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ABSTRACT

Exercise has many systemic effects. Epidemiological studies suggest that exercise can improve the prognosis of people diagnosed with cancer, but the mechanisms are largely unknown. In animal models, exercise has been shown to slow tumor growth by enhancing the immunological response to tumors. The purpose of this thesis was to investigate the effect of acute exercise on circulating immune cell and cytokine levels in humans with newly diagnosed lymphoma or breast cancer.

The thesis included a total of 15 lymphoma patients (mean (SD) age 59 (17) years) and 39 breast cancer patients (57 (10) years), half of whom performed a 10-minute exercise and the other half a 30-minute exercise with bicycle ergometer on a resistance of their own-choosing. The patients were just diagnosed; thus they had not started any cancer treatments. All participants had blood samples taken at rest before pedaling, and for those who completed the 10-minute exercise, also immediately after exercise and 30 minutes after exercise. For those who completed the 30-minute exercise, blood samples were taken halfway through exercise, at the end of exercise, and 30 and 60 minutes after exercise. Circulating immune cell levels were analysed with flow cytometry and cytokines with a cancer-specific cytokine assay.

During exercise, the level of many immune cells, especially lymphocytes, increased in the bloodstream and returned to resting levels 30 minutes after exercise. The number of natural killer cells and $CD8^+$ T cells increased in both patient groups, during the 10- and 30-minute exercises. The responses in immune cells were fairly similar during 10- and 30-minute exercises, but the changes in immune cells correlated positively with the intensity of exercise. Chemokine IP-10 increased during exercise in both lymphoma and breast cancer patients, and in addition eotaxin, IL-1β, IL-13, and MIP-1α increased in breast cancer patients.

Even 10 minutes of moderate intensity exercise mobilizes immune cells in cancer patients. Further research is needed to investigate where mobilized immune cells migrate after exercise as their numbers decrease in the blood, and whether exercise-induced immune cell mobilization slows tumor growth in humans, as it does in mouse models.

KEYWORDS: Acute exercise, Physical activity, Breast cancer, Lymphoma, Immune cells, White blood cells, Cytokines

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TIIVISTELMÄ

Liikunnalla on monia systeemisiä vaikutuksia. Epidemiologisten tutkimusten perusteella tiedetään, että liikunta voi parantaa syöpäpotilaiden ennustetta, mutta ilmiön mekanismeja ei täysin tunneta. Eläinmalleissa liikunnan on nähty hidastavan syöpäkasvaimen kasvua immunologisten mekanismien kautta. Tämän väitöstutkimuksen tarkoitus oli selvittää, miten yksittäinen liikuntasuoritus vaikuttaa verenkierron immuunisolu- ja sytokiinimääriin lymfooma- ja rintasyöpäpotilailla.

Tutkimukseen osallistui 15 lymfoomapotilasta ja 39 rintasyöpäpotilasta, joista puolet suoritti 10 minuutin liikuntarasituksen ja puolet 30 minuutin liikuntarasituksen kuntopyörällä itse valitsemallaan vastuksella. Potilaat olivat juuri saaneet diagnoosin eivätkä siten olleet aloittaneet syöpähoitojaan. Kaikista osallistujista otettiin verinäyte levossa ennen polkemista ja 10 minuutin liikunnan suorittaneilta heti liikunnan jälkeen ja 30 minuuttia liikunnan jälkeen. 30 minuutin liikunnan suorittaneilta otettiin verinäyte puolessa välissä liikuntaa, liikunnan lopussa sekä 30 ja 60 minuuttia liikunnan jälkeen. Verenkierron immuunisolutasot analysoitiin virtaussytometrialla ja sytokiinit syöpäspesifillä sytokiinimäärityksellä.

Liikuntarasituksen aikana monien valkosolujen, etenkin lymfosyyttien, määrät nousivat verenkierrossa ja palasivat takaisin lepotasoon 30 minuuttia liikunnan jälkeen. Yhteistä oli, että molemmissa potilasryhmissä sekä 10 että 30 minuutin liikunnan aikana luonnollisten tappajasolujen ja sytotoksisten $CD8^+$ T solujen määrä nousi liikunnan aikana. Vasteet immuunisoluissa olivat melko samanlaisia 10 ja 30 minuutin liikunnan aikana, mutta immuunisolujen muutokset korreloivat positiivisesti liikunnan intensiteetin kanssa. Kemokiini IP-10 nousi liikunnan aikana sekä lymfooma että rintasyöpäpotilailla ja lisäksi eotaxin, IL-1β, IL-13 ja MIP-1α nousivat liikunnan aikana rintasyöpäpotilailla.

Jo 10 minuutin liikunta kohtalaisella intensiteetillä mobilisoi immuunisoluja syöpäpotilailla. Lisätutkimusta tarvitaan siitä, mihin mobilisoituneet immuunisolut kulkeutuvat liikunnan jälkeen, kun niiden määrä verenkierrossa laskee ja siitä, hidastaako liikuntarasituksesta johtuva immuunisolujen mobilisaatio kasvaimen kasvua ihmisillä kuten hiirimalleissa.

AVAINSANAT: Akuutti liikunta, Fyysinen aktiivisuus, Rintasyöpä, Lymfooma, Immuunisolut, Valkosolut, Sytokiinit

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Abbreviations

APC	Antigen presenting cell
BMI	Body mass index
CRP	C-reactive protein
CTLA-4	Cytotoxic T cell lymphocyte antigen 4
G-CSF	Granulocyte colony-stimulating factor
FasL	Fas ligand
Hb	Hemoglobin
Hct	Hematocrit
HER2	Human epidermal growth factor receptor 2
HR%	Heart rate percentage of age-predicted maximal heart rate
IL	Interleukin
IFN	Interferon
IP-10	Interferon gamma inducible protein
M1	Phenotype 1 macrophage
M2	Phenotype 2 macrophage
MAP	Mean arterial pressure
MCP-1	Monocyte chemoattractant protein 1
MDSC	Myeloid derived suppressor cell
g-MDSC	Granulocytic myeloid derived suppressor cell
MHC	Histocompatibility complex
MIP-1	Macrophage inflammatory protein 1
N1	Phenotype 1 neutrophil
N2	Phenotype 2 neutrophil
NK	Natural killer
PA	Physical activity
PD-1	Programmed cell death protein 1
PDGF	Platelet-derived growth factor
RANTES	Regulated upon activation, normal T cell expressed and secreted
ROS	Reactive oxygen species
RPP	Rate pressure product
TGF	Transforming growth factor

Th	T helper
TME	Tumor microenvironment
TNF	Tumor necrosis factor
TRAIL	Tumor necrosis factor related apoptosis inducing ligand

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Tiia Koivula, Salla Lempiäinen, Petteri Rinne, Maija Hollmén, Carl Johan Sundberg, Helene Rundqvist, Heikki Minn, Ilkka Heinonen. Acute exercise mobilizes $CD8^+$ cytotoxic T cells and NK cells in lymphoma patients. *Frontiers in Physiology*, 2023; 13: 1078512.

II Tiia Koivula, Salla Lempiäinen, Petteri Rinne, Jenna H Rannikko, Maija Hollmén, Carl Johan Sundberg, Helene Rundqvist, Heikki Minn, Ilkka Heinonen. The effect of acute exercise on circulating immune cells in newly diagnosed breast cancer patients. *Scientific Reports,* 2023; 13(1): 6561.

III Tiia Koivula, Salla Lempiäinen, Joona Neuvonen, Jooa Norha, Maija Hollmén, Carl Johan Sundberg, Helene Rundqvist, Heikki Minn, Petteri Rinne, Ilkka Heinonen. The effect of exercise and disease status on mobilization of anti-tumorigenic and pro-tumorigenic immune cells in women with breast cancer. *Frontiers in Immunology*, 2024; 15: 1394420.

IV Tiia Koivula, Jooa Norha, Maija Hollmén, Eeva Juhanoja, Carl Johan Sundberg, Heikki Minn, Helene Rundqvist, Petteri Rinne, Ilkka Heinonen. Immunological changes in the circulation of cancer patients in response to 10- and 30-minute acute exercise. *Manuscript.*

1 Introduction

Cancer is the second leading cause of death worldwide (Ferlay et al., 2024). Breast cancer originates from the breast tissue and is the second most common cancer type diagnosed mostly in women aged 60-70 years (Harbeck et al., 2019). Currently, the 5-year prognosis for breast cancer is approximately 90 %, but it depends largely on the subtype of the cancer as well as the stage of the disease at diagnosis. Lymphoma, cancer that arises from lymphatic tissue, has multiple subtypes, but they can be divided into B cell non-Hodgkin lymphomas, T and natural killer (NK) cell non-Hodgkin lymphomas, and Hogdkin lymphomas based on their origin and occurrence of Reed-Sternberg cells (Swerdlow et al., 2016). The incidence of non-Hodgkin lymphomas increases with age, but for Hodgkin lymphomas, there are two peaks: around 20 years of age and around 60-70 years of age. The prognosis of Hodgkin lymphoma is 85 %, but the survival rate for diffuse large B cell lymphoma, which represents 30-40 % of all lymphoma cases, is only 60-70 % five years after diagnosis (Li et al., 2018).

An immune system acts as a guard in our bodies, searching and destroying pathogens and mutated cells (Mackay et al., 2000). Sometimes, however, due to the complex influence of genetic, environmental, and lifestyle factors, immune system fails in its job and a cancer can arise. Other immune cells are anti-tumoral, meaning that they act to destroy cancer cells and the others are pro-tumoral, meaning that they stimulate the growth of the tumor (Finn, 2012). Anti-tumoral immune cells include for example cytotoxic effector T cells and natural killer (NK) cells, and pro-tumoral immune cells include for example regulatory T cells and myeloid derived suppressor cells (MDSCs). However, most immune cells have both anti-tumoral and pro-tumoral functions, and the activity of these cells is determined by signals from their surroundings. The prognosis of patients with cancer is usually better if there is high number of anti-tumoral immune cells, notably lymphocytes, in the tumor microenvironment (TME) (Mahmoud et al., 2011), and correspondingly the prognosis is worse if there is an abundance of pro-tumoral immune cells in the TME (Bates et al., 2006; Cole et al., 2009).

Increasing body of evidence indicates that lifestyle factors including physical activity can improve outcomes of patients with cancer. Physical activity after cancer

diagnosis decreases cancer-specific mortality by 30 % in breast cancer, colorectal cancer, and prostate cancer (Patel et al., 2019). The exact mechanisms on how physical activity, or exercise, influences patient outcomes are not entirely known. However, regular exercise causes favourable changes in overall homeostasis, and it is hypothesised that some changes in the immune system during and after exercise bout affects tumor development (Hojman, 2017). In mouse models, it has been observed that acute exercise increases the number of circulating anti-tumoral immune cells, and after exercise, these cells are infiltrated to the TME to kill cancer cells (L. Pedersen et al., 2016; Rundqvist et al., 2020). Moreover, exercise can decrease the accumulation of some pro-tumoral immune cells in the TME (Hagar et al., 2019; Wennerberg et al., 2020).

In addition to mouse models, the effect of exercise to immune cells is extensively studied in healthy individuals. Exercise stimulates the neuroendocrine system, which causes hormones such as adrenalin to be released into the bloodstream. Immune cells have receptors to these hormones, and through hormone-receptors interactions, immune cells are mobilized from tissues into the bloodstream (Krüger et al., 2008; Graff et al., 2018). In addition to hormones, increased blood flow and blood pressure, as well as myokines secreted from the contracting muscles mobilize the immune cells (Bay et al., 2020). The response is transient as an elevated number of circulating immune cells during exercise returns to resting levels soon after exercise, when cells are thought to infiltrate back to tissues (Rooney et al., 2018). In healthy individuals, different immune cell populations respond to acute exercise differently due to the fact that different immune cells have different number of receptors to hormones and myokines. Further, the higher the intensity of the exercise, the more different cells are mobilized (Da Silva Neves et al., 2015), because hormone and myokine levels increase with intensity. This effect of acute exercise on immune cells has been studied very little in patients with cancer, even though these patients could potentially benefit from this phenomenon more than healthy individuals.

This PhD study aims to close the gap in literature between methodological pre-clinical studies showing increased tumor killing of immune cells with exercise and epidemiological studies in patients with cancer showing improved outcomes in physically active individuals. Here, circulating immune cell numbers and cytokine levels are examined before, during, and after acute exercise of 10 and 30 minutes in breast cancer and lymphoma patients.

2 Review of the Literature

2.1 Cancer

Cancer is a group of diseases in which mutated cells proliferate uncontrollably (J. S. Brown et al., 2023). Cancer cells have been described to have typical characteristics, hallmarks of cancer, that make them malignant. These include, among others, evasion of growth suppressors, sustained proliferation, resisted cell death, induction of angiogenesis, activation of invasion and metastasis, and avoidance of immune destruction (Hanahan & Weinberg, 2011; Hanahan, 2022). In 2022, nearly 20 million cancer cases were diagnosed, and 9,7 million cancer deaths reported worldwide (Ferlay et al., 2024). In 2040, the incidence of cancer is expected to increase to 28,4 million new cases due to growth and aging of the population and increased prevalence of cancer risk factors (Sung et al., 2021). There is no exact reason for the development of cancer, but it is a sum of many variables and coincidences. It is, however, analysed that smoking, high body weight, and alcohol consumption are the leading risk factors for cancer and that 40 % of cancers could be prevented with favourable lifestyle changes (Islami et al., 2024).

2.1.1 Breast cancer

Breast cancer is a malignancy that arises from cells of breast tissue, from either ducts or lobules. Breast cancers are classified into 4 main types according to their origin and based on the prevalence of hormone receptors and human epidermal growth factor receptor 2 (HER2): Luminal A, Luminal B, HER2 positive, and triple negative breast cancer. Luminal A breast cancers are hormone receptor positive but HER2 negative cancers. Luminal B breast cancers express hormone receptors and are HER2 positive. HER2 positive cancers express HER2 but not hormone receptors, and triple negative cancers do not express either hormone receptors or HER2. (Harbeck et al., 2019)

In 2022, breast cancer was the second most common malignancy worldwide with 2,3 million new cases and 600 thousand cancer deaths (Ferlay et al., 2024). Risk factors for breast cancer include female gender, age, family history of breast cancer, and lifetime estrogen exposure (Vehmanen, 2024). Further, modifiable lifestyle

factors are estimated to explain about a third of breast cancer cases (Arthur et al., 2018). Thus, breast cancer risk can be lowered with regular exercise, maintaining healthy weight, and limiting alcohol and tobacco use.

The most common symptom of breast cancer is a lump in the breast or armpit lymph nodes (Vehmanen, 2024). Other symptoms include abnormal nipple appearance, change in breast skin color, and swelling and rash in the breast. The methods used to diagnose breast cancer include palpation, mammography, ultrasound, and biopsy. The treatment of breast cancer depends on the subtype (Suomen Rintasyöpäryhmä RY, 2024). Most of breast tumors are removed with surgery and treated with radiation therapy afterwards. Drug therapy can be given before or after surgery, depending on the needs. Cytostats reduce the risk of recurrence in all breast cancer types. In addition, hormonal medication can be used for hormone receptor positive breast cancers, and for HER2 positive cancer, there is a precision medicine, HER2 antibody. The prognosis of breast cancer is highly influenced by the subtype and the spread of the disease, but the overall 5-year survival rate is about 90 %.

2.1.2 Lymphoma

Lymphoma is a haematological malignancy that arises from lymphatic tissue. It is not a single disease, but rather a group of different malignant lymphoid tissue tumors. According to the current classification, lymphomas can be divided into B-cell non-Hodgkin lymphomas, T/NK-cell non-Hodgkin lymphomas, and Hodgkin lymphomas (Swerdlow et al., 2016). In 2022, half a million cases of non-Hodgkin lymphoma were diagnosed, and the corresponding number was 80 thousand for Hodgkin lymphoma (Ferlay et al., 2024). In the same year, 250 thousand people died from non-Hodgkin lymphoma and 23 thousand people from Hodgkin lymphoma.

Hodgkin lymphomas are divided into two subtypes: classical Hodgkin lymphoma and nodular lymphocyte predominant Hodgkin lymphoma, both of which originate from B lymphocytes and include neoplastic Reed Sternberg cells (Connors et al., 2020). Although Hodgkin lymphomas are rare overall, it is one of the most common cancers in adolescent and young adults aged 15-34 years. Second incidence peak is in elderly population aged over 60. In addition to age, family history, male gender, and infection of HIV and Epstein-Barr virus are risk factors for Hodgkin lymphoma.

Non-Hodgkin lymphomas can be divided according to their origin into B-, T-, and NK-cell lymphomas (Bowzyk Al-Naeeb et al., 2018). The majority of non-Hodgkin lymphomas arise from B-cell lineage, and the most common subtypes are diffuse large B cell lymphoma and follicular lymphoma. Risk factors for non-Hodgkin lymphoma are age, as it is most common in people 60 or over, certain

chemicals and immune system suppressing medications, as well as HIV and Epstein-Barr virus infections.

The most common symptom of both Hodgkin and non-Hodgkin lymphomas is an asymptomatic enlarged lymph node in neck, armpit, or groin. Some patients also have so-called B symptoms that include fever, night sweats, fatigue, unexplained weight loss, and itching skin. Further, if the tumor is located in mediastinum, first symptoms can be cough, chest pain, and trouble breathing, and tumors in the abdominal area might cause abdominal pain and swelling. (Pasanen, 2022)

The diagnosis of lymphomas is based on a histopathological examination of a biopsy (Joensuu et al., 2013b; Joensuu et al., 2013d). Imaging tests with computer tomography and, if necessary, magnetic resonance imaging and positron emission tomography imaging are used to determine the spread of the disease. Further, bone marrow biopsy is used if needed. The treatments depend on the origin of the tumor, the spread of the disease, the symptoms, and age of the patients, but in general, chemotherapy and radiation therapy are used (Joensuu et al., 2013a; Joensuu et al., 2013c). 5-year survival rate is around 85 % for Hodgkin lymphoma and 65 % for non-Hodgkin lymphoma.

