Schmidt T[1], Hermes A[1], Weisser B[2]

Physical Training Influences the Immune System of Breast Cancer Patients

Der Einfluss von körperlichem Training auf das Immunsystem von Brustkrebspatienten

REVIEW

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1. UNIVERSITY MEDICAL CENTER SCHLESWIG-HOLSTEIN, *Comprehensive Cancer Center (CCC) North, Kiel, Germany*
2. KIEL UNIVERSITY, *Institute of Sports Sciences, Kiel, Germany*

Summary

- **It has been suggested** that physical activity in breast cancer patients can improve not only quality of life, but also other parameters. Influences on physical and psychological levels have been evaluated, but effects on the immune system of breast cancer patients are hardly known. Generally an evaluated dose-response relationship for exercise in oncology barely exists.
- **The effects of physical activity** on the immune system can be formulated only with reservations, but an immunomodulatory effect is expected to occur. Increased immunological anti cancer activity due to physical activity is probably mediated via an increase in number and cytotoxicity of monocytes, natural killer cells and cytokines.
- **A PubMed search** identified relevant trials and meta analyses from 1970 to 2016.
- **This review** summarizes the results of international studies and the current discussion of effects of physical activity on the immune system of breast cancer patients. Highlighted are effects of physical activity on the immune system. 13 original articles and 15 reviews are included in this review. Three original and 13 review articles include other tumor entities besides breast cancer.

KEY WORDS:
Breast Cancer, Immune System, Immune Response, Physical Activity, Physical Intervention

Zusammenfassung

- **Körperliche Aktivität** beeinflusst neben der Lebensqualität von Brustkrebspatienten weitere Parameter auf psychischer und physischer Ebene. Die möglichen Effekte auf das Immunsystem sind hingegen nicht vollständig bekannt, sodass eine Dosis-Wirkung-Beziehung für Sport in der Onkologie bisher kaum existiert.
- **Die immunmodulierenden Auswirkungen** einer körperlichen Aktivität auf das Immunsystem lassen sich nur unter Vorbehalt formulieren. Die veränderten immunologischen Reaktionen werden unter anderem durch die erhöhte Anzahl der Monozyten, als auch durch deren verbesserte Zytotoxität erreicht. Zusätzlich spielt eine erhöhte Zytotoxität der natürlichen Killerzellen und der Zytokine eine Rolle.
- **Dieses Review** fasst die relevanten Studien und Meta-Analysen einer PubMed-Recherche von 1970 bis 2016 zusammen.
- **Dargestellt werden die Ergebnisse** internationaler Studien und die aktuelle Diskussion der Auswirkungen von körperlicher Aktivität auf das Immunsystem von Brustkrebspatienten. 13 Originalarbeiten sowie 15 Übersichtsarbeiten werden in diesem Review aufgenommen. Drei der 13 Originalartikel und 13 Übersichtsartikel befassen sich neben Brustkrebs auch mit weiteren Krebsentitäten.

SCHLÜSSELWÖRTER:
Brustkrebs, Immunsystem, Immunantwort, körperliche Aktivität, Sportintervention

Introduction

Breast cancer is the most frequent cancer disease in women and the incidence is rising (36). Physical exercise is recommended as part of primary prevention in parallel to all medical interventions and to recurrence prophylaxis, as well as for the reduction of side effects. Various studies confirm the positive effects of physical activity in the various therapy phases, and also on the physical, emotional and social level (26, 45, 46).

The influence of physical training on the immune system of healthy athletes has been examined in many studies (9, 31). The effects on the immune system or on the disease prognosis of cancer patients, by contrast, must still be further examined (16). The first results of the effect of physical exercise on the immune system of cancer patients were reported in the 1990s (49). Some authors report that an improved immune function and lower susceptibility for ›

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CORRESPONDING ADDRESS:
Dr. Thorsten Schmidt
University Medical Center Schleswig-Holstein
Comprehensive Cancer Center (CCC) North
Arnold-Heller-Straße 3, Haus 14
24105 Kiel, Germany
✉: thorsten.schmidt@uksh.de

Table 1

Overview of the Original Articles: Effects of physical activity on the immune system of breast cancer patients. NK=Natural Killer Cells, NKT-Cells=Natural Killer-T-Cells, IL-6=Interleukin-6, IL-10=Interleukin-10, TNF-α=Tumor necrosis factor α, CPR=C reactives protein , MIF=Migration inhibition factor.

