):798-806. doi: 10.1002/cncr.31857.

27. Trinh L, Alibhai SMH, Culos-Reed N, Sabiston CM, Jones JM, Rosenberg DE, et al. Associations of light physical activity, moderate-to-vigorous physical activity and sedentary behavior with quality of life in men on androgen deprivation therapy for prostate cancer: a quantile regression analysis. J Behav Med. 2022;45(4):533-43. doi: 10.1007/s10865-022-00285-7.

28. Friedenreich CM, Wang Q, Neilson HK, Kopciuk KA, McGregor SE, Courneya KS. Physical Activity and Survival After Prostate Cancer. Eur Urol. 2016;70(4):576-85. doi: 10.1016/j.eururo.2015.12.032.

29. Fiuza-Luces C, Valenzuela PL, Gálvez BG, Ramírez M, López-Soto A, Simpson RJ, et al. The effect of physical exercise on anticancer immunity. Nat Rev Immunol. 2023. doi: 10.1038/s41577-023-00943-0.

30. Hoffmann C, Weigert C. Skeletal Muscle as an Endocrine Organ: The Role of Myokines in Exercise Adaptations. Cold Spring Harb Perspect Med. 2017;7(11). doi: 10.1101/cshperspect.a029793.

31. Gleeson M, Bishop NC, Stensel DJ, Lindley MR, Mastana SS, Nimmo MA. The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease. Nat Rev Immunol. 2011;11(9):607-15. doi: 10.1038/nri3041.

32. Schenk A, Esser T, Belen S, Gunasekara N, Joisten N, Winker MT, et al. Distinct distribution patterns of exercise-induced natural killer cell mobilization into the circulation and tumor tissue of patients with prostate cancer. Am J Physiol Cell Physiol. 2022;323(3):C879-C84. doi: 10.1152/ajpcell.00243.2022.

33. Untergasser G, Madersbacher S, Berger P. Benign prostatic hyperplasia: age-related tissue-remodeling. Exp Gerontol. 2005;40(3):121-8. doi: 10.1016/j.exger.2004.12.008.

34. Whitaker H, Tam JO, Connor MJ, Grey A. Prostate cancer biology & genomics. Transl Androl Urol. 2020;9(3):1481-91. doi: 10.21037/tau.2019.07.17.

35. Kurita T, Medina RT, Mills AA, Cunha GR. Role of p63 and basal cells in the prostate. Development. 2004;131(20):4955-64. doi: 10.1242/dev.01384.

36. di Sant'Agnese PA. Neuroendocrine cells of the prostate and neuroendocrine differentiation in prostatic carcinoma: a review of morphologic aspects. Urology. 1998;51(5A Suppl):121-4. doi: 10.1016/s0090-4295(98)00064-8.

37. Lamont KR, Tindall DJ. Chapter 5 - Androgen Regulation of Gene Expression. In: Vande Woude GF, Klein G, editors. Advances in Cancer Research. 107: Academic Press; 2010. p. 137-62.

38. Walters KA, Simanainen U, Handelsman DJ. Molecular insights into androgen actions in male and female reproductive function from androgen receptor knockout models. Hum Reprod Update. 2010;16(5):543-58. doi: 10.1093/humupd/dmq003.

39. Swerdloff RS, Dudley RE, Page ST, Wang C, Salameh WA. Dihydrotestosterone: Biochemistry, Physiology, and Clinical Implications of Elevated Blood Levels. Endocr Rev. 2017;38(3):220-54. doi: 10.1210/er.2016-1067.

40. Kaprara A, Huhtaniemi IT. The hypothalamus-pituitary-gonad axis: Tales of mice and men. Metabolism. 2018;86:3-17. doi: 10.1016/j.metabol.2017.11.018.

41. Fiers T, Wu F, Moghetti P, Vanderschueren D, Lapauw B, Kaufman J-M. Reassessing Free-Testosterone Calculation by Liquid Chromatography ─ Tandem Mass Spectrometry Direct Equilibrium Dialysis. J Clin Endocrinol Metab. 2018;103(6):2167-74. doi: 10.1210/jc.2017-02360.

42. Hammond GL. Plasma steroid-binding proteins: primary gatekeepers of steroid hormone action. J Endocrinol. 2016;230(1):R13-R25. doi: 10.1530/joe-16-0070.

43. Bain J. The many faces of testosterone. Clin Interv Aging. 2007;2(4):567-76. doi: 10.2147/CIA.S1417.

44. Brodsky IG, Balagopal P, Nair KS. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men - a clinical research center study. J Clin Endocrinol Metab. 1996;81(10):3469-75. doi: 10.1210/jcem.81.10.8855787.

45. Pike CJ, Nguyen T-VV, Ramsden M, Yao M, Murphy MP, Rosario ER. Androgen cell signaling pathways involved in neuroprotective actions. Horm Behav. 2008;53(5):693-705. doi: 10.1016/j.yhbeh.2007.11.006.

46. Ferlin A, Selice R, Carraro U, Foresta C. Testicular function and bone metabolism ─ beyond testosterone. Nat Rev Endocrinol. 2013;9(9):548-54. doi: 10.1038/nrendo.2013.135.

47. Kelly DM, Jones TH. Testosterone: a metabolic hormone in health and disease. J Endocrinol. 2013;217(3):R25-45. doi: 10.1530/JOE-12-0455.

48. Lee SH, Shen MM. Cell types of origin for prostate cancer. Curr Opin Cell Biol. 2015;37:35-41. doi: 10.1016/j.ceb.2015.10.002.

49. Fine SW. Neuroendocrine tumors of the prostate. Mod Pathol. 2018;31(1):122-32. doi: 10.1038/modpathol.2017.164.

50. Bader DA, McGuire SE. Tumour metabolism and its unique properties in prostate adenocarcinoma. Nat Rev Urol. 2020;17(4):214-31. doi: 10.1038/s41585-020-0288-x.

51. Gottlieb B, Beitel LK, Nadarajah A, Paliouras M, Trifiro M. The androgen receptor gene mutations database: 2012 update. Hum Mutat. 2012;33(5):887-94. doi: 10.1002/humu.22046.

52. Humphrey PA. Histopathology of Prostate Cancer. Cold Spring Harb Perspect Med. 2017;7(10):a030411. doi: 10.1101/cshperspect.a030411.

53. Nelson WG, Antonarakis ES, Carter HB, De Marzo AM, DeWeese TL. 81 - Prostate Cancer. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, editors. Abeloff's Clinical Oncology (Sixth Edition). Philadelphia: Elsevier; 2020. p. 1401-32.e7.

54. Huggins C, Hodges CV. Studies on prostatic cancer. I. The effect of castration, of estrogen and androgen injection on serum phosphatases in metastatic carcinoma of the prostate. CA Cancer J Clin. 1972;22(4):232-40. doi: 10.3322/canjclin.22.4.232.

55. Carpenter V, Saleh T, Min Lee S, Murray G, Reed J, Souers A, et al. Androgen-deprivation induced senescence in prostate cancer cells is permissive for the development of castration-resistance but susceptible to senolytic therapy. Biochem Pharmacol. 2021;193:114765. doi: 10.1016/j.bcp.2021.114765.

56. Castaneda M, den Hollander P, Kuburich NA, Rosen JM, Mani SA. Mechanisms of cancer metastasis. Seminars in Cancer Biology. 2022;87:17-31. doi: 10.1016/j.semcancer.2022.10.006.

57. Halabi S, Kelly WK, Ma H, Zhou H, Solomon NC, Fizazi K, et al. Meta-Analysis Evaluating the Impact of Site of Metastasis on Overall Survival in Men With Castration-Resistant Prostate Cancer. J Clin Oncol. 2016;34(14):1652-9. doi: 10.1200/jco.2015.65.7270.

58. Clarke NW, Hart CA, Brown MD. Molecular mechanisms of metastasis in prostate cancer. Asian J Androl. 2009;11(1):57-67. doi: 10.1038/aja.2008.29.

59. Berish RB, Ali AN, Telmer PG, Ronald JA, Leong HS. Translational models of prostate cancer bone metastasis. Nat Rev Urol. 2018;15(7):403-21. doi: 10.1038/s41585-018-0020-2.

60. Jacob A, Raj R, Allison DB, Myint ZW. Androgen Receptor Signaling in Prostate Cancer and Therapeutic Strategies. Cancers (Basel). 2021;13(21). doi: 10.3390/cancers13215417.

61. Jadvar H, Velez EM, Desai B, Ji L, Colletti PM, Quinn DI. Prediction of Time to Hormonal Treatment Failure in Metastatic Castration-Sensitive Prostate Cancer with 18F-FDG PET/CT. J Nucl Med. 2019;60(11):1524-30. doi: 10.2967/jnumed.118.223263.

62. Montgomery RB, Mostaghel EA, Vessella R, Hess DL, Kalhorn TF, Higano CS, et al. Maintenance of Intratumoral Androgens in Metastatic Prostate Cancer: A Mechanism for Castration-Resistant Tumor Growth. Cancer Res. 2008;68(11):4447-54. doi: 10.1158/0008-5472.CAN-08-0249.

63. Siegel RL, Miller KD, Wagle NS, Jemal A. Cancer statistics, 2023. CA Cancer J Clin. 2023;73(1):17-48. doi: 10.3322/caac.21763.

64. Robert Koch-Institut, Gesellschaft der epidemiologischen Krebsregister in Deutschland e.V. Krebs in Deutschland 2015/2016. 2019. doi: 10.25646/5977.3.

65. Soerjomataram I, Lortet-Tieulent J, Parkin DM, Ferlay J, Mathers C, Forman D, et al. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. Lancet. 2012;380(9856):1840-50. doi: 10.1016/S0140-6736(12)60919-2.

66. Gandaglia G, Leni R, Bray F, Fleshner N, Freedland SJ, Kibel A, et al. Epidemiology and Prevention of Prostate Cancer. Eur Urol Oncol. 2021;4(6):877-92. doi: 10.1016/j.euo.2021.09.006.

67. Brandt A, Bermejo JL, Sundquist J, Hemminki K. Age-specific risk of incident prostate cancer and risk of death from prostate cancer defined by the number of affected family members. Eur Urol. 2010;58(2):275-80. doi: 10.1016/j.eururo.2010.02.002.

68. Clements MB, Vertosick EA, Guerrios-Rivera L, De Hoedt AM, Hernandez J, Liss MA, et al. Defining the Impact of Family History on Detection of High-grade Prostate Cancer in a Large Multi-institutional Cohort. Eur Urol. 2022;82(2):163-9. doi: 10.1016/j.eururo.2021.12.011.

69. Vietri MT, D'Elia G, Caliendo G, Resse M, Casamassimi A, Passariello L, et al. Hereditary Prostate Cancer: Genes Related, Target Therapy and Prevention. Int J Mol Sci. 2021;22(7). doi: 10.3390/ijms22073753.

70. Bergengren O, Pekala KR, Matsoukas K, Fainberg J, Mungovan SF, Bratt O, et al. 2022 Update on Prostate Cancer Epidemiology and Risk Factors - A Systematic Review. Eur Urol. 2023;84(2):191-206. doi: 10.1016/j.eururo.2023.04.021.

71. Siegel DA, O'Neil ME, Richards TB, Dowling NF, Weir HK. Prostate Cancer Incidence and Survival, by Stage and Race/Ethnicity - United States, 2001-2017. MMWR Morb Mortal Wkly Rep. 2020;69(41):1473-80. doi: 10.15585/mmwr.mm6941a1.

72. Ilic D, Neuberger MM, Djulbegovic M, Dahm P. Screening for prostate cancer. Cochrane Database Syst Rev. 2013;2013(1):CD004720. doi: 10.1002/14651858.CD004720.pub3.

73. Welch HG, Albertsen PC. Reconsidering Prostate Cancer Mortality ─ The Future of PSA Screening. N Engl J Med. 2020;382(16):1557-63. doi: 10.1056/NEJMms1914228.

74. Starker A, Buttmann-Schweiger N, Krause L, Barnes B, Kraywinkel K, Holmberg C. [Cancer screening in Germany: availability and participation]. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2018;61(12):1491-9. doi: 10.1007/s00103-018-2842-8.

75. Mottet N, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer-2020 Update. Part 1: Screening, Diagnosis, and Local Treatment with Curative Intent. Eur Urol. 2021;79(2):243-62. doi: 10.1016/j.eururo.2020.09.042.

76. Stephan C, Ralla B, Jung K. Prostate-specific antigen and other serum and urine markers in prostate cancer. Biochim Biophys Acta Rev Cancer. 2014;1846(1):99-112. doi: 10.1016/j.bbcan.2014.04.001.

77. Epstein JI, Egevad L, Amin MB, Delahunt B, Srigley JR, Humphrey PA, et al. The 2014 International Society of Urological Pathology (ISUP) Consensus Conference on Gleason Grading of Prostatic Carcinoma: Definition of Grading Patterns and Proposal for a New Grading System. Am J Surg Pathol. 2016;40(2):244-52. doi: 10.1097/pas.0000000000000530.

78. Kweldam CF, van Leenders GJ, van der Kwast T. Grading of prostate cancer: a work in progress. Histopathology. 2019;74(1):146-60. doi: 10.1111/his.13767.

79. Basha MAA, Hamed MAG, Hussein O, El-Diasty T, Abdelkhalek YI, Hussein YO, et al. 68Ga-PSMA-11 PET/CT in newly diagnosed prostate cancer: diagnostic sensitivity and interobserver agreement. Abdom Radiol. 2019;44(7):2545-56. doi: 10.1007/s00261-019-02006-2.

80. Cheng L, Montironi R, Bostwick DG, Lopez-Beltran A, Berney DM. Staging of prostate cancer. Histopathology. 2012;60(1):87-117. doi: 10.1111/j.1365-2559.2011.04025.x.

81. Brierley JD, Gospodarowicz MK, Wittekind C. TNM classification of malignant tumours. 8th Edition ed. Oxford: John Wiley & Sons; 2017.

82. Anast JW, Andriole GL, Grubb RL. Managing the local complications of locally advanced prostate cancer. Curr Urol Rep. 2007;8(3):211-6. doi: 10.1007/s11934-007-0008-6.

83. McMurtry CT, McMurtry JM. Metastatic Prostate Cancer: Complications and Treatment. J Am Geriatr Soc. 2003;51(8):1136-42. doi: 10.1046/j.1532-5415.2003.51367.x.

84. Saad F, Pouliot F, Danielson B, Catton C, Kapoor A. Symptom assessment to guide treatment selection and determine progression in metastatic castration-resistant prostate cancer: Expert opinion and review of the evidence. Can Urol Assoc J. 2018;12(9):E415-E20. doi: 10.5489/cuaj.5154.

85. Hamdy FC, Donovan JL, Lane JA, Mason M, Metcalfe C, Holding P, et al. Active monitoring, radical prostatectomy and radical radiotherapy in PSA-detected clinically localised prostate cancer: the ProtecT three-arm RCT. Health Technol Assess. 2020;24(37):1-176. doi: 10.3310/hta24370.

86. Van den Broeck T, van den Bergh RCN, Briers E, Cornford P, Cumberbatch M, Tilki D, et al. Biochemical Recurrence in Prostate Cancer: The European Association of Urology Prostate Cancer Guidelines Panel Recommendations. Eur Urol Focus. 2020;6(2):231-4. doi: 10.1016/j.euf.2019.06.004.

87. Cornford P, van den Bergh RCN, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, et al. EAU-EANM-ESTRO-ESUR-SIOG Guidelines on Prostate Cancer. Part II — 2020 Update: Treatment of Relapsing and Metastatic Prostate Cancer. Eur Urol. 2021;79(2):263-82. doi: 10.1016/j.eururo.2020.09.046.

88. Oefelein MG, Feng A, Scolieri MJ, Ricchiutti D, Resnick MI. Reassessment of the definition of castrate levels of testosterone: implications for clinical decision making. Urology. 2000;56(6):1021-4. doi: 10.1016/S0090-4295(00)00793-7.

89. Becker B, Stroever S, Reddy A, Riese WTW. Comparison of Intermittent and Continuous Androgen Deprivation Therapy in Prostate Cancer Patients: An Up-to-Date Meta-analysis for Urologists and Medical Providers. Urol Pract. 2023;10(5):424-34. doi: 10.1097/UPJ.0000000000000424.

90. Fizazi K, Tran N, Fein L, Matsubara N, Rodriguez-Antolin A, Alekseev BY, et al. Abiraterone acetate plus prednisone in patients with newly diagnosed high-risk metastatic castration-sensitive prostate cancer (LATITUDE): final overall survival analysis of a randomised, double-blind, phase 3 trial. Lancet Oncol. 2019;20(5):686-700. doi: 10.1016/S1470-2045(19)30082-8.

91. Sweeney CJ, Martin AJ, Stockler MR, Begbie S, Cheung L, Chi KN, et al. Testosterone suppression plus enzalutamide versus testosterone suppression plus standard antiandrogen therapy for metastatic hormone-sensitive prostate cancer (ENZAMET): an international, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(4):323-34. doi: 10.1016/S1470-2045(23)00063-3.

92. Chi KM, Chowdhury S, Bjartell A, Chung BH, Pereira de Santana Gomes AJ, Given R, et al. Apalutamide in Patients With Metastatic Castration-Sensitive Prostate Cancer: Final Survival Analysis of the Randomized, Double-Blind, Phase III TITAN Study. J Clin Oncol. 2021;39(20):2294-303. doi: 10.1200/JCO.20.03488.

93. Kyriakopoulos CE, Chen YH, Carducci MA, Liu G, Jarrard DF, Hahn NM, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer: Long-Term Survival Analysis of the Randomized Phase III E3805 CHAARTED Trial. J Clin Oncol. 2018;36(11):1060-1. doi: 10.1200/JCO.2017.75.3657.

94. Clarke NW, Ali A, Ingleby FC, Hoyle A, Amos CL, Attard G, et al. Addition of docetaxel to hormonal therapy in low- and high-burden metastatic hormone sensitive prostate cancer: long-term survival results from the STAMPEDE trial. Ann Oncol. 2019;30(12):1992-2003. doi: 10.1093/annonc/mdz396.

95. Gravis G, Boher J-M, Joly F, Soulié M, Albiges L, Priou F, et al. Androgen Deprivation Therapy (ADT) Plus Docetaxel Versus ADT Alone in Metastatic Non castrate Prostate Cancer: Impact of Metastatic Burden and Long-term Survival Analysis of the Randomized Phase 3 GETUG-AFU15 Trial. Eur Urol. 2016;70(2):256-62. doi: 10.1016/j.eururo.2015.11.005.

96. Wenzel M, Nocera L, Collà Ruvolo C, Würnschimmel C, Tian Z, Shariat SF, et al. Overall survival and adverse events after treatment with darolutamide vs. apalutamide vs. enzalutamide for high-risk non-metastatic castration-resistant prostate cancer: a systematic review and network meta-analysis. Prostate Cancer and Prostatic Dis. 2022;25(2):139-48. doi: 10.1038/s41391-021-00395-4.

97. Kawahara T, Saigusa Y, Yoneyama S, Kato M, Kojima I, Yamada H, et al. Development and validation of a survival nomogram and calculator for male patients with metastatic castration-resistant prostate cancer treated with abiraterone acetate and/or enzalutamide. BMC Cancer. 2023;23(1):214. doi: 10.1186/s12885-023-10700-0.

98. Freedland SJ, Davis M, Epstein AJ, Arondekar B, Ivanova JI. Real-world treatment patterns and overall survival among men with Metastatic Castration-Resistant Prostate Cancer (mCRPC) in the US Medicare population. Prostate Cancer and Prostatic Dis. 2023. doi: 10.1038/s41391-023-00725-8.