2.2 Immune system

Immune system's job is to protect us from diseases. Immune cells in the circulation and different tissues detect and respond to pathogens and cancer cells. The immune system is divided into two parts: innate and adaptive immunity. The characteristics of innate immunity are that it is present from birth and that it directs a non-specific and rapid response to pathogens. It includes neutrophils, monocytes, macrophages, eosinophils, basophils, mast cells, dendritic cells, and NK cells. The characteristics of adaptive immunity, on the other hand, are that the immunity develops over time and the response is slower, but specific to each antigen. The function of the adaptive immune system forms a memory trace, so that if the same antigen is encountered again, the body reacts to it faster and more effectively. Immune cells that belong to adaptive immunity are T and B lymphocytes. (Delves & Roitt, 2000)

The interaction between innate and adaptive immune systems are vital for anticancer immunity (Chang & Beatty, 2020). The cancer-immunity cycle is a multistep process, which, if proceed successfully, leads to cancer cell killing (D. S. Chen & Mellman, 2013). First, dendritic cells capture antigens released from dying cancer cells. If dendritic cells interact with other immunity promoting signals such as pro-inflammatory cytokines, they can present the antigens to T cells with histocompatibility complex (MCH) molecules leading to effector T cell priming and activation. At this point, the effectiveness of anti-tumoral immune response is determined based on the balance of activated effector T cells and regulatory T cells.

Next, the activated effector T cells migrate to and infiltrate the tumor microenvironment, and recognize cancer cells by binding to antigens on MHC molecules, resulting in the destruction of target cancer cell. The destruction of cancer cell releases more cancer antigens, which then strengthens the immunity by initiating more cycles. However, the cycle often does not function optimally, because cancer cells have mechanisms to evade immune cell-mediated destruction (Hanahan & Weinberg, 2011). Cancer cells may, for example, reduce the expression of antigens or secrete immunosuppressive factors that reduce the activity of infiltrating anti-tumoral immune cells (Motz & Coukos, 2013). The TME includes both anti-tumoral and pro-tumoral immune cells (**Figure 1**), and abundance or scarcity of these cells in the TME is a predictor for clinical outcome. Typically, high level of effector $CD8^+$ T cells and NK cells in the TME are associated with better prognosis (Ali et al., 2014; Nersesian et al., 2021).

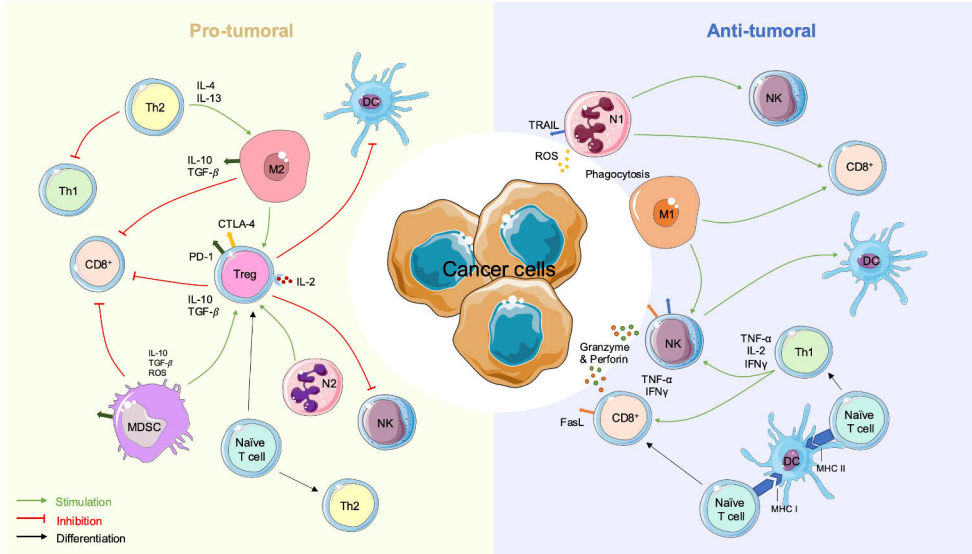

Figure 1. Immune cells in tumor microenvironment. Other cell, such as $CD8^+$ T cells, natural killer (NK) cells, T helper (Th) 1 cells, type 1 neutrophils (N1), type 1 macrophages (M1), and dendritic cells (DC) have anti-tumoral functions in the tumor microenvironment and either directly kill cancer cells or promote the tumor killing activity of other immune cells. On the contrary, other cells such as regulatory T (Treg) cells, myeloid derived suppressor cells (MDSCs), type 2 neutrophils (N2), type 2 macrophages (M2), and Th2 cells have pro-tumoral functions. They for example inhibit anti-tumoral immune cells by expressing immune checkpoint inhibitors and by secreting immunosuppressive cytokines. CTLA, cytotoxic T lymphocyte antigen; FasL, Fas ligand; IFN, interferon; IL, interleukin; MHC, histocompatibility complex; PD, programmed cell death protein; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor; TRAIL, tumor necrosis factor related apoptosis inducing ligand.

2.2.1 Anti-tumoral immune cells

Cytotoxic $CD8^+$ T cells are the most powerful effectors of anticancer immune response. Once activated, $CD8^+$ T cells find cancer cells, bind to their surface with MHC-1, and secrete granules containing granzymes, perforin, cathepsin C, and granulysin that enhance pore formation in cancer cell and subsequent apoptosis. Another cancer cell killing mechanism is the interaction between Fas ligand (FasL) expressed on $CD8^+$ T cells and Fas receptors on cancer cells that lead to fragmentation of cancer cell DNA. (Raskov et al., 2021)

Another cancer-killing cell type is NK cells. NK cells have activating and inhibitory receptors that recognize cancer cells by directly binding to their cell surface ligands. The balance of these receptors determines the activation state of NK cell. One example of activating receptors is CD16, which enhances cytotoxicity and cytokine release. Whereas $CD8^+$ T cells are activated by binding to MCH-1, many of the inhibitory receptors on NK cells recognize MHC-1. Thus, NK cell activity is greater in MHC-1 -deficient cancer cells. In addition to cancer cell ligands, cytokines derived from other immune cells modify the activation of NK cells. Similar to $CD8^+$ T cells, NK cells trigger cancer cell apoptosis by secreting cytotoxic granules containing perforin and granzymes, and by FasL and tumor necrosis factor related apoptosis inducing ligand (TRAIL) interactions. Stimulated NK cells also secrete chemokines and cytokines such as interferon gamma (IFNγ) and tumor necrosis factor alpha (TNF-α) that activate antigen-presenting cells (APCs) and further T cells. (Wolf et al., 2023; Coënon et al., 2024)

2.2.2 Pro-tumoral immune cells

Regulatory T cells are $CD4^+$ T cell subset that promote tumor development by suppressing anticancer immunity in several mechanisms. They express interleukin (IL) 2 receptors and therefore bind and deplete IL-2 from their surroundings, thus reducing availability of this important cytokine of effector T cell activity (Chinen et al., 2016). Further, they secrete immunosuppressive cytokines such as IL-10 and transforming growth factor beta (TFG-β) that downregulate the activity of effector T cells (Taylor et al., 2006), and express immune checkpoint molecules such as cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1) (Matoba et al., 2019), which decrease effector T cell proliferation and induce apoptosis. They can also directly kill effector T cells by secreting granzyme and perforin (Cao et al., 2007).

Myeloid derived suppressor cells (MDSCs) are a collection of immature myeloid cells that also exhibit many immunosuppressive functions that are similar to regulatory T cells. Two subpopulations of MDSCs are identified as granulocytic and

monocytic MDSCs. They secrete IL-10 and TFG-β (Huang et al., 2006), generate reactive oxygen species (ROS) (Kusmartsev et al., 2004), and overexpress arginase-1 and PD-L1 (Rodríguez & Ochoa, 2008; Prima et al., 2017), which all inactivate effector T cells. Further, they are capable of presenting cancer antigens to regulatory T cells enhancing regulatory T cell recruitment and proliferation (Serafini et al., 2008).

2.2.3 Immune cells with both anti- and pro-tumoral functions

Monocytes exhibit different phenotypes and different functions in cancer. Circulating monocytes can be divided into classical, non-classical, and intermediate monocytes, and in the TME, monocytes can differentiate into dendritic cells or macrophages which are further polarized towards M1 or M2 phenotypes. Monocyte-derived dendritic cells display important anti-tumorigenic function as they present tumor antigens to activate $CD8^+$ T cells (Kuhn et al., 2015). Macrophages that are polarized more towards M1 phenotype are pro-inflammatory and typically have anti-tumorigenic functions. They for example phagocytose cancer cells, and recruit $CD8^+$ T cells and NK cell into the TME (J. Liu et al., 2021). On the contrary, anti-inflammatory M2 macrophages inhibit effector T cells with various mechanisms (Nixon et al., 2022; Kersten et al., 2022), and recruit regulatory T cells into the TME (J. Wang et al., 2017). Further, M2 macrophages express PD-1, which in addition to inhibition of T cells, also decreases phagocytosis of other macrophages (Gordon et al., 2017). M1 and M2 phenotypes are the extremes of macrophage activation states, and there is many macrophages with mixed pro- and anti-tumorigenic characteristics (Locati et al., 2020).

$CD4^+$ T cells are characterized as helper T (Th) cells, that provide "help" for $CD8^+$ T cells. However, $CD4^+$ T cells encompasses many subsets with opposing roles in cancer, including regulatory T cells described above, and Th1 cells, Th2 cells, Th9 cells, Th17 cells, and T follicular helper cells (Tay et al., 2021). Anti-tumoral $CD4^+$ T cells recognize cancer antigens through MHC II and can promote $CD8^+$ T cell recruitment and dendritic cell reprogramming (Marzo et al., 2000; Lei et al., 2023), but also use IFNγ, TNF-α, FasL, perforin and granzyme to directly kill cancer cells (Bawden et al., 2024; Oh & Fong, 2021). Th1 cells are characterized by secretion of for example IFNγ, and chemokines such as MCP-1 and MIP-1α, that recruit and activate $CD8^+$ T cells, NK cells, and M1 macrophages (Haabeth et al., 2011). In contrast, Th2 cells suppress anti-tumoral Th1 responses, and promote M2 macrophages (Burkholder et al., 2014). There are, however, few studies reporting that IL-4 secreted by Th2 cells can also exert anti-tumoral responses through recruitment of eosinophils (Mattes et al., 2003; Tepper et al., 1992). Under some conditions, Th17 cells can differentiate to effector cells that produce Th1 cytokines

and thereby recruit $CD8^+$ T cells, NK cells, and dendritic cells to the TME (Kryczek et al., 2009; Hamaï et al., 2012). Some studies have even found that Th17 cells mediate stronger cancer killing responses than Th1 cells (Martin-Orozco et al., 2009; Muranski et al., 2008). Under other conditions, however, Th17 cells express cytokines such as IL-17 that promote angiogenesis and tumor growth (Prabhala et al., 2010).

B cells can be differentiated to many different subtypes (Ma et al., 2024). Some B cells contribute to antitumor immune response by secreting antibodies against cancer antigens and by presenting antigens to T cells (Mazor et al., 2022; Can Cui et al., 2021). Number of cancer types have tertiary lymphoid structures near the tumor, which are immune cell clusters consisting of B cells, T cells, and dendritic cells, and according to current understanding, B cell in these structures promote antitumor responses (Schumacher & Thommen, 2022). However, some B cells exhibit pro-tumoral properties by expressing immune checkpoint molecules and by secreting immunosuppressive cytokines such as IL-10 (Xiao et al., 2016; Ouyang et al., 2016).

Neutrophils are the most abundant immune cell type in blood, and in the TME, they also show high level of plasticity in response to signals that drive their polarization towards pro-tumoral or anti-tumoral phenotypes (Jaillon et al., 2020). Anti-tumoral (N1) neutrophils can directly kill tumor cells through production of tumor-killing substances such as TRAIL and ROS (Koga et al., 2004; Granot et al., 2011), and by phagocytosis (Golay et al., 2013). Moreover, they can act as antigen-presenting cells to T cells (Chang Cui et al., 2021; Chawla et al., 2016), thereby stimulating T cell-mediated killing of tumor cells. In contrast, pro-tumoral (N2) neutrophils promote tumor growth and metastasis by interacting with cancer cells (Yu et al., 2024). Further, they have been observed to recruit regulatory T cells (Zhou et al., 2016) and to inactivate effector T cells by expressing immunosuppressive molecules (T.-T. Wang et al., 2017; Shan et al., 2021).

Eosinophils and basophils are small granulocyte subpopulations, which role in cancer is less investigated, but there are studies reporting both pro-tumoral and anti-tumoral activities of these cells. Eosinophils can enhance $CD8^+$ T cell infiltration to tumors (Carretero et al., 2015), but are also capable of killing tumor cell independently of $CD8^+$ T cells by releasing cytotoxic mediators such as granzyme B (Reichman et al., 2019; Legrand et al., 2010). Their pro-tumoral activities include for example recruitment of regulatory T cells (Zaynagetdinov et al., 2015) and promotion of cancer cell proliferation (Xie et al., 2015; Curran et al., 2011). Similar to eosinophils, basophils release granzyme B (Tschopp et al., 2006) and thereby can kill tumor cells. They also contribute to Th2 activation (Yoshimoto et al., 10 C.E.), are associated with M2 macrophage infiltration (Wu et al., 2022), and can promote angiogenesis by releasing angiogenic factors (Marone et al., 2016).

2.2.4 Cytokines

The cancer-immunity cycle as well as cancer cell initiated immunosuppression depends largely on different immune secretory factors including cytokines that act as messengers between different immune cells and between immune cells and cancer cells (M. Yi et al., 2024). Cytokines include interleukins (IL), chemokines, colony-stimulating factors (CSF), interferons (IFN), tumor necrosis factor (TNF), and transforming growth factors (TGF). To date, there are over 200 cytokines identified. In this paragraph, cytokines involved in the current study in relation to cancer are briefly reviewed.

Interleukins

IL-1 is a pro-inflammatory cytokine that exists in two forms, IL-1α and IL-1β. Overexpression of IL-1β induces cancer development e.g. trough recruitment and activation of MDSCs (Tu et al., 2008) and accumulation of T cell suppressive neutrophils (Kiss et al., 2021), and high level of IL-1β is associated with high tumor grade and poor prognosis (Jin et al., 1997; Wetzler et al., 1994). IL-1ra is an anti-inflammatory cytokine, that binds to same receptor as IL-1, thus acting as a competitive antagonist for IL-1 receptor. It has been observed that IL-1 is highly expressed in human cancer xenografts promoting tumor growth and that IL-1ra inhibits the xenograft growth in IL-1 producing tumors (Elaraj et al., 2006).

IL-4 and IL-13 are immunosuppressive cytokines secreted mainly by Th2 cells. They are inhibitors of cancer antigen presentation (D. S. Chen & Mellman, 2013), and Th2-derived IL-4 and IL-13 also induce M2 macrophage activation and M2-stimulated metastasis (DeNardo et al., 2009; Raes et al., 2005). Blocking of IL-4 and IL-13 results for example in inhibition of anti-apoptotic protein expression, and can thus enhance tumor killing (Natoli et al., 2013).

IL-7 is an important cytokine for T cell function and survival (Vieira et al., 1998). Administration of IL-7 increases $CD4^+$ and $CD8^+$ T cells and decreases the proportion of regulatory T cells in humans (Rosenberg et al., 2006). Further, it enhances cytotoxicity of immune cells by inducing perforin secretion by $CD8^+$ T cells and increasing FasL expression by NK cells (Crawley et al., 2014; Lum et al., 2004). IL-7 also stimulates the expression of other cytokines involved in tumor killing such as IFNγ and IP-10 (Andersson et al., 2009). However, IL-7 has also reported to have pro-tumoral functions. For example, it can induce the survival and proliferation of T-cell acute lymphoblastic leukemia cells (J. T. Barata et al., 2001; A. S. Barata et al., 2011), and invasiveness of prostate cancer cells (Qu et al., 2016; Seol et al., 2019).

IL-9 was originally defined as lymphocyte growth factor, and it is primarily secreted by lymphocytes. IL-9 promotes the recruitment of $CD8^+$ T cell, but also regulatory T cells to the tumors (Lu et al., 2012). However, it seems that IL-9 preferentially recruits $CD8^+$ T cells and thus promotes anti-tumoral responses. Further, $CD8^+$ T cells that produce IL-9 have been identified as superior anti-tumoral cells (Lu et al., 2014). IL-9 can also promote macrophage polarization towards M1 phenotype and enhance macrophages to secrete IP-10 to recruit more $CD8^+$ T cells and NK cells to the TME (Do-Thi et al., 2023). In hematological malignancies, but also in some solid tumors, IL-9 may, however, exert a tumorigenic role by promoting cancer cell growth (Nagato et al., 2005; Kalim et al., 2024).

IL-8 is a pro-inflammatory cytokine that is associated with poor outcome in patients with cancer (Belluomini et al., 2024; Liao et al., 2023). High serum IL-8 is linked to higher neutrophil and monocyte count in blood, and intratumoral IL-8 is linked to neutrophil and monocyte infiltration (Schalper et al., 2020). Further, IL-8 produced by the TME is negatively associated with T cell infiltration (Schalper et al., 2020), and high IL-8 expressing cells downregulate antigen presentation (Yuen et al., 2020).

IL-17 is another pro-inflammatory cytokine that has pro-tumoral effects. In cancer models, IL-17 has been observed to promote tumor growth by e.g. inducing myeloid cell recruitment (Charles et al., 2009) and IL-6 pathway (L. Wang et al., 2009). Serum IL-17 is also associated with poor prognosis in cancers, such as in T-cell lymphoma patients (J. H. Yi et al., 2019).

Chemokines

Chemokines are proteins that control the movement of immune cells. Thus, they promote chemotaxis, the migration of cells in the direction of a chemical signal. Chemokines are divided into four classes, C-chemokine, CC-chemokines, CXC-chemokines, and CX3C-chemokines. Immune cells and stromal cells, but also cancer cells can secrete them. (Nagarsheth et al., 2017)

CCL2 (MCP-1), CCL3 (MIP-1α), CCL4 (MIP-1β), and CCL5 (RANTES) bind to same receptors on immune cells. In cancer, they are all associated with recruitment of $CD8^+$ T cells (Harlin et al., 2009). However, MCP-1 has pro-tumoral effects by also recruiting monocytes and monocytic MDSCs into the TME and has been associated with poor prognosis in breast cancer (Ueno et al., 2000). It also stimulates MIP-1α secretion by macrophages, which further promotes accumulation of macrophages in the TME (Kitamura et al., 2015). In contrast, increased level of MCP-1 together with IFNγ is associated with increased level of tumor-infiltrating T cells and thus correlate with better survival in ovarian cancer (Zhang et al., 2003). RANTES is also involved in monocyte recruitment to the TME, which has been

associated with advanced stages of breast cancer and improved cancer cell survival in lymphoma (Azenshtein et al., 2002; Wilcox et al., 2009). However, RANTES secretion by NK cells leads to dendritic cell accumulation to the tumor site (Böttcher et al., 2018). Therefore, these chemokines contribute to both pro-tumoral and anti-tumoral immunity.