PUBLICATION	NUMBER OF PARTICIPANTS	THERAPY PHASE	INTERVENTION	CELL POPULATION	EFFECT	SIGNIFICANCE
Hagstrom et al. (2016)	39	Rehabilitation	Strength training 3x/week 60min for 16 weeks; the first 8 weeks equipment training then 8 weeks free strength exercises, 3 sets with 8-10 repeats at 80% of 1RM	NK-Cells & NKT-Cell Function, TNF-α, IL-6, IL-10, CRP	Yes (NK-Cells & NKT-Cell Function)	Yes
Zimmer et al. (2016)	18	Rehabilitation	Single intervention: Half-marathon	TNF-α, IL-6, MIF	Yes	No
Evans et al. (2015)	18	3-6 months after treatment	Single interval training on cycle ergometer, 10 load phases for 3min at 60% of Vo_{2max} and pauses of 90sec	NK-Cells	Yes	Yes
Saxton et al. (2014)	85	3-18 months after treatment	6-month progressive aerobic and strength training at 65-85% of maximal heart rate and a nutrition program	Leukocytes, Lymphocytes, Neutrophiles, NK-Cells	Yes (Leukocytes Lymphocytes, Neutrophiles)	Yes
Mohamady et al. (2013)	40	After the mastectomy	Mobilization and mobility training for 3 months daily 2x30min. Additional endurance training (upper body or cycle ergometer) in the final month	NK-Cell-Activity	Yes	Yes
Fairey et al. (2005)	53	Rehabilitation	Cycle ergometer/3x per week for 15 weeks	NK-Cells / Monocytes	Yes	Yes
Hutnick et al. (2005)	49	Rehabilitation	Supervised exercise program; endurance and aerobic training at 60-70% of functional capacity 3x per week	Lymphocytes	Yes	Yes
Niemann et al. (1995)	16	Rehabilitation	Supervised walking training, 60min. 3x per week at 75% of HF_{max} combined with strength training (7 exercises, 2 sets à 12 repeats) for 8 weeks	NK-Cells	No	-
Peters et al. (1995)	24	Rehabilitation	Cycle ergometer, 5x per week for 5 weeks, 30-40min. at 60-80% HF_{max}; followed by 6 months independent training 2-3x per week (moderate intensity)	Monocytes, Leukocytes	Yes	Yes
Peters et al. (1994)	24	Rehabilitation	Cycle ergometer, 5x per week for 5 weeks, 30-40min. at 60-80% HF_{max}; followed by 6 months independent training 2-3x per week (moderate intensity)	NK-Cells	Yes	Yes

cancer are elicited by moderate exercise, and that by contrast a lack of exercise and too-great stress can reduce the immune function and increase the susceptibility to infections (3, 7, 18, 20, 25, 26, 50).

The function of the human immune system is limited by advancing age and by exogenic factors. This appears to be very important in the increased incidence of malignant diseases in elderly people. The immunoreaction may be reduced in part by inactive antigen-specific B- and T-cells, dendritic cells, macrophages, natural killer cells (NK) and neutrophils. Moreover, increased release of cytokines has been reported (3, 42, 43).

Various in-vivo studies addressed the relationship between physical activity and the parameters of the immune system. The results of these studies show that physically-trained rats and mice not only had a higher lymphocyte population, but also presented an improved macrophage function. In another study, it was demonstrated that physical activity significantly increases the number of dendritic cells in rats compared to the control group (21, 22). An anti-inflammatory effect resulting from a reduction of the IL-6 plasma concentration in physical activity was found in mice (28). Moreover, regular movement appears to exert an influence on the activity of NK-cells and thus on tumor growth in mice (32).

Physical exercise can reduce the relative risk of dying from breast cancer by 10-50% (8). The study "The Women's Healthy Eating and Living" reports a survival advantage of up to 50% in women who exercise regularly and maintain a healthy diet (35). Similar positive results were obtained in the "Nurses' Health Study" (13), the "Collaborative Women's Longevity Study" (14) and the "Life after Cancer Epidemiology Study" (48). These studies report a 30-40% reduction in the risk of dying in breast cancer patients who are active at least 1h per week at moderate intensity. The positive results make clear that a lack of exercise, overweight and adiposity can not only increase the risk of suffering breast cancer, but are also associated with an elevated risk of recurrence and increased mortality (36).

Whether the immunological effects of sport and exercise therapy are clinically relevant and contribute to improved breast cancer prognosis, can only be presumed on the basis of studies to date; proof is still outstanding.

This review provides a summary of all studies to date which have addressed the immunological reaction to physical exercise in cancer patients, especially breast cancer patients. An immunomodulating effect of physical exercise is assumed and thus improvement of the course of disease in breast cancer patients is expected. This assumption emphasizes the necessity for validated and individualized sport-therapy concepts, primarily for breast cancer patients.

Method

To prepare this review, a thorough literature search with the following search terms was performed by two independent persons (TS and AH): "Cancer and immune and/or physical training/exercise" and "breast cancer and/or immune and physical training/exercise" and "immune system and cancer and/or sports/exercise" and "immune system and breast cancer and/or sports/exercise". Additional studies were added from references in the identified literature.

All search results were checked with further screening, so that finally 13 original articles and 15 reviews were considered to be relevant.

International original articles and review articles published between 1970 and 2016 were taken into account.

Results

The literature search brought 28 manuscripts, of which 13 were original articles and 15 reviews. These publications are listed and discussed in the present survey article. Three of the original articles and 13 reviews address cancer entities in addition to breast cancer. The study design, the intervention and the effects on the immune cell population are presented (Fig. 1, Tab. 1, 2 and 3).

All reviews confirm the influence of physical activity on the specific cell population of cancer patients. Whereas two review articles do not give any direct information (1, 19), the remaining 13 articles describe a change in the NK cells, monocytes macrophages, lymphocytes or the tumor-associated macrophages, interleukines and the tumor necrosis factor (TNF) (2, 7, 10, 16, 17, 24, 25, 26, 41, 45, 46, 50, 51).

14 overview articles document a positive relationship between physical activity and the cell population, but without providing concrete statements concerning the extent of exercise and the changes in the immune system (1, 3, 10, 16, 17, 19, 24, 25, 26, 41, 45, 46, 50, 51).

The following articles address the influence of physical training on the immune system of breast cancer patients. Three articles include other cancer entities in their studies (4, 37, 47).

Dimeo et al. report a shorter duration of neutropenia through sports activity following high-dosed chemotherapy in various carcinomas. The participants in the intervention group performed daily aerobic endurance training using a bed ergometer. The results show that neutropenia (p=0.01) and thrombocytopenia were shorter in the intervention group. The necessity of a thrombocyte transfusion was also lower in the intervention group than in the control group (p=0.06) (4).

