Physiologic and Molecular Mechanisms Linking Endurance and Resistance Training with Effects for Cancer Patients

Physiologische und molekulare Mechanismen für die Effekte von Kraft- und Ausdauertraining bei Krebspatienten

INTRODUCTION

Over the last decades, epidemiologic studies have shown that physical activity is inversely associated with the disease risk of several cancer sites. The evidence has been classified as convincing for colon cancer, as probable for endometrial and postmenopausal breast cancer, and as limited suggestive for lung, pancreatic, and accepted: June 2014
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SUMMARY

Introduction: Epidemiologic and controlled clinical studies have shown that exercise training before, during and after cancer therapy can have a substantial impact on therapy- and cancer-related symptoms. Further research investigated whether the benefits can be extended to cancer progression, recurrence, and cancer-specific or overall mortality. The underlying biological mechanisms are presumably complex, and may be specific for different types of training and cancer. Methods: A systematic PubMed-based literature review on the effects of exercise training on biomarkers in adult cancer patients was conducted till November 2013. Results: A total of 25 publications on 6 cancer sites were identified. Different biologic mechanisms on the effects of exercise trainings were discussed. Profound hypotheses included the modulation of metabolic factors, immune function, pro- and anti-inflammatory processes, sex hormones, and DNA repair capacities and oxidative stress. Most studies investigated breast cancer patients, endurance training, and changes in metabolic and inflammatory parameters. Results for all mechanisms are inconsistent. Discussion: Compared to the complexity of the topic and due to the paucity of studies in cancer patients the current level of evidence needs to be classified as preliminary. Future well-powered exercise intervention trials with cancer patients should, if feasible, incorporate translational and hypotheses-driven biomarker research. For clinical practice, these identified limitations of knowledge on mechanisms should not slow the increasing acceptance of physical training as safe, well-tolerated and highly effective supportive cancer therapy.

Key Words: Biological mechanisms, exercise training, cancer, clinical studies

ZUSAMMENFASSUNG


Schlüsselwörter: Biologische Mechanismen, körperliches Training, Krebs, klinische Studien

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The complexity of the problem and the potential underlying biological mechanisms are demonstrated in Figure 1. For different types of training, being defined by the specific type, intensity, frequency, and duration, beneficial effects on a broad outcome spectrum have been demonstrated or are currently under investigation in cancer patients. These effects may differ by cancer type, as well as by disease stage and cancer therapy. Compared to the complexity there is a paucity of studies in cancer patients. Only over the past few years, researchers from several disciplines have investigated some cellular and molecular mechanisms directly in cancer patients, with some reviews published prior to 2013 (3, 4). None of the studies could investigate the entire picture, linking training and biologic mediators to clinical outcomes. In general, there is great overlap between the prominent hypotheses on biologic mechanisms for tertiary and primary cancer prevention (19, 28).

Due to the complexity of the issue this paper focuses on training effects on body-fluid biomarkers in adult cancer patients. The primary goal is to present an updated systematic review on the current evidence published until November 2013. Furthermore, limitations of the current evidence are discussed and steps for future research are identified.

**MATERIAL AND METHODS**

In November 2013, a systematic literature review in the MEDLINE database was conducted by using the search syntax of a previous review by Ballard-Barbash and colleagues, extended by the biomarker terms (“dna repair” [Title/Abstract] OR isoprostane [Title/Abstract]) (3). The search covered the time period January 1950 to November 2013 and was limited to English language articles that described studies in humans. Studies in which effects of exercise could have been mixed up with other interventions by study design, such as in combined exercise and dietary intervention programs, as well as biomarkers not based on body fluids, such as bone or breast density, were excluded.

**RESULTS**

Overall, 25 publications were identified that reported some results on blood-based biomarkers in cancer patients from either observational or exercise intervention studies on 6 different cancer sites. An overview of the publications by study type, target mechanism, and cancer site is presented in Table 1. Most manuscripts referred to breast cancer, endurance training interventions, and to insulin-related and inflammatory parameters. Only two covered direct effects on tumor biology (31, 32). The major findings for each biological mechanism will be summarized in the following.

**Modulation of insulin and insulin-related metabolic factors**

Metabolic determinants related to insulin, insulin sensitivity, and the insulin-like-growth factor (IGF) axis have been shown to be associated with cancer etiology, primarily for colon cancer but also for other cancer sites. Exercise may have acute and chronic effects by improving insulin sensitivity. Up to now, a total of 10 publications on exercise training studies in cancer patients have reported results on this pathway. Most studies were performed in breast cancer patients. Endurance and resistance training in breast cancer patients have led to statistically significant changes with reducing IGF-1, increasing the IGF-binding protein IGFBP-3 and reducing the corresponding ratio IGF-1/IGFBP-3 (5, 11, 13). Results reported on insulin were inconsistent, with some studies reporting significant reductions in the exercise group (11, 17), whereas others noting no significant effects (5, 12, 13, 18). With respect to insulin/glucose, only one randomized trial (RCT) with 51 hepatocellular carcinoma patients reported a significantly reduced homeostasis model assessment (HOMA) score for the exercise group compared to the controls at 6 months postoperatively, as well as some improvements on insulin resistance (17). None of the other studies that measured insulin resistance or glucose values have detected significant changes (5, 8, 10, 18, 23, 27).