CXCL10 (IP-10) is a Th1-type chemokine that binds to CXCR3 expressed in $CD8^+$ T cells, Th1 cells, and NK cells (Nagarsheth et al., 2017). Tumor-infiltrating dendritic cells produce IP-10 (Pfirschke et al., 2017), and together with RANTES, stimulates the trafficking of T cells to tumors (D. S. Chen & Mellman, 2013). Further, M1 macrophages express IP-10, which amplifies antitumor responses (Mantovani et al., 2004).

Eotaxin has three forms, CCL11 (Eotaxin 1) CCL24 (Eotaxin 2), and CCL26 (Eotaxin 3). Eotaxin 1 stimulates eosinophil recruitment and degranulation, and thus plays a role in anti-tumoral immunity (Hollande et al., 2019). In breast cancer, high level of Eotaxin 1 is associated with better prognosis, and high Eotaxin 1 expression is linked to increased levels of $CD4^+$ T cells, regulatory T cells, $CD8^+$ T cells, neutrophils, and M1 macrophages (X. Chen et al., 2024). However, in melanoma model, elevated level of Eotaxin 1 was observed to inhibit dendritic cell maturation (Yang et al., 2014). Eotaxin 2 and 3 have been linked to M2 macrophage functions and infiltration, cancer invasion, and metastasis (Lan et al., 2018; M. Cheng et al., 2017).

Interferons, tumor necrosis factor, colony-stimulating factors, and platelet-derived growth factors

Interferons are divided to three types: I, II, and III interferons. IFNγ is a type II interferon that is involved in cancer control, stimulating the killing of cancer cells. It is induced by mitogens and cytokines such as IL-12 and IL-18, that are mainly produced by T cells and NK cells (Seder et al., 1993; Fehniger et al., 1999). $CD8^+$ T cells release IFNγ to target cancer cells to stimulate the killing, but also to neighboring T cells, which stimulates their expansion and differentiation. IFNγ released by NK cells also promotes other cells and their recruitment to the TME. One mechanism of IFNγ in immune cell recruitment is that it regulates the expression of chemokines such as IP-10 and its receptor CXCR3 on T cells, NK cells, monocytes, and dendritic cells (Colvin et al., 2004). Further, it upregulates antigen presentation to T cells by MCH molecules on APCs, enhancing T cell activation (Früh & Yang, 1999). However, IFNγ has also pro-tumoral effects, for example, it has been discovered that it promotes expression of inhibitory molecules such as PD-L1 (Gocher et al., 2022).

Tumor necrosis factor family includes for example TNF-α, FasL, and TRAIL (Chu, 2012). TNF-α can be expressed as a transmembrane protein or enzymatically cleaved into a soluble active form by immune cells and cancer cells. It exhibits both anti-tumoral and pro-tumoral functions. $CD8^+$ T cells and NK cells secrete TNF-α to induce cancel cell apoptosis (Young et al., 2020; Prévost-Blondel et al., 2000; Kashii et al., 1999), and it also acts as a stimulatory factor in cancer antigen presentation by APCs (D. S. Chen & Mellman, 2013). On the other hand, some studies have shown the effect of TNF-α on the activation of MDSCs and regulatory T cells (Hu et al., 2014; Torrey et al., 2017), and if TNF-α is elevated in chronic inflammation, it may prevent carcinogenesis (Landskron et al., 2014).

Colony-stimulating factors stimulate the production of immune cells in the bone marrow. Granulocyte colony-stimulating factor (G-CSF) mostly stimulates granulocyte formation (Lieschke et al., 1994), and is used to treat neutropenia in patients with cancer. However, G-CSF can support tumor growth, cancer cell proliferation, and angiogenesis (Voloshin et al., 2011), and it has been reported to mobilize MDSCs and regulatory T cells (Shojaei et al., 2009; Zou et al., 2004).

PDGF-bb is a member of platelet-derived growth factor (PDGF) family. Cancer cell can produce PDGF-bb, which has been linked to recruitment of different stromal cells to the TME, and it may enable cancer cells to escape from immune surveillance, and stimulate cancer growth, metastasis, and angiogenesis (B. Yi et al., 2002; J. Cheng et al., 2013; Hsu et al., 2019).

2.3 Physical activity

Physical activity (PA) is any movement that expends energy and activates muscles. It can be planned exercise or everyday movements such as walking. World Health Organization's physical activity recommendations include 150-300 minutes of moderate intensity or 75-150 minutes of vigorous intensity aerobic execise or combination thereof, and two sessions of resistance training per week (Bull et al., 2020). There is accumulating evidence of benefits of physical activity on people diagnosed with cancer, and thus the physical activity recommendations are same for patients with cancer as for healthy people (K. L. Campbell et al., 2019). Despite the fact that physical activity is beneficial, majority of cancer patients do not meet the recommendations (Avancini et al., 2020). In Finland, it is suggested that only 10 % of patients with cancer are physically active during cancer treatments (Himberg, 2020).

2.3.1 Physical (in)activity and cancer risk

People who are not physically active have an increased risk of developing cancer. A recent study revealed that 4,8 % of all cancers diagnosed in Australia are attributable to physical inactivity (Ellis et al., 2024). For comparison, tobacco, UV-radiation, and inadequate diet are responsible for more cancer cases (13,4 %, 6,2 %, and 6,1 %, respectively) compared to physical inactivity, but overweight, infections, and alcohol consumption cause fewer cancer cases (3,4 %, 2,9 %, and 2,8 %, respectively) in Australia (Whiteman et al., 2015). However, these percentages vary between countries and studies (Parkin et al., 2011; Jiang et al., 2023). A meta-analysis including 126 studies worldwide showed that people meeting the physical activity recommendations have 7 % reduction in overall cancer risk (L. Liu et al., 2016). The association between physical activity and cancer, however, depends on the cancer type. Cancer types that have been strongly associated with physical activity are breast, colon, bladder, endometrial, esophageal adenocarcinoma, renal, and gastric cancers (McTiernan et al., 2019), and are thus called PA-related cancers. In these cancer types, cancer risk decreases by 10 to 20 % when an individual is physically active. The association is also moderate or limited in lung, hematologic, head and neck, ovary, pancreas, and prostate cancer. Conversely, melanoma is more common in physically active people compared to sedentary ones which is suggested to be a result of increased exposure to UV light while exercising.

Stamatakis et al. have studied the dose dependency of daily physical activity in cancer incidence (Stamatakis et al., 2023). They followed non-exercising individuals for nearly 7 years and found that out of 22 398 participants, 2345 developed cancer. Total incident cancer risk was reduced by 17 to 18 % if an individual engaged a minimum of 3,4 to 3,6 minutes of vigorous intermittent lifestyle physical activity (VILPA) a day. Further, 4,5 VILPA min/day was associated with 31 % to 32 % reduction in PA-related cancer incidence when adjusted for several confounding factors including smoking, alcohol consumption, and family cancer history. Therefore, the higher the amount of VILPA, the higher the risk reduction was. Dose-dependency was also observed in the above mentioned Australian study: if all adults would have engaged ≥30 metabolic equivalent (MET) -hours/week of physical activity 11,9 % of cancers would have been prevented, but if adults only modestly increased the amount of physical activity 4,8 % of cancer cases were preventable (Ellis et al., 2024).

2.3.2 Health benefits of exercise on patients with cancer

Cancer treatments cause many side effects, such as pain, fatigue, depression, and lymphadema, which are often long-term and reduce patients' quality of life

(Penttinen et al., 2010). Further, cancer treatments increase the risk of other cancers as well as diabetes, cardiovascular diseases, and osteoporosis (Jo et al., 2021; Raisi-Estabragh et al., 2023; Z. Chen et al., 2005). There is a strong evidence that chronic exercise before, during, and after cancer treatments can reduce cancer-related fatigue, anxiety, depression, and lymphadema (K. L. Campbell et al., 2019). Further, chronic exercise enhances health-related quality of life, physical functioning, and with moderate evidence, also bone health and sleep. Physical activity might also have a role in preventing other diseases caused by cancer treatments (Scott et al., 2018; Saarto et al., 2011). These exercise benefits affect all patients with cancer as well as cancer survivors, not just PA-related cancers. There is also some evidence that physical activity could reduce cancer recurrence, but studies are conflicting and mostly limited to breast, colorectal, and prostate cancer (Friedenreich et al., 2017).

Physical activity also decreases mortality in patients with breast cancer, colorectal cancer, and prostate cancer (Patel et al., 2019). The reduction in cancer-specific mortality is 31 % in breast cancer, 30 % in colorectal cancer, and 33 % in prostate cancer patients when an individual is physically active after diagnosis, and the percentages for all-cause mortality are even higher. There are also some studies showing similar percentages in non-Hodgkin lymphoma and esophageal cancer (Patel et al., 2019), indicating that chronic exercise may also reduce mortality in other cancer types, but to this day, the evidence is weak. Dose-dependency of physical activity in cancer patients' mortality is still unknown, however, study in healthy people showed that meeting the physical activity recommendations gives nearly maximum longevity benefit, and engaging 3-5 times more gives just a modest benefit increase (Arem et al., 2015).

2.3.3 Anti-tumoral mechanisms of exercise

Despite the strong association between exercise and risk of certain cancers and cancer development, the exact biological mechanisms by which exercise regulates cancer incidence and growth remain unclear. The current understanding is that regular exercise reduces cancer risk by lowering systemic levels of known risk factors and affects cancer development by maintaining homeostasis (McTiernan, 2008; Hojman et al., 2018) (**Figure 2**). In this chapter, suggested mechanisms are discussed.

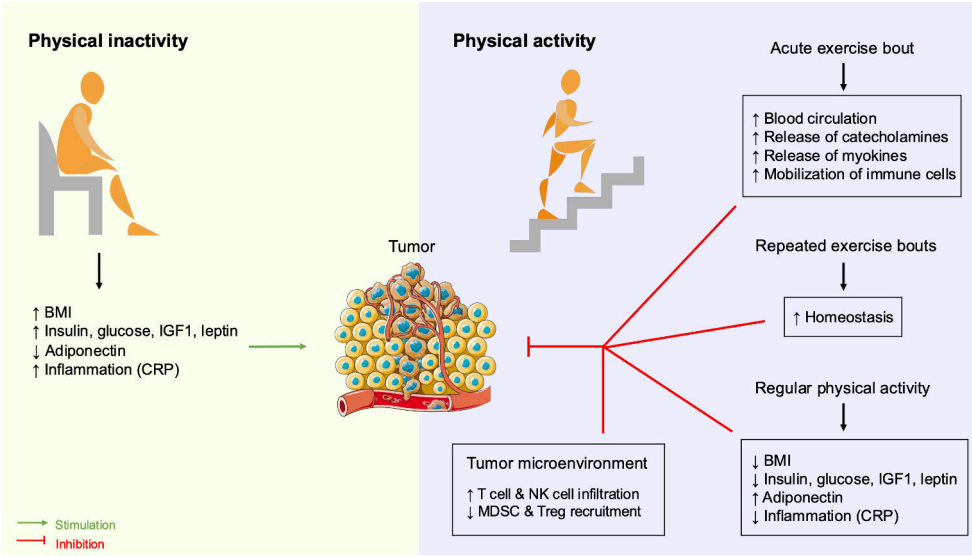

Figure 2. Mechanisms of actions of physical activity in patients with cancer. Prolonged physical inactivity can increase body mass index (BMI) and alter the levels of inflammatory proteins, growth factors, and hormones that promote cancer. Acute exercise increases blood circulation and releases catecholamines and myokines which all mobilize immune cells. Repetitive exercise bouts and regular physical activity can decrease BMI, normalize homeostasis, and improve levels of inflammatory proteins, growth factors, and hormones. Regular exercise may also affect the tumor microenvironment by increasing the infiltration of anti-tumoral immune cells and decreasing the recruitment of pro-tumoral immune cells, but that has not been proven in humans. CRP, C-reactive protein; IGF, insulin-like growth factor; NK cell, natural killer cell; MDSC, myeloid derived suppressor cell; Treg, regulatory T cell. Modified from (Lempiäinen et al, 2021).

2.3.3.1 Obesity, metabolic health, and chronic inflammation

Obesity increases the risk of cancer and promotes cancer development (Bergström et al., 2001; Calle et al., 2003). As adipose tissue expands it becomes dysfunctional and secretes adipokines in altered serum levels (van Kruijsdijk et al., 2009). Leptin is a hormone secreted by adipose tissue that normally decreases appetite and increases metabolism. In obese people, leptin levels can be increased, and studies have shown that leptin can stimulate cancer cell growth (Somasundar et al., 2003) and inhibit cancer cell apoptosis (Hoda et al., 2007). Conversely, obesity can reduce the level of adiponectin, which has an opposite effect to leptin (Yokota et al., 2000). Further, the hypersecretion state observed in obesity causes e.g. hyperinsulinemia and low-grade chronic inflammation, which can favor carcinogenesis (Gunter et al., 2009; Pollak et al., 2004). Thus, systemic levels of inflammatory markers such as C-reactive protein (CRP), TNF-α, and IL-6 are increased in individuals with high body mass index (BMI). TNF-α and IL-6 have contradictory effects in cancer, but elevated

levels of these cytokines as well as CRP are associated with increased cancer risk and cancer mortality (Sangmi et al., 2008; Il'yasova et al., 2005).

Maintaining or achieving a normal body weight by being physically active together with healthy diet maintains normal homeostasis and counteracts these obesity-related metabolic changes that are associated with carcinogenesis. A study with 100 overweight breast cancer survivors showed that 16 weeks of three times per week aerobic and resistance exercise reduces BMI and improves circulating insulin, leptin, adiponectin, CRP, IL-6, and TNF-α levels in exercise group compared to those who did not exercise (Dieli-Conwright et al., 2018).

2.3.3.2 Immunological control of tumor growth

Skeletal muscles are secretory organs, and during exercise, they secrete multiple proteins, lipids, nucleid acids, and metabolites (together called as myokines) to the circulation, which have effects to the immune system (Bente K. Pedersen, 2011). The concentration of IL-6 can increase up to 100-hold when acute exercise is of high intensity and long in duration (Bente K. Pedersen & Febbraio, 2008). Exercise-induced IL-6 acts as an anti-inflammatory mediator by stimulating the release of IL-1ra and IL-10 as well as decreasing the production of TNF-α (Steensberg et al., 2003; Starkie et al., 2003). One important preclinical study revealed that secretion of IL-6 was increased in exercising tumor bearing mice and induced NK cell infiltration into tumors (L. Pedersen et al., 2016). Further, tumor growth rate was decreased in exercising mice compared to sedentary ones, which was a result of enhanced NK cell-dependent tumor killing. Another cytokines induced by acute exercise include for example IL-15 and IL-7 (Haugen et al., 2010; Tamura et al., 2011), which both mediate T cell homeostasis and proliferation (Goldrath et al., 2002; Wallace et al., 2006). Stimulation of double negative T cells with IL-15 enhances their cytotoxicity against tumors by increasing the expression and production of effector molecules (Yao et al., 2019). Another study found that mice with pancreatic cancer that run treadmill had higher level of IL-15Ra-positive $CD8^+$ T cells in tumors compared to untrained mice (Kurz et al., 2022). IL-15Ra-positive $CD8^+$ T cells also had upregulated proliferation and activation markers compared with IL-15Ra-negative cells, reflecting the importance of IL-15 in anti-tumor immunity. Moreover, elevated lactate concentration during exercise increases $CD8^+$ T cell cytotoxicity against tumors *ex vivo* (Rundqvist et al., 2020). In addition to enhancing the recruitment and activity of anti-tumoral immune cells, exercise has been shown to reduce the accumulation of pro-tumoral immune cells, regulatory T cells (Hagar et al., 2019), MDSCs (Wennerberg et al., 2020), and macrophages (Almeida et al., 2009) in tumors in mice.

In humans, blood level of adrenaline increases during exercise, and together with changes in blood pressure, mobilizes immune cells to circulation (B.K. Pedersen & Hoffman-Goetz, 2000). In healthy individuals, the number of many immune cells, including neutrophils, lymphocytes and monocytes are increased in blood during acute exercise, and after exercise cessation, the number decreases to baseline or even below that, suggesting that the cells rapidly return to tissues. The mobilization is dependent on exercise intensity (Da Silva Neves et al., 2015), and some immune cell e.g. NK cells and $CD8^+$ T cells mobilize typically more than $CD4^+$ T cells and B cells (Simpson et al., 2007; Anane et al., 2009; J. P. Campbell et al., 2009; Timmons & Cieslak, 2008). Few studies have also been conducted in cancer survivors and patients. In breast cancer survivors, monocyte number elevated during 45-minute interval training (Khosravi et al., 2021), in pediatric acute lymphoblastic leukemia survivors neutrophil count increased during a 30-minute intermittent run-walk exercise (Ladha et al., 2006), and in prostate cancer patients, T cell and NK cell counts increased during a 45-minute intermittent cycling exercise similarly to healthy controls (Hanson et al., 2023; Hanson et al., 2020). In addition, $CD8^+$ T cells and NK cells increased after watt-max test and interval bicycling exercise in early-stage prostate cancer patients (Schauer et al., 2022).

Circulating immune cell number or activity do not change in response to regular exercise (Khosravi et al., 2019). Hence a recent meta-analysis evaluating the effects of exercise to immune system concluded that exercise does not improve or impair immune system in cancer patients or survivors (Lavín-Pérez et al., 2023). However, Nan Deng et al. found that 12-month aerobic training increased $CD8^+$ T cell and NK cell levels in colon in patients with Lynch syndrome, thus in patients at a high risk of colorectal cancer (Deng et al., 2023), so regular exercise might modify immune cell proportions in tissues. Tumor NK cell infiltration has been studied in patients with prostate cancer undergoing radical prostatectomy, and the study found no difference in NK cell infiltration between a group that did preoperative high-intensity interval training and a group receiving usual care (Djurhuus et al., 2023). However, the number of exercise sessions varied between only 4 and 30 in these patients, and the number of exercise sessions correlated positively with NK cell infiltration. Therefore, although regular execise does not alter immune cell levels in blood, the mobilization and possible tumor infiltration of immune cells observed with acute exercise is suggested to have positive effects to patients with cancer as the phenomenon accumulates in people engaging exercise regularly.