The influence of physical activity on the sleep-promoting cytokines IL-6, TNF-alpha (TNF-α) and on the soluble TNF-alpha receptors (sTNF-R) is described in the study by Sprod et al. In this (two-arm) study, the influence of home-training is compared to the standard treatment with sleep-promoting cytokines. 38 breast and prostate cancer patients were randomized at the start of radiation therapy to a control and an intervention group. The intervention group performed a 4-week exercise program, the control group, by contrast, no additional intervention. IL-6, TNF-α and sTNF-R were measured before and after the intervention. The results of this study emphasize the positive effects of walking and strength training during radiation therapy for breast and prostate cancer patients. The quality of sleep may possibly be positively influenced via regulation of the inflammation mediators (47).

The effect of physical activity on the activity of lymphocytes in breast cancer patients after chemotherapy was investigated by Hutnick et al. 49 breast cancer patients were enrolled in the 6-month intervention study. The intervention group (n=28) performed three supervised training sessions per week, while the control group (n=21) had no sports program. The participants in the intervention group showed a significant percent increase in $CD4^+$- and $CD69^+$-cells. However, if the comparison focuses on the total count, there are no significant differences between the two groups at any time. The plasma- and the mitogen-stimulated IL-6 and the IFγ-production were similar in both groups (15).

The change brought by physical exercise in the immune system of breast cancer patients was the goal of the study by Fairey et al. 52 breast cancer patients were enrolled in the study after the operation and adjuvant therapy. Over a period of 15 weeks, the intervention group (n=25) performed ergometer training three times per week, while the control group (n=28) had no additional intervention. The intensity was defined by the ventilatory equivalent for carbon dioxide. The supervised training started with a 15-minute program from the first to the third weeks. In the subsequent weeks, the training was increased every three weeks by 5 minutes, so that the ergometer training in weeks 12 to 15 lasted 35 minutes. The primary endpoint of the study was the change in NK-cells in peripheral blood. Moreover, other hematological changes were determined. The

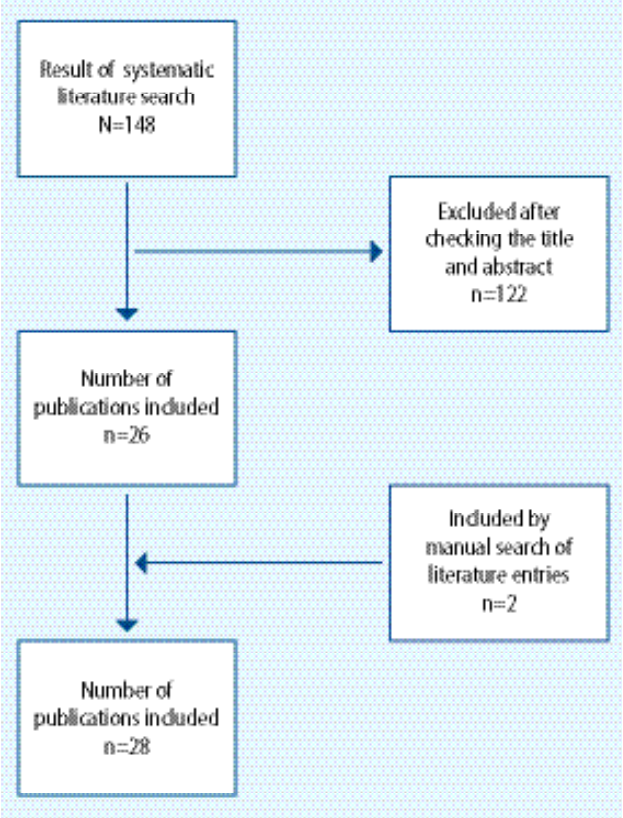

Figure 1
Search tree.

results show a significant increase in NK-cells (p=0.035) and improvement in the proliferation capacity of the lymphocytes (p=0.007) in the intervention group compared to the control group. Monocytes and neutrophils do not differ significantly (6).

Mohamady et al. examined the influence of a sport intervention on the immune system of 40 breast cancer patients following mastectomy. The 3-month training consisted of 30-minute mobilization training twice daily. In the final month, moderate endurance training was performed on an upper-body or cycle ergometer. The results show improvement in NK-cell activity compared to the control group (27).

Evans et al. also reported an increase in NK-cells in both breast cancer patients and participants without an oncological background. The study included 18 subjects, nine breast cancer patients and nine comparable subjects without carcinoma. Unlike other studies, Evans et al. performed single interval training on the cycle ergometer with all subjects. The interval training consisted of 10 exercise phases for three minutes at 60% of the VO_{2max} with 90-second pauses between phases. Blood samples were drawn at four times, prior to the intervention, immediately after the intervention, two hours after the intervention and 24 hours after the intervention. The results show an increase in NK-cells in all subjects. It is noteworthy that the NK-count directly after the intervention is lower in breast cancer patients than in participants without cancer (5).

The study by Peters et al. could demonstrate physical exercise-induced changes, especially in the monocytes and the NK-cells ($CD56^+$). A group of 24 breast cancer patients completed a 7-month training program on a cycle ergometer. The training program was initially conducted in a rehabilitation clinic 5-times per week for 5 weeks with increasing length. Subsequently, it was continued for another 6 months 2-3 times per week in an outpatient group. The blood samples to determine ›

Table 2

Summary of Reviews: Effects of physical activity on the immune system of cancer patients. No info=No data reported, NK=Natural Killer Cells, TNF=Tumor necrosis factor.