**Modulation of inflammatory parameters**

Thus far, only 9 publications systematically investigated effects of exercise on inflammatory markers in cancer patients, mostly with small sample sizes, in diverse cancer types, and reporting inconsistent results. None of the studies performed with breast cancer patients showed significant effects, neither for pro-inflammatory cytokines, e.g. IL-1, TNF-α, IL-6, nor for anti-inflammatory cytokines, such as IL-4 and IL-10 (6, 16, 21). One RCT with 23 colorectal cancer cases after primary therapy yielded reductions of the IL-1ra/IL6 and IL-1ra/IL-1β ratio after two weeks training of moderate intensity (1). With respect to the acute phase protein C-reactive protein (CRP), one prostate cancer and three breast cancer studies reported reductions with exercise (7, 8, 9, 22), whereas the trial in lung cancer patients did not observe any changes (10). In general, further research is needed to better understand the independent contribution of an exercise-induced reduction in visceral fat versus other exercise-induced anti-inflammatory mechanisms (29).
Modulation of immune function
A position paper on the knowledge about the general effects of exercise on immune function concluded that the picture for healthy populations is still diffuse and the evidence for most mechanisms remains tentative (29). In non-hematologic cancer populations, only two studies systematically investigated immune response data directly in cancer patients, primarily referring to endurance training (6, 20). They both found that exercise was associated with a significant change in function in vitro of natural killer cells isolated.

Modulation of DNA repair mechanisms and oxidative stress
This field has hardly been covered in trials with cancer patients. Regarding markers of oxidative stress, only two studies have been performed. One was a RCT with 48 colorectal cancer patients after primary adjuvant cancer therapy who performed a 2-week training with two different intensities (2). They reported a significant decrease of 8-oxo-2′-deoxyguanosine excretion, a marker of oxidative DNA-damage, in the moderate training group and a non-significant increase in the high-intensity group. The other study has been performed in 16 non-small cell lung cancer patients. It reported that moderate to high-intensity cycle ergometer training significantly increased several F2-isoprostanes, markers for oxidative stress (15). Thus, results on the effects of exercise on oxidative stress are currently rare and derived from very small studies.

Modulation of sex hormones
There is broad evidence for associations between circulating concentrations on sex hormone levels, physical activity and cancer risk derived from population-based studies (19). Thus, one might expect some effects in cancer patients, too. However, there are two main differences. First, weight loss/fat loss is generally needed in healthy individuals to modify estrogen levels – this mechanism may be relevant only for some cancer patients; second, as therapy of some tumors also incorporates anti-hormone therapies, such as androgen deprivation for prostate cancer patients, the investigation of isolated effects of exercise on hormone levels is challenging. Thus far, only three prostate cancer patient studies reported results (8, 25, 26). None of these RCTs found significant differences between the training groups and the sedentary control groups for testosterone or prostate-specific antigen (PSA) levels.

DISCUSSION
This review has shown that relatively few studies have yet covered the investigation of biological mechanisms of exercise in human cancer populations. Thus, considering the complexity of the topic, the current evidence is very limited. Besides the low number of studies, investigations covered different cancer types, patients at various stages of disease and treatment, had frequently low sample sizes, and investigated different training settings, different outcomes and biomarkers. Many studies have not primarily been designed to investigate biological mechanisms and some of the studies with non-significant results might have had restricted power to detect relevant differences. Another limitation of the current evidence is that primarily isolated biomarkers have been considered. However, for example, for oxidative stress, there are complex mechanisms of up and down regulation that need to be considered in parallel. Furthermore, many of the discussed mechanisms are currently vivid and quickly developing research fields, where for example for the investigation of immune response numerous further subtypes of cells and new receptors will be discovered in future that may qualify as new targets for investigations. In parallel, the standardization of laboratory methods and reporting of quality control measures need further improvement. This has, for example, been identified as a major issue of concern for current immunologic methods (29).

Table 1: Potential biological mechanisms and overview of published studies (name of first author, publication year and classification of study) in cancer patients on the effects of exercise training, R=randomized controlled trial, O=Observational study, Ic=Intervention study with controls, I=Intervention study without controls.
In addition, the evolving evidence on crosstalk between the above mentioned targets, such as between inflammatory processes, oxidative stress, and DNA repair will add complexity to the analyses.

We restricted this update on observational and controlled clinical studies to adult cancer patients. Advantages of these studies are that they are performed under real life conditions directly in the target population leading to results of direct relevance to humans. Other study concepts and research disciplines can also make essential contributions, such as experimental animal studies. The advantages of these approaches are that they can investigate direct effects in tissue, cells and other biomaterials, for example in knock-out mice with singular genetic manipulations where single pathways can be isolated and investigated. Nevertheless, the application of these models to exercise studies is not trivial. Whereas effects of endurance training can be studied in treadmill experiments for mice, there is no valid approach to mirror resistance training in mice. Additionally, the generalizability of the results to the complex human physical activity behavior, the human body system, and human biomarkers is restricted. Furthermore, potential physiologic and molecular mechanisms that are well-studied in experimental mice. Additionally, the generalizability of the results to the complex human physical activity behavior, the human body system, and human biomarkers is restricted. Furthermore, potential physiologic and molecular mechanisms that are well-studied in experimental mice, there is no valid approach to mirror resistance training in mice. Therefore, generalizability of the results to the complex human physical activity behavior, the human body system, and human biomarkers is restricted. Furthermore, potential physiologic and molecular mechanisms that are well-studied in experimental mice, there is no valid approach to mirror resistance training in mice.

In summary, there are profound hypotheses on potential biological mechanisms of training in cancer patients. However, for almost all potential pathways, the current level of evidence needs to be classified as preliminary. Further well-designed exercise intervention trials of adequate size are needed in cancer patients that, whenever feasible, incorporate high-quality and hypotheses-driven translational and interdisciplinary components for further biomarker research in this field. For the clinical practice, these identified limitations of knowledge on mechanisms should not lead to slowing down the important and increasing acceptance of physical training as save, well-tolerated and highly effective supportive cancer therapy, presumably at all stages of the disease and therapy (24).

Conflict of Interest: The authors declare that they have no conflict of interest.

REFERENCES


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