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Exercise in Cancer Therapy

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An increasing number of epidemiological studies deal with the influence of physical activity in occupation or leisure time on cancer risk. Most of them portend to the fact that physical activity can decrease the risk of developing several types of cancer. In contrast, only a few studies focus on exercise training intervention studies to investigate the effect of physical activity during cancer rehabilitation on physical performance and immune function as well as psychological behavior such as quality of life. A meta-analysis of the literature shows a training-induced increase in the physical fitness of cancer patients in comparison to non-training control groups during and after medical treatment. Although some authors suggest a possible immune-enhancing effect of moderate-endurance exercise in cancer patients, data are ambiguous and portend a lack of knowledge. Based on the literature and our own findings, regular moderate exercise should be recommended in practice and must be batched individually, with special regard to physical fitness.

Key Words: exercise, cancer, therapy, physical performance, immune function

Key Points:

1. Physical activity is able to enhance the physical performance of cancer patients.
2. Exercise training programs for cancer patients should be holistic, including functional and psychosocial aspects.
3. Future research should focus on the amount and content of exercise training to define practical recommendations.

Introduction

In the mortality statistics of industrial nations, cancer takes the second position behind coronary heart diseases (5). Although great scientific advances concerning the early detection and diagnosis of cancer as well as the enlightenment of a genetical background were achieved (e.g., tumor suppressor genes or proto-oncogenes) in a huge number of cancer types, a save therapy concept still does not exist. Therefore, further alternative preventive and rehabilitative strategies are necessary to reduce relapse rates and risk of metastasis on the one hand and to maintain a high quality of life during the possibly prolonged lifetime on the other hand.

In this context, the focus increasingly is on sport that in the meantime rates highly in clinical and ambulant rehabilitation of cancer patients. Besides the well-accepted psychosocial aspects of movement in aftercare and ambulant cancer sports

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groups, the literature hints that physical activity has positive effects on different body systems and may be therapeutically effective.

Clinical Therapy Studies

An increasing number of epidemiological studies deal with an influence of physical activity in occupation or leisure time on cancer risk. Although results in the literature sometimes differ concerning its significance, generally an increased tumor risk is associated with lower physical activity, whilst a tumor protective effect is attributed to high physical activity (46).

In comparison to epidemiological data, only a few studies focus on clinical exercise intervention studies (see Table 1). It is well known that psychological and physical stress due to diagnosis and surgery, as well as chemotherapy and/or radiation, lead to diminished physical function. Inactivity of patients is combined with possible treatment-related negative physical effects such as reduced blood cell counts, fatigue, nausea, vomiting, and pain (7). Furthermore, cancer diagnosis can result in significant reductions of many quality of life–related outcomes including depression, anxiety, changes in body perception, and decreased self-esteem (7). Therefore, the necessity of accompanying measures is obvious to support physical and psychological rehabilitation of cancer patients. In this context, the focus is increasingly on physical activity and physical intervention studies that evaluate the effectiveness of sport in cancer treatment and rehabilitation.

Physical Function

Most clinical studies deal with the effect of an exercise training program on physical functions and psychological well being such as quality of life. Consistent findings in the literature point to a training-induced increase in physical fitness of cancer patients compared to non-trained cancer patients during and after treatment (9–11, 22, 28, 36, 38–41, 45). Moreover, training can have a positive influence on body weight and body composition, whereas obese women seem to profit more than those with normal weight (48).

Enhanced physical fitness was reached by 28 breast-cancer patients who took part in a 10-week structured rehabilitation training program (36). Training was constructed as a holistic exercise program containing gymnastics, games, and endurance exercise and took place twice a week. Because a lymphoedema can be a consequence of treatment for breast cancer and affect quality of life in these patients (18), careful movement must be considered during gymnastics. Therefore, controlled movement without extreme movement sizes are recommended. Whilst enhancement of mobility and communication were aims of gymnastics and games once a week, a consequent moderate endurance program (walking, running) was performed to enhance aerobic capacity. Ten weeks of endurance training were sufficient to significantly enhance maximal oxygen consumption ($\dot{V}O_{2max}$, rel $\dot{V}O_{2max}$) by about 15% and make a 10-km distance possible for the whole group (mean age, 53.9 years).