3 Aims

The aim of this PhD thesis was to investigate whether acute exercise affects the levels of immune cells and cytokines in the bloodstream of patients with newly diagnosed cancer. It was hypothesized that acute exercise temporarily increases the number of circulating immune cells in patients with cancer, and that the increases in immune cells correlate positively with exercise intensity. Further, it was hypothesized that acute exercise has also an effect to circulating cytokine levels, but the response in cytokines is smaller compared to immune cells.

The specific aims were:

Study I: To investigate the effect of acute 10-minute exercise to immune cells in the circulation of lymphoma patients.

Study II: To investigate the effect of acute 10-minute exercise to immune cells in the circulation of breast cancer patients.

Study III: To investigate the effect of acute 30-minute exercise to immune cells in the circulation of breast cancer patients.

Study IV: To investigate the effect of acute 30-minute exercise to immune cells in the circulation of lymphoma patients, and the effect of 10- and 30-minute exercises to circulating cytokines in lymphoma and breast cancer patients.

4 Materials and Methods

The thesis work included data obtained from four different observational studies where the effect of acute exercise on circulating immune cells and cytokines were measured. Each participant served their own control (immune cell/cytokine level at rest vs. level during and after exercise). The studies were conducted at Turku PET Centre (Turku, Finland) between September 2020 and December 2023. Good clinical practice and the Declaration of Helsinki were followed. The studies were approved by the Ethics Committee of the Hospital District of Southwestern Finland (72/2018) (12/2020) (100/2020). The studies are registered in the international register of clinical trials (Clinicaltrials.gov NCT03987724, NCT04416087, and NCT04990856).

4.1 Participants

Study I included 7 lymphoma patients, study II included 20 breast cancer patients, study III included 19 breast cancer patients, and study IV included 8 lymphoma patients. All participants were recruited from Turku University Hospital. The inclusion criteria in all studies were 18-70 years of age and additionally in studies I and IV a disease of newly diagnosed Hodgkin lymphoma, recurrent Hodgkin lymphoma and non-Hodgkin lymphoma with neck and thorax involvement, and in studies II and III a newly diagnosed breast cancer. Thus, all participants were diagnosed with cancer days-weeks before they were recruited to the study, and they had not started their cancer treatments at the time of the study visit. The exclusion criteria in all of the studies were abnormal fatigue, anemia, or physical dysfunction due to the disease that would have affected to their ability to perform the exercise. All participants participated voluntarily by signing an informed consent form after reviewing the study information sheet and hearing an explanation about the study from the investigators.

4.2 Exercise studies

4.2.1 Study I and II

The participants visited Turku PET Centre once 1 day to 1 week before the actual study day during which they tested pedalling a supine bicycle ergometer (Tunturi E30^{R}, Hungary). During that testing, a pedalling power for the actual study was determined. Testing was started with minimal power production (watts) and was gradually increased until the patient was confident that the chosen power would feel moderately heavy but be so that they could pedal the bicycle ergometer for 10 minutes without developing fatigue. Higher power production levels were also tested to make sure that the choice was correct and not too light. During the testing, it was also monitored that the chosen power production would modestly increase participants heart rate, typically above 100 bpm. Participants were advised to abstain from strong physical exertion, alcohol consumption, and caffeine for 24 hours prior to the study day.

On the study day, participants conducted a 10-minute exercise with a supine bicycle ergometer with the power production level of their choosing. Participants' heart rate was measured with pulse oximeter (Palmsat 2500, Nonin, Plymouth, United States) during the exercise and at rest before and after the exercise. Blood pressure was measured with Apteq AE701f blood pressure monitor (Rossmax Swiss GmbH, Berneck, Switzerland) also during the exercise and at rest before and after the exercise. To determine the strenuousness of the exercise, participants rated their perceived exertion on a Borg Scale (6-20).

4.2.2 Study III and IV

Each participant visited Turku PET Centre once for the study. Participants performed a 30-minute exercise with a cycle ergometer (Gymstick Vapor 10.0, Gymstick International Oy, Lahti, Finland). Participants were allowed to choose the resistance and cadence of pedalling themselves, and they were allowed to modify the resistance as many times as they liked during the exercise. However, the participants were asked to reach a heart rate that was 70 % of their age predicted maximal heart rate at some point during the exercise. The corresponding heart rate was calculated for each patient with the following formula: (220-age) * 0,7. Lactate concentration (Lactate Scout 4, EKF Diagnostics, Barleben, Germany) and blood pressure (Apteq AE701f, Rossmax Swiss GmbH Berneck, Switzerland) were measured at rest before the exercise, at half-way during the exercise, at the end of the exercise, and again at rest 30 minutes and 60 minutes after the execise. Heart rate was measured with pulse

oximeter (Palmsat 2500, Nonin, Plymouth, United States) at rest before the exercise and 30 minutes and 60 minutes after the exercise. Additionally, heart rate was continuously measured during the exercise with Polar H10 heart rate sensor (Polar Electro Oy, Kempele, Finland). Participants' rating of perceived exertion was determined with Borg Scale (6-20).

4.3 Blood samples

An intravenous catheter was inserted for each participant before the exercise in all the studies. In studies I and II, venous blood samples were collected at three time points: at rest before the exercise, immediately after the exercise, and 30 minutes after the exercise. In studies III and IV, venous blood samples were collected at five different time points: at rest before the exercise, at half-way during the exercise, at the end of the exercise, 30 minutes after the exercise, and 60 minutes after the exercise.

4.3.1 Flow cytometry

Participants' white blood cell subset levels were determined with flow cytometry in all the studies. For that, whole blood sample per each time point was processed either on the same day or stored in the refrigerator with 4 % formaldehyde (Thermo Fisher Scientific, Kandel, Germany) and processed on the next day.

For all study samples, Fc Block (BD Biosciences, San Jose, United States) was added to 100 µl of whole blood and incubated for 10 minutes at room temperature (RT). Thereafter, the samples were stained with fluorophore-labelled CD monoclonal antibodies (BD Biosciences, San Jose, United States) and incubated for 20 minutes in dark in RT. Antibodies used in all the studies were CD45, CD3, CD4, CD8, CD14, CD16, CD19, CD56, CD64. Additionally, CD11b, CD25, CD33, CD66b, CD183, CD194, CD196, and HLA-DR were used in studies III and IV. Red blood cells were lysed with 1X FACS lysing solution (BD Biosciences, San Jose, United States). Samples were washed with PBS (Thermo Fisher Scientific, Waltham, United States) and the cell pellet suspended in 300 µl PBS. Some of the samples in studies III and IV were further processed for FoxP3 staining. For that, the samples were incubated with Fixation/Permeabilization working solution (Thermo Fisher Scientific, Waltham, USA), incubated with FoxP3-antibody (BD Biosciences, San Jose, United States) and washed with 1X Permeabilization buffer (Thermo Fisher Scientific, Waltham, USA). Samples from all the studies were run with a BD LSR Fortessa™ flow cytometer (Biosciences, San Jose, United States). Gating strategy of

studies I and II are presented in **Figure 3** and gating strategy of studies III and IV in **Figure 4**.

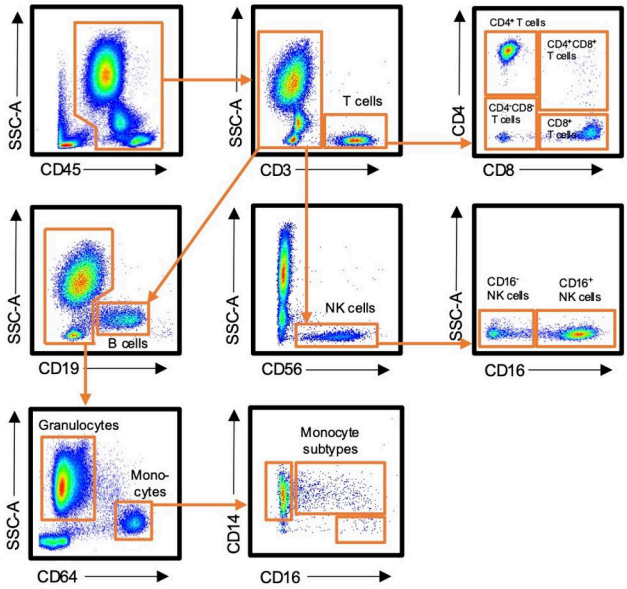

Figure 3. Gating strategy of studies I and II. Modified from Original publications I and II.

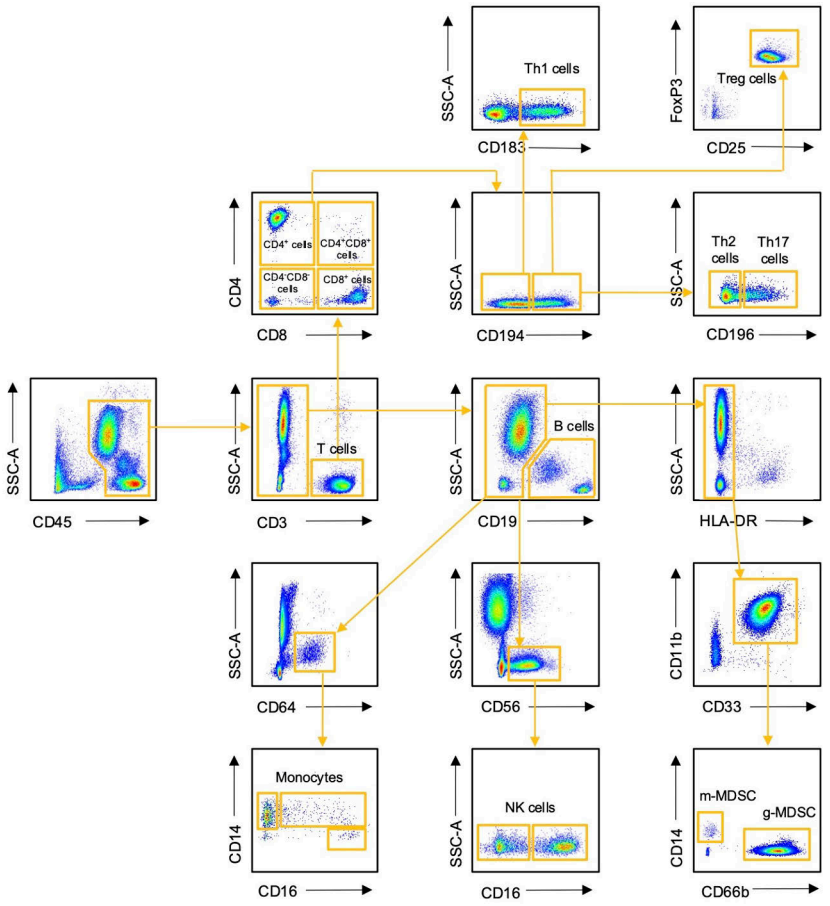

Figure 4. Gating strategy of studies III and IV. From Original publication III.

4.3.2 Complete blood count

Complete blood count was analysed in Turku University Hospital Laboratory in studies III and IV. White blood cell counts were analysed using flow cytometry method (Sysmex XN analyser, Sysmex, Kobe, Japan). Red blood cell count was determined by the hydrodynamically focused DC detection method (Sysmex XN analyzer, Sysmex, Kobe, Japan). Hematocrit (Hct) was calculated via the red blood cell pulse height detection method (Sysmex XN analyzer, Sysmex, Kobe, Japan). Hemoglobin (Hb) was determined by the sodium lauryl sulphate method (Sysmex XN analyzer, Sysmex, Kobe, Japan).

4.3.3 Cytokine analysis

Venous blood samples collected in all the studies were also used for cytokine analysis. After sample collection, the blood samples were kept at room temperature for 30 minutes. Thereafter, the samples were centrifuged at 2800 rpm for 10 minutes to separate serum from whole blood. 1ml serum was collected from each sample and stored in -80°C freezer. Later, the levels of cytokines were detected from the serum samples with Bio-Plex Human cytokine assay (Bio-rad, Hercules, USA).

4.4 Cancer biomarkers

Characterization of breast cancer biomarkers were determined at Pathology Laboratory of Turku University Hospital as part of the patients' routine diagnostics. Paraffin embedded cancer specimens were stained using Ventana Benchmark Ultra (Roche Diagnostics) for immunohistochemistry with estrogen receptor (ER) (SP1), progesterone receptor (PR) (IE2), HER2 (4B5), and Ki-67 (30–9) antibodies (Ventana/Roche Diagnostics). Positive staining at HER2 immunohistochemistry was always confirmed by *in situ* hybridization according to national and international guidelines. The degree of histological differentiation of carcinoma was determined according to Scaff-Bloom-Richardson and staging by the UICC TNM classification.

4.5 Calculations

To characterize the intensity of exercise in all studies, heart rate percentage of age-predicted maximal heart rate (HR%), rate pressure product (RPP), and mean arterial pressure (MAP) were calculated. Age-predicted maximal heart rate was determined by subtracting age from 220, and HR% was calculated by dividing mean exercising heart rate by the age-predicted maximal heart rate. RPP was calculated by multiplying systolic blood pressure by heart rate. MAP was calculated as (diastolic blood pressure * 2 + systolic blood pressure)/3.

In studies III and IV, the change in plasma volume (PV) during and after exercise bout was taken into consideration and calculated with the following formula: $\Delta PV = (Hb_{pre}*(1-Hct_{post}))/(Hb_{post}*(1-Hct_{pre}))-1$. White blood cell (WBC) counts were adjusted to reflect the exercise-induced shifts in plasma volume with the following formula: $WBC_{corrected} = WBC_{uncorrected}*(1+\Delta PV)$. Further, in studies III and IV, immune cell subset levels obtained from flow cytometry measurements were corrected with total leukocyte count obtained from complete blood count. For the correction the following formula was used: $WBC_{corrected}$ = total leukocyte count*WBC% of $CD45^+$ cells.

4.6 Statistical analysis

4.6.1 Sample size

The sample size for each study was determined by power calculations for the primary outcome of the studies that these studies are a part of that is tumor blood flow. In regards to aiming to show increased tumor blood flow in lymphoma patients in response to acute exercise, it was calculated that if tumor blood flow is doubled from its normal resting values of 36 ml/100g/min (Komar et al., 2008), 5,25 participants are needed to show statistical increase for studies I and IV ($\alpha = 0,05$, $\beta = 0,9$). Similarly, if tumor blood flow in breast cancer patients is doubled from its normal values of 30-32 ml/100g/min (Mankoff et al., 2002; Mankoff et al., 2003), 12,8 participants are needed for studies II and III ($\alpha = 0,05$, $\beta = 0,9$). To secure enough statistical power for other variables, 8 participants were recruited to studies I and IV and 20 participants for studies II and III.

4.6.2 Analyses

Two-way t-test was used to compare exercise intensity variables between exercise and baseline. The effect of acute exercise on immune cells in each study was analysed with repeated measured ANOVA. To determine the effect of 10- and 30-minute acute exercise on white blood cell counts and cytokine levels, linear mixed models were used. Pearson or Spearman correlations were used to evaluate the associations between exercise intensity and cancer biomarkers and immune cell changes. The level of statistical significance was set at $p<0,05$. All statistical analyses were performed with Graphpad prism 8.0 (Graphpad Software, Massachusetts, United States), IBM SPSS Statistics 27.0 (IBM Corp., New York, United States), and SAS 9.4 (SAS Institute Inc., North Carolina, United States)

5 Results

5.1 Participant characteristics

Total of 56 participants were recruited, of which 54 were included in this study since blood sample collection was unsuccessful in two of the participants. In all studies, participants' heart rate and blood pressure increased during exercise (**Table 1**).

Table 1. Participant characteristics at baseline and during exercise.

	Study I	**Study II**	**Study III**	**Study IV**
N	7	20	19	8
Cancer, type	Lymphoma	Breast	Breast	Lymphoma
Age, years	51 (21)	58 (11)	56 (8)	66 (8)
Height, cm	176 (14)	165 (5)	164 (5)	179 (5)
Weight, kg	84 (17)	76 (13)	77 (15)	82 (11)
BMI, kg/m^2	27 (4)	28 (5)	29 (5)	25 (3)
HR, bpm	77 (15)	66 (9)	69 (10)	64 (8)
SBP, mmHg	129 (15)	140 (30)	122 (16)	113 (15)
DBP, mmHg	69 (9)	75 (12)	69 (7)	58 (8)
RPP, bpm*mmHg	9894 (2065)	9249 (2679)	7928 (1936)	8731 (2111)
MAP, mmHg	89 (11)	96 (17)	86 (9)	91 (11)
Lactate, mmol/l			1.2 (0.5)	1.1 (0.4)
Exercise measurements:				
HR, bpm	109 (21)**	114 (17)***	127 (19)**	98 (12)***
HR%, bpm	65 (13)	70 (10)	77 (12)	64 (8)
SBP, mmHg	155 (31)*	158 (30)***	165 (22)***	147 (15)**
DBP, mmHg	84 (23)	89 (29)**	111 (17)***	83 (12)**
RPP, bpm*mmHg	16883 (4391)**	17996 (4718)***	20576 (6748)***	13518 (3752)**
MAP, mmHg	128 (77)	112 (28)***	125 (22)***	105 (25)*
RPE, Borg scale (6-20)	13 (2)	12 (2)	14 (2)	11 (3)
Lactate, mmol/l			3.7 (1.5)***	2.2 (0.6)**

BMI, body mass index; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; RPP, rate pressure product; MAP, mean arterial pressure; HR%, heart rate percentage of age-predicted maximal heart rate; RPE, rate of perceived exertion. Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 within a study (two-tailed paired t-test).

5.2 Plasma volume change

The complete blood count obtained in studies III and IV allowed the calculation of plasma volume change. In patients with breast cancer in study III, plasma volume decreased 17 % during the exercise, and was 2 % and 5 % above baseline at 30 minutes and at 60 minutes post-exercise, respectively (**Figure 5A**). In patients with lymphoma in study IV, plasma volume decreased 11 % during the exercise, and was 8 % and 12 % above baseline at 30 minutes and at 60 minutes post-exercise, respectively (**Figure 5B**). Immune cell changes were corrected for plasma volume changes to ensure that the increases in immune cell numbers during exercise were associated with a mobilization of the cells and not the decrease in plasma volume. Table 2 represents percentage changes in immune cells during a 30-minute exercise when analysed with uncorrected values and plasma volume corrected values in breast cancer and lymphoma patients. The changes in uncorrected immune cells are significantly greater than the changes in corrected immune cells (**Table 2**).