99. Armstrong AJ, Lin P, Tombal B, Saad F, Higano CS, Joshua AM, et al. Five-year Survival Prediction and Safety Outcomes with Enzalutamide in Men with Chemotherapy-naive

Metastatic Castration-resistant Prostate Cancer from the PREVAIL Trial. Eur Urol. 2020;78(3):347-57. doi: 10.1016/j.eururo.2020.04.061.

100. Nuhn P, De Bono JS, Fizazi K, Freedland SJ, Grilli M, Kantoff PW, et al. Update on Systemic Prostate Cancer Therapies: Management of Metastatic Castration-resistant Prostate Cancer in the Era of Precision Oncology. Eur Urol. 2019;75(1):88-99. doi: 10.1016/j.eururo.2018.03.028.

101. de Bono JS, Oudard S, Ozguroglu M, Hansen Sr, Machiels J-P, Kocak I, et al. Prednisone plus cabazitaxel or mitoxantrone for metastatic castration-resistant prostate cancer progressing after docetaxel treatment: a randomised open-label trial. Lancet. 2010;376(9747):1147-54. doi: 10.1016/S0140-6736(10)61389-X.

102. de Bono JS, Logothetis CJ, Molina A, Fizazi K, North S, Chu L, et al. Abiraterone and increased survival in metastatic prostate cancer. N Engl J Med. 2011;364(21):1995-2005. doi: 10.1056/NEJMoa1014618.

103. Scher HI, Fizazi K, Saad F, Taplin M-E, Sternberg CN, Miller K, et al. Increased Survival with Enzalutamide in Prostate Cancer after Chemotherapy. N Engl J Med. 2012;367(13):1187-97. doi: 10.1056/NEJMoa1207506.

104. Ryan CJ, Smith MR, Fizazi K, Saad F, Mulders PFA, Sternberg CN, et al. Abiraterone acetate plus prednisone versus placebo plus prednisone in chemotherapy-naive men with metastatic castration-resistant prostate cancer (COU-AA-302): final overall survival analysis of a randomised, double-blind, placebo-controlled phase 3 study. Lancet Oncol. 2015;16(2):152-60. doi: 10.1016/S1470-2045(14)71205-7.

105. Beer TM, Armstrong AJ, Rathkopf D, Loriot Y, Sternberg CN, Higano CS, et al. Enzalutamide in Men with Chemotherapy-naive Metastatic Castration-resistant Prostate Cancer: Extended Analysis of the Phase 3 PREVAIL Study. Eur Urol. 2017;71(2):151-4. doi: 10.1016/j.eururo.2016.07.032.

106. Mateo J, Carreira S, Sandhu S, Miranda S, Mossop H, Perez-Lopez R, et al. DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer. N Engl J Med. 2015;373(18):1697-708. doi: 10.1056/NEJMoa1506859.

107. Hussain M, Mateo J, Fizazi K, Saad F, Shore N, Sandhu S, et al. Survival with Olaparib in Metastatic Castration-Resistant Prostate Cancer. N Engl J Med. 2020;383(24):2345-57. doi: 10.1056/NEJMoa2022485

108. Hegemann M, Bedke J, Stenzl A, Todenhöfer T. Denosumab treatment in the management of patients with advanced prostate cancer: clinical evidence and experience. Ther Adv Urol. 2017;9(3-4):81-8. doi: 10.1177/1756287216686018.

109. Iversen P, G. MD, See WA, Morris T, Armstrong J, Wirth MP, et al. Antiandrogen monotherapy in patients with localized or locally advanced prostate cancer: final results from the bicalutamide Early Prostate Cancer programme at a median follow-up of 9.7 years. BJU Int. 2010;105(8):1074-81. doi: 10.1111/j.1464-410X.2010.09319.x.

110. See W, Iversen P, Wirth M, McLeod D, Garside L, Morris T. Immediate Treatment with Bicalutamide 150mg as Adjuvant Therapy Significantly Reduces the Risk of PSA Progression in Early Prostate Cancer. Eur Urol. 2003;44(5):512-8. doi: 10.1016/S0302-2838(03)00366-X.

111. Capper CP, Rae JM, Auchus RJ. The Metabolism, Analysis, and Targeting of Steroid Hormones in Breast and Prostate Cancer. Horm Cancer. 2016;7(3):149-64. doi: 10.1007/s12672-016-0259-0.

112. He Y, Xu W, Xiao YT, Huang H, Gu D, Ren S. Targeting signaling pathways in prostate cancer: mechanisms and clinical trials. Signal Transduct Target Ther. 2022;7(1):198. doi: 10.1038/s41392-022-01042-7.

113. Schröder F, Crawford ED, Axcrona K, Payne H, Keane TE. Androgen deprivation therapy: past, present and future. BJU Int. 2012;109:1-12. doi: 10.1111/j.1464-410X.2012.11215.x.

114. Desai K, McManus JM, Sharifi N. Hormonal Therapy for Prostate Cancer. Endocr Rev. 2021;42(3):354-73. doi: 10.1210/endrev/bnab002.

115. Conn PM, Crowley WF. Gonadotropin-Releasing Hormone and Its Analogues. N Engl J Med. 1991;324(2):93-103. doi: 10.1056/nejm199101103240205.

116. Kittai AS, Blank J, Graff JN. Gonadotropin-Releasing Hormone Antagonists in Prostate Cancer. Oncology (Williston Park). 2018;32(12):604-6.

117. Van Poppel H, Abrahamsson P-A. Considerations for the use of gonadotropin-releasing hormone agonists and antagonists in patients with prostate cancer. Int J Urol. 2020;27:830-7. doi: 10.1111/iju.14303.

118. U.S. Food and Drug Administration. FDA approves relugolix for advanced prostate cancer [updated 18.12.2020; cited 28.01.2024]. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-relugolix-advanced-prostate-cancer.

119. European Medicines Agency. Orgovyx [updated 21.12.2023; cited 28.01.2024]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/orgovyx.

120. Tran C, Ouk S, Clegg NJ, Chen Y, Watson PA, Arora V, et al. Development of a Second-Generation Antiandrogen for Treatment of Advanced Prostate Cancer. Science. 2009;324(5928):787-90. doi: 10.1126/science.1168175.

121. Bubley GJ, Balk SP. Association Between Androgen Receptor Splice Variants and Prostate Cancer Resistance to Abiraterone and Enzalutamide. J Clin Oncol. 2017;35(19):2103-5. doi: 10.1200/jco.2017.72.8808.

122. Alex AB, Pal SK, Agarwal N. CYP17 inhibitors in prostate cancer: latest evidence and clinical potential. Ther Adv Med Oncol. 2016;8(4):267-75. doi: 10.1177/1758834016642370.

123. Boukovala M, Spetsieris N, Efstathiou E. Systemic Treatment of Prostate Cancer in Elderly Patients: Current Role and Safety Considerations of Androgen-Targeting Strategies. Drugs Aging. 2019;36(8):701-17. doi: 10.1007/s40266-019-00677-6.

124. Schweizer MT, Gulati R, Mostaghel EA, Nelson PS, Montgomery RB, Yu EY, et al. Docetaxel-related toxicity in metastatic hormone-sensitive and metastatic castration-resistant prostate cancer. Med Oncol. 2016;33(7):77. doi: 10.1007/s12032-016-0793-1.

125. Chang C, Yeh S, Lee SO, Chang TM. Androgen receptor (AR) pathophysiological roles in androgen-related diseases in skin, bone/muscle, metabolic syndrome and neuron/immune systems: lessons learned from mice lacking AR in specific cells. Nucl Recept Signal. 2013;11:e001. doi: 10.1621/nrs.11001.

126. Sutinen P, Malinen M, Palvimo JJ. Androgen Receptor. In: Simoni M, Huhtaniemi IT, editors. Endocrinology of the Testis and Male Reproduction. Cham: Springer International Publishing AG; 2017.

127. Rizk J, Sahu R, Duteil D. An overview on androgen-mediated actions in skeletal muscle and adipose tissue. Steroids. 2023;199:109306. doi: 10.1016/j.steroids.2023.109306.

128. White JP, Gao S, Puppa MJ, Sato S, Welle SL, Carson JA. Testosterone regulation of Akt/mTORC1/FoxO3a signaling in skeletal muscle. Mol Cell Endocrinol. 2013;365(2):174-86. doi: 10.1016/j.mce.2012.10.019.

129. Galvao DA, Spry NA, Taaffe DR, Newton RU, Stanley J, Shannon T, et al. Changes in muscle, fat and bone mass after 36 weeks of maximal androgen blockade for prostate cancer. BJU Int. 2008;102(1):44-7. doi: 10.1111/j.1464-410X.2008.07539.x.

130. Smith MR, Saad F, Egerdie B, Sieber PR, Tammela TL, Ke C, et al. Sarcopenia during androgen-deprivation therapy for prostate cancer. J Clin Oncol. 2012;30(26):3271-6. doi: 10.1200/JCO.2011.38.8850.

131. Galvao DA, Taaffe DR, Spry N, Joseph D, Turner D, Newton RU. Reduced muscle strength and functional performance in men with prostate cancer undergoing androgen suppression: a comprehensive cross-sectional investigation. Prostate Cancer Prostatic Dis. 2009;12(2):198-203. doi: 10.1038/pcan.2008.51.

132. Kimura Y, Yamada M, Ohji S, Ishiyama D, Nishio N, Otobe Y, et al. Presence of sarcopenic obesity and evaluation of the associated muscle quality in Japanese older men with prostate cancer undergoing androgen deprivation therapy. J Geriatr Oncol. 2019;10(5):835-8. doi: 10.1016/j.jgo.2019.03.017.

133. Haseen F, Murray LJ, Cardwell CR, O'Sullivan JM, Cantwell MM. The effect of androgen deprivation therapy on body composition in men with prostate cancer: systematic review and meta-analysis. J Cancer Surviv. 2010;4(2):128-39. doi: 10.1007/s11764-009-0114-1.

134. Hamilton EJ, Gianatti E, Strauss BJ, Wentworth J, Lim-Joon D, Bolton D, et al. Increase in visceral and subcutaneous abdominal fat in men with prostate cancer treated with androgen deprivation therapy. Clin Endocrinol. 2011;74(3):377-83. doi: 10.1111/j.1365-2265.2010.03942.x.

135. Di Lorenzo G, Autorino R, Perdonà S, De Placido S. Management of gynaecomastia in patients with prostate cancer: a systematic review. Lancet Oncol. 2005;6(12):972-9. doi: 10.1016/S1470-2045(05)70464-2.

136. Kim DK, Lee JY, Kim KJ, Hong N, Kim JW, Hah YS, et al. Effect of Androgen-Deprivation Therapy on Bone Mineral Density in Patients with Prostate Cancer: A Systematic Review and Meta-Analysis. J Clin Med. 2019;8(1):113. doi: 10.3390/jcm8010113.

137. Maillefert JF, J. S, Michel F, Saussine C, Javier RM, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol. 1999;161(4):1219-22.

138. Ioannidis G, Papaioannou A, Hopman WM, Akhtar-Danesh N, Anastassiades T, Pickard L, et al. Relation between fractures and mortality: results from the Canadian Multicentre Osteoporosis Study. CMAJ. 2009;181(5):265-71. doi: 10.1503/cmaj.081720.

139. Iki M, Fujita Y, Tamaki J, Kouda K, Yura A, Sato Y, et al. Incident fracture associated with increased risk of mortality even after adjusting for frailty status in elderly Japanese men: the Fujiwara-kyo Osteoporosis Risk in Men (FORMEN) Cohort Study. Osteoporosis Int. 2017;28(3):871-80. doi: 10.1007/s00198-016-3797-y.

140. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, Sforza A, et al. Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. Eur J Endocrinol. 2011;165(5):687-701. doi: 10.1530/EJE-11-0447.

141. Ohlsson C, Barrett-Connor E, Bhasin S, Orwoll E, Labrie F, Karlsson MK, et al. High serum testosterone is associated with reduced risk of cardiovascular events in elderly men: the MrOS (Osteoporotic Fractures in Men) study in Sweden. J Am Coll Cardiol. 2011;58(16):1674-81. doi: 10.1016/j.jacc.2011.07.019.

142. Keating NL, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. J Clin Oncol. 2006;24(27):4448-56. doi: 10.1200/JCO.2006.06.2497.

143. O'Farrell S, Garmo H, Holmberg L, Adolfsson J, Stattin P, Van Hemelrijck M. Risk and timing of cardiovascular disease after androgen-deprivation therapy in men with prostate cancer. J Clin Oncol. 2015;33(11):1243-51. doi: 10.1200/JCO.2014.59.1792.

144. Chen D-Y, Lee C-H, Tsai M-L, Hsieh M-J, Chuang C-K, Pang S-T, et al. Cancer Therapy-Related Cardiac Dysfunction in Patients With Prostate Cancer Undergoing Androgen Deprivation Therapy. J Am Heart Assoc. 2023;12(19):e030447. doi: 10.1161/JAHA.123.030447.

145. Keating NL, O'Malley AJ, Freedland SJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy: observational study of veterans with prostate cancer. J Natl Cancer Inst. 2010;102(1):39-46. doi: 10.1093/jnci/djp404.

146. Hu JC, Williams SB, O'Malley AJ, Smith MR, Nguyen PL, Keating NL. Androgen-deprivation therapy for nonmetastatic prostate cancer is associated with an increased risk of peripheral arterial disease and venous thromboembolism. Eur Urol. 2012;61(6):1119-28. doi: 10.1016/j.eururo.2012.01.045.

147. Dolmatova E, Waheed N, Olson BM, Patel SA, Mandawat A. The Intersection of Prostate Cancer and Hypertension: a Call to Action. Curr Treat Options Oncol. 2023;24(7):892-905. doi: 10.1007/s11864-023-01094-z.

148. Stilley JA, Guan R, Duffy DM, Segaloff DL. Signaling through FSH receptors on human umbilical vein endothelial cells promotes angiogenesis. J Clin Endocrinol Metab. 2013;99(5):E813-20. doi: 10.1210/jc.2013-3186

149. Expert Panel on Detection, Evaluation, Treatment of High Blood Cholesterol in Adults,. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA. 2001;285(19):2486-97. doi: 10.1001/jama.285.19.2486.

150. Braga-Basaria M, Dobs AS, Muller DC, Carducci MA, John M, Egan J, et al. Metabolic syndrome in men with prostate cancer undergoing long-term androgen-deprivation therapy. J Clin Oncol. 2006;24(24):3979-83. doi: 10.1200/JCO.2006.05.9741.

151. Zhu X, Wu S. Risk of hypertension in Cancer patients treated with Abiraterone: a meta-analysis. Clin Hypertens. 2019;25:5. doi: 10.1186/s40885-019-0110-3

152. Zhu X, Wu S. Increased Risk of Hypertension with Enzalutamide in Prostate Cancer: A Meta-Analysis. Cancer Invest. 2019;37(9):478-88. doi: 10.1080/07357907.2019.1670203.

153. Huang YT, Li CC, Chou YH, Ke HL, Chen CY. Health-related quality of life of exposed versus non-exposed androgen deprivation therapy patients with prostate cancer: a cross-sectional study. Int J Clin Pharm. 2019;41(4):993-1003. doi: 10.1007/s11096-019-00854-y.

154. Dacal K, Sereika SM, Greenspan SL. Quality of life in prostate cancer patients taking androgen deprivation therapy. J Am Geriatr Soc. 2006;54(1):85-90. doi: 10.1111/j.1532-5415.2005.00567.x.

155. Alibhai SM, Breunis H, Timilshina N, Naglie G, Tannock I, Krahn M, et al. Long-term impact of androgen-deprivation therapy on physical function and quality of life. Cancer. 2015;121(14):2350-7. doi: 10.1002/cncr.29355.

156. Bower JE. Cancer-related fatigue — mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014;11(10):597-609. doi: 10.1038/nrclinonc.2014.127.

157. Rodriguez Antolin A, Martinez-Pineiro L, Jimenez Romero ME, Garcia Ramos JB, Lopez Bellido D, Munoz Del Toro J, et al. Prevalence of fatigue and impact on quality of life in castration-resistant prostate cancer patients: the VITAL study. BMC Urol. 2019;19(1):92. doi: 10.1186/s12894-019-0527-8.

158. Ternov KK, Sønksen J, Fode M, Lindberg H, Kistorp C, Bisbjerg R, et al. Fatigue, health-related quality-of-life and metabolic changes in men treated with enzalutamide or abiraterone acetate plus prednisone for metastatic castration-resistant prostate cancer: A randomised clinical trial (HEAT). Eur J Cancer. 2022;171:75-84. doi: 10.1016/j.ejca.2022.04.034.

159. Agarwal N, McQuarrie K, Bjartell A, Chowdhury S, Pereira de Santana Gomes AJ, Chung BH, et al. Apalutamide plus Androgen Deprivation Therapy for Metastatic Castration-Sensitive Prostate Cancer: Analysis of Pain and Fatigue in the Phase 3 TITAN Study. J Urol. 2021;206(4):914-23. doi: 10.1097/JU.0000000000001841

160. Jones JM, Kohli M, Loprinzi CL. Androgen deprivation therapy-associated vasomotor symptoms. Asian J Androl. 2012;14(2):193-7. doi: 10.1038/aja.2011.101.

161. Corona G, Filippi S, Comelio P, Bianchi N, Frizza F, Dicuio M, et al. Sexual function in men undergoing androgen deprivation therapy. Int J Impot Res. 2021;33(4):439-47. doi: 10.1038/s41443-021-00418-7.

162. Holtfrerich SKC, Knipper S, Purwins J, Castens J, Beyer B, Schlomm T, et al. The impact of long-term androgen deprivation therapy on cognitive function and socioeconomic

decision making in prostate cancer patients. Psychooncology. 2020;29(8):1338-46. doi: 10.1002/pon.5442.

163. Huang SW, Chen LC, Tseng CS, Chen CH, Yuan LH, Shau WY, et al. Risk of cognitive impairment in men with advanced prostate cancer treated with NHAs: A systematic review and network meta-analysis. Clin Transl Sci. 2023;16(2):313-25. doi: 10.1111/cts.13451.

164. Jones LW, Eves ND, Haykowsky M, Freedland SJ, Mackey JR. Exercise intolerance in cancer and the role of exercise therapy to reverse dysfunction. Lancet Oncol. 2009;10(6):598-605. doi: 10.1016/S1470-2045(09)70031-2.

165. Aversa Z, Costelli P, Muscaritoli M. Cancer-induced muscle wasting: latest findings in prevention and treatment. Ther Adv Med Oncol. 2017;9(5):369-82. doi: 10.1177/1758834017698643.

166. Gong J, Payne D, Caron J, Bay CP, McGregor BA, Hainer J, et al. Reduced Cardiorespiratory Fitness and Increased Cardiovascular Mortality After Prolonged Androgen Deprivation Therapy for Prostate Cancer. JACC CardioOncol. 2020;2(4):553-63. doi: 10.1016/j.jaccao.2020.08.011.

167. Gourdin T. Recent progress in treating advanced prostate cancer. Curr Opin Oncol. 2020;32(3):210-5. doi: 10.1097/CCO.0000000000000624.

168. Myint ZW, Momo HD, Otto DE, Yan D, Wang P, Kolesar JM. Evaluation of Fall and Fracture Risk Among Men With Prostate Cancer Treated With Androgen Receptor Inhibitors: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(11):e2025826. doi: 10.1001/jamanetworkopen.2020.25826.