In a study of Nieman and colleagues (n = 16), endurance training was organized as a walking program of 30 min three times a week for 8 weeks. Intensity was adjusted individually at about 75% of the maximal heart rate. During the 60-min training session, aerobic exercise was combined with strength training. Training

Table 1 For Exercise in Cancer Therapy

Authors	Tumour	Involved patients	Training program	Results
Winningham et al. 1989	Mamma	24 women (stage 2) undergoing chemotherapy	Controlled study: 10-12 weeks aerobic interval training 3x/week for 20-30 min at 60-85% of the maximal heart rate	• Training has a positive influence on body weight and composition, especially exercising obese women profit from the program
Peters et al. 1994, 1995; Lötzerich/ Peters 1997	Mamma	49 women completed chemotherapy and radiation	Controlled study: 7 months endurance exercise program on a bicycle ergometer, 2-3 x/week with moderate intensity with an average duration of 33 min	• Increased training dependent immune function (phagocytosis of monocytes and granulocytes as well as cytotoxicity of natural killer cells) • Training based reduction of physical complaints • Positive correlation of training frequency and satisfaction of life
Nieman et al. 1995	Mamma	16 women completed chemotherapy and radiation	Controlled study: 8 weeks of exercise, 3 x/week as a combination of 30 min walking and 30 min strength training with an intensity of 75 % of the maximal heart	• Increase of physical performance (walking distance test) • Decrease of heart rate at defined exercise • Increase of leg strength • No training dependent effect on NK-cell number and function
Dimeo et al. 1997a	Various tumours	32 patients after high-dose chemotherapy and autologous stem cell transplantation	Controlled study: 6 weeks walking on a treadmill following an interval pattern, 5 x/weeks with an intensity corresponding to 90 ± 5 % of the maximal heart rate Exercise started with 5x3 min with nterruptions for rest and developed ito 1x30min walking continuously	• Training dependent increase of maximal physical performance (walking speed) and hemoglobin concentration • No patient of the exercise group reported fatigue or limitations in activities of daily living at the end of the project in comparison to the control group (25% reported fatigue)

Authors	Tumour	Involved patients	Training program	Results
Dimeo et al. 1997b	Various tumours	70 patients after high-dose chemotherapy and autologous stem cell transplantation	Controlled study: Biking on an ergometer in a supine position during hospitalisation (± 2 weeks), 30 min daily with an interval pattern (15x1 min exercise with 1 minute rest between) with moderate to low intensity	• Reduced training dependent decrease of physical performance during hospitalisation • Training dependent reduced duration of neutropenia, thrombopenia, reduced days of hospitalisation, severity of diarrhea and severity of pain
Schulz et al. 1998	Mamma	28 women completed chemotherapy and radiation	Uncontrolled study: 10 weeks of a structured rehabilitation training program, 2 x/week with a holistic concept: 1 x/week gymnastics and games 1 x/week aerobic exercise	• Increased quality of life expressed by reduced anxiety and reduced depression • Increased physical performance
Dimeo et al. 1999	Various tumours	59 patients receiving high-dose chemotherapy followed by auto-logous stem cell transplantation	Controlled study: Biking on an ergometer in a supine position during hospitalisation 30 minutes daily with an interval pattern (15x1 min exercise with 1 min rest between) with moderate to low intensity (detailed information of duration/weeks of training session is missing)	• Higher increase of fatigue and somatic complaints in the control group at day of discharge in comparison to the exercise group • Training dependent improvement of several scores of psychological distress
Schulz et al. 1999	Colorectal tumours	49 patients finished chemotherapy and radiation	Controlled study: 6 weeks endurance exercise program on a bicycle ergometer, 5 x/week with a moderate intensity with an average duration of 38min	• No training dependent effect on immune function • Enhanced physical performance