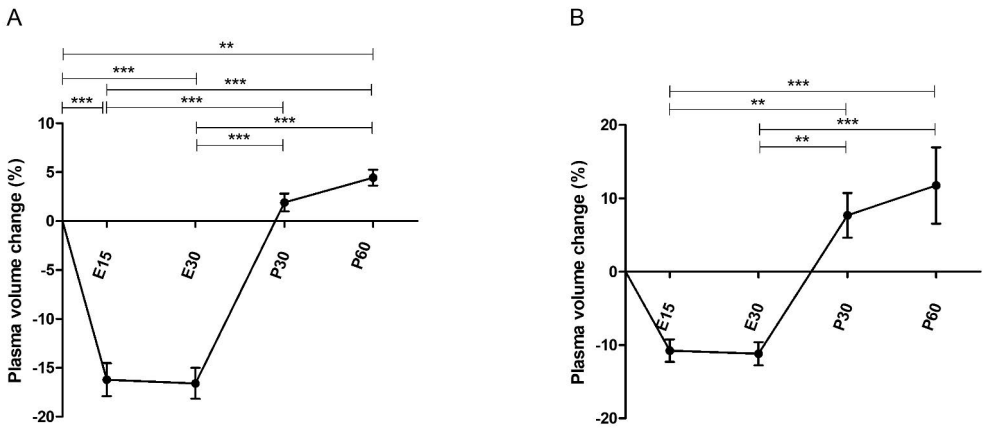

Figure 5. Plasma volume change during and after a 30-minute exercise in (A) breast cancer patients and (B) lymphoma patients. **p<0.01, ***p<0.001. E15, at 15-minute timepoint during a 30-min exercise; E30, timepoint when exercise was about to be finished; P30, 30 minutes after a 30-minute exercise; P60, 60 minutes after a 30-minute exercise.

Table 2. Immune cell percentage changes during a 30-minute exercise with plasma volume corrected and uncorrected values.

	Uncorrected (%)	Plasma volume corrected (%)	p-value
Total leukocytes	41 (25)	19 (17)	<0.0001
Neutrophils	41 (25)	19 (19)	<0.0001
Lymphocytes	53 (42)	29 (32)	<0.0001
Monocytes	23 (27)	4 (20)	<0.0001
Eosinophils	46 (152)	22 (124)	0.0004
Basophils	51 (90)	29 (69)	<0.0001

Values are mean (standard deviation).

5.3 Immune cell responses

In study I, the number of $CD8^+$ T cells and $CD56^+$ NK cells increased immediately after 10-minute exercise in lymphoma patients (**Table 3**). Moreover, the proportion of $CD56^+CD16^+$ NK cells of total leukocytes ($CD45^+$ cells) and the proportion of $CD8^+$ T cells of total T cells ($CD3^+$ cells) increased immediately after the exercise (**Table 4**). The proportion of $CD4^+$ T cells of total T cells decreased immediately after the exercise.

Table 3. Immune cell responses to acute 10-minute exercise in lymphoma patients.

	Baseline (cells/µl)	Immediately after exercise (cells/µl)	30 min after exercise (cells/µl)
$CD45^+$	2917 (2494)	3000 (2448)	2626 (2222)
$CD3^+$	215 (109)	248 (125)	208 (111)
$CD4^+$	112 (63)	118 (79)	107 (66)
$CD8^+$	80 (43)	101 (46)**	77 (42)
$CD4^+CD8^+$	11 (17)	13 (19)	10 (14)
$CD4^-CD8^-$	10 (8)	14 (14)	11 (10)
$CD19^+$	176 (128)	165 (129)	153 (116)
$CD56^+$	94 (51)	162 (94)**	92 (57)
$CD56^+CD16^+$	52 (42)	111 (94)*	53 (48)
$CD56^+CD16^-$	41 (39)	51 (43)*	38 (34)
$CD64^+$	185 (161)	175 (143)	179 (155)
$CD14^+CD16^-$	137 (124)	132 (116)	132 (131)
$CD14^+CD16^+$	37 (35)	33 (27)	34 (26)
$CD14^-CD16^+$	2 (2)	3 (2)	3 (2)
$CD64^-$SSC-A^{high}	2234 (2114)	2116 (1859)	2011 (1943)

Values are mean (standard deviation). *p<0.05, **p<0.01 compared to baseline.

Table 4. Immune cell proportional responses to acute 10-minute exercise in lymphoma patients.

	Baseline	Immediately after exercise	30 min after exercise
% of $CD45^+$ cells			
$CD3^+$	12 (8.1)	12 (7.2)	11 (6.8)
$CD4^+$	5.7 (4.1)	5.0 (3.1)	5.2 (3.2)
$CD8^+$	4.8 (3.3)	5.3 (3.3)	4.4 (2.9)
$CD4^+CD8^+$	0.5 (0.9)	0.6 (1.0)	0.5 (0.7)
$CD4^-CD8^-$	0.6 (0.5)	0.7 (0.7)	0.6 (0.6)
$CD19^+$	9.7 (8.6)	8.5 (7.2)	8.8 (6.7)
$CD56^+$	5.2 (3.5)	7.7 (4.5)*	5.2 (4.1)
$CD56^+CD16^+$	2.8 (2.3)	5.0 (3.6)*	3.1 (3.0)
$CD56^+CD16^-$	2.4 (2.3)	2.7 (2.3)	2.1 (1.9)
$CD64^+$	7.6 (2.8)	7.4 (3.3)	8.3 (3.8)
$CD14^+CD16^-$	5.9 (2.4)	5.8 (2.9)	6.2 (3.2)
$CD14^+CD16^+$	1.2 (0.5)	1.1 (0.4)	1.4 (1.0)
$CD14^-CD16^+$	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)
$CD64^-$SSC-A^{high}	67 (16)	66 (10)	64 (13)
% of total T ($CD3^+$) cells			
$CD4^+$	51 (11)	45 (12)***	50 (10)
$CD8^+$	40 (10)	45 (12)**	40 (9)
$CD4^+CD8^+$	3.7 (4.8)	4.1 (5.5)	3.7 (4.6)
$CD4^-CD8^-$	5.6 (4.1)	6.0 (3.9)	5.8 (4.1)

Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline.

In study II, the number of total leukocytes ($CD45^+$ cells), $CD8^+$ T cells, $CD19^+$ B cells, $CD56^+CD16^+$ NK cells, and $CD14^+CD16^+$ monocytes increased immediately after 10-minute exercise in breast cancer patients (**Table 5**). The proportion of $CD56^+CD16^+$ NK cells of total leukocytes and the proportion of $CD8^+$ T cells of total T cells increased immediately after the exercise (**Table 6**).

Table 5. Immune cell responses to acute 10-minute exercise in breast cancer patients.

	Baseline (cells/µl)	Immediately after exercise (cells/µl)	30 min after exercise (cells/µl)
$CD45^+$	1325 (849)	1715 (1202)**	1624 (1094)
$CD3^+$	205 (157)	244 (178)	226 (161)
$CD4^+$	126 (109)	166 (125)	157 (115)
$CD8^+$	50 (50)	67 (56)*	57 (48)
$CD4^+CD8^+$	3 (5)	4 (6)	3 (4)
$CD4^-CD8^-$	6 (6)	8 (7)	7 (5)
$CD19^+$	104 (80)	123 (93)*	114 (81)
$CD56^+$	72 (60)	144 (114)***	77 (60)
$CD56^+CD16^+$	52 (50)	109 (104)***	59 (53)
$CD56^+CD16^-$	20 (23)	24 (26)	17 (16)
$CD64^+$	73 (54)	88 (86)	92 (65)
$CD14^+CD16^-$	61 (44)	70 (56)*	72 (53)
$CD14^+CD16^+$	8 (6)	12 (9)	13 (9)
$CD14^-CD16^+$	2 (2)	2 (2)	3 (2)
$CD64^-$SSC-A^{high}	807 (581)	1007 (790)	1077 (763)

Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline.

Table 6. Immune cell proportional responses to acute 10-minute exercise in breast cancer patients.

	Baseline	Immediately after exercise	30 min after exercise
% of $CD45^+$ cells			
$CD3^+$	16 (9.5)	14 (6.2)	16 (9.2)
$CD4^+$	10 (6.9)	9.4 (3.9)	11 (6.3)
$CD8^+$	4.0 (3.0)	4.1 (2.7)	4.0 (2.8)
$CD4^+CD8^+$	0.3 (0.3)	0.2 (0.2)	0.2 (0.2)
$CD4^-CD8^-$	0.8 (1.2)	0.6 (0.5)	0.6 (0.9)
$CD19^+$	6.9 (2.8)	6.3 (2.9)	6.2 (2.3)
$CD56^+$	7.3 (5.1)	10 (6.5)**	7.4 (6.7)
$CD56^+CD16^+$	4.9 (3.6)	8.3 (6.5)***	5.5 (5.3)
$CD56^+CD16^-$	2.3 (2.6)	1.9 (1.5)	1.9 (2.6)
$CD64^+$	5.5 (2.0)	5.2 (1.7)	5.3 (1.9)
$CD14^+CD16^-$	4.6 (1.6)	4.2 (1.4)	4.2 (1.5)
$CD14^+CD16^+$	0.5 (0.4)	0.6 (0.3)	0.6 (0.4)
$CD14^-CD16^+$	0.2 (0.1)	0.2 (0.2)	0.2 (0.2)
$CD64^-$SSC-A^{high}	58 (19)	56 (16)	60 (20)
% of total T ($CD3^+$) cells			
$CD4^+$	66 (19)	68 (11)	70 (9.6)
$CD8^+$	23 (11)	26 (10)*	25 (8.5)
$CD4^+CD8^+$	1.8 (1.7)	1.7 (1.7)	1.5 (1.5)
$CD4^-CD8^-$	4.4 (4.7)	4.2 (4.1)	3.5 (2.8)

Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline. Modified from Original publication II.

In study III, the number of total leukocytes, neutrophils, lymphocytes, monocytes, basophils, $CD3^+$ total T cells, $CD4^+$ T cells, Th2 cells, Th17 cells, $CD8^+$ T cells, $CD4^-CD8^-$ T cells, $CD56^+$ NK cells, and $CD14^-CD16^+$ monocytes increased during 30-minute exercise in breast cancer patients (**Table 7**). Further, the proportion of lymphocytes and $CD56^+CD16^+$ NK cells of total leukocytes and the proportion of $CD8^+$ T cells of total T cells increased during the exercise (**Table 8**). The proportion of neutrophils, monocytes, eosinophils, $CD19^+$ B cells, and granulocytic MDSCs (gMDSCs) of total leukocytes and the proportion of $CD4^+$ T cells of total T cells decreased during the exercise. In turn, after the exercise, the proportion of lymphocytes and $CD56^+CD16^+$ NK cells of total leukocytes decreased, and the proportion of neutrophils increased. Moreover, the proportion of Th2 cells increased at 30 minutes after the exercise.

Table 7. Immune cell responses to acute 30-minute exercise in breast cancer patients.

	Baseline (cells/µl)	E15 (cells/µl)	E30 (cells/µl)	P30 (cells/µl)	P60 (cells/µl)
Total leukocytes	5747 (1546)	6905(1587)***	6843 (1750)*	5939 (1777)	6160 (1750)
Neutrophils	3378 (1186)	3935 (1384)*	4039 (1391)	3707 (1450)	3865 (1423)
Lymphocytes	1658 (482)	2182 (441)***	2094(497)***	1576 (483)	1629 (533)
Monocytes	492 (226)	556 (245)***	517 (273)	457 (282)	480 (331)
Eosinophils	185 (167)	180 (136)**	171 (143)**	156 (143)	172 (129)
Basophils	32 (18)	41 (17)	38 (16)	38 (15)	36 (13)
$CD3^+$	1507 (591)	1845 (711)***	1720 (675)*	1684 (774)	1574 (738)
$CD4^+$	979 (517)	1122 (548)	1056 (530)	1051 (529)	1003 (533)
Th1	107 (77)	119 (78)	107 (66)	118 (77)	115 (81)
Th2	164 (161)	192 (165)**	175 (119)	192 (168)	176 (130)
Th17	44 (38)	54 (47)**	47 (34)	52 (47)	48 (39)
Treg	31 (26)	30 (34)	33 (31)	43 (50)	36 (44)
$CD8^+$	460 (277)	629 (430)**	580 (377)*	568 (349)	503 (347)
$CD4^+CD8^+$	22 (59)	41 (115)	36 (103)	26 (75)	16 (28)
$CD4^-CD8^-$	51 (37)	71 (63)**	62 (46)	56 (49)	48 (37)
$CD19^+$	551 (679)	529 (370)	507 (460)	439 (377)	463 (432)
$CD56^+$	398 (301)	778 (391)***	831 (511)**	307 (207)	360 (257)
$CD56^+CD16^+$	208 (150)	521 (284)***	566 (285)***	163 (95)	185 (112)
$CD56^+CD16^-$	187 (252)	252 (261)**	260 (266)*	146 (154)	173 (203)
$CD14^+CD16^-$	84 (168)	86 (170)	89 (191)	87 (208)	110 (262)
$CD14^+CD16^+$	20 (33)	25 (44)	24 (46)	22 (44)	24 (51)
$CD14^-CD16^+$	8.0 (10)	10 (12)*	11 (16)	7.9 (11)	8.2 (10)
MDSC	2532 (1654)	2289 (1509)	2360 (1476)	2341 (1645)	2467 (1498)
gMDSC	2484 (1662)	2250 (1518)	2321 (1489)	2312 (1651)	2430 (1499)
mMDSC	3.2 (7.3)	2.9 (7.0)	3.4 (9.3)	2.3 (6.2)	2.0 (4.4)

E15, at 15-minute timepoint during a 30-min exercise; E30, timepoint when exercise was about to be finished; P30, 30 minutes after a 30-minute exercise; P60, 60 minutes after a 30-minute exercise. Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline.

Table 8. Immune cell proportional responses to acute 30-minute exercise in breast cancer patients.

	Baseline	E15	E30	P30	P60
% of total leukocytes					
Neutrophils	58 (7.6)	56 (8.5)*	58 (7.9)	62 (8.6)**	62 (8.6)**
Lymphocytes	30 (7.7)	33 (8.3)***	32 (7.7)	28 (8.1)*	27 (8.3)*
Monocytes	8.5 (2.7)	8.0 (2.4)*	7.4 (2.2)**	7.5 (2.3)***	7.6 (2.7)***
Eosinophils	3.2 (2.9)	2.7 (2.2)*	2.6 (2.3)	2.8 (2.5)	3.0 (2.4)
Basophils	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.7 (0.3)	0.6 (0.2)
$CD3^+$	27 (11)	28 (12)	26 (11)	30 (13)	27 (12)
$CD4^+$	17 (8.0)	17 (8.4)	16 (8.2)	18 (8.7)	17 (8.7)
Th1	1.8 (1.3)	1.7 (1.1)	1.6 (1.0)	1.8 (1.3)	1.7 (1.3)
Th2	2.7 (1.8)	2.7 (1.8)	2.6 (1.5)	3.3 (2.2)*	3.0 (1.9)
Th17	0.8 (0.5)	0.8 (0.6)	0.7 (0.5)	0.9 (0.7)	0.8 (0.6)
Treg	0.6 (0.5)	0.5 (0.5)	0.5 (0.5)	0.8 (0.9)	0.6 (0.7)
$CD8^+$	8.7 (6.5)	9.5 (7.4)	8.8 (6.4)	10.1 (6.0)	8.8 (6.3)
$CD4^+CD8^+$	0.5 (1.6)	0.6 (1.9)	0.6 (1.8)	0.6 (1.8)	0.3 (0.7)
$CD4^-CD8^-$	0.9 (0.6)	1.0 (0.7)	0.9 (0.6)	1.0 (0.6)	0.8 (0.5)
$CD19^+$	8.8 (6.6)	7.7 (3.8)*	7.4 (5.1)	7.3 (4.7)	7.3 (4.7)
$CD56^+$	6.9 (5.1)	11 (4.7)***	12 (5.3)**	5.0 (2.5)*	5.8 (3.7)
$CD56^+CD16^+$	3.5 (1.8)	7.5 (3.7)***	7.9 (4.4)***	2.6 (1.0)*	2.9 (1.4)
$CD56^+CD16^-$	3.4 (4.7)	3.6 (3.8)	3.7 (3.7)	2.4 (2.2)	2,.8 (3.2)
$CD14^+CD16^-$	1.3 (2.3)	1.1 (1.8)	1.0 (1.8)	1.1 (2.2)	1.4 (2.6)
$CD14^+CD16^+$	0.3 (0.4)	0.3 (0.4)	0.3 (0.4)	0.3 (0.5)	0.3 (0.5)
$CD14^-CD16^+$	0.1 (0.2)	0.1 (0.1)	0.1 (0.2)	0.1 (0.1)	0.1 (0.1)
MDSC	45 (27)	33 (21)***	35 (21)**	41 (28)	41 (26)
gMDSC	44 (27)	32 (21)***	34 (21)**	40 (28)	41 (26)
mMDSC	0.1 (0.1)	0.0 (0.1)	0.1 (0.2)	0.0 (0.1)	0.0 (0.1)
% of total T cells					
$CD4^+$	65 (15)	62 (17)**	62 (16)*	64 (11)	65 (13)
$CD8^+$	31 (15)	33 (16)**	33 (16)*	32 (11)	30 (13)
$CD4^+CD8^+$	2.6 (8.2)	3.4 (11)	3.2 (11)	2.8 (9.6)	2.6 (8.3)
$CD4^-CD8^-$	3.3 (1.7)	3.7 (2.5)	3.7 (2.4)	3.2 (1.9)	3.1 (1.7)
% of helper T cells					
Th1	12 (8.1)	12 (7.5)	11 (7.5)	11 (7.6)	12 (8.5)
Th2	18 (15)	18 (14)	18 (13)	19 (16)	18 (16)
Th17	4.6 (2.9)	4.9 (3.5)	5.0 (3.7)	5.0 (3.5)	5.2 (4.4)
Treg	3.4 (2.3)	2.8 (2.1)	3.5 (2.8)	4.5 (4.4)	3.8 (3.5)

E15, at 15-minute timepoint during a 30-min exercise; E30, timepoint when exercise was about to be finished; P30, 30 minutes after a 30-minute exercise; P60, 60 minutes after a 30-minute exercise. Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline. Modified from Original publication III.