169. Hanson ED, Stopforth CK, Alzer M, Carver J, Lucas AR, Whang YE, et al. Body composition, physical function and quality of life in healthy men and across different stages of prostate cancer. Prostate Cancer Prostatic Dis. 2021;24(3):725-32. doi: 10.1038/s41391-020-00317-w.

170. Morgans AK, Renzulli J, 2nd, Olivier K, Shore ND. Risk of Cognitive Effects in Comorbid Patients With Prostate Cancer Treated With Androgen Receptor Inhibitors. Clin Genitourin Cancer. 2021;19(5):467 e1- e11. doi: 10.1016/j.clgc.2021.03.014.

171. Parkin J, Cohen B. An overview of the immune system. Lancet. 2001;357(9270):1777-89. doi: 10.1016/S0140-6736(00)04904-7.

172. Coussens LM, Werb Z. Inflammation and cancer. Nature. 2002;420(6917):860-7. doi: 10.1038/nature01322.

173. Das D, Karthik N, Taneja R. Crosstalk Between Inflammatory Signaling and Methylation in Cancer. Front Cell Dev Biol. 2021;9:756458. doi: 10.3389/fcell.2021.756458.

174. Nicholson LB. The immune system. Essays Biochem. 2016;60(3):275-301. doi: 10.1042/EBC20160017.

175. Van Parijs L, Abbas AK. Homeostasis and self-tolerance in the immune system: turning lymphocytes off. Science. 1998;280(5361):243-8.

176. Kawai T, Akira S. Innate immune recognition of viral infection. Nat Immunol. 2006;7(2):131-7. doi: 10.1038/ni1303.

177. Sim MJW, Sun PD. T Cell Recognition of Tumor Neoantigens and Insights Into T Cell Immunotherapy. Front Immunol. 2022;13. doi: 10.3389/fimmu.2022.833017.

178. Clark R, Kupper T. Old Meets New: The Interaction Between Innate and Adaptive Immunity. J Invest Dermatol. 2005;125(4):629-37. doi: 10.1111/j.0022-202X.2005.23856.x.

179. Janeway CAJ, Travers P, Walport M. Principles of innate and adaptive immunity. Immunobiology: The Immune System in Health and Disease. 5th ed. New York: Garland Science; 2001.

180. Charles A. Janeway J, Medzhitov R. Innate Immune Recognition. Annu Rev Immunol. 2002;20(1):197-216. doi: 10.1146/annurev.immunol.20.083001.084359.

181. Akira S, Uematsu S, Takeuchi O. Pathogen Recognition and Innate Immunity. Cell. 2006;124(4):783-801. doi: 10.1016/j.cell.2006.02.015.

182. Marshall JS, Warrington R, Watson W, Kim HL. An introduction to immunology and immunopathology. Allergy Asthma Clin Immunol. 2018;14(Suppl 2):49. doi: 10.1186/s13223-018-0278-1.

183. Bonilla FA, Oettgen HC. Adaptive immunity. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S33-40. doi: 10.1016/j.jaci.2009.09.017.

184. Harding CV, Unanue ER. Cellular mechanisms of antigen processing and the function of class I and II major histocompatibility complex molecules. Cell Regul. 1990;1(7):499-509. doi: 10.1091/mbc.1.7.499.

185. Mueller SN, Gebhardt T, Carbone FR, Heath WR. Memory T Cell Subsets, Migration Patterns, and Tissue Residence. Annu Rev Immunol. 2013;31(1):137-61. doi: 10.1146/annurev-immunol-032712-095954.

186. Cancro MP, Tomayko MM. Memory B cells and plasma cells: The differentiative continuum of humoral immunity. Immunol Rev. 2021;303(1):72-82. doi: 10.1111/imr.13016.

187. Chaplin DD. Overview of the immune response. J Allergy Clin Immunol. 2010;125(2 Suppl 2):S3-23. doi: 10.1016/j.jaci.2009.12.980.

188. Engel P, Boumsell L, Balderas R, Bensussan A, Gattei V, Horejsi V, et al. CD Nomenclature 2015: Human Leukocyte Differentiation Antigen Workshops as a Driving Force in Immunology. J Immunol. 2015;195(10):4555-63. doi: 10.4049/jimmunol.1502033.

189. Cumano A, Berthault C, Ramond C, Petit M, Golub R, Bandeira A, et al. New Molecular Insights into Immune Cell Development. Annu Rev Immunol. 2019;37(1):497-519. doi: 10.1146/annurev-immunol-042718-041319.

190. Romito A, Cobellis G. Pluripotent Stem Cells: Current Understanding and Future Directions. Stem Cells Int. 2016;2016:9451492. doi: 10.1155/2016/9451492.

191. Fang P, Li X, Dai J, Cole L, Camacho JA, Zhang Y, et al. Immune cell subset differentiation and tissue inflammation. J Hematol Oncol. 2018;11(1):97. doi: 10.1186/s13045-018-0637-x.

192. Dranoff G. Cytokines in cancer pathogenesis and cancer therapy. Nat Rev Cancer. 2004;4(1):11-22. doi: 10.1038/nrc1252.

193. Schmitz ML, Weber A, Roxlau T, Gaestel M, Kracht M. Signal integration, crosstalk mechanisms and networks in the function of inflammatory cytokines. Biochim Biophys Acta. 2011;1813(12):2165-75. doi: 10.1016/j.bbamcr.2011.06.019.

194. Thorner J, Hunter T, Cantley LC, Sever R. Signal transduction: From the atomic age to the post-genomic era. Cold Spring Harb Perspect Biol. 2014;6(12):a022913. doi: 10.1101/cshperspect.a022913.

195. Zhang JM, An J. Cytokines, inflammation, and pain. Int Anesthesiol Clin. 2007;45(2):27-37. doi: 10.1097/AIA.0b013e318034194e.

196. Jakubzick CV, Randolph GJ, Henson PM. Monocyte differentiation and antigen-presenting functions. Nat Rev Immunol. 2017;17(6):349-62. doi: 10.1038/nri.2017.28.

197. Song L, Dong G, Guo L, Graves DT. The function of dendritic cells in modulating the host response. Mol Oral Microbiol. 2018;33(1):13-21. doi: 10.1111/omi.12195.

198. Urb M, Sheppard DC. The role of mast cells in the defence against pathogens. PLoS Pathog. 2012;8(4):e1002619. doi: 10.1371/journal.ppat.1002619.

199. Acharya KR, Ackerman SJ. Eosinophil Granule Proteins: Form and Function. J Biol Chem. 2014;289(25):17406-15. doi: 10.1074/jbc.R113.546218.

200. Gatault S, Legrand F, Delbeke M, Loiseau S, Capron M. Involvement of eosinophils in the anti-tumor response. Cancer Immunol Immunother. 2012;61(9):1527-34. doi: 10.1007/s00262-012-1288-3.

201. Wu SY, Fu T, Jiang YZ, Shao ZM. Natural killer cells in cancer biology and therapy. Mol Cancer. 2020;19(1):120. doi: 10.1186/s12943-020-01238-x.

202. Pallmer K, Oxenius A. Recognition and Regulation of T Cells by NK Cells. Front Immunol. 2016;7. doi: 10.3389/fimmu.2016.00251.

203. Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. Trends Immunol. 2001;22(11):633-40. doi: 10.1016/s1471-4906(01)02060-9

204. Iwasaki A, Medzhitov R. Control of adaptive immunity by the innate immune system. Nat Immunol. 2015;16(4):343-53. doi: 10.1038/ni.3123.

205. Taniuchi I. CD4 Helper and CD8 Cytotoxic T Cell Differentiation. Annu Rev Immunol. 2018;36(1):579-601. doi: 10.1146/annurev-immunol-042617-053411.

206. Overgaard NH, Jung J-W, Steptoe RJ, Wells JW. CD4+/CD8+ double-positive T cells: more than just a developmental stage? J Leukoc Biol. 2015;97(1):31-8. doi: 10.1189/jlb.1RU0814-382.

207. Corthay A, Skovseth DK, Lundin KU, Røsjø E, Omholt H, Hofgaard PO, et al. Primary Antitumor Immune Response Mediated by CD4+ T Cells. Immunity. 2005;22(3):371-83. doi: 10.1016/j.immuni.2005.02.003.

208. Sackstein R, Schatton T, Barthel SR. T-lymphocyte homing: an underappreciated yet critical hurdle for successful cancer immunotherapy. Lab Invest. 2017;97(6):669-97. doi: 10.1038/labinvest.2017.25.

209. Basu R, Whitlock BM, Husson J, Le Floc'h A, Jin W, Oyler-Yaniv A, et al. Cytotoxic T Cells Use Mechanical Force to Potentiate Target Cell Killing. Cell. 2016;165(1):100-10. doi: 10.1016/j.cell.2016.01.021.

210. Gordy C, He Y-W. Endocytosis by target cells: an essential means for perforin- and granzyme-mediated killing. Cell Mol Immunol. 2012;9(1):5-6. doi: 10.1038/cmi.2011.45.

211. Fu Q, Fu T-M, Cruz AC, Sengupta P, Thomas SK, Wang S, et al. Structural Basis and Functional Role of Intramembrane Trimerization of the Fas/CD95 Death Receptor. Mol Cell. 2016;61(4):602-13. doi: 10.1016/j.molcel.2016.01.009.

212. Wiedemann A, Depoil D, Faroudi M, Valitutti S. Cytotoxic T lymphocytes kill multiple targets simultaneously via spatiotemporal uncoupling of lytic and stimulatory synapses. Proc Natl Acad Sci. 2006;103(29):10985-90. doi: 10.1073/pnas.0600651103.

213. Raskov H, Orhan A, Christensen JP, Gogenur I. Cytotoxic CD8+ T cells in cancer and cancer immunotherapy. Br J Cancer. 2021;124(2):359-67. doi: 10.1038/s41416-020-01048-4.

214. Xie N, Shen G, Gao W, Huang Z, Huang C, Fu L. Neoantigens: promising targets for cancer therapy. Signal Transduct Target Ther. 2023;8(1):9. doi: 10.1038/s41392-022-01270-x.

215. Poncette L, Bluhm J, Blankenstein T. The role of CD4 T cells in rejection of solid tumors. Curr Opin Immunol. 2022;74:18-24. doi: 10.1016/j.coi.2021.09.005.

216. Speiser DE, Chijioke O, Schaeuble K, Munz C. CD4+ T cells in cancer. Nat Cancer. 2023;4(3):317-29. doi: 10.1038/s43018-023-00521-2.

217. Zhu J, Yamane H, Paul WE. Differentiation of Effector CD4 T Cell Populations. Annu Rev Immunol. 2010;28(1):445-89. doi: 10.1146/annurev-immunol-030409-101212.

218. Kammertoens T, Friese C, Arina A, Idel C, Briesemeister D, Rothe M, et al. Tumour ischaemia by interferon-gamma resembles physiological blood vessel regression. Nature. 2017;545(7652):98-102. doi: 10.1038/nature22311.

219. Jou E. Type 1 and type 2 cytokine-mediated immune orchestration in the tumour microenvironment and their therapeutic potential. Explor Target Antitumor Ther. 2023;4(3):474-97. doi: 10.37349/etat.2023.00146.

220. Onishi RM, Gaffen SL. Interleukin-17 and its target genes: mechanisms of interleukin-17 function in disease. Immunology. 2010;129(3):311-21. doi: 10.1111/j.1365-2567.2009.03240.x.

221. Vignali DA, Collison LW, Workman CJ. How regulatory T cells work. Nat Rev Immunol. 2008;8(7):523-32. doi: 10.1038/nri2343.

222. Reth M. Antigen Receptors on B Lymphocytes. Annu Rev Immunol. 1992;10(1):97-121. doi: 10.1146/annurev.iy.10.040192.000525.

223. Tanaka S, Baba Y. B Cell Receptor Signaling. In: Wang J-Y, editor. B Cells in Immunity and Tolerance. Singapore: Springer Singapore; 2020. p. 23-36.

224. LeBien TW, Tedder TF. B lymphocytes: how they develop and function. Blood. 2008;112(5):1570-80. doi: 10.1182/blood-2008-02-078071.

225. Schroeder HW, Cavacini L. Structure and function of immunoglobulins. J Allergy Clin Immunol. 2010;125(2):S41-S52. doi: 10.1016/j.jaci.2009.09.046.

226. Germain C, Gnjatic S, Tamzalit F, Knockaert S, Remark R, Goc Jrm, et al. Presence of B Cells in Tertiary Lymphoid Structures Is Associated with a Protective Immunity in Patients with Lung Cancer. Am J Respir Crit Care Med. 2014;189(7):832-44. doi: 10.1164/rccm.201309-1611OC.

227. Wang S-s, Liu W, Ly D, Xu H, Qu L, Zhang L. Tumor-infiltrating B cells: their role and application in anti-tumor immunity in lung cancer. Cell Mol Immunol. 2019;16(1):6-18. doi: 10.1038/s41423-018-0027-x.

228. Maiorino L, Daßler-Plenker J, Sun L, Egeblad M. Innate Immunity and Cancer Pathophysiology. Annu Rev Pathol. 2022;17:425-57. doi: 10.1146/annurev-pathmechdis-032221-115501.

229. Zhao SG, Lehrer J, Chang SL, Das R, Erho N, Liu Y, et al. The Immune Landscape of Prostate Cancer and Nomination of PD-L2 as a Potential Therapeutic Target. J Natl Cancer Inst. 2018;111(3):301-10. doi: 10.1093/jnci/djy141.

230. Kwon O-J, Zhang L, Ittmann MM, Xin L. Prostatic inflammation enhances basal-to-luminal differentiation and accelerates initiation of prostate cancer with a basal cell origin. Proc Natl Acad Sci USA. 2014;111(5):E592-E600. doi: 10.1073/pnas.1318157111.

231. Gurel B, Lucia MS, Thompson IM, Jr, Goodman PJ, Tangen CM, Kristal AR, et al. Chronic Inflammation in Benign Prostate Tissue Is Associated with High-Grade Prostate Cancer in the Placebo Arm of the Prostate Cancer Prevention Trial. Cancer Epidemiol Biomarkers Prev. 2014;23(5):847-56. doi: 10.1158/1055-9965.EPI-13-1126.

232. Shinohara DB, Vaghasia AM, Yu S-H, Mak TN, Brüggemann H, Nelson WG, et al. A mouse model of chronic prostatic inflammation using a human prostate cancer-derived isolate of Propionibacterium acnes. Prostate. 2013;73(9):1007-15. doi: 10.1002/pros.22648.

233. Sarkar P, Malik S, Banerjee A, Datta C, Pal DK, Ghosh A, et al. Differential Microbial Signature Associated With Benign Prostatic Hyperplasia and Prostate Cancer. Front Cell Infect Microbiol. 2022;12. doi: 10.3389/fcimb.2022.894777.

234. Kirby RS, Lowe D, Bultitude MI, Shuttleworth KE. Intra-prostatic urinary reflux: an aetiological factor in abacterial prostatitis. Br J Urol. 1982;54:729-31. doi: 10.1111/j.1464-410x.1982.tb13635.x.

235. Ferrucci D, Silva SP, Rocha A, Nascimento L, Vieira AS, Taboga SR, et al. Dietary fatty acid quality affects systemic parameters and promotes prostatitis and pre-neoplastic lesions. Sci Rep. 2019;9(1):19233. doi: 10.1038/s41598-019-55882-5.

236. Nava Rodrigues D, Rescigno P, Liu D, Yuan W, Carreira S, Lambros MB, et al. Immunogenomic analyses associate immunological alterations with mismatch repair defects in prostate cancer. J Clin Invest. 2018;128(10):4441-53. doi: 10.1172/JCI121924.

237. Baylin SB, Jones PA. Epigenetic Determinants of Cancer. Cold Spring Harb Perspect Biol. 2016;8(9):a019505. doi: 10.1101/cshperspect.a019505.

238. Elkahwaji JE, Zhong W, Hopkins WJ, Bushman W. Chronic bacterial infection and inflammation incite reactive hyperplasia in a mouse model of chronic prostatitis. Prostate. 2007;67(1):14-21. doi: 10.1002/pros.20445.

239. Lindmark F, Jonsson B-A, Bergh A, Stattin P, Zheng SL, Meyers DA, et al. Analysis of the macrophage scavenger receptor 1 gene in Swedish hereditary and sporadic prostate cancer. Prostate. 2004;59(2):132-40. doi: 10.1002/pros.10367.

240. Wang J, Yuan W, Yue C, Dai F, Gao S, Mi Y, et al. RNASEL 1623A>C variant is associated with the risk of prostate cancer in African descendants. J Cell Biochem. 2019;120(7):11955-64. doi: 10.1002/jcb.28479.

241. Ammirante M, Luo J-L, Grivennikov S, Nedospasov S, Karin M. B-cell-derived lymphotoxin promotes castration-resistant prostate cancer. Nature. 2010;464(7286):302-5. doi: 10.1038/nature08782.

242. Shalapour S, Font-Burgada J, Di Caro G, Zhong Z, Sanchez-Lopez E, Dhar D, et al. Immunosuppressive plasma cells impede T-cell-dependent immunogenic chemotherapy. Nature. 2015;521(7550):94-8. doi: 10.1038/nature14395.

243. Gentles AJ, Newman AM, Liu CL, Bratman SV, Feng W, Kim D, et al. The prognostic landscape of genes and infiltrating immune cells across human cancers. Nature Medicine. 2015;21(8):938-45. doi: 10.1038/nm.3909.

244. Masetti M, Carriero R, Portale F, Marelli G, Morina N, Pandini M, et al. Lipid-loaded tumor-associated macrophages sustain tumor growth and invasiveness in prostate cancer. J Exp Med. 2021;219(2). doi: 10.1084/jem.20210564.

245. Yang L, Zhang Y. Tumor-associated macrophages: from basic research to clinical application. J Hematol Oncol. 2017;10(1):58. doi: 10.1186/s13045-017-0430-2.

246. Coffelt SB, Wellenstein MD, de Visser KE. Neutrophils in cancer: neutral no more. Nat Rev Cancer. 2016;16(7):431-46. doi: 10.1038/nrc.2016.52.

247. Yang D, Liu J, Qian H, Zhuang Q. Cancer-associated fibroblasts: from basic science to anticancer therapy. Exp Mol Med. 2023;55(7):1322-32. doi: 10.1038/s12276-023-01013-0.

248. Shariat SF, Andrews B, Kattan MW, Kim J, Wheeler TM, Slawin KM. Plasma levels of interleukin-6 and its soluble receptor are associated with prostate cancer progression and metastasis. Urology. 2001;58(6):1008-15. doi: 10.1016/S0090-4295(01)01405-4.

249. Nguyen DP, Li J, Tewari AK. Inflammation and prostate cancer: the role of interleukin 6 (IL-6). BJU Int. 2014;113(6):986-92. doi: 10.1111/bju.12452.

250. Culig Z, Puhr M. Interleukin-6: A multifunctional targetable cytokine in human prostate cancer. Mol Cell Endocrinol. 2012;360(1):52-8. doi: 10.1016/j.mce.2011.05.033.

251. Castro F, Cardoso AP, Goncalves RM, Oliveira MJ. Interferon-Gamma at the Crossroads of Tumor Immune Surveillance or Evasion. Front Immunol. 2018;9. doi: 10.3389/fimmu.2018.00847.

252. Hernandez C, Huebener P, Schwabe RF. Damage-associated molecular patterns in cancer: a double-edged sword. Oncogene. 2016;35(46):5931-41. doi: 10.1038/onc.2016.104.

253. Stultz J, Fong L. How to turn up the heat on the cold immune microenvironment of metastatic prostate cancer. Prostate Cancer and Prostatic Dis. 2021;24(3):697-717. doi: 10.1038/s41391-021-00340-5.