PUBLICATION	TUMOR ENTITY	THERAPY PAHSE	INTERVENTION	CELL POPULATION	EFFECT	SIGNIFICANCE
Cao Dinh et al. (2016)	Various entities and diseases	no info	Endurance- und aerobic training	NK-Cells, NK-Cells Activity	Yes	Yes
Kruijsen-Yesarsma et al. (2013)	Various entities	During and after therapy	Endurance- und strength training	NK-Cells, Monocyten, Macrophages, Lymphocytes	Yes	no info
Maddocks et al. (2013)	Various Entities	in early stage of disease	no info	C-reactive protein and other inflammation markers	Yes	No
Goh et al. (2012)	Mammary carcinoma	no info	no info	Tumor-associated Macrophages	Yes	no info
Walsh et al. (2011)	no info	no info	no info	NK-Cells, Monocytes, Leukocytes	Yes	no info
Schmitz et al. (2010)	Mammary carcinoma	no info	no info	NK-Cells	Yes	no info
De Backer et al. (2009)	Mammary and prostate carcinoma	After therapy	Strength training 1-3 Sets 8-12 Repeats 3-24 weeks 1-5 units/ week Intensity 25%-85% 1RM	no info	Yes	no info
McTiernan, et al. (2008)	no info	no info	no info	NK-Cells, Lymphocytes, Monocytes	Yes	no info
Kruk et al. (2006)	Mammary and colon carcinoma	no info	30-60 minutes per day	NK-Cells, Monocytes, Macrophages, Lymphocytes	Yes	no info
McTiernan, et al. (2004)	Various entities	no info	Endurance training on cycle ergometer	NK-Cells, Monocytes, Macrophages, Lymphocytes	Yes	Yes
Fairey et al. (2002)	Mammary carcinoma and leukemia	During and after therapy	Endurance training on cycle ergometer 60-80% Hf_{max}, 30-60min; 2-29 weeks	NK-Cells, Monocytes, Lymphocytes	Yes	no info
Shephard et al. (1998)	Mammary, colon, lung carcinoma gynecol. tumors	no info	no info	NK-Cells, Monocytes, Macrophages, Lymphocytes, (Interleukine, TNF)	Yes	no info
Shephard et al. (1995)	no info	no info	Physical activity	NK-Cells, Monocytes, Macrophages, Lymphocytes, (Interleukine, TNF)	Yes	no info
Lee et al. (1995)	Mammary, colon and prostate carcinoma	Preventive	no info	no info	Yes	no info
Woods et al. (1994)	no info	no info	no info	Monocytes, Macrophages	Yes	no info

the cell counts of monocytes and NK-cells were examined at three time points: at the start of the study, after 5 weeks and at the end of the study. The results showed an increase in granulocytes (initial: 61.3±7.9%, after 5 weeks: 60.0±9.7% and after 7 months 65.4±6.8%) ($p<0.05$) and a decrease in lymphocytes and monocytes ($p<0.05$). In addition, a constant NK-cell count with elevated cytotoxic activity was determined. At the start of the study, the basal activity of the NK-cells in cancer patients (18.9% lysis) showed lower performance capacity than in healthy persons (30-35% lysis). After the 7-month intervention program, the NK-cells of the cancer patients showed a cytotoxic activity of 28.3% lysis capacity and thus attain the range of the healthy subjects ($p>0.05$) (33, 34).

Hagstrom et al. could also determine a positive effect of physical training on the immune system. 39 breast cancer patients were randomized to an intervention and a control group. The 20 participants in the intervention group completed equipment training over 16 weeks at 80% of the "one repetition maximum". The NK-cells, the "natural killer T-cells" (NKT) and the inflammation markers, TNF-α, IL-6, IL-10 and CRP (C reactive protein) were measured before and after the intervention. The results showed a change in NK and in the NKT-function. Compared to the control group, the intervention group had a lower expression of TNF-α on the NK-cells ($p=0.005$) and on the NKT-cells ($p=0.04$) at the end of the study. There were no other significant differences (11).

Zimmer et al. investigated the short-term effect of a half-marathon on the immune system of breast cancer patients. Blood samples were drawn from nine breast cancer patients in follow-up care and nine healthy athletes before, 15 minutes after and 24h after a half-marathon. The focus of this investigation is on the leukocytes (granulocytes, monocytes, lymphocytes), the T-cells and the anti-inflammatory cytokines. No significant difference was observed at any time between breast cancer patients and healthy athletes (52).

Nieman et al. found no influence of physical activity on the immune system in their study. 16 breast cancer patients were randomized in this study to an intervention and a control group, of whom only 12 completed the study. Nieman et al. focus the study on the physical performance capacity, the cell count of lymphocytes and the activity of the NK-cells. The intervention group completed a 60-miniute supervised strength and endurance training over 8 weeks, 3-times per week. The results showed an improvement in physical performance capacity and a significant improvement in the 6m-walking test ($p=0.02$) in the intervention group. No increase in lymphocytes and NK-cells was observed. The T-lymphocyte count and the activity of the NK cells also remained stable (29).

Saxton et al. were also unable to confirm the expected influence of their intervention on the NK-cells. 85 breast cancer patients were randomized to an intervention and a control group. The intervention consisted of a 6-month progressive aerobic and strength training at 65-85 % of maximal heart rate, and a nutritional program. The results showed a change in neither the count nor the activity of the NK-cells compared to the control group. However, the leukocyte, lymphocyte and neutrophil counts in the control group increased compared to the intervention group. But no unequivocal conclusions can be drawn, since it is not apparent whether the sports and/or the nutritional program were responsible for the results (38).