Authors	Tumour	Involved patients	Training program	Results
Schwarz 1999, 2000	Mamma	27 women receiving chemotherapy	Uncontrolled study: 8 weeks of a home based training program during chemotherapy with a self made exercise program with instruction to exercise 3-4 x/ week, each session 15-30 min aerobically	• 60% of all patients showed an increase of physical function (increased walking distance) and a reduced weight gain • Positive effect on quality of life mainly due to the influence on the fatigue syndrome • Training is able to diminish intensity of fatigue by a change of body perception
Shore/ Shephard 1999	Leukaemia	6 children within five years after diagnosis	Controlled study: 12 weeks of an endurance based holistic exercise program (various kinds of sports), 3 x/week, each session for 30 min at 70-85 % of the maximal heart rate	• Low level of VO_2max at the beginning • Training dependent increase of VO^2max • Training based positive influence on body fat and anxiety • Low level of immune function in children who still received chemotherapy • Acute exercise caused further impairment of immune response
Kelm et al. 2000	Rectum	1 men metastatic tumour undergoing chemotherapy	Uncontrolled study/case report: 13 weeks of strength and endurance exercise training, 2 x/week at 40-60 % of the postoperative defined maximal physical performance	• Increase of strength and endurance improvement (reduced heart rate and lactate at defined exercise) • Increased percentage of NK-cells • Increased quality of life
Na et al. 2000	Stomach	35 patients directly after surgery	Controlled study: Moderate exercise (arm or bicycle ergometer) twice a day, 5 days a week for 2 weeks, beginning from postoperative day 2 with an intensity of 60 % of the maximal heart rate	• All patients (exercise and control group) showed reduced NK-cell activity until postoperative day 7 • After 2 weeks training dependent enhanced NK-cell activity

Authors	Tumour	Involved patients	Training program	Results
Lübbe et al. 2001	Lung	56 patients	Uncontrolled study: Stationary rehabilitation program including individual aerobic endurance exercise as well as other components	• Increase of quality of life subscales "vitality" and "mental health" during rehabilitation • Improved lung function parameters
Schwarz et al. 2001	Mamma	72 women receiving chemotherapy	Uncontrolled study: 8 weeks of a home based exercise program with instruction to exercise 3-4 x/weeks, each session 15-30 min aerobically	• Exercise reduced fatigue • With increased duration of exercise intensity of fatigue declined
Segal et al. 2001 aerobic	Mamma	123 women (stage 1+2) partly receiving chemotherapy	Controlled study: 3 groups: control group, self directed exercise and supervised exercise group 26 weeks of exercise intervention 3-5 times a week aerobically	• Decreased physical function of the control group, increased physical function of both intervention groups (self directed > supervised) • No changes in quality of life • Supervised exercise group showed increased capacity and reduced body weight

was able to increase the walking test distance and reduce the heart rate in a defined physical stress test after training intervention. Moreover, increased quadriceps strength, measured with a computerized testing station, could be measured at the end of the study (28).

Effects of a home-based training program were investigated in comparison to a standardized guided training program. Altogether, 27 breast-cancer patients (tested prior to the first chemotherapy treatment) took part in an 8-week home-based exercise program. It was recorded in detail concerning type, duration, and intensity of training and led to increased physical fitness (38–40). Women who adopted the exercise program showed significant increases in functional ability, expressed as an increased walking distance in the post test and less weight gain (39, 40).

Within stationary rehabilitation, including physiotherapy, psycho-oncological, socio-medical, and educational as well as recreational components, an individual aerobic endurance exercise program was undertaken with 56 lung-cancer patients (26). The participants (13 female, 43 male) averaged 62 years of age and took part in the program for a minimum of 21 days. Improved lung function (forced vital capacity in %, forced expiratory volume in 1 s) due to training was accompanied by the enhancement of the questionnaire subscales *vitality* and *mental health.* Nothing can be said in detail concerning which part of the stationary rehabilitation program was responsible for the enhanced lung function. Since effects of holistic programs are difficult to interpret and attributing effects to the different parts of the training concept is often impossible, most scientific clinical studies deal with the effects of endurance exercise on physical and/or psychological function.