254. Petitprez F, Fossati N, Vano Y, Freschi M, Becht E, Lucianò R, et al. PD-L1 Expression and CD8+ T-cell Infiltrate are Associated with Clinical Progression in Patients with Node-positive Prostate Cancer. Eur Urol Focus. 2019;5(2):192-6. doi: 10.1016/j.euf.2017.05.013.

255. Kiniwa Y, Miyahara Y, Wang H, Peng W, Peng G, Wheeler T, et al. CD8+ Foxp3+ regulatory T cells mediate immunosuppression in prostate cancer. Clin Cancer Res. 2007;13(23):6947-58. doi: 0.1158/1078-0432.CCR-07-0842.

256. Davidsson S, Andren O, Ohlson A-L, Carlsson J, Andersson S-O, Giunchi F, et al. FOXP3+ regulatory T cells in normal prostate tissue, postatrophic hyperplasia, prostatic intraepithelial neoplasia, and tumor histological lesions in men with and without prostate cancer. Prostate. 2018;78(1):40-7. doi: 10.1002/pros.23442.

257. Davidsson S, Ohlson A-L, Andersson S-O, Fall K, Meisner A, Fiorentino M, et al. CD4 helper T cells, CD8 cytotoxic T cells, and FOXP3+ regulatory T cells with respect to lethal prostate cancer. Mod Pathol. 2013;26(3):448-55. doi: 10.1038/modpathol.2012.164.

258. Park A, Lee Y, Kim MS, Kang YJ, Park Y-J, Jung H, et al. Prostaglandin E2 Secreted by Thyroid Cancer Cells Contributes to Immune Escape Through the Suppression of Natural Killer (NK) Cell Cytotoxicity and NK Cell Differentiation. Front Immunol. 2018;9:1859. doi: 10.3389/fimmu.2018.01859.

259. Young A, Ngiow SF, Gao Y, Patch A-M, Barkauskas DS, Messaoudene M, et al. A2AR Adenosine Signaling Suppresses Natural Killer Cell Maturation in the Tumor Microenvironment. Cancer Res. 2018;78(4):1003-16. doi: 10.1158/0008-5472.CAN-17-2826.

260. Concha-Benavente F, Kansy B, Moskovitz J, Moy J, Chandran U, Ferris RL. PD-L1 Mediates Dysfunction in Activated PD-1+ NK Cells in Head and Neck Cancer Patients. Cancer Immunol Res. 2018;6(12):1548-60. doi: 10.1158/2326-6066.CIR-18-0062.

261. Al Absi A, Wurzer H, Guerin C, Hoffmann C, Moreau F, Mao X, et al. Actin Cytoskeleton Remodeling Drives Breast Cancer Cell Escape from Natural Killer-Mediated Cytotoxicity. Cancer Res. 2018;78(19):5631-43. doi: 10.1158/0008-5472.CAN-18-0441.

262. Anand U, Dey A, Chandel AKS, Sanyal R, Mishra A, Pandey DK, et al. Cancer chemotherapy and beyond: Current status, drug candidates, associated risks and progress in targeted therapeutics. Genes Dis. 2023;10(4):1367-401. doi: 10.1016/j.gendis.2022.02.007.

263. Shahrasbi A, Armin AR, Ardebili A, Rafie KS, Ansari M, Rabani M. Hematologic Adverse Effects following Systemic Chemotherapy. J Oncol Med & Pract. 2017;2(1):110-2. doi: 10.4172/2576-3857.1000110.

264. Sharma A, Jasrotia S, Kumar A. Effects of Chemotherapy on the Immune System: Implications for Cancer Treatment and Patient Outcomes. Naunyn Schmiedebergs Arch Pharmacol. 2023. doi: 10.1007/s00210-023-02781-2.

265. Kongsted P, Svane IM, Lindberg H, Sengeløv L. Predictors of Chemotherapy-Induced Toxicity and Treatment Outcomes in Elderly Versus Younger Patients With Metastatic Castration-Resistant Prostate Cancer. Clin Genitourin Cancer. 2016;14(6):e559-e68. doi: 10.1016/j.clgc.2016.03.018.

266. De Ruysscher D, Niedermann G, Burnet NG, Siva S, Lee AWM, Hegi-Johnson F. Radiotherapy toxicity. Nat Rev Dis Primers. 2019;5(1):13. doi: 10.1038/s41572-019-0064-5.

267. Gubbels Bupp MR, Jorgensen TN. Androgen-Induced Immunosuppression. Front Immunol. 2018;9:794. doi: 10.3389/fimmu.2018.00794.

268. Mierzejewska K, Borkowska S, Suszynska E, Suszynska M, Poniewierska-Baran A, Maj M, et al. Hematopoietic Stem/Progenitor Cells Express Several Functional Sex Hormone Receptors ─ Novel Evidence for a Potential Developmental Link Between Hematopoiesis and Primordial Germ Cells. Stem Cells Dev. 2015;24(8):927-37. doi: 10.1089/scd.2014.0546.

269. Ben-Batalla I, Vargas-Delgado ME, von Amsberg G, Janning M, Loges S. Influence of Androgens on Immunity to Self and Foreign: Effects on Immunity and Cancer. Front Immunol. 2020;11:1184. doi: 10.3389/fimmu.2020.01184.

270. Malkin CJ, Pugh PJ, Jones RD, Kapoor D, Channer KS, Jones TH. The Effect of Testosterone Replacement on Endogenous Inflammatory Cytokines and Lipid Profiles in Hypogonadal Men. J Clin Endocrinol Metab. 2004;89(7):3313-8. doi: 10.1210/jc.2003-031069.

271. Conteduca V, Brighi N, Schepisi G, De Giorgi U. Immunogenomic profiles associated with response to life-prolonging agents in prostate cancer. Br J Cancer. 2023;129(7):1050-60. doi: 10.1038/s41416-023-02354-3.

272. Gannon PO, Poisson AO, Delvoye N, Lapointe R, Mes-Masson A-M, Saad F. Characterization of the intra-prostatic immune cell infiltration in androgen-deprived prostate cancer patients. J Immunol Methods. 2009;348(1):9-17. doi: 10.1016/j.jim.2009.06.004.

273. Guan X, Polesso F, Wang C, Sehrawat A, Hawkins RM, Murray SE, et al. Androgen receptor activity in T cells limits checkpoint blockade efficacy. Nature. 2022;606(7915):791-6. doi: 10.1038/s41586-022-04522-6.

274. Page ST, Plymate SR, Bremner WJ, Matsumoto AM, Hess DL, Lin DW, et al. Effect of medical castration on CD4+CD25+ T cells, CD8+ T cell IFN-γ expression, and NK cells: a physiological role for testosterone and/or its metabolites. Am J Physiol Endocrinol Metab. 2006;290(5):E856-E63. doi: 10.1152/ajpendo.00484.2005.

275. Araujo B. de Lima V, Hansen M, Spanggaard I, Rohrberg K, Reker Hadrup S, Lassen U, et al. Immune Cell Profiling of Peripheral Blood as Signature for Response During Checkpoint Inhibition Across Cancer Types. Front Oncol. 2021;11. doi: 10.3389/fonc.2021.558248.

276. Jørgensen N, Lænkholm A-V, Sækmose SG, Hansen LB, Hviid TVF. Peripheral blood immune markers in breast cancer: Differences in regulatory T cell abundance are related to clinical parameters. Clin Immunol. 2021;232:108847. doi: 10.1016/j.clim.2021.108847.

277. Romagnani S. T-cell subsets (Th1 versus Th2). Ann Allergy Asthma Immunol. 2000;85(1):9-21. doi: 10.1016/S1081-1206(10)62426-X.

278. Spellberg B, Edwards JE. Type 1/Type 2 Immunity in Infectious Diseases. Clin Infect Dis. 2001;32(1):76-102. doi: 10.1086/317537.

279. Bais AG, Beckmann I, Lindemans J, Ewing PC, Meijer CJLM, Snijders PJF, et al. A shift to a peripheral Th2-type cytokine pattern during the carcinogenesis of cervical cancer becomes manifest in CIN III lesions. J Clin Pathol. 2005;58(10):1096-100. doi: 10.1136/jcp.2004.025072.

280. Tosolini M, Kirilovsky A, Mlecnik B, Fredriksen T, Mauger Sp, Bindea G, et al. Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer. Cancer Res. 2011;71(4):1263-71. doi: 10.1158/0008-5472.CAN-10-2907.

281. Xiao Y, Huang Y, Jiang J, Chen Y, Wei C. Identification of the prognostic value of Th1/Th2 ratio and a novel prognostic signature in basal-like breast cancer. Hereditas. 2023;160(1):2. doi: 10.1186/s41065-023-00265-0.

282. Zheng R, Wang F, Huang Y, Xiang Q, Dai H, Zhang W. Elevated Th17 cell frequencies and Th17/Treg ratio are associated with airway hyperresponsiveness in asthmatic children. J Asthma. 2021;58(6):707-16. doi: 10.1080/02770903.2020.1737710.

283. Cupp MA, Cariolou M, Tzoulaki I, Aune D, Evangelou E, Berlanga-Taylor AJ. Neutrophil to lymphocyte ratio and cancer prognosis: an umbrella review of systematic reviews and meta-analyses of observational studies. BMC Medicine. 2020;18(1):360. doi: 10.1186/s12916-020-01817-1.

284. Li B, Zhou P, Liu Y, Wei H, Yang X, Chen T, et al. Platelet-to-lymphocyte ratio in advanced Cancer: Review and meta-analysis. Clinica Chimica Acta. 2018;483:48-56. doi: 10.1016/j.cca.2018.04.023.

285. Hu B, Yang X-R, Xu Y, Sun Y-F, Sun C, Guo W, et al. Systemic Immune-Inflammation Index Predicts Prognosis of Patients after Curative Resection for Hepatocellular Carcinoma. Clin Cancer Res. 2014;20(23):6212-22. doi: 10.1158/1078-0432.CCR-14-0442.

286. Holinstat M. Normal platelet function. Cancer Metastasis Rev. 2017;36(2):195-8. doi: 10.1007/s10555-017-9677-x.

287. Guo W, Lu X, Liu Q, Zhang T, Li P, Qiao W, et al. Prognostic value of neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio for breast cancer patients: An updated meta-analysis of 17079 individuals. Cancer Med. 2019;8(9):4135-48. doi: 10.1002/cam4.2281.

288. Tian B-W, Yang Y-F, Yang C-C, Yan L-J, Ding Z-N, Liu H, et al. Systemic immune-inflammation index predicts prognosis of cancer immunotherapy: systemic review and meta-analysis. Immunotherapy. 2022;14(18):1481-96. doi: 10.2217/imt-2022-0133.

289. Li J, Cao D, Huang Y, Xiong Q, Tan D, Liu L, et al. The Prognostic and Clinicopathological Significance of Systemic Immune-Inflammation Index in Bladder Cancer. Front Immunol. 2022;13:865643. doi: 10.3389/fimmu.2022.865643.

290. Qi W, Zhou Y, Liu Z, Wang J, Lv G, Zhong M, et al. Revealing the prognostic and clinicopathological significance of systemic immune-inflammation index in patients with different stage prostate cancer: A systematic review and meta-analysis. Front Med (Lausanne). 2022;9:1052943. doi: 10.3389/fmed.2022.1052943.

291. Tang L, Li X, Wang B, Luo G, Gu L, Chen L, et al. Prognostic Value of Neutrophil-to-Lymphocyte Ratio in Localized and Advanced Prostate Cancer: A Systematic Review and Meta-Analysis. PLOS ONE. 2016;11(4):e0153981. doi: 10.1371/journal.pone.0153981.

292. Diaz MA, Zubicaray J, Molina B, Abad L, Castillo A, Sebastian E, et al. Haploidentical Stem Cell Transplantation in Children With Hematological Malignancies Using αβ+ T-Cell Receptor and CD19+ Cell Depleted Grafts: High CD56dim/CD56bright NK Cell Ratio Early Following Transplantation Is Associated With Lower Relapse Incidence and Better Outcome. Front Immunol. 2019;10. doi: 10.3389/fimmu.2019.02504.

293. Walzik D, Joisten N, Zacher J, Zimmer P. Transferring clinically established immune inflammation markers into exercise physiology: focus on neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio and systemic immune-inflammation index. Eur J Appl Physiol. 2021;121(7):1803-14. doi: 10.1007/s00421-021-04668-7.

294. Caspersen CJ, Powell KE, Christenson GM. Physical activity, exercise, and physical fitness: definitions and distinctions for health-related research. Public Health Rep. 1985;100(2):126-31.

295. Bull FC, Al-Ansari SS, Biddle S, Borodulin K, Buman MP, Cardon G, et al. World Health Organization 2020 guidelines on physical activity and sedentary behaviour. Br J Sports Med. 2020;54(24):1451-62. doi: 10.1136/bjsports-2020-102955.

296. Patel AV, Friedenreich CM, Moore SC, Hayes SC, Silver JK, Campbell KL, et al. American College of Sports Medicine Roundtable Report on Physical Activity, Sedentary Behavior, and Cancer Prevention and Control. Med Sci Sports Exerc. 2019;51(11):2391-402. doi: 10.1249/MSS.0000000000002117.

297. Campbell KL, Winters-Stone KM, Wiskemann J, May AM, Schwartz AL, Courneya KS, et al. Exercise Guidelines for Cancer Survivors: Consensus Statement from International Multidisciplinary Roundtable. Med Sci Sports Exerc. 2019;51(11):2375-90. doi: 10.1249/MSS.0000000000002116.

298. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F, et al. ESPEN guidelines on nutrition in cancer patients. Clin Nutr. 2017;36(1):11-48. doi: 10.1016/j.clnu.2016.07.015.

299. Cave J, Paschalis A, Huang CY, West M, Copson E, Jack S, et al. A systematic review of the safety and efficacy of aerobic exercise during cytotoxic chemotherapy treatment. Support Care Cancer. 2018;26(10):3337-51. doi: 10.1007/s00520-018-4295-x.

300. Capozzi LC, Daun JT, Ester M, Mosca S, Langelier D, Francis GJ, et al. Physical Activity for Individuals Living with Advanced Cancer: Evidence and Recommendations. Semin Oncol Nurs. 2021;37(4):151170. doi: 10.1016/j.soncn.2021.151170.

301. Oldervoll LM, Loge JH, Lydersen S, Paltiel H, Asp MB, Nygaard UV, et al. Physical Exercise for Cancer Patients with Advanced Disease: A Randomized Controlled Trial. Oncologist. 2011;16(11):1649-57. doi: 10.1634/theoncologist.2011-0133.

302. Sweegers MG, Altenburg TM, Chinapaw MJ, Kalter J, Verdonck de Leeuw IM, Courneya KS, et al. Which exercise prescriptions improve quality of life and physical function in patients with cancer during and following treatment? A systematic review and meta-analysis of randomised controlled trials. Br J Sports Med. 2018;52(8):505-13. doi: 10.1136/bjsports-2017-097891.

303. 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(13):812-. doi: 10.1136/bjsports-2018-099191.

304. Norton K, Norton L, Sadgrove D. Position statement on physical activity and exercise intensity terminology. J Sci Med Sport. 2010;13(5):496-502. doi: 10.1016/j.jsams.2009.09.008.

305. Campbell KL, Cormie P, Weller S, Alibhai SMH, Bolam KA, Campbell A, et al. Exercise Recommendation for People With Bone Metastases: Expert Consensus for Health Care Providers and Exercise Professionals. JCO Oncology Practice. 2022;18(5):e697-e709. doi: 10.1200/op.21.00454.

306. Galvao DA, Taaffe DR, Spry N, Cormie P, Joseph D, Chambers SK, et al. Exercise Preserves Physical Function in Prostate Cancer Patients with Bone Metastases. Med Sci Sports Exerc. 2018;50(3):393-9. doi: 10.1249/MSS.0000000000001454.

307. Rief H, Petersen LC, Omlor G, Akbar M, Bruckner T, Rieken S, et al. The effect of resistance training during radiotherapy on spinal bone metastases in cancer patients - A randomized trial. Radiother Oncol. 2014;112(1):133-9. doi: 10.1016/j.radonc.2014.06.008.

308. Sprave T, Rosenberger F, Verma V, Förster R, Bruckner T, Schlampp I, et al. Paravertebral Muscle Training in Patients with Unstable Spinal Metastases Receiving Palliative Radiotherapy: An Exploratory Randomized Feasibility Trial. Cancers. 2019;11(11):1771. doi: 10.3390/cancers11111771

309. Courneya KS, Stevinson C, McNeely ML, Sellar CM, Friedenreich CM, Peddle-McIntyre CJ, et al. Effects of supervised exercise on motivational outcomes and longer-term behavior. Med Sci Sports Exerc. 2012;44(3):542-9. doi: 10.1249/MSS.0b013e3182301e06.

310. Fang YY, Wang CP, Chen YJ, Lou PJ, Ko JY, Lin JJ, et al. Physical activity and fitness in survivors of head and neck cancer. Support Care Cancer. 2021;29(11):6807-17. doi: 10.1007/s00520-021-06192-y.

311. Lally P, Miller NE, Lawrence C, Beeken RJ, Fisher A. Associations of self-reported and device-assessed physical activity with fatigue, quality of life, and sleep quality in adults living with and beyond cancer. J Sport Health Sci. 2023. doi: 10.1016/j.jshs.2023.05.001.

312. Coletta AM, Marquez G, Thomas P, Thoman W, Bevers T, Brewster AM, et al. Clinical factors associated with adherence to aerobic and resistance physical activity guidelines among cancer prevention patients and survivors. PLOS ONE. 2019;14(8):e0220814. doi: 10.1371/journal.pone.0220814.

313. Santa Mina D, Guglietti CL, Alibhai SM, Matthew AG, Kalnin R, Ahmad N, et al. The effect of meeting physical activity guidelines for cancer survivors on quality of life following radical prostatectomy for prostate cancer. J Cancer Surviv. 2014;8(2):190-8. doi: 10.1007/s11764-013-0329-z.

314. Guinan EM, Devenney K, Quinn C, Sheill G, Eochagain CM, Kennedy MJ, et al. Associations Among Physical Activity, Skeletal Related Events, and Patient Reported Outcomes in Patients with Bone Metastases. Semin Oncol Nurs. 2022;38(2):151274. doi: 10.1016/j.soncn.2022.151274.

315. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical activity and survival after prostate cancer diagnosis in the health professionals follow-up study. J Clin Oncol. 2011;29(6):726-32. doi: 10.1200/JCO.2010.31.5226.

316. Toohey K, Hunter M, Paterson C, Mortazavi R, Singh B. Exercise Adherence in Men with Prostate Cancer Undergoing Androgen Deprivation Therapy: A Systematic Review and Meta-Analysis. Cancers. 2022;14(10):2452. doi: 10.3390/cancers14102452.

317. Sheill G, Brady L, Hayes B, Baird A-M, Guinan E, Vishwakarma R, et al. ExPeCT: a randomised trial examining the impact of exercise on quality of life in men with metastatic prostate cancer. Support Care Cancer. 2023;31(5):292. doi: 10.1007/s00520-023-07740-4.

318. Courneya KS, Segal RJ, Reid RD, Jones LW, Malone SC, Venner PM, et al. Three independent factors predicted adherence in a randomized controlled trial of resistance exercise training among prostate cancer survivors. J Clin Epidemiol. 2004;57(6):571-9. doi: 10.1016/j.jclinepi.2003.11.010.

319. Rosenberger M, Fulton JE, Buman MP, Troiano RP, Grandner MA, Buchner DM, et al. The 24-Hour Activity Cycle: A New Paradigm for Physical Activity. Med Sci Sports Exerc. 2019;51(3):454-64. doi: 10.1249/mss.0000000000001811.