Six studies report changes in lymphocyte subpopulations (5, 6, 15, 33, 34, 38). There is evidence that regular exercise has no influence on the $CD3^+$T-lymphocyte (6, 15) and the $CD56^+$-cell counts (6, 33, 34). Two of these studies also point out that

Table 3

Summary of original articles: Effects of physical activity on the immune system of cancer patients. no info=no data reported, NK=Natural Killer Cells, IL-6=Interleukin-6, TNF-α=Tumor necrosis factor α, sTNF-R=soluble TNF-alpha-receptors.

PUBLICATION	TUMOR ENTITY	THERAPY PHASE	INTERVENTION	CELL POPULATION	EFFECT	SIGNIFICANCE
Sprod et al. (2010)	Mammary and prostate carcinoma	After first diagnosis Radiation of at least six weeks	Endurance: Walking units daily increased by 5-20% steps Strength training (upper body): 11 exercises, increase to 4 Sets à 15 repeats	Interleukin-6 (IL-6) Tumor necrosis factor alpha (TNF-α) soluble TNF-alpha-receptors (sTNF-R)	Yes (IL-6, TNF α)	No
Rogers et al. (2008)	no info	no info	no info	NK-Cells, Monocytes, Macrophages	Yes	no info
Dimeo et al. 1997	Mammary carcinoma and other entities	During hospitalization	Bed-, cycle ergometer; daily 30min 50% HF Reserve	Period of Neutropenia	Yes	Yes

regular exercise apparently brings no changes in the $CD4^+$-/$CD8^+$- and $CD20^+$-B-lymphocytes (6, 15). Five studies describe a change in cell function, for example the cytotoxic activity of NK-cells (6, 11, 15, 27, 33).

Ten studies address especially the effects of physical training on the immune system of breast cancer patients (5, 6, 11, 15, 27, 30, 33, 34, 38, 52). The results of these studies show that the NK cell populations increase or their function improves due to different sports interventions. Fairey et al. and Peters et al. report in addition a change in the lymphocyte population (5, 33). Both the NK-cells and also the lymphocytes play an important role in the immune system and the immunoreaction. Improvement in the function or the number of cells can work against a recurrence.

Discussion

The studies and reviews described present the influence of physical exercise on the immune system, the effect on the cellular level and the changes in cytotoxins in various cancer forms. The focus of this review is on breast cancer.

Despite different intervention programs, all of the studies included expect physical exercise to bring improvement in the immunostatus of breast cancer patients, as well as in the other types of carcinoma considered. The possible effects of movement and physical exercise are, on the one hand, an increase in cells, on the other hand, improvement of the function of monocytes, macrophages, NK-cells and increased release of cytokines. The relevant exercise-induced immunomodifications in cancer still remain unclear (22, 45).

Various clinical studies show that physical exercise supports the activity of the cellular immune function and exerts a positive influence on the immune system with respect to tumor formation (42, 43, 45, 46). The intensity and duration play an important role in influencing the immune system.

To date, only a few scientific results are available on which to evaluate the dosage or a suitable sport and exercise intervention. An intensive and long-lasting intervention program leads to improved activity in various areas of the immune system (2, 25). A program which is too intensive and too long, on the other hand, can also have negative effects at the immune-system level.

Training at moderate intensity appears to exert a stimulating and activating effect (12). It is still not known whether endurance training or strength training is the more important for immunostimulation.

The influence of physical exercise on the change in the immune system takes place at the cellular level. An increase in cells or improved cell function can be demonstrated in various studies (5, 6, 11, 15, 27, 33, 34). In addition to adaptation of the immune system, the cytokines have an additional positive secondary effect on the well-being of cancer patients (reduction of fatigue, reduction of cancer cachexia) (39, 46). The immune function and reaction can be improved by an increase in cells and improvement in the function of monocytes, macrophages and NK-cells (3, 23, 42, 43, 45, 46).

The different results of the available studies can be attributed to the various study designs. This review concentrates on the phase after operation, chemotherapy or radiation therapy. The sport and exercise programs in the studies cited differ in several points, so that comparability is limited (6, 45). The intervention programs differ with respect to their intensity, duration of the individual training sessions, their frequency and the overall extent of physical activity. While Peters et al. set the intensity of endurance training at 60-85% of maximal heart rate, Nieman et al. choose an intensity of 75% of maximal heart rate. Other differences can be observed with respect to the length of the individual training sessions (30-60 minutes), the frequency (three times per week – five times per week) and the overall duration (between 8 weeks and 7 months).

A further common limitation of all cited studies is the lack of attention to additional activity on the job, in everyday life and leisure. Endurance training was selected as the intervention in most cases (4, 5, 6, 15, 27, 29, 33, 34, 47, 52). This was conducted in six studies on an ergometer (4, 5, 6, 27, 33, 34), in one study as an aerobic program (15) and in two other studies as walking sessions (47) or on a treadmill (29). Two studies combined cardio-training with a strengthening program (29, 38). One study supplemented endurance training with mobilization and mobility training (27). Strength training was selected as intervention only in the study by Hagstrom et al. (11), and Zimmer et al. chose a single half-marathon as intervention (52). The terms "physical training" and "physical exercise" do not allow deduction of which specific training methods and what intensity are involved (17, 26, 45).

The original articles and reviews do not adequately state the times at which blood samples were drawn (directly after training, 24h after training or at some other time). The changes in the immune system are short-lived and are often determined by the type and duration of activity. Here, again, determination of the optimal "training dosage" appears to be decisive.

