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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

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SUMMARY

Introduction: Epidemiologic and controlled clinical studies have shown that exercise training before, during and after a 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

Problemstellung: Epidemiologische und kontrollierte klinische Studien verdeutlichen, dass körperliches Training vor, während und nach einer Krebstherapie wichtige Einflüsse auf verschiedene krebs- und therapiebedingte Symptome habe kann. Zunehmend erforscht wird auch, ob sich der Nutzen bis auf das Rekurrenzrisiko, die krankheitsspezifische Mortalität und die Gesamtmortalität ausdehnt. Die zu Grunde liegenden biologischen Mechanismen gelten als komplex und sind spezifisch für verschiedene Trainingsformen aber auch Krebsarten zu untersuchen. Methoden: Es wurde ein systematischer Literaturreview in der Datenbank PubMed zu den Effekten von körperlichem Training auf Biomarker bei erwachsenen Krebspatienten bis November 2013 durchgeführt. Ergebnisse: Insgesamt wurden 25 Publikationen zu 6 verschiedenen Krebsarten identifiziert. Dabei wurden verschiedene biologische Mechanismen für die Effekte von körperlichem Training bei Krebspatienten diskutiert. Zu den fundierten Hypothesen gehören die Modulationen von metabolischen Faktoren, Geschlechtshormonen, der Immunfunktion, von pro- und anti-inflammatorischen Prozessen sowie von DNA-Reparaturkapazitäten und oxidativem Stress. Die meisten Studien beschäftigten sich mit Brustkrebs, Ausdauertraining und Veränderungen von metabolischen oder inflammatorischen Parametern. Die Ergebnisse sind meist nicht eindeutig. Diskussion: Verglichen mit der Komplexität des Themas und auf Grund der geringen Anzahl von Publikationen ist die aktuelle Evidenzlage als vorläufig einzustufen. Hinreichend große, klinische Sportinterventionsstudien sollten nach Möglichkeit durch die Sammlung von Biomaterialien vermehrt translationale und hypothesengestützte Biomarkerforschung beinhalten. Die aufgezeigte Forschungslücke im Bereich der biologischen Mechanismen darf nicht als Argumentationshilfe dienen, um Krebspatienten den zunehmend belegten Nutzen von Kraft- und Ausdauertraining als gutverträglicher und hocheffektiver Supportivtherapie vorzuenthalten.

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

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

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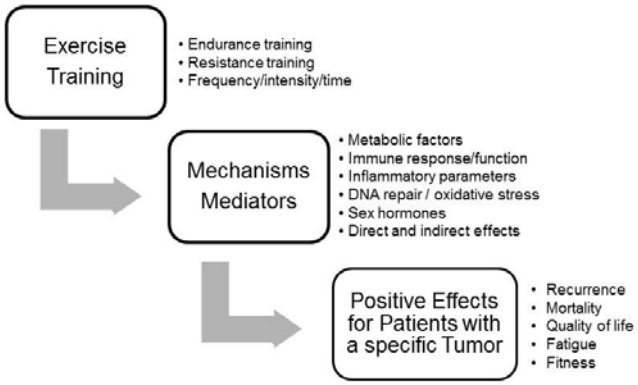

Figure 1: Overview of the potential underlying biological mechanism for the positive effects of exercise training on several outcomes for cancer patients.

premenopausal breast cancer (30). In addition, since the past decade, about 80-100 clinical studies in cancer patients have shown that endurance and resistance training before, during and after a cancer therapy can have a substantial impact on therapy- and cancer-related symptoms. (14,24). Furthermore, there is growing interest in determining whether the benefits of exercise training can be extended to cancer progression, recurrence, and cancer-specific or overall mortality. These outcomes have thus far been studied in about 30 observational studies, primarily in breast cancer patients (3).

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 cytocines, e.g. IL-1, TNF-α, IL-6, nor for anti-inflammatory cytocines, 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.

Target	Total number of publications	Studied Cancer Site			
		Breast	Prostate	Colorectal	Others
Insulin-related metabolic factors, IGF signal transduction	10	Fairey 2003 (R) Irwin 2005 (O) Schmitz 2005 (R) Ligibel 2008 (R) Irwin 2009 (R) Janelsins 2011 (R) Tosti 2011 (Ic)	Galvao 2010 (R)		Lung: Hwang 2012 (R) Hepatocellular: Kaibori 2013 (R)
Inflammatory parameters	9	Fairey 2005a (R) Fairey 2005b (R) Payne 2008 (R) Pierce 2009 (O) George 2010 (O) Jones-S 2012 (R)	Galvao 2010 (R)	Allgayer 2004 (R)	Lung: Hwang 2012 (R)
Immune response	2	Fairey 2005a (R)			Stomach: Na 2000 (R)
DNA repair and oxidative stress	2			Allgayer 2008 (R)	Lung: Jones-L 2011 (I)
Sex hormones	4		Galvao 2010 (R) Segal 2003 (R) Segal 2009 (R) Burton 2012 (O)		
Direct effects on tumor biology	2	Zeng 2012 (O+R)			Stomach: Yuasa 2009 (O)

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 studies have not been investigated in humans, and vice versa (14). It can be expected, that an overarching research agenda incorporating several research disciplines would result in major progress.