320. Lynch BM, Dunstan DW, Winkler E, Healy GN, Eakin E, Owen N. Objectively assessed physical activity, sedentary time and waist circumference among prostate cancer survivors: findings from the National Health and Nutrition Examination Survey (2003-2006). Eur J Cancer Care (Engl). 2011;20(4):514-9. doi: 10.1111/j.1365-2354.2010.01205.x.

321. Gaskin CJ, Craike M, Mohebbi M, Salmon J, Courneya KS, Broadbent S, et al. Associations of objectively measured moderate-to-vigorous physical activity and sedentary behavior with quality of life and psychological well-being in prostate cancer survivors. Cancer Causes Control. 2016;27(9):1093-103. doi: 10.1007/s10552-016-0787-5.

322. Ainsworth B, Cahalin L, Buman M, Ross R. The Current State of Physical Activity Assessment Tools. Prog Cardiovasc Dis. 2015;57(4):387-95. doi: 10.1016/j.pcad.2014.10.005.

323. Warren JM, Ekelund U, Besson H, Mezzani A, Geladas N, Vanhees L. Assessment of physical activity – a review of methodologies with reference to epidemiological research: a report of the exercise physiology section of the European Association of Cardiovascular Prevention and Rehabilitation. Eur J Cardiovasc Prev Rehabil. 2010;17(2):127-39. doi: 10.1097/HJR.0b013e32832ed875.

324. Shephard RJ. Limits to the measurement of habitual physical activity by questionnaires. Br J Sports Med. 2003;37(3):197-206. doi: 10.1136/bjsm.37.3.197.

325. Karuturi M, Wong ML, Hsu T, Kimmick GG, Lichtman SM, Holmes HM, et al. Understanding cognition in older patients with cancer. J Geriatr Oncol. 2016;7(4):258-69. doi: 10.1016/j.jgo.2016.04.004.

326. Chen KY, Bassett DR. The Technology of Accelerometry-Based Activity Monitors: Current and Future. Med Sci Sports Exerc. 2005;37(11):S490-S500. doi: 10.1249/01.mss.0000185571.49104.82.

327. Liu F, Wanigatunga AA, Schrack JA. Assessment of Physical Activity in Adults Using Wrist Accelerometers. Epidemiol Rev. 2021;43(1):65-93. doi: 10.1093/epirev/mxab004.

328. Sloane R, Clutter Snyder D, Demark-Wahnefried W, Lobach D, Kraus WE. Comparing the 7-day physical activity recall with a triaxial accelerometer for measuring time in exercise. Med Sci Sports Exerc. 2009;41(6):1334.40. doi: 10.1249/MSS.0b013e3181984fa8.

329. Golsteijn RHJ, Bolman C, Volders E, Peels DA, de Vries H, Lechner L. Short-term efficacy of a computer-tailored physical activity intervention for prostate and colorectal cancer patients and survivors: a randomized controlled trial. Int J Behav Nutr Phys Act. 2018;15(1):106. doi: 10.1186/s12966-018-0734-9.

330. Winters-Stone KM, Neil SE, Campbell KL. Attention to principles of exercise training: a review of exercise studies for survivors of cancers other than breast. Br J Sports Med. 2014;48(12):987-95. doi: 10.1136/bjsports-2012-091732.

331. Nilsen TS, Scott JM, Michalski M, Capaci C, Thomas S, Herndon JE, et al. Novel Methods for Reporting of Exercise Dose and Adherence: An Exploratory Analysis. Med Sci Sports Exerc. 2018;50(6):1134-41. doi: 10.1249/MSS.0000000000001545.

332. Fairman CM, Nilsen TS, Newton RU, Taaffe DR, Spry N, Joseph D, et al. Reporting of Resistance Training Dose, Adherence, and Tolerance in Exercise Oncology. Med Sci Sports Exerc. 2020;52(2):315-22. doi: 10.1249/MSS.0000000000002127.

333. Cannioto RA, Hutson A, Dighe S, McCann W, McCann SE, Zirpoli GR, et al. Physical Activity Before, During, and After Chemotherapy for High-Risk Breast Cancer:

Relationships With Survival. J Natl Cancer Inst. 2020;113(1):54-63. doi: 10.1093/jnci/djaa046.

334. Schmitz KH, Campbell AM, Stuiver MM, Pinto BM, Schwartz AL, Morris GS, et al. Exercise is medicine in oncology: Engaging clinicians to help patients move through cancer. CA Cancer J Clin. 2019;69(6):468-84. doi: 10.3322/caac.21579.

335. Bonn SE, Sjölander A, Lagerros YT, Wiklund F, Stattin P, Holmberg E, et al. Physical Activity and Survival among Men Diagnosed with Prostate Cancer. Cancer Epidemiol Biomarkers Prev. 2015;24(1):57-64. doi: 10.1158/1055-9965.EPI-14-0707.

336. Wang Y, Jacobs EJ, Gapstur SM, Maliniak ML, Gansler T, McCullough ML, et al. Recreational Physical Activity in Relation to Prostate Cancer-specific Mortality Among Men with Nonmetastatic Prostate Cancer. Eur Urol. 2017;72(6):931-9. doi: 10.1016/j.eururo.2017.06.037.

337. Dai JY, Wang B, Wang X, Cheng A, Kolb S, Stanford JL, et al. Vigorous Physical Activity Is Associated with Lower Risk of Metastatic-Lethal Progression in Prostate Cancer and Hypomethylation in the CRACR2A Gene. Cancer Epidemiol Biomarkers Prev. 2019;28(2):258-64. doi: 10.1158/1055-9965.EPI-18-0622.

338. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical Activity after Diagnosis and Risk of Prostate Cancer Progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor. Cancer Res. 2011;71(11):3889-95. doi: 10.1158/0008-5472.CAN-10-3932.

339. Eschke RCKR, Lampit A, Schenk A, Javelle F, Steindorf K, Diel P, et al. Impact of Physical Exercise on Growth and Progression of Cancer in Rodents ─ A Systematic Review and Meta-Analysis. Front Oncol. 2019;9:35. doi: 10.3389/fonc.2019.00035.

340. Esser KA, Harpole CE, Prins GS, Diamond AM. Physical activity reduces prostate carcinogenesis in a transgenic model. Prostate. 2009;69(13):1372-7. doi: 10.1002/pros.20987.

341. Rundqvist H, Augsten M, Stromberg A, Rullman E, Mijwel S, Kharaziha P, et al. Effect of acute exercise on prostate cancer cell growth. PLOS ONE. 2013;8(7):e67579. doi: 10.1371/journal.pone.0067579.

342. Kang D-W, 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(10):1487-95. doi: 10.1001/jamaoncol.2021.3067.

343. Edmunds K, Tuffaha H, Scuffham P, Galvao DA, Newton RU. The role of exercise in the management of adverse effects of androgen deprivation therapy for prostate cancer: a rapid review. Support Care Cancer. 2020;28(12):5661-71. doi: 10.1007/s00520-020-05637-0.

344. Newton RU, Galváo DA. Accumulating Evidence for Physical Activity and Prostate Cancer Survival: Time for a Definitive Trial of Exercise Medicine? Eur Urol. 2016;70(4):586-7. doi: 10.1016/j.eururo.2016.04.018.

345. Piraux E, Caty G, Aboubakar Nana F, Reychler G. Effects of exercise therapy in cancer patients undergoing radiotherapy treatment: a narrative review. SAGE Open Med. 2020;8. doi: 10.1177/2050312120922657.

346. Ross R, Blair SN, Arena R, Church TS, Despres JP, Franklin BA, et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A Scientific Statement From the American Heart Association. Circulation. 2016;134(24):e653-e99. doi: 10.1161/CIR.0000000000000461.

347. Singh F, Newton RU, Galvao DA, Spry N, Baker MK. A systematic review of pre-surgical exercise intervention studies with cancer patients. Surg Oncol. 2013;22(2):92-104. doi: 10.1016/j.suronc.2013.01.004.

348. Groen WG, Naaktgeboren WR, van Harten WH, van Vulpen JK, Kool N, Sonke GS, et al. Physical Fitness and Chemotherapy Tolerance in Patients with Early-Stage Breast Cancer. Med Sci Sports Exerc. 2022;54(4):537-42. doi: 10.1249/mss.0000000000002828.

349. Sardinha LB, Santos DA, Marques EA, Mota J. Criterion-referenced fitness standards for predicting physical independence into later life. Exp Gerontol. 2015;61:142-6. doi: 10.1016/j.exger.2014.12.012.

350. Blair SN, Kohl HW, Paffenbarger RS, Clark DG, Cooper KH, Gibbons LW. Physical fitness and all-cause mortality. A prospective study of healthy men and women. JAMA. 1989;262(17):2395-401. doi: 10.1001/jama.262.17.2395.

351. Ortega FB, Ruiz JR, Castillo MJ, Sjostrom M. Physical fitness in childhood and adolescence: a powerful marker of health. Int J Obes (Lond). 2008;32(1):1-11. doi: 10.1038/sj.ijo.0803774.

352. Kell RT, Bell G, Quinney A. Musculoskeletal Fitness, Health Outcomes and Quality of Life. Sports Med. 2001;31(12):863-73. doi: 10.2165/00007256-200131120-00003.

353. Farnsworth CPTDD, Cannon M. Chapter 39 - Exercise Prescription. In: Seidenberg PH, Beutler AI, editors. The Sports Medicine Resource Manual. Philadelphia: W.B. Saunders; 2008. p. 497-506.

354. Painter P, L. SA, Carey S. Physical functioning: definitions, measurement, and expectations. Adv Ren Replace Ther. 1999;6(2):110-23. doi: 10.1016/s1073-4449(99)70028-2.

355. Beaudart C, Dawson A, Shaw SC, Harvey NC, Kanis JA, Binkley N, et al. Nutrition and physical activity in the prevention and treatment of sarcopenia: systematic review. Osteoporos Int. 2017;28(6):1817-33. doi: 10.1007/s00198-017-3980-9.

356. Dipietro L, Campbell WW, Buchner DM, Erickson KI, Powell KE, Bloodgood B, et al. Physical Activity, Injurious Falls, and Physical Function in Aging: An Umbrella Review. Med Sci Sports Exerc. 2019;51(6):1303-13. doi: 10.1249/mss.0000000000001942.

357. Billot M, Calvani R, Urtamo A, Sánchez-Sánchez JL, Ciccolari-Micaldi C, Chang M, et al. Preserving Mobility in Older Adults with Physical Frailty and Sarcopenia: Opportunities, Challenges, and Recommendations for Physical Activity Interventions. Clin Interv Aging. 2020;15:1675-90. doi: 10.2147/cia.S253535.

358. Franklin BA, Eijsvogels TMH, Pandey A, Quindry J, Toth PP. Physical activity, cardiorespiratory fitness, and cardiovascular health: A clinical practice statement of the American Society for Preventive Cardiology Part II: Physical activity, cardiorespiratory fitness, minimum and goal intensities for exercise training, prescriptive methods, and special patient populations. Am J Prev Cardiol. 2022;12:100425. doi: 10.1016/j.ajpc.2022.100425.

359. Lahart IM, Metsios GS, Nevill AM, Carmichael AR. Physical activity for women with breast cancer after adjuvant therapy. Cochrane Database Syst Rev. 2018(1). doi: 10.1002/14651858.CD011292.pub2.

360. Faithfull S, Lemanska A, Poole K, Aning J, Manders R, Marshall J, et al. Obesity and low levels of physical activity impact on cardiopulmonary fitness in older men after treatment for prostate cancer. Eur J Cancer Care (Engl). 2021;30(6):e13476. doi: 10.1111/ecc.13476.

361. Phillips SM, Stampfer MJ, Chan JM, Giovannucci EL, Kenfield SA. Physical activity, sedentary behavior, and health-related quality of life in prostate cancer survivors in the health professionals follow-up study. J Cancer Surviv. 2015;9(3):500-11. doi: 10.1007/s11764-015-0426-2.

362. Thorsen L, Courneya KS, Stevinson C, Fossa SD. A systematic review of physical activity in prostate cancer survivors: outcomes, prevalence, and determinants. Support Care Cancer. 2008;16(9):987-97. doi: 10.1007/s00520-008-0411-7.

363. Chen Z, Zhang Y, Lu C, Zeng H, Schumann M, Cheng S. Supervised Physical Training Enhances Muscle Strength but Not Muscle Mass in Prostate Cancer Patients Undergoing

Androgen Deprivation Therapy: A Systematic Review and Meta-Analysis. Front Physiol. 2019;10:843. doi: 10.3389/fphys.2019.00843.

364. Nilsen TS, Thorsen L, Fosså SD, Wiig M, Kirkegaard C, Skovlund E, et al. Effects of strength training on muscle cellular outcomes in prostate cancer patients on androgen deprivation therapy. Scand J Med Sci Sports. 2016;26(9):1026-35. doi: 10.1111/sms.12543.

365. Andersen MF, Midtgaard J, Bjerre ED. Do Patients with Prostate Cancer Benefit from Exercise Interventions? A Systematic Review and Meta-Analysis. Int J Environ Res Public Health. 2022;19(2). doi: 10.3390/ijerph19020972.

366. Van Blarigan EL, Kenfield SA, Olshen A, Panchal N, Encabo K, Tenggara I, et al. Effect of a Home-based Walking Intervention on Cardiopulmonary Fitness and Quality of Life Among Men with Prostate Cancer on Active Surveillance: The Active Surveillance Exercise Randomized Controlled Trial. Eur Urol Oncol. 2023. doi: 10.1016/j.euo.2023.10.012.

367. Owen PJ, Daly RM, Livingston PM, Fraser SF. Lifestyle guidelines for managing adverse effects on bone health and body composition in men treated with androgen deprivation therapy for prostate cancer: an update. Prostate Cancer Prostatic Dis. 2017;20(2):137-45. doi: 10.1038/pcan.2016.69.

368. Harrison MR, Davis PG, Khouri MG, Bartlett DB, Gupta RT, Armstrong AJ, et al. A randomized controlled trial comparing changes in fitness with or without supervised exercise in patients initiated on enzalutamide and androgen deprivation therapy for non-metastatic castration-sensitive prostate cancer (EXTEND). Prostate Cancer Prostatic Dis. 2022;25(1):58-64. doi: 10.1038/s41391-022-00519-4.

369. Nieman DC, Wentz LM. The compelling link between physical activity and the body's defense system. J Sport Health Sci. 2019;8(3):201-17. doi: 10.1016/j.jshs.2018.09.009.

370. Shephard RJ. Adhesion Molecules, Catecholamines and Leucocyte Redistribution During and Following Exercise. Sports Med. 2003;33(4):261-84. doi: 10.2165/00007256-200333040-00002.

371. Fischer CP. Interleukin-6 in acute exercise and training: what is the biological relevance? Exerc Immunol Rev. 2006;12:6-33.

372. Steensberg A, Fischer CP, Keller C, Møller K, Pedersen BK. IL-6 enhances plasma IL-1ra, IL-10, and cortisol in humans. Am J Physiol Endocrinol Metab. 2003;285(2):E433-E7. doi: 10.1152/ajpendo.00074.2003.

373. Bay ML, Heywood S, Wedell-Neergaard A-S, Schauer T, Lehrskov LL, Christensen RHj, et al. Human immune cell mobilization during exercise: effect of IL-6 receptor blockade. Exp Physiol. 2020;105(12):2086-98. doi: 10.1113/EP088864.

374. Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metab. 2016;23(3):554-62. doi: 10.1016/j.cmet.2016.01.011.

375. Koelwyn GJ, Quail DF, Zhang X, White RM, Jones LW. Exercise-dependent regulation of the tumour microenvironment. Nat Rev Cancer. 2017;17(10):620-32. doi: 10.1038/nrc.2017.78.

376. Schauer T, Djurhuus SS, Simonsen C, Brasso K, Christensen JF. The effects of acute exercise and inflammation on immune function in early-stage prostate cancer. Brain Behav Immun Health. 2022;25:100508. doi: 10.1016/j.bbih.2022.100508.

377. Hanson ED, Sakkal S, Que S, Cho E, Spielmann G, Kadife E, et al. Natural killer cell mobilization and egress following acute exercise in men with prostate cancer. Exp Physiol. 2020;105(9):1524-39. doi: 10.1113/EP088627.

378. Hanson ED, Sakkal S, Bates-Fraser LC, Que S, Cho E, Spielmann G, et al. Acute exercise induces distinct quantitative and phenotypical T cell profiles in men with prostate cancer. Front Sports Act Living. 2023;5:1173377. doi: 10.3389/fspor.2023.1173377.

379. Galvao DA, Nosaka K, Taaffe DR, Peake J, Spry N, Suzuki K, et al. Endocrine and immune responses to resistance training in prostate cancer patients. Prostate Cancer Prostatic Dis. 2008;11(2):160-5. doi: 10.1038/sj.pcan.4500991.

380. Kim JS, Taaffe DR, Galvao DA, Hart NH, Gray E, Ryan CJ, et al. Exercise in advanced prostate cancer elevates myokine levels and suppresses in-vitro cell growth. Prostate Cancer Prostatic Dis. 2022;25(1):86-92. doi: 10.1038/s41391-022-00504-x.

381. Kaushik D, Shah PK, Mukherjee N, Ji N, Dursun F, Kumar AP, et al. Effects of yoga in men with prostate cancer on quality of life and immune response: a pilot randomized controlled trial. Prostate Cancer Prostatic Dis. 2022;25(3):531-8. doi: 10.1038/s41391-021-00470-w.

382. Winker M, Stossel S, Neu MA, Lehmann N, El Malki K, Paret C, et al. Exercise reduces systemic immune inflammation index (SII) in childhood cancer patients. Support Care Cancer. 2022;30(4):2905-8. doi: 10.1007/s00520-021-06719-3.

383. Weyh C, Kruger K, Strasser B. Physical Activity and Diet Shape the Immune System during Aging. Nutrients. 2020;12(3). doi: 10.3390/nu12030622.

384. Nieman D, Henson D, Gusewitch G, Warren B, Dotson R, Butterworth D, et al. Physical activity and immune function in elderly women. Med Sci Sports Exerc. 1993;25(7):823-31. doi: 10.1249/00005768-199307000-00011.

385. Bartlett DB, Fox O, McNulty CL, Greenwood HL, Murphy L, Sapey E, et al. Habitual physical activity is associated with the maintenance of neutrophil migratory dynamics in healthy older adults. Brain Behav Immun Health. 2016;56:12-20. doi: 10.1016/j.bbi.2016.02.024.

386. Duggal NA, Pollock RD, Lazarus NR, Harridge S, Lord JM. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. Aging Cell. 2018;17(2):e12750. doi: 10.1111/acel.12750.

387. Liu Z, Liang Q, Ren Y, Guo C, Ge X, Wang L, et al. Immunosenescence: molecular mechanisms and diseases. Signal Transduct Target Ther. 2023;8(1):200. doi: 10.1038/s41392-023-01451-2.

388. Zemlin C, Stuhlert C, Schleicher JT, Wormann C, Altmayer L, Lang M, et al. Longitudinal Assessment of Physical Activity, Fitness, Body Composition, Immunological Biomarkers, and Psychological Parameters During the First Year After Diagnosis in Women With Non-Metastatic Breast Cancer: The BEGYN Study Protocol. Front Oncol. 2021;11:762709. doi: 10.3389/fonc.2021.762709.

389. 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(5):e022899. doi: 10.1136/bmjopen-2018-022899.

390. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-81. doi: 10.1016/j.jbi.2008.08.010.

391. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. Can J Appl Sport Sci. 1985;10(3):141-6.