In study IV, total leukocytes, lymphocytes, $CD3^+$ total T cells, $CD4^+$ T cells, Th17 cells, regulatory T cells, $CD8^+$ T cells, $CD4^-CD8^-$ T cells, NK cells, and $CD14^-CD16^+$ monocytes increased during 30-minute exercise in lymphoma patients (**Table 9**). Further, the number of $CD14^+CD16^+$ monocytes increased after the exercise, and the number of monocytes and basophils decreased after the exercise. The proportion of $CD8^+$ T cells, $CD4^-CD8^-$ T cells and $CD56^+$ NK cells of total leukocytes increased, and the proportion of monocytes and basophils decreased during the exercise (**Table 10**). Moreover, the proportion of neutrophils increased, and the proportion of NK cells decreased after the exercise.

Table 9. Immune cell responses to acute 30-minute exercise in lymphoma patients.

	Baseline (cells/µl)	**E15 (cells/µl)**	**E30 (cells/µl)**	**P30 (cells/µl)**	**P60 (cells/µl)**
Total leukocytes	5763 (2183)	6491 (2098)	6536 (2395)*	5959 (2745)	6164 (1534)
Neutrophils	3546 (1960)	3977 (2235)	4095 (2461)	4079 (2726)	4112 (1263)
Lymphocytes	1400 (386)	1649 (509)*	1652 (526)	1178 (460)	1241 (324)
Monocytes	561 (148)	583 (140)	554 (153)	472 (147)*	562 (188)
Eosinophils	189 (136)	189 (158)	187 (160)	189 (179)	194 (169)
Basophils	49 (23)	44 (20)	40 (18)	41 (23)*	40 (22)*
$CD3^+$	1095 (442)	1358 (417)*	1512(496)***	1181 (387)	1270 (310)
$CD4^+$	594 (241)	694 (227)	779 (220)**	706 (253)	753 (168)*
Th1	136 (79)	148 (83)	152 (86)	140 (91)	149 (62)
Th2	127 (85)	105 (54)	164 (77)	173 (103)	166 (86)
Th17	40 (36)	41 (31)	63 (42)*	53 (38)	59 (35)
Treg	87 (30)	104 (52)	117 (40)*	107 (51)	119 (48)*
$CD8^+$	425 (289)	601 (313)**	677 (362)***	461 (211)	509 (196)
$CD4^-CD8^-$	29 (16)	46 (27)	68 (56)***	37 (32)	38 (22)
$CD19^+$	466 (310)	496 (237)	471 (209)	407 (264)	401 (148)
$CD56^+$	475 (217)	658 (350)***	596 (389)*	387 (302)	402 (223)
$CD56^+CD16^+$	210 (139)	328 (174)***	297 (165)**	137 (86)*	137 (89)*
$CD56^+CD16^-$	266 (100)	327 (266)**	295 (280)	233 (256)	240 (285)
$CD14^+CD16^-$	252 (163)	241 (157)	217 (163)	233 (136)	267 (166)
$CD14^+CD16^+$	46 (34)	55 (39)	45 (33)	67 (68)*	70 (62)*
$CD14^-CD16^+$	11 (4)	15 (5)*	12 (5)	13 (8)	15 (10)*

E15, at 15-minute timepoint during a 30-min exercise; E30, timepoint when exercise was about to be finished; P30, 30 minutes after a 30-minute exercise; P60, 60 minutes after a 30-minute exercise. Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline.

Table 10. Immune cell proportional responses to acute 30-minute exercise in lymphoma patients.

	Baseline	E15	E30	P30	P60
% of total leukocytes					
Neutrophils	58 (7.6)	58 (8.5)	59 (7.9)	64 (8.6)*	64 (8.6)*
Lymphocytes	26 (7.7)	29 (8.3)	28 (7.7)	23 (8.1)	22 (8.2)
Monocytes	11 (2.7)	9.6 (2.4)*	9.2 (2.2)**	9.0 (2.3)***	9.7 (2.7)
Eosinophils	3.4 (2.9)	3.0 (2.2)	2.9 (2.3)*	3.3 (2.5)	3.3 (2.4)
Basophils	0.8 (0.3)	0.7 (0.3)*	0.6 (0.3)**	0.7 (0.3)	0.7 (0.2)**
$CD3^+$	22 (11)	24 (11)	26 (13)	23 (9.4)	23 (6.6)
$CD4^+$	12 (6.2)	12 (5.2)	14 (5.1)	14 (4.8)	14 (3.7)
Th1	2.7 (2.2)	2.6 (1.9)	2.7 (1.9)	2.8 (2.2)	2.7 (1.6)
Th2	2.4 (1.6)	1.9 (1.3)	2.7 (1.2)	3.0 (1.5)	2.8 (1.4)
Th17	0.8 (1.0)	0.8 (0.7)	1.0 (0.7)	0.9 (0.6)	1.1 (0.7)
Treg	1.7 (0.9)	1.8 (1.1)	2.1 (1.2)	2.1 (1.3)	2.2 (1.3)
$CD8^+$	9.0 (7.0)	11 (7.0)	12 (8.2)*	9.3 (5.3)	9.2 (4.4)
$CD4^-CD8^-$	0.5 (0.4)	0.7 (0.4)	1.0 (0.6)***	0.6 (0.4)	0.6 (0.2)
$CD19^+$	7.6 (2.7)	7.3 (2.2)	7.0 (2.2)	6.5 (2.0)	7.1 (1.5)
$CD56^+$	8.5 (5.5)	11 (5.3)*	9.1 (5.3)	6.6 (4.2)*	5.8 (2.9)**
$CD56^+CD16^+$	4.4 (3.3)	5.4 (3.4)	5.0 (3.3)	2.5 (2.0)**	2.1 (1.5)**
$CD56^+CD16^-$	4.4 (7.5)	4.6 (3.2)	4.3 (3.1)	3.6 (2.6)**	3.3 (0.7)**
$CD14^+CD16^-$	4.6 (2.2)	3.8 (1.6)	3.0 (1.5)*	5.6 (3.2)	7.6 (4.9)**
$CD14^+CD16^+$	0.8 (0.3)	0.8 (0.4)	0.6 (0.3)	1.0 (0.6)*	1.0 (0.5)
$CD14^-CD16^+$	0.2 (0.04)	0.2 (0.04)	0.2 (0.04)	0.2 (0.05)	0.2 (0.1)
% of total T cells					
$CD4^+$	57 (22)	56 (16)	58 (17)	64 (16)	66 (16)
$CD8^+$	37 (17)	42 (12)*	43 (10)*	38 (10)	38 (8.9)
$CD4^-CD8^-$	2.6 (0.9)	3.6 (2.8)	4.6 (4.4)*	3.0 (2.7)	3.1 (2.2)
% of helper T cells					
Th1	23 (13)	21 (12)	20 (11)	19 (13)	20 (10)
Th2	20 (9.3)	15 (6.5)	21 (9.4)	23 (10)	22 (12)
Th17	7.4 (5.9)	6.4 (4.9)	10 (8.0)	8.0 (6.1)	8.6 (6.0)
Treg	16 (7.1)	15 (5.2)	15 (6.7)	15 (5.1)	16 (8.3)

E15, at 15-minute timepoint during a 30-min exercise; E30, timepoint when exercise was about to be finished; P30, 30 minutes after a 30-minute exercise; P60, 60 minutes after a 30-minute exercise. Values are mean (standard deviation). *p<0.05, **p<0.01, ***p<0.001 compared to baseline.

To compare immune cell responses to 10-minute and 30-minute exercises, immune cell changes in lymphoma patients from study I was compared to study IV, and similarly in breast cancer patients, study II was compared to study III.

Additionally, some immune cell changes were compared between 15- and 30-minute timepoints during the 30-minute exercise, as they were not analysed in the 10-minute exercise study. All immune cells responded similarly to 10- and 30-minute exercises in lymphoma patients (**Table 11**). In breast cancer patients, the increases in $CD4^+$ T cells and NK cells were significantly greater during the 30-minute exercise compared to the 10-minute exercise (**Table 12**). Moreover, the mobilization of $CD14^-CD16^+$ monocytes was different in breast cancer patients between the studies. The number of $CD14^-CD16^+$ monocytes increased only at 30 minutes after the 10-minute exercise in study II, but increased during 30-minute exercise and decreased back to baseline 30 minutes after the 30-minute exercise in study III.

Table 11. Immune cell percentage responses to 10- and 30-minute exercises in lymphoma patients.

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values		
				group	time	group*time
Total leukocytes	15 min	29 (9.4)	-0.1 (7.3)	0.970	**<0.0001**	0.999
	30 min	29 (14)	-0.1 (7.3)			
Neutrophils	15 min	27 (11)	0.1 (18)	0.838	**<0.0001**	0.887
	30 min	30 (16)	0.1 (18)			
Lymphocytes	15 min	42 (42)	-19 (24)	0.932	**<0.0001**	0.988
	30 min	39 (45)	-19 (24)			
Monocytes	15 min	18 (15)	-21 (16)	0.756	**<0.0001**	0.698
	30 min	12 (20)	-21 (16)			
Eosinophils	15 min	5.0 (31)	-19 (36)	0.981	**0.0070**	0.998
	30 min	4.2 (31)	-19 (36)			
Basophils	15 min	0.8 (4.3)	-15 (15)	0.839	0.0775	0.935
	30 min	-3.7 (48)	-15 (15)			
$CD3^+$	10 min	19 (38)	-7.2 (19)	0.234	**0.0062**	0.244
	30 min	65 (86)	0.9 (22)			
$CD4^+$	10 min	4.2 (31)	-7.9 (17)	0.090	0.0642	0.131
	30 min	59 (69)	26 (67)			
Th1	15 min	20 (14)	-2.1 (54)	0.970	0.1224	0.992
	30 min	22 (65)	-2.6 (54)			
Th2	15 min	-4.3 (50)	18 (38)	0.302	0.2351	0.176
	30 min	32 (28)	17 (38)			

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values		
				group	time	group*time
Th17	15 min	25 (41)	28 (51)	0.430	**0.0119**	0.331
	30 min	63 (74)	28 (51)			
Treg	15 min	33 (35)	14 (35)	0.827	**0.0028**	0.925
	30 min	39 (84)	14 (35)			
$CD8^+$	10 min	32 (42)	-3.8 (18)	0.178	**<0.0001**	0.096
	30 min	84 (78)	0.5 (21)			
$CD4^-CD8^-$	10 min	37 (26)	4.0 (18)	0.249	**0.0015**	0.053
	30 min	155 (189)	6.7 (76)			
$CD19^+$	10 min	-5.6 (12)	-13 (20)	0.417	0.0703	0.198
	30 min	27 (70)	-18 (17)			
$CD56^+$	10 mi	85 (82)	-4.6 (32)	0.065	**<0.0001**	0.227
	30 min	43 (31)	-33 (21)			
$CD56^+CD16^+$	10 min	109 (64)	-0.4 (41)	**0.020**	**<0.0001**	0.093
	30 min	60 (39)	-45 (16)			
$CD56^+CD16^-$	10 min	39 (66)	-6.9 (22)	0.246	**0.0003**	0.523
	30 min	24 (27)	-31 (21)			
$CD14^+CD16^-$	10 min	3.5 (27)	-3.8 (26)	0.683	0.9178	0.547
	30 min	-7.6 (21)	-1.4 (30)			
$CD14^+CD16^+$	10 min	-5.7 (16)	-3.7 (42)	0.151	0.6698	0.422
	30 min	10 (26)	19 (24)			
$CD14^-CD16^+$	10 min	42 (33)	50 (118)	0.206	0.1611	0.447
	30 min	23 (24)	4.7 (22)			

Values are mean (standard deviation).

Table 12. Immune cell percentage responses to 10- and 30-minute exercise in breast cancer patients.

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values group	time	group*time
Total leukocytes	15 min	47 (26)	2.8 (14)	0.896	**<0.0001**	0.983
	30 min	46 (27)	2.4 (14)			
Neutrophils	15 min	41 (24)	9.5 (20)	0.727	**<0.0001**	0.692
	30 min	46 (27)	9.3 (20)			
Lymphocytes	15 min	64 (37)	-5.7 (13)	0.704	**<0.0001**	0.850
	30 min	59 (41)	-5.9 (13)			
Monocytes	15 min	39 (26)	-7.9 (16)	0.363	**<0.0001**	0.238
	30 min	28 (29)	-8.8 (16)			
Eosinophils	15 min	19 (32)	-20 (27)	0.708	**<0.0001**	0.665
	30 min	10 (44)	-19 (27)			
Basophils	15 min	72 (98)	32 (79)	0.754	**<0.0001**	0.856
	30 min	59 (82)	29 (79)			
$CD3^+$	10 min	18 (45)	10 (41)	0.165	**0.0001**	0.116
	30 min	46 (41)	12 (39)			
$CD4^+$	10 min	11 (22)	17 (53)	0.276	**0.0016**	**0.030**
	30 min	41 (37)***,^^	10 (43)			
Th1	15 min	28 (29)	33 (63)	0.808	**0.0007**	0.931
	30 min	23 (32)	33 (63)			
Th2	15 min	41 (33)	17 (39)	0.626	**<0.0001**	0.775
	30 min	33 (38)	17 (39)			
Th17	15 min	48 (38)	18 (48)	0.499	**<0.0001**	0.567
	30 min	34 (36)	18 (48)			
Treg	15 min	20 (38)	40 (90)	0.770	**0.0129**	0.931
	30 min	29 (36)	40 (90)			
$CD8^+$	10 min	34 (124)	25 (69)	0.461	**0.0047**	0.473
	30 min	66 (65)	23 (50)			
$CD4^-CD8^-$	10 min	22 (51)	8.4 (41)	0.200	**0.0002**	0.100
	30 min	60 (77)	10 (49)			
$CD19^+$	10 min	14 (36)	8.3 (35)	0.290	**0.0106**	0.115
	30 min	14 (32)	-11 (20)			

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values group	time	group*time
$CD56^+$	10 min	91 (90)***	8.1 (33)	0.229	**<0.0001**	**0.002**
	30 min	167 (119)***,^^^	-20 (29)			
$CD56^+CD16^+$	10 min	130 (163)**	16 (46)	0.222	**<0.0001**	**0.019**
	30 min	267 (283) ***,^^	-21 (32)			
$CD56^+CD16^-$	10 min	18 (54)	-3.8 (38)	**0.044**	**<0.0001**	**0.001**
	30 min	82 (81) ***,^^^	-7.1 (38)			
$CD14^+CD16^-$	10 min	16 (61)	16 (59)	0.741	**0.0176**	0.191
	30 min	40 (68)	3.3 (54)			
$CD14^+CD16^+$	10 min	63 (104)	40 (70)	0.439	**0.0002**	0.612
	30 min	60 (79)	13 (50)			
$CD14^-CD16^+$	10 min	24 (66)	32 (77)*	0.752	**0.0001**	**0.004**
	30 mi	68 (62)***,^	0.7 (36)			

Values are mean (standard deviation). **p<0.01, ***p<0.001 change from baseline. ^p<0.05, ^^p<0.01, ^^^p<0.001 between groups.

5.3.1 Correlation analyses

The mobilization of total leukocytes, T cells, B cells, and NK cells during the 10-minute exercise correlated positively with various variables of the intensity of the exercise (**Table 13**). During the 30-minute exercise, there was fewer significant correlations (**Table 14**). The mobilization of lymphocytes correlated positively with exercising RPP and lactate concentration, the mobilization of monocytes correlated positively with exercising heart rate and HR%, and the mobilization of basophils correlated positively with exercising RPP and MAP (**Table 14**).

Table 13. Correlations between exercise intensity variables and mobilization of immune cells during a 10-minute exercise in patients with breast cancer.

	SBP (mmHg)	DBP (mmHg)	HR (bpm)	HR% (bpm)	RPP (bpm*mmHg)	MAP (mmHg)
$CD45^+$	**0.65****	**0.56****	**0.47***	**0.58****	**0.70*****	**0.58****
$CD3^+$	**0.75*****	**0.88*****	0.37	**0.48***	**0.81*****	**0.86*****
$CD4^+$	**0.60****	**0.73*****	0.31	0.44	**0.65****	**0.71*****
$CD8^+$	**0.49***	**0.58****	0.44	**0.49***	**0.62****	**0.56****
$CD4^+CD8^+$	**0.50***	**0.39**	0.19	0.43	**0.51***	0.45
$CD4^-CD8^-$	**0.65****	**0.68*****	**0.48***	**0.59****	**0.77*****	**0.69*****
$CD19^+$	**0.54***	**0.58****	0.41	**0.54***	**0.64****	**0.59****
$CD56^+$	**0.50***	**0.58****	**0.50***	**0.61****	**0.65****	**0.49***
$CD56^+CD16^+$	**0.47***	0.44	**0.50***	**0.61****	**0.62****	**0.46***
$CD56^+CD16^-$	**0.53***	**0.50***	0.32	0.41	**0.58****	**0.53***
$CD64^-$SSC-A^{high}	0.32	0.25	0.27	0.39	0.39	0.28
$CD64^+$	0.28	0.19	0.08	0.27	0.26	0.23
$CD14^+CD16^-$	0.12	0.07	0.34	0.38	0.27	0.09
$CD14^+CD16^+$	0.30	0.19	0.03	0.24	0.25	0.24
$CD14^-CD16^+$	0.11	0.11	-0.17	0.07	0.01	0.11

SBP, Systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; HR%, heart rate percentage of age-predicted maximal heart rate; RPP, rate pressure product; MAP, mean arterial pressure. Values are Pearson correlation coefficients. *p<0.05, **p<0.01, ***p<0.001. Modified from Original publication II.

Table 14. Correlations between exercise intensity variables and mobilization of immune cells during a 30-minute exercise in patients with breast cancer.