Segal and colleagues (41) found an increased aerobic capacity after 26 weeks of endurance exercise training. Over 123 breast-cancer patients with or without adjuvant chemotherapy were randomly assigned to a control group, a self-directed exercise intervention, or a supervised exercise intervention group. The self-directed group received instructions and were asked to train five times a week at home following a detailed exercise prescription and to make a training protocol. Women of the supervised group trained three times with a standardized training protocol including warm-up and cool down. Two further training sessions per week at home were recommended to reach the same training frequency.

Women of the control group showed a diminished aerobic capacity at the end of the project, indicating that a reduced therapy-related physical performance persisted for several months. Physical training was able to enhance performance and reduce therapy-related physical symptoms that could be shown in both training groups. Women who organized their training in person reached higher fitness levels than those women participating in the guided exercise program (41). A possible explanation by the authors for these surprising result was that the self-directed program included many features such as written guidelines for home exercise, education about pulse check, and frequent telephone calls, to realize effective home training. This well-attended program, in addition to the opportunity to exercise under convenient conditions (at home or in community facilities, individual scheduling), could be responsible for the high motivation of participants, followed by the positive results of the training program.

Positive changes in physical fitness could also be reached by a well-dosed endurance program during or after chemotherapy (9–11). The studies by Dimeo and colleagues generally involved patients with a wide range of different tumors. They were treated with high-dose chemotherapy followed by autologous peripheral blood

stem cell transplantation. During 6 weeks of a specially designed rehabilitation program, 16 patients underwent a walking program on a treadmill after completing high-dose chemotherapy, while a group of the same size served as controls. The walking program followed an interval training pattern and was performed five times a week. Duration of exercise was gradually increased so that 30 min of continuous walking could be reached at the end of the project. Intensity of training was adjusted relatively high—about 90% of the maximal heart rate. A higher velocity in a speed test and an increase in therapy-related diminished hemoglobin levels could be found at the end of the exercise program in the training group compared to the controls (11).

In a second study, the same working group started the exercise program during chemotherapy (11). For the exercise intervention, a bike ergometer in supine position was used and intensity of training adjusted to a moderate level (50% of cardiac reserve). Fifteen repetitions of 1 min of cycling were interrupted by 1 min of rest to allow patients to recover from exercise. Daily exercise was continued for the duration of hospitalization. A prolongation of test distance and an increase in walking speed could be found in the intervention group compared to the controls (11). Furthermore, therapy-induced symptoms such as neutropenia or thrombopenia could be diminished, and the severity of diarrhea as well as pain were reduced. These positive effects could lead to a diminution of hospitalization, leading to cost savings (11). Training-dependent adaptation, including increased stress resistance, must be taken into account.

An enhancement of physical performance was also reached by 25 female and male colon-cancer patients. In this study, standardized exercise training was performed on a bicycle ergometer once a day for about 40 min. With an exercise frequency of 5 days a week for 5 weeks at a moderate training level (average heart rate < 110 $b \cdot min^{-1}$), a workload of more than 1 W/kg body weight and a duration of more than 35 min were reached (37).

In addition, 7 months of moderate cycling two to three times a week was able to increase physical performance of 24 breast-cancer patients (24). At the end of the training session, increased duration of training (from an average of about 12 min to 33 min) was accompanied by an increased workload (from 0.4 up to 0.9 W/kg bodyweight). Correspondingly, heart rate during exercise stayed at the same level (between 120 and 130 $b \cdot min^{-1}$), thus indicating training progress. A training-induced increase in physical performance could provoke a feeling of fitness accompanied by reduced physical complaints (33).

Not only adult cancer patients seem to profit physically from an exercise training program; so do children and adolescents with leukemia (45). Illness-dependent reduced oxygen transport capacity was increased by training, and a positive influence on body fat and anxiety also occurred in the training group.