392. Amireault S, Godin G, Lacombe J, Sabiston CM. Validation of the Godin-Shephard Leisure-Time Physical Activity Questionnaire classification coding system using accelerometer assessment among breast cancer survivors. J Cancer Surviv. 2015;9(3):532-40. doi: 10.1007/s11764-015-0430-6.

393. Rock CL, Doyle C, Demark-Wahnefried W, Meyerhardt J, Courneya KS, Schwartz AL, et al. Nutrition and physical activity guidelines for cancer survivors. CA Cancer J Clin. 2012;62(4):243-74. doi: 10.3322/caac.21142.

394. Godin G. The Godin-Shephard Leisure-Time Physical Activity Questionnaire. Health & Fitness Journal of Canada. 2011;4(1):18-22. doi: 10.14288/hfjc.v4i1.82.

395. Amireault S, Godin G. The Godin-Shephard leisure-time physical activity questionnaire: validity evidence supporting its use for classifying healthy adults into active and insufficiently active categories. Percept Mot Skills. 2015;120(2):604-22. doi: 10.2466/03.27.PMS.120v19x7.

396. Migueles JH, Rowlands AV, Huber F, Sabia S, van Hees VT. GGIR: A Research Community–Driven Open Source R Package for Generating Physical Activity and Sleep Outcomes From Multi-Day Raw Accelerometer Data. J Meas Phys Behav. 2019;2(3):188-96. doi: 10.1123/jmpb.2018-0063.

397. Ahmadi MN, Hamer M, Gill JMR, Murphy M, Sanders JP, Doherty A, et al. Brief bouts of device-measured intermittent lifestyle physical activity and its association with major adverse cardiovascular events and mortality in people who do not exercise: a prospective cohort study. Lancet Public Health. 2023;8(10):e800-e10. doi: 10.1016/S2468-2667(23)00183-4.

398. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing. Vienna, Austria. 2023. https://www.R-project.org/.

399. Posit team. RStudio: Integrated Development Environment for R. Posit Software, PBC. Boston, MA. 2023. http://www.posit.co/.

400. van Hees VT, Fang Z, Langford J, Assah F, Mohammad A, da Silva ICM, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. J Appl Physiol (1985). 2014;117(7):738-44. doi: 10.1152/japplphysiol.00421.2014.

401. van Hees VT, Gorzelniak L, Dean León EC, Eder M, Pias M, Taherian S, et al. Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity. PLOS ONE. 2013;8(4):e61691. doi: 10.1371/journal.pone.0061691.

402. van Hees VT, Sabia S, Anderson KN, Denton SJ, Oliver J, Catt M, et al. A Novel, Open Access Method to Assess Sleep Duration Using a Wrist-Worn Accelerometer. PLOS ONE. 2015;10(11):e0142533. doi: 10.1371/journal.pone.0142533.

403. Hildebrand M, van Hees VT, Hansen BH, Ekelund U. Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. Med Sci Sports Exerc. 2014;46(9):1816-24. doi: 10.1249/MSS.0000000000000289.

404. Hildebrand M, Hansen BH, van Hees VT, Ekelund U. Evaluation of raw acceleration sedentary thresholds in children and adults. Scand J Med Sci Sports. 2017;27(12):1814-23. doi: 10.1111/sms.12795.

405. Migueles JH, Cadenas-Sanchez C, Alcantara JMA, Leal-Martin J, Manas A, Ara I, et al. Calibration and Cross-Validation of Accelerometer Cut-Points to Classify Sedentary Time and Physical Activity from Hip and Non-Dominant and Dominant Wrists in Older Adults. Sensors (Basel). 2021;21(10). doi: 10.3390/s21103326.

406. Migueles JH, Aadland E, Andersen LB, Brond JC, Chastin SF, Hansen BH, et al. GRANADA consensus on analytical approaches to assess associations with accelerometer-determined physical behaviours (physical activity, sedentary behaviour and sleep) in epidemiological studies. Br J Sports Med. 2022;56(7):376-84. doi: 10.1136/bjsports-2020-103604.

407. Mahnke YD, Beddall MH, Roederer M. OMIP-017: Human CD4+ helper T-cell subsets including follicular helper cells. Cytometry. 2013;83(5):439-40. doi: 10.1002/cyto.a.22269.

408. Das K, Krzywinski M, Altman N. Quantile regression. Nat Methods. 2019;16(6):451-2. doi: 10.1038/s41592-019-0406-y.

409. Vallance JK, Friedenreich CM, Wang Q, Matthews CE, Yang L, McNeely ML, et al. Associations of device-measured physical activity and sedentary time with quality of life and fatigue in newly diagnosed breast cancer patients: Baseline results from the AMBER cohort study. Cancer. 2023;129(2):296-306. doi: 10.1002/cncr.34531.

410. Kokla M, Virtanen J, Kolehmainen M, Paananen J, Hanhineva K. Random forest-based imputation outperforms other methods for imputing LC-MS metabolomics data: a comparative study. BMC Bioinformatics. 2019;20(1):492. doi: 10.1186/s12859-019-3110-0.

411. Chin W. The Partial Least Squares Approach to Structural Equation Modeling. In: Marcoulides GA, editor. Modern Methods for Business Research. Mahwah, NJ: Lawrence Erlbaum Associates; 1998. p. 295-336.

412. Kucheryavskiy S. mdatools ─ R package for chemometrics. Chemometrics and Intelligent Laboratory Systems. 2020;198. doi: 10.1016/j.chemolab.2020.103937.

413. Richardson JTE. Eta squared and partial eta squared as measures of effect size in educational research. Educ Res Rev. 2011;6(2):135-47. doi: 10.1016/j.edurev.2010.12.001.

414. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd ed. New York, NY: Routledge; 1988.

415. Kassambara A. rstatix: Pipe-Friendly Framework for Basic Statistical Tests. 2023. https://rpkgs.datanovia.com/rstatix/.

416. Mir N, Burke O, Yates S, Rajasekaran T, Chan J, Szmulewitz R, et al. Androgen receptor pathway inhibitors, prostate cancer, and older adults: a global Young International Society of Geriatric Oncology drug review. Ther Adv Med Oncol. 2023;15:1-18. doi: 10.1177/17588359221149887.

417. Bylow K, Mohile SG, Stadler WM, Dale W. Does androgen-deprivation therapy accelerate the development of frailty in older men with prostate cancer?: a conceptual review. Cancer. 2007;110(12):2604-13. doi: 10.1002/cncr.23084.

418. Papadopoulos E, Leach HJ, Tomlinson G, Durbano S, Danyluk JM, Sabiston CM, et al. Factors predicting gains in moderate-to-vigorous physical activity in prostate cancer survivors on androgen deprivation therapy. Support Care Cancer. 2022;30(11):9011-8. doi: 10.1007/s00520-022-07300-2.

419. Salerno EA, Culakova E, Kleckner AS, Heckler CE, Lin PJ, Matthews CE, et al. Physical Activity Patterns and Relationships With Cognitive Function in Patients With Breast Cancer Before, During, and After Chemotherapy in a Prospective, Nationwide Study. J Clin Oncol. 2021;39(29):3283-92. doi: 10.1200/jco.20.03514.

420. Galvao DA, Newton RU, Gardiner RA, Girgis A, Lepore SJ, Stiller A, et al. Compliance to exercise-oncology guidelines in prostate cancer survivors and associations with psychological distress, unmet supportive care needs, and quality of life. Psychooncology. 2015;24(10):1241-9. doi: 10.1002/pon.3882.

421. Ozdemir K, Keser I, Sen I, Ozgur Tan M. Investigating the relationships between quality of life, fatigue and leisure time physical activity in prostate cancer patients. J Back Musculoskelet Rehabil. 2019;32(3):497-503. doi: 10.3233/BMR-181220.

422. Sung MR, Patel MV, Djalalov S, Le LW, Shepherd FA, Burkes RL, et al. Evolution of Symptom Burden of Advanced Lung Cancer Over a Decade. Clin Lung Cancer. 2017;18(3):274-80.e6. doi: 10.1016/j.cllc.2016.12.010.

423. Michael YL, Wu C, Pan K, Seguin-Fowler RA, Garcia DO, Zaslavsky O, et al. Postmenopausal Breast Cancer and Physical Function Change: A Difference-in-Differences Analysis. J Am Geriatr Soc. 2020;68(5):1029-36. doi: 10.1111/jgs.16323.

424. Herbolsheimer F, Riepe MW, Peter R. Cognitive function and the agreement between self-reported and accelerometer-accessed physical activity. BMC Geriatr. 2018;18(1):56. doi: 10.1186/s12877-018-0747-x.

425. Lange M, Joly F, Vardy J, Ahles T, Dubois M, Tron L, et al. Cancer-related cognitive impairment: an update on state of the art, detection, and management strategies in cancer survivors. Ann Oncol. 2019;30(12):1925-40. doi: 10.1093/annonc/mdz410.

426. Gao Z, Liu W, McDonough DJ, Zeng N, Lee JE. The Dilemma of Analyzing Physical Activity and Sedentary Behavior with Wrist Accelerometer Data: Challenges and Opportunities. J Clin Med. 2021;10(24). doi: 10.3390/jcm10245951.

427. Ayabe M, Kumahara H, Morimura K, Tanaka H. Epoch length and the physical activity bout analysis: An accelerometry research issue. BMC Res Notes. 2013;6(1):20. doi: 10.1186/1756-0500-6-20.

428. Jakicic JM, Kraus WE, Powell KE, Campbell WW, Janz KF, Troiano RP, et al. Association between Bout Duration of Physical Activity and Health: Systematic Review. Med Sci Sports Exerc. 2019;51(6):1213-9. doi: 10.1249/MSS.0000000000001933.

429. Migueles JH, Cadenas-Sanchez C, Ekelund U, Delisle Nystrom C, Mora-Gonzalez J, Lof M, et al. Accelerometer Data Collection and Processing Criteria to Assess Physical Activity and Other Outcomes: A Systematic Review and Practical Considerations. Sports Med. 2017;47(9):1821-45. doi: 10.1007/s40279-017-0716-0.

430. Neishabouri A, Nguyen J, Samuelsson J, Guthrie T, Biggs M, Wyatt J, et al. Quantification of acceleration as activity counts in ActiGraph wearable. Sci Rep. 2022;12(1):11958. doi: 10.1038/s41598-022-16003-x.

431. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. CMAJ. 2006;174(6):801-9. doi: 10.1503/cmaj.051351.

432. Felipe B. Schuch, Davy Vancampfort, Joseph Firth, Simon Rosenbaum, Philip B. Ward, Edson S. Silva, et al. Physical Activity and Incident Depression: A Meta-Analysis of Prospective Cohort Studies. Am J Psychiatry. 2018;175(7):631-48. doi: 10.1176/appi.ajp.2018.17111194.

433. Friedenreich CM, Ryder-Burbidge C, McNeil J. Physical activity, obesity and sedentary behavior in cancer etiology: epidemiologic evidence and biologic mechanisms. Mol Oncol. 2021;15(3):790-800. doi: 10.1002/1878-0261.12772.

434. Perry AS, Dooley EE, Master H, Spartano NL, Brittain EL, Gabriel KP. Physical Activity Over the Lifecourse and Cardiovascular Disease. Circ Res. 2023;132(12):1725-40. doi: 10.1161/CIRCRESAHA.123.322121.

435. Zhao X, Hu F. Relationship Between Physical Fitness, Anthropometric Measurement, and Bone Health in Adult Men. Clin Nurs Res. 2023;32(4):733-41. doi: 10.1177/10547738211060937.

436. Li R, Xia J, Zhang XI, Gathirua-Mwangi WG, Guo J, Li Y, et al. Associations of Muscle Mass and Strength with All-Cause Mortality among US Older Adults. Med Sci Sports Exerc. 2018;50(3):458-67. doi: 10.1249/MSS.0000000000001448.

437. Robsahm TE, Falk RS, Heir T, Sandvik L, Vos L, Erikssen JE, et al. Measured cardiorespiratory fitness and self-reported physical activity: associations with cancer risk and death in a long-term prospective cohort study. Cancer Med. 2016;5(8):2136-44. doi: 10.1002/cam4.773.

438. Mueller S, Winzer EB, Duvinage A, Gevaert AB, Edelmann F, Haller B, et al. Effect of High-Intensity Interval Training, Moderate Continuous Training, or Guideline-Based Physical Activity Advice on Peak Oxygen Consumption in Patients With Heart Failure With Preserved Ejection Fraction: A Randomized Clinical Trial. JAMA. 2021;325(6):542-51. doi: 10.1001/jama.2020.26812.

439. Peck SS, Esmaeilzadeh M, Rankin K, Shalmon T, Fan CS, Somerset E, et al. Self-Reported Physical Activity, QoL, Cardiac Function, and Cardiorespiratory Fitness in Women With HER2+ Breast Cancer. JACC CardioOncol. 2022;4(3):387-400. doi: 10.1016/j.jaccao.2022.06.006.

440. Blair CK, Morey MC, Desmond RA, Cohen HJ, Sloane R, Snyder DC, et al. Light-intensity activity attenuates functional decline in older cancer survivors. Med Sci Sports Exerc. 2014;46(7):1375-83. doi: 10.1249/MSS.0000000000000241.

441. Li J, Cao D, Huang Y, Chen Z, Wang R, Dong Q, et al. Sleep duration and health outcomes: an umbrella review. Sleep Breath. 2022;26(3):1479-501. doi: 10.1007/s11325-021-02458-1.

442. Palesh OG, Roscoe JA, Mustian KM, Roth T, Savard J, Ancoli-Israel S, et al. Prevalence, Demographics, and Psychological Associations of Sleep Disruption in Patients With Cancer: University of Rochester Cancer Center ─ Community Clinical Oncology Program. J Clin Oncol. 2010;28(2):292-8. doi: 10.1200/jco.2009.22.5011.

443. Berger AM, Mooney K, Alvarez-Perez A, Breitbart WS, Carpenter KM, Cella D, et al. Cancer-Related Fatigue, Version 2.2015. J Natl Compr Canc Netw. 2015;13(8):1012-39. doi: 10.6004/jnccn.2015.0122.

444. Bandara V, Capp A, Ahmed G, Arm J, Martin J. Assessment and predictors of fatigue in men with prostate cancer receiving radiotherapy and androgen deprivation therapy. J Med Imaging Radiat Oncol. 2019;63(5):683-90. doi: 10.1111/1754-9485.12922.

445. Bergin ART, Hovey E, Lloyd A, Marx G, Parente P, Rapke T, et al. Docetaxel-related fatigue in men with metastatic prostate cancer: a descriptive analysis. Support Care Cancer. 2017;25(9):2871-9. doi: 10.1007/s00520-017-3706-8.

446. Sparasci D, Napoli I, Rossi L, Pereira-Mestre R, Manconi M, Treglia G, et al. Prostate Cancer and Sleep Disorders: A Systematic Review. Cancers (Basel). 2022;14(7):1784. doi: 10.3390/cancers14071784.

447. Mondal S, Edwards S, Wibowo E, Ahmed H, Wassersug RJ, Ellis J, et al. Evaluating Patterns and Factors Related to Sleep Disturbances in Prostate Cancer Patients. Healthcare (Basel). 2022;10(5):832. doi: 10.3390/healthcare10050832.

448. Wiggins EK, Oyekunle T, Howard LE, Markt SC, Mucci LA, Bliwise DL, et al. Sleep quality and prostate cancer aggressiveness: Results from the REDUCE trial. Prostate. 2020;80(15):1304-13. doi: 10.1002/pros.24052.

449. van Coevorden-van Loon EMP, Horemans HHLD, Heijenbrok-Kal MH, van den Berg-Emons RJG, Rozenberg R, Vincent AJPE, et al. Physical fitness and its association with fatigue in patients with low-grade glioma. Disabil Rehabil. 2023;45(20):3323-9. doi: 10.1080/09638288.2022.2125084.

450. Marker RJ, Ostendorf DM, Leach HJ, Peters JC. Cancer-related fatigue mediates the relationships between physical fitness and attendance and quality of life after participation in a clinical exercise program for survivors of cancer. Qual Life Res. 2022;31(11):3201-10. doi: 10.1007/s11136-022-03173-4.

451. Schofield C, Newton RU, Cohen PA, Galvao DA, McVeigh JA, Hart NH, et al. Activity Behaviors and Physiological Characteristics of Women With Advanced-Stage Ovarian Cancer: A Preliminary Cross-sectional Investigation. Int J Gynecol Cancer. 2018;28(3):604-13. doi: 10.1097/IGC.0000000000001197.

452. Demark-Wahnefried W, Clipp EC, Morey MC, Pieper CF, Sloane R, Snyder DC, et al. Physical function and associations with diet and exercise: Results of a cross-sectional survey among elders with breast or prostate cancer. Int J Behav Nutr Phys Act. 2004;1(1):16. doi: 10.1186/1479-5868-1-16.

453. O'Neill D, Forman DE. The importance of physical function as a clinical outcome: Assessment and enhancement. Clin Cardiol. 2020;43(2):108-17. doi: 10.1002/clc.23311.

454. Kenkhuis MF, Klingestijn M, Fanshawe AM, Breukink SO, Janssen-Heijnen MLG, Keulen ETP, et al. Longitudinal associations of sedentary behavior and physical activity with body composition in colorectal cancer survivors up to 2 years post treatment. J Cancer Res Clin Oncol. 2023;149(7):4063-75. doi: 10.1007/s00432-022-04267-9.

455. Wang Y-C, Bohannon RW, Li X, Sindhu B, Kapellusch J. Hand-Grip Strength: Normative Reference Values and Equations for Individuals 18 to 85 Years of Age Residing in the United States. J Orthop Sports Phys Ther. 2018;48(9):685-93. doi: 10.2519/jospt.2018.7851.

456. El Assar M, Álvarez-Bustos A, Sosa P, Angulo J, Rodríguez-Mañas L. Effect of Physical Activity/Exercise on Oxidative Stress and Inflammation in Muscle and Vascular Aging. Int J Mol Sci. 2022;23(15):8713. doi: 10.3390/ijms23158713.

457. Dungey M, Young HML, Churchward DR, Burton JO, Smith AC, Bishop NC. Regular exercise during haemodialysis promotes an anti-inflammatory leucocyte profile. Clin Kidney J. 2017;10(6):813-21. doi: 10.1093/ckj/sfx015.

458. Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. J Leukoc Biol. 2019;106(2):309-22. doi: 10.1002/JLB.4RI0818-311R.

459. Kitamura T, Doughty-Shenton D, Cassetta L, Fragkogianni S, Brownlie D, Kato Y, et al. Monocytes Differentiate to Immune Suppressive Precursors of Metastasis-Associated Macrophages in Mouse Models of Metastatic Breast Cancer. Front Immunol. 2018;8. doi: 10.3389/fimmu.2017.02004.

460. Chun E, Lavoie S, Michaud M, Gallini CA, Kim J, Soucy G, et al. CCL2 Promotes Colorectal Carcinogenesis by Enhancing Polymorphonuclear Myeloid-Derived Suppressor Cell Population and Function. Cell Reports. 2015;12(2):244-57. doi: 10.1016/j.celrep.2015.06.024.

461. Hayashi T, Fujita K, Nojima S, Hayashi Y, Nakano K, Ishizuya Y, et al. Peripheral blood monocyte count reflecting tumor-infiltrating macrophages is a predictive factor of adverse pathology in radical prostatectomy specimens. Prostate. 2017;77(14):1383-8. doi: 10.1002/pros.23398.