The cited reviews focus on the effect of physical exercise on the immune system of breast cancer patients. Although the quality of the studies has improved with time, further investigations and studies are necessary to optimize and broaden the possibilities of sport and exercise therapy on the quality of life, chance of survival and risk of recurrence. In addition to breast cancer, other types of cancer (such as prostate and colon carcinoma) are taken into account. The data in the additionally-named carcinomas on the topic "Effects of physical activity on the immune system" are similarly as heterogeneous as for breast cancer.

The discussion in all publications on this topic is found to be difficult and complicated, since each article has its own ›

methodical limitations, which makes the discussion and interpretation of the results more difficult. The results of the various study designs point to possibilities and tendencies. The individual lifestyle of the individual subject, along with other secondary diseases, cannot be ruled out as possible disruptive factors.

Conclusion

This review demonstrates the complexity of the topic. The authors reach different results due to various study designs and the limitations of the various individual studies. Future studies should address more homogeneous subject groups so that specific exercise recommendations can be made. Scientific and more specific statements about the effect of targeted sports intervention after a breast cancer diagnosis are possible only after further prospective, standardized and controlled clinical studies confirming the assumption of an immunomodulating effect of physical activity. Investigation of the dose/effect relationship of sports in breast cancer or various carcinoma entities in general should additionally be the focus of future studies to enable more precise statements on the intensity, duration and extent of sport activities.

Conflict of Interest

The authors have no conflict of interest.

References

(1) **BACKER DE IC, SCHEP G, BACKX FJ, VREUGDENHIL G, KUIPERS H.** Resistance training in cancer survivors: A systematic review. Int J Sports Med. 2009; 30: 703-712. doi:10.1055/s-0029-1225330

(2) **BAUER T, WEISSER B.** Effect of aerobic endurance exercise on immune function in elderly athletes. Praxis. 2002; 91: 153-158. doi:10.1024/0369-8394.91.5.153

(3) **CAO DINH H, BEYER I, METS T, ONYEMA OO, NJEMINI R, RENMANS W, DE WAELE M, JOCHMANS K, VANDER MEERES S, BAUTMANS I.** Effects of Physical Exercise on Markers of Cellular Immunosenecence: A Systematic Review. Calcif Tissue Int. 2016; 6: 1-23.

(4) **DIMEO F, FETSCHER S, LANGE W, MERTELSMANN R, KEUL J.** Effects of aerobic exercise on the physical performance and incidence of treatment related complications after high dose chemotherapy. Blood. 1997; 90: 3390-3394.

(5) **EVANS AS, HACKNEY AC, MCMURRAY RG, RANDELL SH, MUSS HB, DEAL AM, BATTAGLINI CL.** Impact of Acute Intermittent Exercise on Natural Killer Cells in Breast Cancer Survivors. Integr Cancer Ther. 2015; 14: 436-445. doi:10.1177/1534735415580681

(6) **FAIREY AS, COURNEYA KS, FIELD CJ, BELL GJ, JONES LW, MACKEY JR.** Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. J Appl Physiol. 2005; 98: 1534-1540. doi:10.1152/japplphysiol.00566.2004

(7) **FAIREY AS, COURNEYA KS, FIELD CJ, MACKEY JR.** Physical exercise and immune system function in cancer survivors: A comprehensive review and future directions. Cancer. 2002; 94: 539-551. doi:10.1002/cncr.10244

(8) **FRIEDENREICH CM, CUST AE.** Physical activity and breast cancer risk: impact of timing, type and dose of activity and population subgroup effects. Br J Sports Med. 2008; 42: 636-647. doi:10.1136/bjsm.2006.029132

(9) **GLEESON M, WALSH NP.** The BASES expert statement on exercise, immunity, and infection. J Sports Sci. 2012; 30: 321-324. doi:10.1080/02640414.2011.627371

(10) **GOH J, KIRK EA, LEE SX, LADIGES WC.** Exercise, physical activity and breast cancer: The role of tumor associated macrophages. Exerc Immunol Rev. 2012; 18: 158-176.

(11) **HAGSTROM AD, MARSHAL PWM, LONSDALE C, PAPALIA S, CHEEMA BS, TOBEN C, BAUNE BT, SINGH MAF, GREEN S.** The effect of resistance training on markers of immune function and inflammation in previously sedentary women recovering from breast cancer: a randomized controlled trial. Breast Cancer Res Treat. 2016; 155: 471-482. doi:10.1007/s10549-016-3688-0

(12) **HAYES SC, SPENCE RR, GALVAO DA, NEWTON RU.** Australian Association for Exercise and Sport Science position stand: Optimising cancer outcomes through exercise. J Sci Med Sport. 2009; 12: 428-434. doi:10.1016/j.jsams.2009.03.002

(13) **HOLMES M, CHEN WDF, KROENKE C, COLDITZ G.** Physical activity and survival after breast cancer diagnosis. JAMA. 2005; 293: 2479-2486. doi:10.1001/jama.293.20.2479

(14) **HOLICK CN, NEWCOMB PA, TRENTHAM-DIETZ A, TITUS-ERNSTOFF L, BERSCH AJ, STAMPFER MJ, BARON JA, EGAN KM, WILLETT WC.** Physical activity and survival after diagnosis of invasive breast cancer. Cancer Epidemiol Biomarkers Prev. 2008; 17: 379-386. doi:10.1158/1055-9965.EPI-07-0771

(15) **HUTNICK NA, WILLIAMS NI, KRAEMER WJ, ORSEGA-SMITH E, DIXON RH, BLEZNAK AD, MASTRO AM.** Exercise and lymphocyte activation following chemotherapy for breast cancer. Med Sci Sports Exerc. 2005; 37: 1827-1835. doi:10.1249/01.mss.0000175857.84936.1a

(16) **KRUIJSEN JAARSMA M, RÉVÉSZ D, BIERINGS MB, BUFFART LM, TAKKEN T.** Effects of exercise on immune function in patients with cancer: A systematic review. Exerc Immunol Rev. 2013; 19: 120-143.