	HR (bmp)	HR% (bmp)	RPP (bmp*mmHg)	MAP (mmHg)	Lactate (mmol/l)	EE ($kcal*min^{-1}$)
Total leukocytes	0.31	0.36	0.44	0.24	0.38	0.26
Neutrophils	0.15	0.18	0.04	-0.03	0.22	0.08
Lymphocytes	0.34	0.43	**0.58***	0.43	**0.50***	0.37
Monocytes	**0.51***	**0.52***	0.47	-0.12	0.19	0.40
Eosinophils	0.12	0.15	0.40	0.38	0.11	0.17
Basophils	0.29	0.40	**0.61***	**0.68****	0.43	0.39
$CD3^+$	0.20	0.24	0.30	0.32	0.18	0.29
$CD4^+$	0.12	0.14	0.35	0.46	0.17	0.18
Th1	0.23	0.21	0.30	0.29	0.10	0.20
Th2	0.24	0.23	0.37	0.37	0.10	0.18
Th17	0.39	0.39	0.52	0.36	0.22	0.26
Treg	0.00	0.04	0.08	0.20	-0.17	-0.05
$CD8^+$	0.25	0.30	0.15	0.16	0.14	0.35

	HR (bmp)	HR% (bmp)	RPP (bmp*mmHg)	MAP (mmHg)	Lactate (mmol/l)	EE (kcal*min^{-1})
$CD4^+CD8^+$	0.37	**0.51***	0.34	0.04	**0.57***	0.11
$CD4^-CD8^-$	0.16	0.12	-0.00	-0.23	0.23	0.09
$CD19^+$	0.25	0.23	0.33	0.24	-0.03	0.16
$CD56^+$	-0.11	-0.06	-0.14	-0.07	0.41	-0.08
$CD56^+CD16^+$	-0.07	-0.01	-0.08	0.00	**0.50***	-0.07
$CD56^+CD16^-$	-0.19	-0.18	-0.28	-0.24	0.09	-0.11
$CD14^+CD16^-$	0.38	0.39	0.28	-0.30	-0.03	0.42
$CD14^+CD16^+$	0.36	0.39	0.35	-0.30	0.15	0.44
$CD14^-CD16^+$	0.26	0.31	0.01	-0.28	0.22	0.38
MDSC	0.22	0.16	-0.40	-0.51	0.10	0.15
g-MDSC	0.20	0.14	-0.43	-0.54	0.10	0.14
m-MDSC	-0.30	-0.12	-0.34	-0.10	-0.01	-0.40

HR, heart rate; HR%, heart rate percentage of age-predicted maximal heart rate; RPP, rate pressure product; MAP, mean arterial pressure; EE, energy expenditure. Values are Pearson correlation coefficients. *p<0.05, **p<0.01. Modified from Original publication III.

In studies II and III, correlations between immune cell mobilization and breast cancer biomarkers were analysed. Mobilization of $CD4^+$ T cells and $CD8^+$ T cells correlated positively with HER2 positivity during the 10-minute exercise (**Table 15**). In addition, the mobilization of $CD8^+$ T cells correlated negatively with estrogen receptor positivity. During the 30-minute exercise, the mobilization of neutrophils correlated positively with breast cancer grade and proliferation index (Ki-67) (**Table 16**). Breast cancer grade also correlated positively with granulocytic MDSCs and negatively with monocytic MDSCs. Further, mobilization of Th17 cells, regulatory T cells, and $CD8^+$ T cells correlated negatively with progesterone receptor positivity.

Table 15. Correlations between breast cancer disease status and mobilization of immune cells during a 10-minute exercise.

	Grade (scale 1-3)	Tumor size (scale 1-3)	ER (%)	PR (%)	HER2 (pos/neg)	Ki-67 (%)
$CD45^+$	0.17	0.17	-0.13	-0.33	0.18	0.01
$CD3^+$	-0.01	0.23	-0.16	-0.19	0.17	0.01
$CD4^+$	0.12	0.02	-0.35	-0.08	**0.52***	0.21
$CD8^+$	0.19	-0.05	**-0.54***	-0.27	**0.61****	0.28
$CD4^+CD8^+$	0.08	0.06	0.12	-0.27	0.03	-0.05
$CD4^-CD8^-$	0.18	0.05	-0.28	-0.29	0.32	0.23
$CD19^+$	0.19	0.32	-0.02	-0.18	0.17	-0.08
$CD56^+$	-0.18	-0.05	-0.23	-0.13	0.19	-0.13
$CD56^+CD16^+$	-0.19	-0.06	-0.21	-0.10	0.17	-0.14

	Grade (scale 1-3)	Tumor size (scale 1-3)	ER (%)	PR (%)	HER2 (pos/neg)	Ki-67 (%)
$CD56^+CD16^-$	0.03	0.08	-0.25	-0.38	0.33	0.11
$CD64^-SSC\text{-}A^{high}$	0.18	0.09	0.06	-0.27	0.08	-0.09
$CD64^+$	0.15	0.08	0.25	-0.20	0.05	-0.15
$CD14^+CD16^-$	0.12	0.07	0.28	-0.18	0.03	-0.16
$CD14^+CD16^+$	0.36	0.23	-0.08	-0.34	0.10	0.10
$CD14^-CD16^+$	0.15	0.21	0.44	0.12	0.06	-0.32

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Ki-67, proliferation index. Values are Spearman and Pearson correlation coefficients. *p<0.05, **p<0.01. Modified from Original publication II.

Table 16. Correlations between breast cancer disease status and mobilization of immune cells during a 30-minute exercise.

	Grade (scale 1-3)	Tumor size (scale 1-3)	ER (%)	PR (%)	HER2 (pos/neg)	Ki-67 (%)
Total leukocytes	0.38	-0.07	-0.09	-0.32	0.09	0.36
Neutrophils	**0.49***	-0.02	-0.25	-0.30	0.19	**0.52***
Lymphocytes	0.02	-0.20	0.16	-0.29	-0.19	-0.03
Monocytes	0.02	-0.28	0.10	-0.04	0.03	0.42
Eosinophils	0.11	0.13	0.00	0.17	0.00	-0.12
Basophils	0.43	0.16	0.02	-0.38	0.08	0.09
$CD3^+$	0.37	0.30	-0.24	**-0.53***	0.41	0.19
$CD4^+$	0.19	0.38	-0.12	-0.35	0.28	0.12
Th1	0.12	0.06	0.06	-0.15	0.12	0.11
Th2	0.17	0.11	-0.02	-0.20	0.15	0.11
Th17	0.11	0.02	0.02	**-0.50***	0.17	0.04
Treg	0.28	0.26	-0.45	**-0.47***	0.44	0.25
$CD8^+$	0.36	0.15	-0.29	**-0.59****	0.38	0.21
$CD4^+CD8^+$	-0.30	-0.23	0.07	-0.28	-0.03	-0.10
$CD4^-CD8^-$	0.15	-0.38	-0.14	-0.29	-0.25	0.05
$CD19^+$	0.05	-0.16	-0.06	-0.03	-0.28	0.06
$CD56^+$	-0.24	-0.35	0.25	0.08	-0.34	-0.01
$CD56^+CD16^+$	-0.18	-0.30	0.21	-0.02	-0.31	-0.00
$CD56^+CD16^-$	-0.32	-0.30	0.30	0.33	-0.28	-0.04
$CD14^+CD16^-$	0.09	-0.13	0.04	-0.33	0.22	0.33
$CD14^+CD16^+$	0.16	-0.14	0.12	-0.29	0.13	0.33
$CD14^-CD16^+$	0.04	-0.20	0.23	-0.12	-0.13	0.24
MDSC	0.49	0.02	-0.39	-0.32	0.26	0.20
g-MDSC	**0.54***	-0.04	-0.40	-0.33	0.26	0.20
m-MDSC	**-0.54***	0.02	0.05	0.05	-0.13	-0.39

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; Ki-67, proliferation index. Values are Spearman and Pearson correlation coefficients. *p<0.05, **p<0.01. Modified from Original publication III.

5.4 Cytokine responses

Similar to immune cells, circulating cytokine responses were compared between 10-minute and 30-minute exercises in patients with lymphoma and breast cancer. In lymphoma patients, there was no change in cytokine levels in response to exercise except in IP-10, which increased similarly during 10- and 30-minute exercises (**Table 17**). In breast cancer patients, the level of IP-10 and Eotaxin increased significantly more during the 30-minute exercise compared to the 10-minute exercise (**Table 18**). Further, the levels of IL-1β, IL-13, and MIP-1α increased during exercise and the levels of PDGF-bb, MIP-1β, and TNF-α decreased at 30 minutes post exercise in breast cancer patients.

Table 17. Circulating cytokine percentage responses to 10- and 30-minute exercise in lymphoma patients.

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values		
				group	time	group*time
IL-1β	10 min	22 (59)	32 (62)	0.263	0.217	0.983
	30 min	-6.5 (18)	8.5 (35)			
IL-1ra	10 min	29 (98)	-8.9 (12)	0.494	0.622	0.277
	30 min	4.3 (4.8)	81 (222)			
IL-4	10 min	15 (48)	-5.3 (47)	0.800	0.732	0.405
	30 min	-2.1 (16)	4.3 (29)			
IL-7	10 min	2.5 (40)	28 (113)	0.845	0.473	0.900
	30 min	18 (73)	25 (67)			
IL-8	10 min	2.5 (38)	8.0 (32)	0.531	0.367	0.625
	30 min	-10 (20)	3.3 (21)			
IL-9	10 min	-2.0 (6.6)	-3.4 (5.0)	0.225	0.704	0.430
	30 min	2.0 (6.9)	0.8 (8.7)			
IL-13	10 min	73 (148)	73 (149)	0.330	0.071	0.240
	30 min	106 (295)	356 (566)			
IL-17	10 min	34 (53)	46 (93)	0.315	0.089	0.493
	30 min	9.4 (22)	15 (37)			
Eotaxin	10 min	0.3 (15)	-2.6 (15)	0.583	0.895	0.813
	30 mi	2.2 (12)	2.0 (11)			

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values		
				group	time	group*time
G-CSF	15 min	-6.3 (19)	1.1 (22)	0.559	0.944	0.457
	30 min	4.6 (21)	0.6 (15)			
IFN-y	10 min	-2.0 (38)	3.5 (15)	0.898	0.976	0.887
	30 min	4.9 (22)	0.8 (56)			
IP-10	10 min	13 (14)	0.8 (9.3)	0.431	**0.013**	0.560
	30 min	6.0 (13)	-1.1 (15)			
MCP-1	10 min	-20 (23)	-14 (24)	0.439	0.124	0.672
	30 min	-14 (29)	0.5 (40)			
MIP-1α	10 min	-14 (17)	-12 (18)	0.317	0.217	0.365
	30 min	0.9 (17)	-7.4 (29)			
PDGF-bb	10 min	5.2 (27)	-1.5 (5.3)	0.833	0.754	0.981
	30 min	5.3 (31)	1.3 (25)			
MIP-1β	10 min	0.9 (3.9)	-2.5 (4.8)	0.994	0.722	0.247
	30 min	-1.7 (7.6)	0.1 (5.5)			
RANTES	10 min	-2.2 (11)	-1.6 (8.4)	0.574	0.186	0.248
	30 min	-3.8 (10)	5.2 (10)			
TNF-α	10 min	4.9 (7.1)	0.1 (11)	0.246	0.545	0.254
	30 min	-2.9 (8.9)	-3.2 (10)			

Values are mean (standard deviation).

Table 18. Circulating cytokine percentage responses to 10- and 30-minute exercise in breast cancer patients.

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values		
				group	time	group*time
IL-1β	10 min	43 (110)	10 (50)	0.303	**0.003**	0.417
	30 min	28 (77)	-16 (31)			
IL-1ra	10 min	59 (164)	35 (112)	0.593	0.057	0.890
	30 min	88 (216)	51 (180)			
IL-4	10 min	18 (89)	-19 (42)	0.092	0.147	0.125
	30 min	67 (173)	70 (205)			

		Exercise – Baseline (%)	30 min post – Baseline (%)	p-values		
				group	time	group*time
IL-7	10 min	6.2 (45)	9.2 (56)	0.365	0.375	0.680
	30 min	28 (101)	17 (65)			
IL-8	10 min	-1.9 (78)	-7.5 (72)	0.317	0.772	0.535
	30 min	20 (71)	19 (105)			
IL-9	10 min	3.0 (16)	-0.4 (7.3)	0.198	0.069	0.303
	30 min	-0.4 (17)	-7.8 (18)			
IL-13	10 min	41 (166)	29 (122)	0.534	**0.041**	0.389
	30 min	107 (267)	24 (120)			
IL-17	10 min	56 (135)	85 (275)	0.083	0.333	0.141
	30 min	-8.1 (34)	-12 (36)			
Eotaxin	10 min	5.3 (15)	-2.0 (11)	0.154	**<0.0001**	**0.042**
	30 min	16 (20)***,^^	-0.3 (12)			
G-CSF	10 min	13 (72)	1.9 (40)	0.607	0.127	0.486
	30 min	19 (111)	-22 (36)			
IFN-y	10 min	2.9 (62)	5.8 (76)	0.610	0.444	0.432
	30 min	28 (95)	-1.9 (47)			
IP-10	10 min	2.8 (14)	0.9 (7.8)	0.085	**<0.0001**	**0.002**
	30 min	18 (21)***,^^^	1.3 (17)			
MCP-1	10 min	11 (40)	-3.4 (34)	0.416	0.827	0.098
	30 min	-8.2 (27)	-0.7 (36)			
MIP-1α	10 min	33 (137)	-5.1 (20)	0.990	**0.043**	0.929
	30 min	40 (144)	-12 (34)			
PDGF-bb	10 min	8.8 (26)	-5.5 (20)	0.200	**0.002**	0.494
	30 min	0.9 (26)	-14 (23)			
MIP-1β	10 min	-2.8 (10)	-0.3 (8.1)	0.192	**0.049**	0.100
	30 min	-3.3 (7.2)	-6.1 (10)			
RANTES	10 min	1.1 (13)	0.0 (9.1)	0.284	0.562	0.227
	30 min	-4.8 (7.4)	-0.3 (13)			
TNF-α	10 min	3.5 (21)	-4.8 (11)	0.218	**0.002**	0.526
	30 min	-0.8 (8.5)	-10 (16)			

Values are mean (standard deviation). ***p<0.001 change from baseline. ^^p<0.01, ^^^p<0.001 between groups.

6 Discussion

Several studies have observed improved outcomes in patients with cancer who are physically active, but these studies do not reveal the underlying mechanisms. Studies conducted in mouse models have demonstrated that positive immunological changes occur during and after acute exercise that eventually decrease tumor growth. Before the start of conducting the current study, the only knowledge on immune cell responses to exercise in humans was from healthy individuals. Therefore, this thesis aimed to shrink the gap between epidemiological studies conducted in people diagnosed with cancer and mechanistical preclinical studies and deepen our knowledge of how acute exercise affects immune system in patients with cancer.

Here, many different immune cells were found to be highly responsive to acute exercise both in lymphoma and breast cancer patients. The number of circulating cytotoxic immune cells, $CD8^+$ T cells and NK cells, was increased during exercise in each study, thus in lymphoma and breast cancer patients during 10- and 30-minute exercises. Immune cells responded similarly during 10- and 30-minute exercises, but many changes also correlated positively with the intensity of exercise. Circulating cytokine levels did not change as much as immune cell levels, but significant increases were found in chemokine IP-10 in both patient groups.

6.1 Acute exercise mobilizes different immune cells

In study I, acute 10-minute exercise increased the number of circulating $CD8^+$ T cells and $CD56^+$ NK cells in lymphoma patients that was observed immediately after exercise. In study II, 10-minute exercise also increased the number of $CD8^+$ T cells and NK cells, but additionally total leukocytes, $CD19^+$ B cells, and $CD14^+CD16^-$ monocytes in breast cancer patients. In study III, total leukocytes, neutrophils, lymphocytes, monocytes, basophils, $CD4^+$ T cells, Th2 cells, Th17 cells, $CD8^+$ T cells, $CD4^-CD8^-$ T cells, and NK cells increased during 30-minute exercise in breast cancer patients, and in study IV, total leukocytes, lymphocytes, $CD4^+$ T cells, Th17 cells, $CD8^+$ T cells, $CD4^-CD8^-$ T cells, regulatory T cells, and NK cells increased during the 30-minute exercise in lymphoma patients. There are, therefore, some

differences between the studies, but what is common to the studies is that the number of $CD8^+$ T cells and NK cells and the proportion of NK cells of total leukocytes and proportion of $CD8^+$ T cells of total T cells increased during exercise. This is encouraging to patients with cancer, as these cells are the most important in killing cancer cells. The result is also in line with previous studies conducted in healthy individuals, where NK cells and $CD8^+$ T cells are proved to be the most responsive immune cells to exercise stimuli (Simpson et al., 2007; Anane et al., 2009; J. P. Campbell et al., 2009; Timmons & Cieslak, 2008).

Regulatory T cells inhibit the anti-tumoral function of $CD8^+$ T cells and NK cells, and therefore their increase during exercise could reduce the positive effects of $CD8^+$ T cell and NK cell mobilization. Here the number of regulatory T cells increased in lymphoma patients but not in breast cancer patients. One reason for this difference might be their baseline values. In lymphoma patients, 16 % of circulating $CD4^+$ T cells were regulatory T cells whereas in breast cancer patients, regulatory T cells represented only 3 % of $CD4^+$ T cells. In healthy individuals, about 10-15 % of $CD4^+$ T cells are regulatory T cells, and in malignancies, the proportion tends to increase (Saleh & Elkord, 2020). Thus, the proportion of regulatory T cells was really low in breast cancer patients. However, also based on previous literature, any clear conclusions can not be drawn on regulatory T cell mobilization during exercise, as there are studies showing increase, decrease, and no change during and after acute exercise (Proschinger et al., 2021).

In both 10-minute and 30-minute exercise studies, more immune cell subsets were mobilized in patients with breast cancer than in patients with lymphoma, which is most likely a result from different exercise intensities. Any proper analyses could not be done on immune cell mobilization between different diagnosis, thus lymphoma and breast cancer, because gender can also play a role and all breast cancer patients were women and all lymphoma patients expect one were men.

In all the studies except for study IV, all significant changes in absolute cell numbers were observed only during or immediately after exercise, and the numbers were back to baseline at 30 and 60 minutes post-exercise. In study IV, however, the number of total monocytes and basophils did not change during exercise but decreased at 30 minutes post-exercise. Further, the number of regulatory T cells, which increased during exercise, decreased back to baseline at 30 minutes post-exercise and increased again at 60 minutes post-exercise. The general pattern of immune cell mobilization was, however, similar to what is seen in numerous other studies in healthy individuals: the number of immune cells, especially lymphocytes, increase during acute exercise and rapidly decrease after exercise (Graff et al., 2018; Anane et al., 2009; Rooney et al., 2018). The decrease during recovery has been studied before, and it is proposed that the cells infiltrate back to tissues such as to lungs, bone marrow, and Peyer's patches (Krüger et al., 2008), but also to tumors (L.

Pedersen et al., 2016; Gomes-Santos et al., 2024), or go through apoptosis (Mooren et al., 2002).