In summary, consistent findings in the literature point out that moderate exercise during therapy and rehabilitation is able to enhance physical performance, which is mostly affected by illness and therapy. Reduced physical fitness often is combined with impaired activities of daily living. Consistent findings in the literature show that during rehabilitation, cancer patients can physically profit from independent exercise programs, whether a holistic- or an endurance-orientated program is used.

Immune Function

Although an impaired immune function is discussed in relation to cancer development, only a few studies focus on training-dependent changes of immune cells and immune functions in cancer patients.

It is well known from healthy individuals that in parallel to adaptations of the hormonal system, changes of specific parameters of the immune system occur during and after exercise. Many training studies deal with qualitative and quantitative changes in the immune system after an acute bout of exercise. Besides frequently occurring changes in leukocyte and lymphocyte subpopulations (17, 25, 30, 43), the stimulating influence of moderate exercise on functions of different immune cells could have implications for cancer rehabilitation. In parallel to an exercise-induced increased phagocytotic activity of the monocyte/macrophage system, an enhanced cytotoxicity of natural killer cells was found in healthy individuals (1, 12, 13, 31, 47). Furthermore, long-term training programs are able to enhance natural cytotoxicity of NK cells in vitro against K 562 tumor cells (8, 29).

According to the immune surveillance theory, an important role concerning cancerogenesis is attributed to natural killer cells (6). Therefore, stimulation of these cells is desirable and may be reached by regular endurance training of moderate intensity.

At the beginning of an exercise-intervention study with postmenopausal breast-cancer patients (n = 49), natural killer-cell functions of all patients were diminished compared to healthy people. Whilst the activity of NK cells remains unchanged in patients of the control group, phagocytotic activity of monocytes and granulocytes was increased by 7 months of regular and moderate-endurance training. Furthermore, at the end of the study, natural-killer cytotoxicity of the intervention group was significantly enhanced by training (32, 33) and reached NK-cell function, which was comparable to the results of healthy people mentioned in the literature (4). In contrast, 8 weeks of a holistic exercise training (endurance and strength training) were unable to provoke a training-induced increase of natural killer-cell cytotoxicity in breast-cancer patients (n = 16; 28).

Much epidemiological data suggests that risk for cancer of the gastrointestinal system can be reduced by physical activity; therefore, evaluation of therapeutical effects of a standardized exercise program were analyzed through an exercise intervention study in colon-cancer patients (n = 49). Five weeks of regular endurance exercise did not provoke important immunological changes—neither an increase in natural killer-cell cytotoxicity nor an increase in phagocytotic activity of granulocytes and monocytes (37).

While only colon-cancer patients with early tumor stages were involved in this study, Kelm and colleagues (22) investigated the effect of an exercise program on a 58-year-old man undergoing chemotherapy with metastatic carcinoma of the rectum. Thirteen weeks of strength and endurance exercise twice a week were followed by an increased number of natural killer cells. This immunological activation was accompanied by increased physical performance and strength as well as enhanced quality of life.

In contrast to the above-mentioned studies, Na and colleagues (27) conducted their exercise program with stomach-cancer patients (n = 35) directly after they underwent surgical operations (second day). Half of the group trained moderately (60% of maximal heart rate) twice a day on an arm or bicycle ergometer five times a

week for 2 weeks. While natural killer-cell cytotoxicity was diminished in all patients (control and exercise groups) at the beginning of the study, it was significantly enhanced after 2 weeks of training compared to the control group.

In agreement with these studies, children and adolescents with leukemia showed a weak immune function at the beginning of their exercise intervention study (45). Whilst results from the literature concerning an influence of endurance exercise on immune function in cancer patients point to a stimulating effect or no effect in leukemia children (n = 3 control group, n = 3 exercise group), a slight impairment of immune function was found due to exercise. Intensity of exercise was adjusted to about 70 to 85% of the maximal heart rate, which seemed very intensive for young cancer patients. Patients with leukemia and lymphoma, as well as patients undergoing chemotherapy, must be treated very carefully with regard to exercise. In practical experience, moderate- to low-intensity exercise is recommended.