(17) **KRUK J, ABOUL ENEIN HY.** Physical activity in the prevention of cancer. Asian Pac J Cancer Prev. 2006; 7: 11-21.

(18) **KYU HH, BACHMANN VF, ALEXANDRE LT, MUMFORD JE, AFSHIN A, ESTEP K, VEERMANN JV, DELWICHE K, IANNARONE M, MOYER ML, CERCY K, VOS T, MURRAY CJL, FOROUZANFAR MH.** Physical activity and risk of breast cancer, colon cancer, diabetes, ischemic heart disease, and ischemic stroke events: systematic review and dose-response meta-analysis for the Global Burden of Disease Study 2013. BMJ. 2016; 354: i3857. doi:10.1136/bmj.i3857

(19) **LEE IM.** Exercise and physical health: Cancer and immune function. Res Q Exerc Sport. 1995; 66: 286-291. doi:10.1080/02701367.1995.10607913

(20) **LEITZMANN M, POWERS H, ANDERSON AS, SCOCCIANTI C, BERRINO F, BOUTRON-RUAULT MC, CECCHINI M, ESPINA C, KEY TJ, NORAT T, WISEMAN M, ROMIEU I.** European Code against Cancer 4th Edition: Physical activity and cancer. Cancer Epidemiology. 2015; 39: S46-S55.

(21) **LIAO HF, CHIANG LM, YEN CC, CHEN YY, ZHUANG RR, LAI LY, CHIANG J, CHEN YJ.** Effect of a periodized exercise training and active recovery program on antitumor activity and development of dendritic cells. J Sports Med Phys Fitness. 2006; 46: 307-314.

(22) **LIMA DE C, ALVES LE, LAGHER F, MACHADO AF, BONATTO SJ, KUCZERA D, FERREIRA DE SOUZA C, PEQUITO DC, MURITIBA AL, NUNES EA.** Anaerobic exercise reduces tumor growth, cancer cachexia and increases macrophage and lymphocyte response in Walker 256 tumor bearing rats. Eur J Appl Physiol. 2008; 104: 957-964. doi:10.1007/s00421-008-0849-9

(23) **LOPRINZI PD, CARDINAL BJ.** Erratum to: Self efficacy mediates the relationship between behavioral processes of change and physical activity in older breast cancer survivors. Breast Cancer. 2013; 20: 47-52. doi:10.1007/s12282-011-0298-x

(24) **MADDOCKS M, JONES LW, WILCOCK A.** Immunological and hormonal effects of exercise: implications for cancer cachexia. Curr Opin Support Palliat Care. 2013; 7: 376-382. doi:10.1097/SPC.0000000000000010

(25) **MCTIERNAN A.** Physical activity after cancer: physiologic outcomes. Cancer Invest. 2004; 22: 68-81. doi:10.1081/CNV-120027581

(26) **MCTIERNAN A.** Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008; 8: 205-211. doi:10.1038/nrc2325

(27) **MOHAMADY TM, BORHAN WH, ABDALLAH W, ABDELGHANI S.** Effect of selected exercise program on natural killer cytotoxic cells activity of post-mastectomy patients. BJBAS (Beni-Suef University Journal of Bacis and Appllied Sciences). 2013; 2: 114-119.

(28) **MURPHY EA, DAVIS JM, BARRILLEAUX TL, MCCLELLAN JL, STEINER JL, CARMICHAEL MD, PENA MM, HERBERT JR, GREEN JE.** Benefits of exercise training on breast cancer progression and inflammation in C3(1)SV40Tag mice. Cytokine. 2011; 55: 274-279. doi:10.1016/j.cyto.2011.04.007

(29) **NIEMAN DC, COOK VD, HENSON DA, SUTTLES J, REJESKI WJ, RIBISL PM, FAGOAGA OR, NEHLSEN-CANNARELLA SL.** Moderate exercise training and natural killer cell cytotoxic activity in breast cancer patients. Int J Sports Med. 1995; 16: 334-337. doi:10.1055/s-2007-973015

(30) **NIEMAN DC, HENSON DA.** Role of endurance exercise in immune senescence. Med Sci Sports Exerc. 1994; 26: 172-181. doi:10.1249/00005768-199402000-00007

(31) **PEDERSEN BK, BRUUNSGAARD H.** How physical exercise influences the establishment of infections. Sports Med. 1995; 19: 393-400. doi:10.2165/00007256-199519060-00003

(32) **PEDERSEN L, IDORN M, OLOFSSON GH, LAUENBORG B, NOOKAEW I, HANSEN RH, JOHANNESEN HH, BECKER JC, PEDERSEN KS, DETHLEFSEN JN, GEHL, J, PEDERSEN BK, STRATEN THOR P, HOJMAN P.** Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. Cell Metab. 2016; 23: 554-562. doi:10.1016/j.cmet.2016.01.011

(33) **PETERS C, LOTZERICH H, NIEMEIER B, SCHÜLE K, UHLENBRUCK G.** Influence of a moderate exercise training on natural killer cytotoxicity and personality traits in cancer patients. Anticancer Res. 1994; 14: 1033-1036.

(34) **PETERS C, LOTZERICH H, NIEMEIER B, SCHÜLE K, UHLENBRUCK G.** Exercise, cancer and the immune response of monocytes. Anticancer Res. 1995; 15: 175-179.