At the time of starting these studies, there was no publications on immune cell mobilization in patients with cancer. Now, others have also studied the phenomenon with similar results. Neutrophils, monocytes, total lymphocytes, $CD8^+$ T cells, and NK cells were found increased after watt-max test and interval bicycling exercise in patients with newly diagnosed early-stage prostate cancer that had not started anti-cancer therapy (Schauer et al., 2022). In patients with newly diagnosed myeloma, neutrophils, monocytes, total lymphocytes, $CD4^+$ T cells, $CD8^+$ T cells, B cells, NK cells, and MDSCs were increased immediately after 30-minute cycling exercise at an intensity of 15 % above anaerobic threshold (Collier-Bain, Emery, Brown, et al., 2024), and in similar protocol, neutrophils, monocytes, total lymphocytes, NK cells, and MDSCs were also increased in newly diagnosed chronic lymphocytic leukemia patients (Collier-Bain, Emery, Causer, et al., 2024). In the current study, MDSCs were analysed in breast cancer patients performing the 30-minute exercise, and it was found that the absolute number of MDSCs did not change but the proportion of MDSCs of total leukocytes decreased during the exercise. In above mentioned studies, MDSCs increased by 70 % in chronic lymphocytic leukemia patients and 49 % in myeloma patients, thus the difference is substantial. The effect of exercise on MDSCs is studied very little and thus any conclusions can not be made. However, similar to regulatory T cells, MDSCs have the ability to inhibit $CD8^+$ T cells and NK cells, and thus when mobilized, they may decrease the maximum potential that exercise potentially has to boosting $CD8^+$ T cell- and NK cell-mediated tumor killing.

In the current studies, immune cell mobilization in patients with lymphoma and breast cancer was not compared to healthy individuals, but the results found here in patients with cancer are similar to what is previously reported in healthy people (Graff et al., 2018; Anane et al., 2009), and so it seems that the stimulatory effect of exercise to immune cells is not diminished by cancer disease. There was, however, few correlations between immune cell changes and breast cancer disease status, such as $CD8^+$ T cells negatively correlating with estrogen and progesterone receptor positivity, but these results should be replicated in other studies to argue that disease status affects cell mobilization. There are few studies that have compared immune cell responses between cancer survivors and healthy controls. In prostate cancer survivors, T cell and NK cell mobilization during acute exercise is similar to controls (Hanson et al., 2023; Hanson et al., 2020), and in breast cancer survivors, NK cell mobilization is similar to controls (Evans et al., 2015), but the mobilization of mucosal associated invariant T cells is attenuated (Hanson et al., 2021).

Consequently, mobilization of immune cells in response to acute exercise occurs rapidly after initiation of exercise and is a transient phenomenon. Mobilization of

immune cells in patients with lymphoma and breast cancer is similar to what is observed in people with other cancer diagnoses and in healthy individuals. Small differences seen between this and other acute exercise studies result most likely from different exercise protocols, but also for example from participants' gender (F. F. Brown et al., 2014; Adammek et al., 2024), and history of infections (Turner et al., 2010; LaVoy et al., 2017).

6.1.1 The effect of duration and intensity of exercise on immune cell mobilization

Previous studies in healthy individuals report that immune cell mobilization is dependent on the intensity and modality of acute exercise, and the conclusion is that the mobilization is greater during high intensity exercise compared to exercise with low intensity (Da Silva Neves et al., 2015), and during endurance exercise compared to resistance exercise (Schlagheck et al., 2020). Daud et al. have studied immune cell responses after different durations (10, 20, and 30 minutes) and intensities (50, 60, and 70 % of VO2peak), and observed that the number of total leukocytes, neutrophils, lymphocytes, and monocytes increased after exercise of all intensities and durations (Daud et al., 2019). The mobilization of all these cells was dependent on the duration of exercise, and only the mobilization of lymphocytes and monocytes was dependent on the intensity of exercise. Further, they found that the mobilization of the immune cells differed between exercise intensities only after 10-minute exercise and not after 20- and 30-minute exercises, indicating that the intensity of exercise plays a bigger role when the duration of exercise is shorter.

In the current studies, participants were cycling at an intensity of their own choosing, but in studies I and II it was monitored that their heart rate was increased moderately, typically above 100, and in studies III and IV, the participants were advised to reach a heart rate that was 70 % of their maximal (220-age) heart rate. In the studies, the variables used to describe exercise intensity were heart rate, heart rate percentage of age-predicted maximal heart rate (HR%), blood pressure, RPP, MAP, and Borg scale. In addition, lactate concentration was measured in studies III and IV. In lymphoma patients performing the 10-minute exercise, increase in $CD8^+$ T cells did not correlate with any exercise intensity variable and increase in NK cells correlated only with diastolic blood pressure. However, in breast cancer patients performing the 10-minute exercise, increase in total leukocytes and NK cells correlated positively with heart rate, HR%, blood pressure, RPP, and MAP. Further, increases in $CD8^+$ T cells and $CD19^+$ B cells correlated positively with the same variables except with absolute heart rate. In breast cancer patients performing the 30-minute exercise, there was fewer significant correlations. For example,

mobilization of $CD8^+$ T cells did not correlate with any exercise intensity variable and $CD56^+CD16^+$ NK cells correlated only with lactate concentration measured at the end of the exercise. The mobilization of total leukocytes and neutrophils also did not correlate with any variable, but the mobilization of total lymphocytes correlated with RPP and lactate concentration, and the mobilization of monocytes correlated with heart rate and HR%. These findings are in line with Duad et al. study as it seems that the intensity of exercise had more pronounced effect to immune cell mobilization during the shorter, 10-minute exercise, and only the mobilization of lymphocytes and monocytes correlated with exercise intensity during the longer 30-minute exercise. When immune cell mobilization was compared between 10- and 30-minute exercises in lymphoma and breast cancer patients, only the increases in $CD4^+$ T cells and NK cells were greater during the 30-minute exercise compared to 10-minute exercise in breast cancer patients, so it seems that the mobilization of most immune cells was not dependent on the duration of the exercise in this study. Further, the intensity of exercise measured as HR% was higher in breast cancer patients performing the 30-minute exercise compared to the 10-minute exercise (77 % and 70 %, respectively), so it is unclear whether the differences seen in the mobilization of $CD4^+$ T cells and NK cells between 10- and 30-minute exercises were dependent on the intensity or the duration of the exercise. In lymphoma patients, immune cell responses did not differ between exercise durations in any of the immune cells studied, but also the intensity of exercise was similar between 10- and 30-minute studies in lymphoma patients (65 % and 64 %, respectively).

Altogether, it seems that 10 minutes of exercise is enough to stimulate immune cells in people diagnosed with cancer, and especially if the duration of exercise is limited to 10-minutes, the higher the intensity, the more the immune cells are mobilized.

6.2 Some cytokine levels are altered with exercise

Here in lymphoma patients, time effect was significant only for chemokine IP-10 which increased similarly during 10- and 30-minute exercises. In breast cancer patients, the time effect was significant for IL-1β, IL-13, Eotaxin, IP-10, MIP-1α, MIP-1β, PDGF-bb, and TNFα. The level of IL-1β, IL-13, Eotaxin, IP-10, and MIP-1α increased during exercise, and the level of MIP-1β, PDGF-bb, and TNFα decreased 30 minutes after exercise. Further, the group*time effect was significant for Eotaxin and IP-10, as their number increased more during the 30-minute exercise compared to 10-minute exercise. The responses of some cytokines to acute exercise has been studied relatively well in healthy individuals, however, with conflicting results. The level of muscle-derived IL-6 increases dramatically in many studies, but results from other cytokines tend show more heterogeneousness (Moldoveanu et al.,

2012). It has been suggested that IL-1β and TNFα levels do not respond to moderate exercise, but increase with prolonged exercise, such as marathons (Docherty et al., 2022; Ostrowski et al., 1999). However, in the current study, IL-1β increased during moderate intensity exercise, and another study found no change during or after 2.5 hour long run at 75 % of VO2max, thus a prolonged exercise (Ostrowski et al., 1998). The same study also found no change in TNFα or MIP-1β levels (Ostrowski et al., 1998). The effect of acute exercise on chemokines has not been studied much. One study in healthy women report no change in IP-10 levels immediately after moderate or high intensity exercise (Quintana-Mendias et al., 2023). Another study in healthy men showed no change in IP-10, Eotaxin, or MIP-1β after 60 minute walking or running exercise (Gagnon et al., 2014). However, MIP-1β was seen increased during a marathon run (Ostrowski et al., 2001). Further, it is widely accepted that IL-1ra levels increase after exercise that contributes to anti-inflammatory milieu observed after exercise (Bente K. Pedersen & Febbraio, 2008). Here in breast cancer patients, there was only a trend towards IL-ra increase ($p=0.057$). The effect of acute exercise on cytokines has not been studied in individuals diagnosed with cancer, so the results found in the current study can not be compared to other than results from healthy individuals.

The origin of these increased levels is unknown, but it might be that they are simply a result from increased circulating levels of immune cells that secrete them, especially as increased cytokine levels were observed only during and immediately after exercise, when immune cell levels are also increased. Similarly, decreases in cytokine levels were only observed at 30-minutes post-exercise when immune cell levels also decreased back to baseline or even below baseline. Th2 cells are the primary source of IL-13 (Zhu, 2015), and in the current study, Th2 cells were increased in breast cancer patients, not in lymphoma patients, similar to IL-13. Similarly, monocytes secrete IL-1β (Hadadi et al., 2016), and both IL-1β and total monocytes were increased only in breast cancer patients. Another source for cytokines is contracting muscles (Lightfoot & Cooper, 2016), so some cytokines measured in blood may originally be from skeletal muscle cells. Cytokine secretion in response to activity change in immune cells might not occur within 10- or 30-minute exercise or even 30 minutes post-exercise. For example, T cell-derived IFNγ can be detected extracellularly only 6 hours after T cell receptor activation, and its level peaks after 12-24 hours (Gocher et al., 2022). However, some immune cells, notably granulocytes can storage cytokines in secretory granules, and release them within minutes of receptor stimulation (Lacy & Stow, 2011). Further, although circulating cytokine levels might not change in response to exercise, it is possible that the expression of different cytokines changes within immune cells, and thus exercise could modulate immune cell activity (LaVoy et al., 2017; Zaldivar et al., 2006). Unfortunately, based on the changes in cytokine level in this study, it is not

possible to determine whether the activity of the immune cells was changed during or after the exercises.

All cytokines which level was altered during and following the acute exercise in the current study have the ability to contribute to tumor growth. For example, IL-1β and IL-13 are associated with immunosuppression in cancer (Kiss et al., 2021; DeNardo et al., 2009), and Eotaxin, IP-10, MIP-1α, and MIP-1β act as chemoattractants to different immune cells (Garcia-Zepeda et al., 1996; Sallusto et al., 1997; Loetscher et al., 1996; Menten et al., 2002). Based on the circulating levels only, any conclusions can not be drawn on their effect on cancer in response to exercise. However, IP-10 has been observed to be increased in tumors of exercising mice, which leads to enhanced NK cell and $CD8^+$ T cell infiltration (L. Pedersen et al., 2016; Miao et al., 2024). The next step would be to examine cytokines in the TME in exercising humans.

6.3 Clinical significance

Cancer evades immune surveillance, inhibits anti-tumoral cells and stimulates pro-tumoral cells, which promotes tumor growth. However, in mouse models, exercise has been observed to have the opposite effect. Exercise enhances $CD8^+$ T cell- and NK cell-mediated tumor-killing by mobilizing and redistributing these cells to tumors in mice (L. Pedersen et al., 2016; Rundqvist et al., 2020). Further, accumulation of regulatory T cell and MDSC is decreased in exercising tumor bearing mice (Hagar et al., 2019; Wennerberg et al., 2020). In the present study, immune cell counts are increased in the circulation during acute exercise, but it is unknown where the cells go after the exercise as their number in blood decreases. In humans, immune cell infiltration to tumors has been studied only a little. In patients with prostate cancer, high intensity interval training protocol before surgery did not increase NK cell infiltration to tumor when compared to control group, but the times the patients exercised before the surgery correlated positively with NK cell infiltration (Djurhuus et al., 2023). Another study examined $CD8^+$ T cell infiltration in colorectal tumors and found that people who reported engaging recreational physical activity more than 3 times per week had higher density of $CD8^+$ T cells in their tumors compared to those reporting no recreational physical activity (Renman et al., 2021). Thus, it is unlikely that one exercise bout would increase immune cell infiltration to tumors significantly, but with regular exercise, NK cell and $CD8^+$ T cell infiltration might be enhanced in humans as seen in mouse models, and that could lead to better tumor killing. It must be kept in mind, however, that the infiltration of these anti-tumoral cell might not be enough to improve immune surveillance because their activity is often inhibited in the tumor site. Thus, in addition to examining NK cell and $CD8^+$ T cell infiltration, the balance and

proportion of other cell in the TME should also be taken into consideration. For example, in the current study, the regulatory T cell number increased during and after 30-minute exercise in lymphoma patients, and it would be of interest to also examine their trafficking to see whether they can infiltrate the tumor after exercise.

There are also preliminary results that immunological changes induced by exercise could improve the effectiveness of immuno-oncological therapies (Gustafson et al., 2021). One study showed that NK cells and monocytes isolated from exercising myeloma patients are linked to improved efficacy of daratumumab-mediated antibody-dependent cellular cytotoxicity *in vitro* (Collier-Bain, Emery, Brown, et al., 2024), and similarly, isolated mobilized NK cell enhanced rituximab-mediated cytotoxicity in chronic lymphocytic leukemia cells *ex vivo* (Collier-Bain, Emery, Causer, et al., 2024). Further, the efficacy of PD-1 treatment can be improved when coupled with exercise (Wennerberg et al., 2020). Lymphocyte harvesting is used as a part of some cancer treatments, such as CAR-T cell therapy. Acute exercise could be used to increase lymphocyte numbers in blood right before or during the harvesting, so that more immune cell can be collected. Further, it seems that the cytotoxic activity of immune cells can be enhanced with exercise before harvesting (Schauer et al., 2022; Bigley et al., 2014; Batatinha et al., 2023; Baker et al., 2024), and that cytokines IL-7 and IL-15, which are also known as myokines, can enhance the proliferation, survival, and effector function of CAR-T cells (Xu et al., 2014).

Therefore, although the current study did not include analyses of patient outcomes, treatment efficacy, or cancer-killing activity of immune cells, it can be hypothesized that the mobilization of immune cells as observed here in patients with lymphoma and breast cancer could beneficially influence these aspects.

6.4 Strengths and limitations

One limitation is that the relative intensity of exercise was not similar in each participant in any of the studies which might have contributed to heterogenous immune cell responses between the participants. Standardization of the exercise intensity would have required maximal fitness tests to be performed before the actual study visit and because of the limited time-window for the studies between diagnosis and start of cancer treatments, it would have been very challenging to schedule and perform. However, the exercise intensity not being the same for each participant allowed the examination of correlations between immune cell mobilization and exercise intensity. Secondly, complete blood counts were analysed only in studies III and IV. The strength is that it was then possible to calculate changes in plasma volume and correct the changes in immune cells with the plasma volume change. That was not, however, possible in studies I and II. It was also observed that the absolute number of immune cells at baseline was lower after sample preparation than

what is normally seen in blood. Thus, in studies III and IV the number of immune cells analysed with flow cytometry were corrected with immune cell numbers obtained from complete blood count to reflect more correct absolute counts. This again was not possible in studies I and II because of not analysing the complete blood count and thus the absolute numbers are much lower.

A key strength is that the protocol for studies III and IV was optimized after completion of studies I and II. As mentioned, the complete blood count was added to analyses, but also the timing of blood sampling and the flow cytometry panels were adjusted. Two samples during the 30-minute exercise revealed much more information than just one sample immediately after exercise, and additional time point at 60 minutes post-exercise also allowed the longer observation period. Further, inclusion of different helper T cells, especially regulatory T cells, as well as MDSCs in the analyses provided deeper knowledge on participants' immune profiles. However, additional analysis on immune cell trafficking or activity would have provided even more insight on the topic and possible clinical significance. The studies also did not include any measures of the tumor itself, which is a limitation. Thus, the clinical significance of the studies and the discussion section of this thesis are rather descriptive.

6.5 Future directions

The study shows that immune cells are mobilized in people diagnosed with cancer as seen before in healthy individuals and in tumor mouse models. In order for mobilized immune cells to affect tumor growth and patient outcomes, they must infiltrate the TME to interact with tumor cells. In this study, circulating immune cell numbers were increased during exercise, but they rapidly egress after the exercises. Thereby it is hypothesised that immune cells infiltrate back to tissues following the exercise, but their exact destination is unknown. Future studies in humans should try to investigate immune cell trafficking after exercise and examine whether immune cell infiltration is increased in the tumors with exercise. There are few studies that have already looked tumor content after exercise, and this far no clear increase in infiltrating cell counts is seen after exercise. However, positive correlations have been observed between the amount of exercise and infiltration of cytotoxic immune cells. The timing between exercise and examination of tumor immune infiltration may play a key role in whether to see responses or not. Thus, studies examining different exercise modalities and/or intensities and immune cell infiltration at different times after exercise should be conducted to get a better, comprehensive, understanding of immune cell responses to exercise. Further, there are many factors such as extracellular matrix stiffness that can play a role in whether the mobilized cells can infiltrate the TME. Dense extracellular matrix has been associated with

hindered T cell infiltration to tumors and correspondingly decreased matrix density is associated with increased T cell infiltration (Nicolas-Boluda et al., 2021). Thus, in addition to studying the responses of aerobic or resistance exercise to the TME, it could be of interest to also investigate the effects of stretching to immune cell infiltration.

7 Summary/Conclusions

This study shows that acute exercise is a strong stimulus for immune cells in patients with cancer. The number of many different immune cells increase in the circulation during acute exercise, but the phenomenon is transient, as the numbers decrease back to baseline quickly during recovery. NK cells and $CD8^+$ T cells are the most responsive cells as their number increase in lymphoma and breast cancer patients during both 10- and 30-minute exercises. Further, the higher the intensity, the more the cells are increased in blood, especially during the shorter, 10-minute exercise. The level of IP-10 also increased in both lymphoma and breast cancer patients, and the levels of Eotaxin, IL-1β, IL-13, and MIP-1α increased also in breast cancer patients.

Based on preclinical studies, the current knowledge is that exercise-induced mobilization and redistribution of $CD8^+$ T cells and NK cells reduces tumor growth. Moreover, the level of IP-10 increases in tumors in mice with exercise and recruits cytotoxic cells. Therefore, the mobilization of immune cells, especially cytotoxic immune cells, observed in this study, can enhance immune surveillance against tumors. However, in the future it should be studied whether mobilized immune cells infiltrate the tumor in patients with cancer after acute exercise and can thus destroy cancer cells. Advising patients with cancer to be physically active early on after diagnosis may be beneficial.

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March 3, 2025
Tiia Koivula

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