462. Magrowski Ł, Masri O, Ciepaeł J, Depowska G, Nowicka Z, Stando R, et al. Pre-Treatment Hemoglobin Concentration and Absolute Monocyte Count as Independent Prognostic Factors for Survival in Localized or Locally Advanced Prostate Cancer Patients Undergoing Radiotherapy. Biomedicines. 2022;10(10):2514. doi: 10.3390/biomedicines10102514.

463. Wang Y-Q, Zhu Y-J, Pan J-H, Xu F, Shao X-G, Sha J-J, et al. Peripheral monocyte count: an independent diagnostic and prognostic biomarker for prostate cancer ─ a large Chinese cohort study. Asian J Androl. 2017;19(5):579-85. doi: 10.4103/1008-682x.186185.

464. Åberg A-M, Bergström SH, Thysell E, Tjon-Kon-Fat L-A, Nilsson JA, Widmark A, et al. High Monocyte Count and Expression of S100A9 and S100A12 in Peripheral Blood Mononuclear Cells Are Associated with Poor Outcome in Patients with Metastatic Prostate Cancer. Cancers. 2021;13(10):2424. doi: 10.3390/cancers13102424.

465. Wadley AJ, Roberts MJ, Creighton J, Thackray AE, Stensel DJ, Bishop NC. Higher levels of physical activity are associated with reduced tethering and migration of pro-inflammatory monocytes in males with central obesity. Exerc Immunol Rev. 2021;27:54-66.

466. Timmerman KL, Flynn MG, Coen PM, Markofski MM, Pence BD. Exercise training-induced lowering of inflammatory (CD14+CD16+) monocytes: a role in the anti-inflammatory influence of exercise? J Leukoc Biol. 2008;84(5):1271-8. doi: 10.1189/jlb.0408244.

467. Mulder K, Patel AA, Kong WT, Piot C, Halitzki E, Dunsmore G, et al. Cross-tissue single-cell landscape of human monocytes and macrophages in health and disease. Immunity. 2021;54(8):1883-900.e5. doi: 10.1016/j.immuni.2021.07.007.

468. Schlecker E, Stojanovic A, Eisen C, Quack C, Falk CS, Umansky V, et al. Tumor-Infiltrating Monocytic Myeloid-Derived Suppressor Cells Mediate CCR5-Dependent Recruitment of Regulatory T Cells Favoring Tumor Growth. J Immunol. 2012;189(12):5602-11. doi: 10.4049/jimmunol.1201018.

469. Tiemessen MM, Jagger AL, Evans HG, van Herwijnen MJC, John S, Taams LS. CD4+CD25+Foxp3+ regulatory T cells induce alternative activation of human monocytes/macrophages. Proc Natl Acad Sci USA. 2007;104(49):19446-51. doi: doi:10.1073/pnas.0706832104.

470. Liyanage UK, Moore TT, Joo H-G, Tanaka Y, Herrmann V, Doherty G, et al. Prevalence of Regulatory T Cells Is Increased in Peripheral Blood and Tumor Microenvironment of Patients with Pancreas or Breast Adenocarcinoma. J Immunol. 2002;169(5):2756-61. doi: 10.4049/jimmunol.169.5.2756.

471. Ichihara F, Kono K, Takahashi A, Kawaida H, Sugai H, Fujii H. Increased populations of regulatory T cells in peripheral blood and tumor-infiltrating lymphocytes in patients with gastric and esophageal cancers. Clin Cancer Res. 2003;9(12):4404-8.

472. Hiraoka N, Onozato K, Kosuge T, Hirohashi S. Prevalence of FOXP3+ Regulatory T Cells Increases During the Progression of Pancreatic Ductal Adenocarcinoma and Its Premalignant Lesions. Clin Cancer Res. 2006;12(18):5423-34. doi: 10.1158/1078-0432.CCR-06-0369.

473. Karpisheh V, Mousavi SM, Naghavi Sheykholeslami P, Fathi M, Mohammadpour Saray M, Aghebati-Maleki L, et al. The role of regulatory T cells in the pathogenesis and treatment of prostate cancer. Life Sci. 2021;284:119132. doi: 10.1016/j.lfs.2021.119132.

474. Emery A, Moore S, Turner JE, Campbell JP. Reframing How Physical Activity Reduces The Incidence of Clinically-Diagnosed Cancers: Appraising Exercise-Induced Immuno-Modulation As An Integral Mechanism. Front Oncol. 2022;12:788113. doi: 10.3389/fonc.2022.788113.

475. Gustafson MP, DiCostanzo AC, Wheatley CM, Kim C-H, Bornschlegl S, Gastineau DA, et al. A systems biology approach to investigating the influence of exercise and fitness on the composition of leukocytes in peripheral blood. J Immunother Cancer. 2017;5(1):30. doi: 10.1186/s40425-017-0231-8.

476. Templeton AJ, McNamara MA, Seruga B, Vera-Badillo FE, Aneja P, Ocana A, et al. Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. J Natl Cancer Inst. 2014;106(6). doi: 10.1093/jnci/dju124.

477. Merrill RM, Bird JS. Effect of young age on prostate cancer survival: a population-based assessment (United States). Cancer Causes Control. 2002;13(5):435-43. doi: 10.1023/a:1015764507609.

478. Cao J, Zhu X, Zhao X, Li X-F, Xu R. Neutrophil-to-Lymphocyte Ratio Predicts PSA Response and Prognosis in Prostate Cancer: A Systematic Review and Meta-Analysis. PLOS ONE. 2016;11(7):e0158770. doi: 10.1371/journal.pone.0158770.

479. You Y, Chen Y, Fang W, Li X, Wang R, Liu J, et al. The association between sedentary behavior, exercise, and sleep disturbance: A mediation analysis of inflammatory biomarkers. Front Immunol. 2023;13. doi: 10.3389/fimmu.2022.1080782.

480. Mavropalias G, Sim M, Taaffe DR, Galvao DA, Spry N, Kraemer WJ, et al. Exercise medicine for cancer cachexia: targeted exercise to counteract mechanisms and treatment side effects. J Cancer Res Clin Oncol. 2022;148(6):1389-406. doi: 10.1007/s00432-022-03927-0.

481. Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. Cell Metab. 2018;27(1):10-21. doi: 10.1016/j.cmet.2017.09.015.

482. Dalla Via J, Owen PJ, Daly RM, Mundell NL, Livingston PM, Rantalainen T, et al. Musculoskeletal Responses to Exercise Plus Nutrition in Men with Prostate Cancer on Androgen Deprivation: A 12-Month RCT. Med Sci Sports Exerc. 2021;53(10):2054-65. doi: 10.1249/mss.0000000000002682.

483. Evans JW. Periodized Resistance Training for Enhancing Skeletal Muscle Hypertrophy and Strength: A Mini-Review. Front Physiol. 2019;10. doi: 10.3389/fphys.2019.00013.

484. Mølmen KS, Øfsteng SJ, Rønnestad BR. Block periodization of endurance training ─ a systematic review and meta-analysis. Open Access J Sports Med. 2019;10:145-60. doi: 10.2147/OAJSM.S180408.

485. Rhea MR, Alderman BL. A Meta-Analysis of Periodized versus Nonperiodized Strength and Power Training Programs. Res Q Exercise and Sport. 2004;75(4):413-22. doi: 10.1080/02701367.2004.10609174.

486. Bates-Fraser LC, Riley S, Stopforth C, Moertl K, Edgar K, Stoner L, et al. Home-based exercise improves quality of life in breast and prostate cancer survivors: A meta-analysis. PLOS ONE. 2023;18(4):e0284427. doi: 10.1371/journal.pone.0284427.

487. Lopez P, Taaffe DR, Newton RU, Galvao DA. Resistance Exercise Dosage in Men with Prostate Cancer: Systematic Review, Meta-analysis, and Meta-regression. Med Sci Sports Exerc. 2021;53(3):459-69. doi: 10.1249/mss.0000000000002503.

488. Ramos JS, Dalleck LC, Tjonna AE, Beetham KS, Coombes JS. The Impact of High-Intensity Interval Training Versus Moderate-Intensity Continuous Training on Vascular Function: a Systematic Review and Meta-Analysis. Sports Med. 2015;45(5):679-92. doi: 10.1007/s40279-015-0321-z.

489. Hwang CL, Lim J, Yoo JK, Kim HK, Hwang MH, Handberg EM, et al. Effect of all-extremity high-intensity interval training vs. moderate-intensity continuous training on aerobic fitness in middle-aged and older adults with type 2 diabetes: A randomized controlled trial. Exp Gerontol. 2019;116:46-53. doi: 10.1016/j.exger.2018.12.013.

490. Zhu Q, Xiong X, Zheng Q, Deng Q, Hao Y, Liu D, et al. High-intensity interval training versus moderate-intensity continuous training for localized prostate cancer under active surveillance: a systematic review and network meta-analysis. Prostate Cancer and Prostatic Dis. 2024. doi: 10.1038/s41391-024-00801-7.

491. Herranz-Gómez A, Cuenca-Martínez F, Suso-Martí L, Varangot-Reille C, Calatayud J, Blanco-Díaz M, et al. Effectiveness of HIIT in patients with cancer or cancer survivors: An umbrella and mapping review with meta-meta-analysis. Scand J Med Sci Sports. 2022;32(11):1522-49. doi: 10.1111/sms.14223.

492. Djurhuus SS, Simonsen C, Toft BG, Thomsen SN, Wielsøe S, Røder MA, et al. Exercise training to increase tumour natural killer-cell infiltration in men with localised prostate cancer: a randomised controlled trial. BJU Int. 2023;131(1):116-24. doi: 10.1111/bju.15842.

493. Bartlett DB, Hanson ED, Lee JT, Wagoner CW, Harrell EP, Sullivan SA, et al. The Effects of 16 Weeks of Exercise Training on Neutrophil Functions in Breast Cancer Survivors. Front Immunol. 2021;12. doi: 10.3389/fimmu.2021.733101.

494. Fathollahi Shoorabeh F, Dabidiroshan V, Sheikh Saraf B, Nuri R. Investigating the Effects of Regular Resistance Training and Prostatic Massage on Proinflammatory Markers and Serum Prostate-Specific Antigen Levels in Males with Prostate Cancer. Middle East J Rehabil Health. 2016;3(1):e33651. doi: 10.17795/mejrh-33651.

495. Yin X, Xiao Y, Li F, Qi S, Yin Z, Gao J. Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Prostate Cancer: A Systematic Review and Meta-analysis. Medicine (Baltimore). 2016;95(3):e2544. doi: 10.1097/md.0000000000002544.

496. Kruijsen-Jaarsma M, Révész D, Bierings MB, Buffart LM, Takken T. Effects of exercise on immune function in patients with cancer: a systematic review. Exerc Immunol Rev. 2013;19:120-43.

497. Valenzuela PL, Saco-Ledo G, Santos-Lozano A, Morales JS, Castillo-García A, Simpson RJ, et al. Exercise Training and Natural Killer Cells in Cancer Survivors: Current Evidence and Research Gaps Based on a Systematic Review and Meta-analysis. Sports Med Open. 2022;8(1):36. doi: 10.1186/s40798-022-00419-w.

498. Rumpf C, Proschinger S, Schenk A, Bloch W, Lampit A, Javelle F, et al. The Effect of Acute Physical Exercise on NK-Cell Cytolytic Activity: A Systematic Review and Meta-Analysis. Sports Med. 2021;51(3):519-30. doi: 10.1007/s40279-020-01402-9.

499. Clifford BK, Kaakoush NO, Tedla N, Goldstein D, Simar D. The effect of exercise intensity on the inflammatory profile of cancer survivors: A randomised crossover study. Eur J Clin Invest. 2023;53(7):e13984. doi: 10.1111/eci.13984.

500. Kraemer MB, Priolli DG, Reis IGM, Pelosi AC, Garbuio ALP, Messias LHD. Home-based, supervised, and mixed exercise intervention on functional capacity and quality of life of colorectal cancer patients: a meta-analysis. Sci Rep. 2022;12(1):2471. doi: 10.1038/s41598-022-06165-z.

501. Larsen RF, Jarden M, Minet LR, Frølund UC, Abildgaard N. Supervised and home-based physical exercise in patients newly diagnosed with multiple myeloma – a randomized controlled feasibility study. Pilot Feasibility Stud. 2019;5(1):130. doi: 10.1186/s40814-019-0518-2.

502. Swartz MC, Lewis ZH, Lyons EJ, Jennings K, Middleton A, Deer RR, et al. Effect of Home- and Community-Based Physical Activity Interventions on Physical Function Among Cancer Survivors: A Systematic Review and Meta-Analysis. Arch Phys Med Rehabil. 2017;98(8):1652-65. doi: 10.1016/j.apmr.2017.03.017.

503. Scheiermann C, Frenette PS, Hidalgo A. Regulation of leucocyte homeostasis in the circulation. Cardiovasc Res. 2015;107(3):340-51. doi: 10.1093/cvr/cvv099.

504. Hwang M, Canzoniero JV, Rosner S, Zhang G, White JR, Belcaid Z, et al. Peripheral blood immune cell dynamics reflect antitumor immune responses and predict clinical response to immunotherapy. J Immunother Cancer. 2022;10(6):e004688. doi: 10.1136/jitc-2022-004688.

505. Dumeaux V, Fjukstad B, Fjosne HE, Frantzen J-O, Holmen MM, Rodegerdts E, et al. Interactions between the tumor and the blood systemic response of breast cancer patients. PLOS Comput Biol. 2017;13(9):e1005680. doi: 10.1371/journal.pcbi.1005680.

506. Sharma D, Farrar JD. Adrenergic regulation of immune cell function and inflammation. Semin Immunopathol. 2020;42(6):709-17. doi: 10.1007/s00281-020-00829-6.

507. Belardelli F. Role of interferons and other cytokines in the regulation of the immune response. APMIS. 1995;103:161-79. doi: 10.1111/j.1699-0463.1995.tb01092.x.

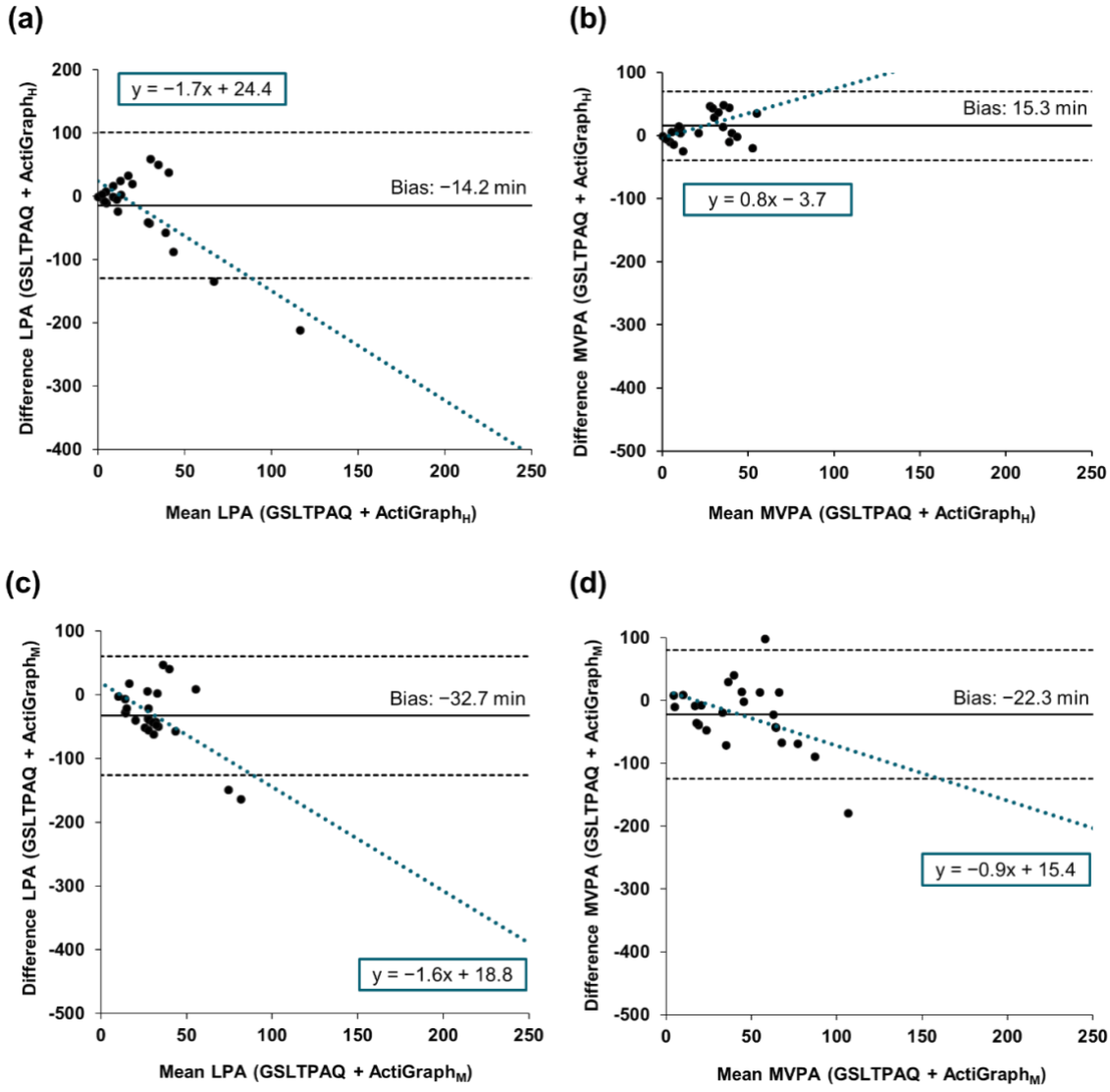
508. Holmen Olofsson G, Mikkelsen MK, Ragle A-M, Christiansen AB, Olsen AP, Heide-Ottosen L, et al. High Intensity Aerobic exercise training and Immune cell Mobilization in patients with lung cancer (HI AIM) – a randomized controlled trial. BMC Cancer. 2022;22(1):246. doi: 10.1186/s12885-022-09349-y.

509. Kjeldsted E, Ammitzbøll G, Jørgensen LB, Lodin A, Bojesen RD, Ceballos SG, et al. Neo-train: study protocol and feasibility results for a two-arm randomized controlled trial investigating the effect of supervised exercise during neoadjuvant chemotherapy on tumour response in patients with breast cancer. BMC Cancer. 2023;23(1):777. doi: 10.1186/s12885-023-11284-5.

510. Ünsal Delialioğlu S, Mandıroğlu S, Göksel F. Awareness and attitudes of oncology physicians recommending exercise to patients with cancer. Turk J Phys Med Rehabil. 2022;68(1):70-5. doi: 10.5606/tftrd.2022.7120.

511. Mina DS, Sabiston CM, Au D, Fong AJ, Capozzi LC, Langelier D, et al. Connecting people with cancer to physical activity and exercise programs: a pathway to create accessibility and engagement. Curr Oncol. 2018;25(2):149-62. doi: 10.3747/co.25.3977.

Supplementary material



Supplemental Figure 1. Bland-Altman plots showing the agreement between daily accelerometer-derived and self-reported physical activity. Accelerometer-derived physical activity estimates were calculated using minimal requirements of 10 min bouts. Agreement of **(a)** light physical activity (LPA) estimates from the Godin-Shephard Leisure-Time Physical Activity Questionnaire (GSLTPAQ) and ActiGraph$_H$, **(b)** moderate-to-vigorous physical activity (MVPA) estimates from the GSLTPAQ and ActiGraph$_H$, **(c)** LPA estimates from the GSLTPAQ and ActiGraph$_M$ and **(d)** LPA estimates from the GSLTPAQ and ActiGraph$_M$. The unit of measurement for physical activity depicted in all plots is minutes (min). Dashed lines in black represent the upper and lower limits of agreement. Dotted lines in blue represent regression lines and blue boxes include regression line equations.