(35) **PIERCE JP, STEFANICK ML, FLATT SW, NATARAJAN L, STERNFELD B, MADLENSKY L, AL-DELAIMY WK, THOMSON CA, KEALEY S, HAJEK R, PARKER BA, NEWMAN VA, CAAN B, ROCK CL.** Greater survival after breast cancer in physically active women with high vegetable fruit intake regardless of obesity. J Clin Oncol. 2007; 25: 2345-2351. doi:10.1200/JCO.2006.08.6819

(36) **RACK B, ANDERGASSEN U, NEUGEBAUER J, SALMEN J, HEPP P, SOMMER H, LICHENTEGGER W, FRIESE K, BECKMANN MW, HAUNER D, HAUNER H, JANNI W.** The German SUCCESS C Study The First European Lifestyle Study on Breast Cancer. Breast Care, 2010; 5: 395-400. doi:10.1159/000322677

(37) **ROGERS CJ, COLBERT LH, GREINER JW, PERKINS SN, HURSTING SD.** Physical activity and cancer prevention. Pathways and targets for intervention. Sports Med. 2008; 38: 271-296. doi:10.2165/00007256-200838040-00002

(38) **SAXTON JM, SCOTT EJ, DALEY AJ, WOODROOF MN, MUTRIE N, CRANK H, POWERS HJ, COLEMAN RE.** Effects of an exercise and hypocaloric healthy eating intervention on indices of psychological health status, hypothalamic-pituitary-adrenal axis regulation and immune function after early-stage breast cancer: a randomized controlled trial. Breast Cancer. 2014; 16: R39.

(39) **SCHMIDT T, WEISSER B, JONAT W, BAUMANN FT, MUNDHENKE C.** Gentle strength training in rehabilitation of breast cancer patients compared to conventional therapy. Anticancer Res. 2012; 32: 3229-3233.

(40) **SCHMITZ KH, COURNEYA KS, MATTHEWS C, DEMARK-WAHNEFRIED W, GALVÃO DA, PINTO BM, IRWIN ML, WOLIN KY, SEGAL RJ, LUCIA A, SCHNEIDER CM, VON GRUENIGEN VE, SCHWARTZ AL; AMERICAN COLLEGE OF SPORTS MEDICINE.** American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010; 42: 1409-1426. doi:10.1249/MSS.0b013e3181e0c112

(41) **SCHMITZ KH, SPECK RM.** Risks and benefits of physical activity among breast cancer survivors who have completed treatment. Womens Health (Lond Engl). 2010; 6: 221-238. doi:10.2217/whe.10.1

(42) **SENCHINA DS, KOHUT ML.** Immunological outcomes of exercise in older adults. Clin Interv Aging. 2007; 2: 3-16. doi:10.2147/ciia.2007.2.1.3

(43) **SHEPHARD RJ, RHIND S, SHEK PN.** Exercise and the immune system. Natural killer cells, interleukins and related responses. Sports Med. 1994; 18: 340-369. doi:10.2165/00007256-199418050-00006

(44) **SHEPHARD RJ, SHEK PN.** Potential impact of physical activity and sport on the immune system a brief review. Br J Sports Med. 1994; 28: 247-255. doi:10.1136/bjsm.28.4.247

(45) **SHEPHARD RJ, SHEK PN.** Cancer, immune function, and physical activity. Can J Appl Physiol. 1995; 20: 1-25. doi:10.1139/h95-001

(46) **SHEPHARD RJ, SHEK PN.** Associations between physical activity and susceptibility to cancer: Possible mechanisms. Sports Med. 1998; 26: 293-315. doi:10.2165/00007256-199826050-00002

(47) **SPROD LK, PALESH OG, JANELSINS MC, PEPPONE LJ, HECKLER CE, ADAMS MJ, MORROW GR, MUSTIAN KM.** Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. Community Oncol. 2010; 7: 463-471. doi:10.1016/S1548-5315(11)70427-2

(48) **STERNFELD B, WELTZIEN E, QUESENBERRY CP JR, CASTILLO AL, KWAN M, SLATTERY ML, CAAN BJ.** Physical activity and risk of recurrence and mortality in breast cancer survivors: Findings from the LACE study. Cancer Epidemiol Biomarkers Prev. 2009; 18: 87-95. doi:10.1158/1055-9965.EPI-08-0595

(49) **UHLENBRUCK G, ORDER U.** Can endurance sports stimulate immune mechanisms against cancer and metastasis? Int J Sports Med. 1991; 12: S63-S68. doi:10.1055/s-2007-1024753

(50) **WALSH NP, GLEESON M, SHEPHARD RJ, GLEESON M, WOODS JA, BISHOP NC, FLESHNER M, GREEN C, PEDERSEN BK, HOFFMAN-GOETE L, ROGERS CJ, NORTHOFF H, ABBASI A, SIMON P.** Position statement. Part one: Immune function and exercise. Exerc Immunol Rev. 2011; 17: 6-63.

(51) **WOODS JA, DAVIS JM.** Exercise, monocyte/macrophage function, and cancer. Med Sci Sports Exerc. 1994; 26: 147-156. doi:10.1249/00005768-199402000-00004

(52) **ZIMMER P, BAUMANN FT, BLOCH W, ZOPF EM, SCHULZ S, LATSCH J, SCHOLLMAYER F, SHIMABUKURO-VORNHAGEN A, VON BERGWELT-BAILDON M, SCHENK A.** Impact of a half marathon on cellular immune system, pro-inflammatory cytokine levels, and recovery behavior of breast cancer patients in the aftercare compared to healthy controls. Eur J Haematol. 2016; 96: 152-159. doi:10.1111/ejh.12561