Scientific data concerning exercise- or training-induced changes of immune function in cancer patients still portend a lack of knowledge. Only a few studies focus on these topics, and they differ concerning the kind of cancer, the number of patients involved, the stage of cancer progress, as well as the method of exercise intervention.

In summary, evidence strongly suggests a possible immune-enhancing effect by moderate-endurance exercise of cancer patients found in those controlled studies with larger group sizes (27, 32, 33). In this context, it is difficult to interpret the results of studies involving less than 20 patients. Furthermore, the necessity of long-term intervention studies to induce possible changes in immune functions becomes clear and corresponds to the results in the literature concerning healthy people. Long-term intervention studies with a standardized training program are needed to validate this point of view.

Psychological Changes

Parallel to the positive influence of sports on physical performance and immune function from a medical point of view, the positive psychological effects of physical activity in training groups must be considered (44). Scientific results from the psycho-immunology literature show the influence of emotions on immune functions and reflect the strict connection between the psyche and immune system. Emotional reactions are accompanied by changes in endocrine profiles, which alone or with exercise are able to influence several parameters of cellular immunity (14–16, 21) such as the activity of natural killer cells (16, 19, 20).

Exercise may influence quality of life during cancer therapy and rehabilitation in different ways (7). Breast-cancer patients involved in physical exercise programs showed less depression and anxiety, in particular disorientation, compared to controls (10, 34, 36, 42) and trained more regularly if they received recommendations for organizing the training (42).

Increased functional and emotional scales (EORTC-QLQ), indicating reduced anxiety and depression, resulted from training. Furthermore, training-dependent enhanced quality of life (SF-36) was based on higher physical functioning, general health perception, as well as enhanced psychological well-being (36).

Training-dependent positive effects on quality of life sometimes affect the fatigue syndrome. Fatigue is a common side effect of cancer treatment that impacts quality of life. Exercise training is one way to reduce fatigue (9–11). Reduced

fatigue can come about through changed perception (39, 40). Because increased duration of training was strongly related to a diminution of fatigue intensity (38), long-time training intervention should be recommended in the rehabilitation of cancer patients.

Furthermore, regular training with a frequency of two and more sessions a week seems to be important. A strong positive correlation was found between training frequency and satisfaction of life, indicating that a training frequency of two to three times a week should be recommended in general practice (32, 33).

Motivation is a very important aspect of long-lasting exercise training programs. Whilst adults can be convinced of the health benefits of physical exercise training, children and adolescents must be motivated by movement itself at the beginning of the exercise program. Training programs for these specific groups cannot be standardized, only endurance-orientated, but they must be playful and diversified using a holistic program. Attention to these aspects resulted in a positive influence on anxiety in the small group of leukemia children who took part in an exercise training program (45).

Psychological reactions associated with cancer such as anxiety, helplessness, or depression are related to a worse prognosis (3) and a shorter survival time (2), whereas cancer patients without anxiety and depression showed longer survival time (23). Therefore, psychosocial health should be a regular consideration in each training session in cancer rehabilitation.

Conclusions

For a long time, survival time was the most important criteria for the selection of therapy in cancer treatment; today, associated quality of life is increasingly important. Contemporary medical rehabilitation of patients combines functional wellness with holistic and psychosocial concerns. But quality of life must be seriously considered during the attained lifetime (35). Based on the psychosocial effects of sports in the rehabilitation of cancer, more than 550 ambulant sport groups adapted for cancer patients are now established in Germany.

The clinical data suggest that regular physical activity should be recommended to cancer patients. Consistent findings point out that training intensity should be moderate to allow weak patients to participate. Furthermore, appropriate intensity must be determined individually and adapted to therapy-related changes in physical fitness. Although data of immunological studies promote an endurance-based exercise program, a holistic approach, including endurance training, seems to adequately increase cardiovascular fitness and reduce movement restrictions. Last but not least, patient motivation is of major importance for successful training because, as indicated by the epidemiological data reviewed here, the training period should be long-term, with a frequency of two to three times per week.

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