Supplemental Table 1. Partial least squares regression results on the association of immune cells and inflammation markers with accelerometer-derived physical activity estimates from ActiGraph$_H$ and ActiGraph$_M$.

Model information	Model statistics (ActiGraph$_H$)					Model information	Model statistics (ActiGraph$_M$)				
	R^2	Regression coeff. β	95% CI	t-value	p-value		R^2	Regression coeff. β	95% CI	t-value	p-value
Platelets [a]	0.32					**Platelets** [a]	0.32				
BMI		−0.32	−0.53, −0.11	−3.15	**.004**	BMI		−0.32	−0.53, −0.11	−3.15	**.004**
Time since diagnosis		−0.42	−0.72, −0.11	−2.83	**.009**	Time since diagnosis		−0.42	−0.72, −0.11	−2.83	**.009**
Leukocytes [a]	0.22					**Leukocytes** [a]	0.22				
Sedentary behaviour		0.19	−0.08, 0.47	1.46	.157	Sedentary behaviour		0.19	−0.08, 0.47	1.46	.157
ADT		0.28	−0.03, 0.60	1.86	.074	ADT		0.28	−0.03, 0.60	1.86	.074
Prostate cancer stage		0.23	−0.05, 0.51	1.69	.104	Prostate cancer stage		0.23	−0.05, 0.51	1.69	.104
Neutrophils [a]	0.26					**Neutrophils** [a]	0.26				
Sleep		−0.18	−0.47, 0.11	−1.29	.209	Sleep		−0.18	−0.47, 0.11	−1.29	.209
ADT		0.25	0, 0.50	2.09	**.047**	ADT		0.25	0, 0.50	2.09	**.047**
Prostate cancer stage		0.32	0.05, 0.59	2.43	**.022**	Prostate cancer stage		0.32	0.05, 0.59	2.43	**.022**
Neutrophils (relative)	0.41					**Neutrophils (relative)**	0.43				
Sleep		−0.19	−0.32, −0.06	−3.05	**.005**	Sleep		−0.23	−0.39, −0.07	−2.92	**.007**
MVPA		0.21	−0.03, 0.46	1.82	.081	Age		−0.31	−0.53, −0.09	−2.87	**.008**
Age		−0.26	−0.45, −0.08	−2.89	**.008**	Prostate cancer stage		0.26	0.09, 0.43	3.15	**.004**
Prostate cancer stage		0.22	0.09, 0.35	3.52	**.002**	Time since diagnosis		−0.19	−0.41, 0.03	−1.74	.095
Monocytes	0.38					**Monocytes**	0.38				
Sleep		0.19	−0.16, 0.54	1.08	.290	Sedentary behaviour		0.18	0.03, 0.33	2.47	**.020**
Light physical activity		−0.19	−0.36, −0.03	−2.40	**.024**	Light physical activity		−0.22	−0.48, 0.04	−1.73	.095
Age		0.25	0.02, 0.48	2.18	**.039**	Age		0.22	0, 0.44	2.02	.054
Time since diagnosis		0.29	−0.51, 1.08	0.71	.482	Time since diagnosis		0.25	−0.43, 0.93	0.73	.473
Monocytes (relative)	0.42					**Monocytes (relative)**	0.43				
Sleep		0.24	−0.04, 0.52	1.72	.098	Light physical activity		−0.22	−0.46, 0.02	−1.91	.068
Age		0.29	0.09, 0.49	2.93	**.007**	Sleep		0.19	−0.03, 0.41	1.74	.095
Time since diagnosis		0.36	−0.20, 0.93	1.30	.205	Age		0.23	0.07, 0.38	2.98	**.006**
						Time since diagnosis		0.29	−0.16, 0.73	1.31	.203

Model information	Model statistics (ActiGraph$_H$)					Model information	Model statistics (ActiGraph$_M$)				
	R^2	Regression coeff. β	95% CI	t-value	p-value		R^2	Regression coeff. β	95% CI	t-value	p-value
Lymphocytes	0.18					**Lymphocytes**	0.17				
Sedentary behaviour		0.15	−0.05, 0.35	1.50	.146	Sedentary behaviour		0.15	−0.02, 0.31	1.86	.074
MVPA		−0.15	−0.35, 0.06	−1.47	.155	MVPA		−0.13	−0.28, 0.02	−1.73	.096
Age		0.14	−0.07, 0.34	1.37	.182	Age		0.13	−0.08, 0.35	1.27	.214
ADT		0.26	−0.20, 0.72	1.16	.256	ADT		0.25	−0.23, 0.73	1.10	.282
Lymphocytes (relative)	0.11					**Lymphocytes (relative)**	0.09				
MVPA		−0.15	−0.50, 0.20	−0.87	.392	Age		0.20	−0.17, 0.57	1.14	.267
Age		0.16	−0.10, 0.42	1.27	.216	Prostate cancer stage		−0.16	−0.43, 0.10	−1.27	.216
Prostate cancer stage		−0.13	−0.33, 0.08	−1.31	.202						
NK cells [a]	0.27					**NK cells** [a]	0.27				
Age		0.32	0.08, 0.56	2.75	**.011**	Age		0.32	0.08, 0.56	2.75	**.011**
Prostate cancer stage		−0.31	−0.50, −0.12	−3.35	**.002**	Prostate cancer stage		−0.31	−0.50, −0.12	−3.35	**.002**
NK^{dim} cells [a]	0.28					**NK^{dim} cells** [a]	0.28				
Age		0.33	0.09, 0.57	2.80	**.009**	Age		0.33	0.09, 0.57	2.80	**.009**
Prostate cancer stage		−0.31	−0.50, −0.12	−3.34	**.003**	Prostate cancer stage		−0.31	−0.50, −0.12	−3.34	**.003**
NK^{bright} cells	0.07					**NK^{bright} cells**	0.09				
Sedentary behaviour		−0.07	−0.49, 0.35	−0.33	.747	Sedentary behaviour		−0.11	−0.61, 0.39	−0.42	.681
Light physical activity		0.09	−0.44, 0.62	0.32	.751	Light physical activity		0.17	−0.32, 0.67	0.71	.487
Age		−0.08	−0.23, 0.07	−1.17	.252	ADT		0.13	−0.17, 0.42	0.93	.363
ADT		0.12	−0.14, 0.37	0.97	.343						
Time since diagnosis		−0.08	−0.36, 0.20	−0.59	.561						
B cells [a]	0.14					**B cells** [a]	0.14				
Sleep		−0.14	−0.53, 0.25	−0.73	.472	Sleep		−0.14	−0.53, 0.25	−0.73	.472
ADT		0.24	0.03, 0.46	2.33	**.028**	ADT		0.24	0.03, 0.46	2.33	**.028**
Prostate cancer stage		0.17	−0.13, 0.47	1.18	.250	Prostate cancer stage		0.17	−0.13, 0.47	1.18	.250
T cells [a]	0.22					**T cells** [a]	0.22				
Sedentary behaviour		0.20	−0.14, 0.55	1.22	.234	Sedentary behaviour		0.20	−0.14, 0.55	1.22	.234
ADT		0.41	0.02, 0.80	2.15	**.041**	ADT		0.41	0.02, 0.80	2.15	**.041**

Model information	Model statistics (ActiGraph$_H$)					Model information	Model statistics (ActiGraph$_M$)				
	R^2	Regression coeff. β	95% CI	t-value	p-value		R^2	Regression coeff. β	95% CI	t-value	p-value
Tc cells	0.20					**Tc cells**	0.21				
Sedentary behaviour		0.15	0.01, 0.29	2.14	**.042**	Sedentary behaviour		0.17	0.01, 0.33	2.23	**.035**
Light physical activity		−0.13	−0.22, −0.04	−2.91	**.007**	MVPA		−0.17	−0.27, −0.07	−3.51	**.002**
MVPA		−0.10	−0.23, 0.03	−1.62	.118	Age		0.17	−0.05, 0.38	1.58	.127
Age		0.14	−0.04, 0.31	1.60	.122	Prostate cancer stage		0.16	−0.07, 0.39	1.43	.164
Prostate cancer stage		0.13	−0.06, 0.32	1.39	.176						
Th cells [a]	0.27					**Th cells** [a]	0.27				
ADT		0.52	0.19, 0.85	3.24	**.003**	ADT		0.52	0.19, 0.85	3.24	**.003**
Th1 cells [a]	0.19					**Th1 cells** [a]	0.19				
Age		0.39	−0.03, 0.81	1.89	.070	Age		0.39	−0.03, 0.81	1.89	.070
ADT		0.25	−0.33, 0.82	0.88	.387	ADT		0.25	−0.33, 0.82	0.88	.387
Th2 cells	0.30					**Th2 cells**	0.25				
MVPA		−0.27	−0.57, 0.04	−1.76	.090	Light physical activity		0.20	0.01, 0.40	2.14	**.042**
ADT		0.24	0.02, 0.47	2.20	**.037**	ADT		0.22	0.05, 0.38	2.73	**.011**
BMI		0.30	−0.48, 1.09	0.77	.448	BMI		0.27	−0.45, 0.98	0.75	.460
Prostate cancer stage		0.25	−0.10, 0.61	1.45	.160	Prostate cancer stage		0.23	−0.10, 0.55	1.40	.175
Th17 cells	0.40					**Th17 cells**	0.35				
MVPA		−0.31	−0.64, 0.02	−1.89	.070	ADT		0.43	0.04, 0.82	2.25	**.033**
ADT		0.40	0, 0.80	2.04	.051	BMI		0.53	−0.34, 1.40	1.23	.230
BMI		0.49	−0.29, 1.27	1.28	.213						
Treg cells [a]	0.29					**Treg cells** [a]	0.29				
Sleep		−0.24	−0.47, −0.01	−2.15	**.041**	Sleep		−0.24	−0.47, −0.01	−2.15	**.041**
Age		−0.17	−0.40, 0.07	−1.48	.152	Age		−0.17	−0.40, 0.07	−1.48	.152
ADT		0.26	0.03, 0.49	2.37	**.026**	ADT		0.26	0.03, 0.49	2.37	**.026**
Prostate cancer stage		0.15	−0.07, 0.38	1.38	.179	Prostate cancer stage		0.15	−0.07, 0.38	1.38	.179
Treg cells (% lymphocytes)	0.34					**Treg cells (% lymphocytes)**	0.31				
Sedentary behaviour		−0.21	−0.35, −0.07	−2.99	**.006**	Sedentary behaviour		−0.19	−0.31, −0.07	−3.23	**.003**
Light physical activity		0.23	0.13, 0.33	4.73	**< .001**	MVPA		0.21	0.14, 0.28	5.95	**<.001**
Age		−0.27	−0.48, −0.06	−2.64	**.014**	Age		−0.26	−0.46, −0.06	−2.66	**.013**

Model information	Model statistics (ActiGraph$_H$)					Model information	Model statistics (ActiGraph$_M$)				
	R^2	Regression coeff. β	95% CI	t-value	p-value		R^2	Regression coeff. β	95% CI	t-value	p-value
NLR	0.32					**NLR**	0.21				
MVPA		0.31	−0.10, 0.73	1.54	.135	MVPA		0.17	−0.34, 0.68	0.68	.505
Age		−0.23	−0.44, −0.03	−2.32	**.028**	Age		−0.25	−0.47, −0.04	−2.41	**.024**
Prostate cancer stage		0.20	0.01, 0.39	2.18	**.038**	Prostate cancer stage		0.22	0.01, 0.43	2.11	**.045**
PLR	0.18					**PLR**	0.20				
MVPA		0.22	−0.10, 0.54	1.41	.169	Age		−0.32	−0.93, 0.30	−1.04	.307
Age		−0.20	−0.55, 0.14	−1.21	.236	ADT		−0.38	−0.90, 0.14	−1.49	.148
ADT		−0.25	−0.74, 0.24	−1.05	.306	BMI		−0.25	−0.87, 0.38	−0.81	.428
BMI		−0.16	−0.54, 0.23	−0.85	.402						
SII	0.32					**SII**	0.25				
MVPA		0.25	−0.11, 0.61	1.41	.170	Sleep		−0.15	−0.40, 0.09	−1.28	.213
Age		−0.23	−0.40, −0.06	−2.73	**.011**	Age		−0.24	−0.44, −0.04	−2.51	**.019**
Time since diagnosis		−0.15	−0.32, 0.02	−1.85	.076	Time since diagnosis		−0.16	−0.33, 0.01	−1.94	.063
Prostate cancer stage		0.19	0.01, 0.37	2.15	**.041**	Prostate cancer stage		0.20	0, 0.41	2.03	.053
NK^{dim}/NK^{bright} ratio [a]	0.34					**NK^{dim}/NK^{bright} ratio** [a]	0.34				
Age		0.45	0.23, 0.66	4.22	**< .001**	Age		0.45	0.23, 0.66	4.22	**< .001**
Prostate cancer stage		−0.25	−0.43, −0.07	−2.89	**.008**	Prostate cancer stage		−0.25	−0.43, −0.07	−2.89	**.008**
Th1/Th2 ratio [a]	0.23					**Th1/Th2 ratio** [a]	0.23				
Sleep		0.17	0.05, 0.28	2.86	**.008**	Sleep		0.17	0.05, 0.28	2.86	**.008**
Age		0.30	−0.01, 0.61	2.00	.056	Age		0.30	−0.01, 0.61	2.00	.056
Prostate cancer stage		−0.19	−0.33, −0.05	−2.80	**.009**	Prostate cancer stage		−0.19	−0.33, −0.05	−2.80	**.009**
Th17/Treg ratio	0.17					**Th17/Treg ratio**	0.18				
MVPA		−0.14	−0.29, 0.01	−1.87	.072	Sleep		0.20	−0.15, 0.55	1.19	.244
Sleep		0.15	−0.09, 0.40	1.27	.216	Age		0.19	−0.09, 0.48	1.39	.175
Age		0.15	−0.13, 0.42	1.10	.281	BMI		0.18	−0.47, 0.83	0.56	.580
BMI		0.14	−0.39, 0.67	0.52	.607	Prostate cancer stage		−0.16	−0.67, 0.36	−0.64	.528
Prostate cancer stage		−0.12	−0.61, 0.37	−0.52	.610						

Notes: Variables used for prediction models included physical activity estimates (sedentary behaviour, light physical activity, MVPA, sleep) and covariates (age, BMI, prostate cancer stage, time on ADT, time since diagnosis). Final models only included variables identified as important predictors by a variable importance for projection (VIP) score ≥ 1.

Abbreviations: β: regression coefficient; ADT: androgen deprivation therapy; BMI: body mass index; CI: confidence interval; MVPA: moderate-to-vigorous physical activity; NK cell: natural killer cell; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SII: systemic immune-inflammation index; Tc: cytotoxic T cell; Th cell: T helper cell; Treg: regulatory T cell.

[a] None of the physical activity variables were considered important predictors (VIP score < 1) and consequently excluded, resulting in identical models for $ActiGraph_H$ and $ActiGraph_M$.

Supplemental Table 2. Physical fitness, immune cells and inflammation markers of participants in the intervention and control arm at baseline and the 6-month visit.

	Intervention arm (n = 8)		Control arm (n = 11)	
	Baseline	**6 months**	**Baseline**	**6 months**
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Physical fitness				
Relative VO_2peak, $ml \cdot min^{-1} \cdot kg^{-1}$	26.2 ± 3.9	29.1 ± 3.3	27.2 ± 6.1	26.8 ± 6.7
400 metre walk time, s	242.3 ± 41.4	248.0 ± 37.9	243.7 ± 41.3	234.9 ± 32.0
Relative leg extension 1RM, $kg \cdot kg^{-1}$	1.0 ± 0.3	1.2 ± 0.2	0.9 ± 0.2	1.0 ± 0.2
Handgrip strength, kg [a]	44.1 ± 5.6	49.0 ± 4.9	46.3 ± 7.8	47.5 ± 6.2
Immune cells				
Platelets, $10^3 \cdot \mu L^{-1}$	222.8 ± 42.7	207.0 ± 22.7	212.8 ± 33.6	224.2 ± 46.7
Leukocytes, $10^3 \cdot \mu L^{-1}$	5.71 ± 1.67	5.39 ± 1.63	6.11 ± 2.24	6.05 ± 2.28
Neutrophils, $10^3 \cdot \mu L^{-1}$	3.12 ± 0.96	2.84 ± 0.73	3.73 ± 1.60	3.44 ± 1.74
Monocytes, $10^3 \cdot \mu L^{-1}$	0.54 ± 0.20	0.51 ± 0.15	0.52 ± 0.16	0.57 ± 0.20
Lymphocytes, $10^3 \cdot \mu L^{-1}$	1.72 ± 0.80	1.79 ± 0.82	1.65 ± 0.72	1.81 ± 0.62
NK cells, % lymphocytes	18.1 ± 9.0	17.0 ± 8.1	16.7 ± 9.3	16.4 ± 7.0
NK^{dim} cells, % NK	96.0 ± 3.2	95.5 ± 3.3	95.6 ± 2.2	95.7 ± 1.8
NK^{bright} cells, % NK	2.7 ± 2.1	2.9 ± 2.0	3.5 ± 1.8	3.2 ± 1.4
B cells, % lymphocytes	12.5 ± 8.8	12.6 ± 8.7	13.5 ± 6.9	12.9 ± 6.1
T cells, % lymphocytes	63.2 ± 11.0	63.4 ± 10.7	64.4 ± 10.5	65.0 ± 10.9
Tc cells, % lymphocytes	23.7 ± 9.8	24.7 ± 9.9	24.8 ± 10.9	25.4 ± 11.3
Th cells, % lymphocytes	39.0 ± 6.8	38.3 ± 6.9	39.1 ± 9.1	39.2 ± 7.2
Th1 cells, % lymphocytes	5.1 ± 2.1	5.0 ± 1.8	3.5 ± 1.8	4.2 ± 1.9
Th2 cells, % lymphocytes	2.6 ± 0.9	2.4 ± 0.5	2.9 ± 1.7	3.0 ± 1.7
Th17 cells, % lymphocytes	1.7 ± 0.6	1.5 ± 0.4	1.6 ± 0.8	1.8 ± 0.8
Treg cells, % lymphocytes	3.9 ± 1.4	3.7 ± 1.4	3.5 ± 1.1	3.5 ± 0.9
Inflammation markers				
Neutrophil-to-lymphocyte ratio (NLR)	2.03 ± 0.73	1.85 ± 0.87	2.48 ± 1.18	1.96 ± 0.77
Platelet-to-lymphocyte ratio (PLR)	154.2 ± 68.8	148.0 ± 92.1	152.6 ± 70.1	139.4 ± 66.7
Systemic immune-inflammation index (SII)	446.6 ± 166.5	389.6 ± 215.0	514.6 ± 227.2	438.6 ± 204.4
NK^{dim}/NK^{bright} ratio	63.8 ± 58.4	52.2 ± 46.4	46.3 ± 51.9	36.5 ± 17.7
Th1/Th2 ratio	2.33 ± 1.59	2.18 ± 1.11	1.56 ± 1.19	1.84 ± 1.42
Th17/Treg ratio	0.45 ± 0.09	0.44 ± 0.13	0.52 ± 0.33	0.55 ± 0.32

Abbreviations: 1RM: one-repetition maximum; NK: natural killer; NLR: neutrophil-to-lymphocyte ratio; PLR: platelet-to-lymphocyte ratio; SD: standard deviation; SII: systemic immune-inflammation index; Tc: cytotoxic T; Th: T helper; Treg: regulatory T; VO_2peak: peak oxygen consumption.