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

1. **Allgayer H, Nicolaus S, Schreiber S.** Decreased interleukin-1 receptor antagonist response following moderate exercise in patients with colorectal carcinoma after primary treatment. Cancer Detect Prev. 2004;28:208-213. doi:10.1016/j.cdp.2004.02.001
2. **Allgayer H, Owen RW, Nair J, Spiegelhalder B, Streit J, Reichel C, and Bartsch H.** Short-term moderate exercise programs reduce oxidative DNA damage as determined by high-performance liquid chromatography-electrospray ionization-mass spectrometry in patients with colorectal carcinoma following primary treatment. Scand J Gastroenterol. 2008;43:971-978. doi:10.1080/00365520701766111
3. **Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM.** Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. J Natl Cancer Inst. 2012;104:815-840. doi:10.1093/jnci/djs207
4. **Betof AS, Dewhirst MW, Jones LW.** Effects and potential mechanisms of exercise training on cancer progression: a translational perspective. Brain Behav Immun. 2013;30(Suppl):S75-S87. doi:10.1016/j.bbi.2012.05.001
5. **Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Mackey JR.** Effects of exercise training on fasting insulin, insulin resistance, insulin-like growth factors, and insulin-like growth factor binding proteins in postmenopausal breast cancer survivors: a randomized controlled trial. Cancer Epidemiol Biomarkers Prev. 2003;12:721-727.
6. **Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, and Mackey JR:** Randomized controlled trial of exercise and blood immune function in postmenopausal breast cancer survivors. J Appl Physiol. 2005a;98:1534-1540. doi:10.1152/japplphysiol.00566.2004
7. **Fairey AS, Courneya KS, Field CJ, Bell GJ, Jones LW, Martin BS, and Mackey JR.** Effect of exercise training on C-reactive protein in postmenopausal breast cancer survivors: a randomized controlled trial. Brain Behav Immun. 2005b;19:381-388. doi:10.1016/j.bbi.2005.04.001
8. **Galvao DA, Taaffe DR, Spry N, Joseph D, Newton RU.** Combined resistance and aerobic exercise program reverses muscle loss in men undergoing androgen suppression therapy for prostate cancer without bone metastases: a randomized controlled trial. J Clin Oncol. 2010;28:340-347. doi:10.1200/JCO.2009.23.2488
9. **George SM, Neuhouser ML, Mayne ST, Irwin ML, Albanes D, Gail MH, Alfano CM, Bernstein L, McTiernan A, Reedy J, Smith AW, Ulrich CM, Ballard-Barbash R.** Postdiagnosis diet quality is inversely related to a biomarker of inflammation among breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2010;19:2220-2228. doi:10.1158/1055-9965.EPI-10-0464
10. **Hwang CL, Yu CJ, Shih JY, Yang PC, Wu YT.** Effects of exercise training on exercise capacity in patients with non-small cell lung cancer receiving targeted therapy. Support Care Cancer. 2012;20:3169-3177. doi:10.1007/s00520-012-1452-5
11. **Irwin ML, McTiernan A, Bernstein L, Gilliland FD, Baumgartner R, Baumgartner K, Ballard-Barbash R.** Relationship of obesity and physical activity with C-peptide, leptin, and insulin-like growth factors in breast cancer survivors. Cancer Epidemiol Biomarkers Prev. 2005;14:2881-2888. doi:10.1158/1055-9965.EPI-05-0185
12. **Irwin ML, Varma K, Alvarez-Reeves M, Cadmus L, Wiley A, Chung GG, Dipietro L, Mayne ST, and Yu H.** Randomized controlled trial of aerobic exercise on insulin and insulin-like growth factors in breast cancer survivors: the Yale Exercise and Survivorship study. Cancer Epidemiol Biomarkers Prev. 2009;18:306-313. doi:10.1158/1055-9965.EPI-08-0531
13. **Janelsins MC, Davis PG, Wideman L, Katula JA, Sprod LK, Peppone LJ, Palesh OG, Heckler CE, Williams JP, Morrow GR, and Mustian KM.** Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. Clin Breast Cancer. 2011;11:161-170. doi:10.1016/j.clbc.2011.03.013
14. **Jones LW, Alfano CM.** Exercise-oncology research: past, present, and future. Acta Oncol. 2013;52:195-215. doi:10.3109/0284186X.2012.742564
15. **Jones LW, Liang Y, Pituskin EN, Battaglini CL, Scott JM, Hornsby WE, and Haykowsky M.** Effect of exercise training on peak oxygen consumption in patients with cancer: a meta-analysis. Oncologist. 2011;16:112-120. doi:10.1634/theoncologist.2010-0197
16. **Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML.** Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. Cancer Prev Res (Phila). 2013;6:109-118. doi:10.1158/1940-6207.CAPR-12-0278
17. **Kaibori M, Ishizaki M, Matsui K, Nakatake R, Yoshiuchi S, Kimura Y, and Kwon AH.** Perioperative exercise for chronic liver injury patients with hepatocellular carcinoma undergoing hepatectomy. Am J Surg. 2013;206:202-209. doi:10.1016/j.amjsurg.2012.07.035
18. **Ligibel JA, Campbell N, Partridge A, Chen WY, Salinardi T, Chen H, Adloff K, Keshaviah A, Winer EP.** Impact of a mixed strength and endurance exercise intervention on insulin levels in breast cancer survivors. J Clin Oncol. 2008;26:907-912. doi:10.1200/JCO.2007.12.7357
19. **McTiernan A.** Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008;8:205-211. doi:10.1038/nrc2325
20. **Na YM, Kim MY, Kim YK, Ha YR, Yoon DS.** Exercise therapy effect on natural killer cell cytotoxic activity in stomach cancer patients after curative surgery. Arch Phys Med Rehabil. 2000;81:777-779. doi:10.1016/S0003-9993(00)90110-2

21. **Payne JK, Held J, Thorpe J, Shaw H.** Effect of exercise on biomarkers, fatigue, sleep disturbances, and depressive symptoms in older women with breast cancer receiving hormonal therapy. Oncol Nurs Forum. 2008;35:635-642. doi:10.1188/08.ONF.635-642
22. **Pierce BL, Neuhouser ML, Wener MH, Bernstein L, Baumgartner RN, Ballard-Barbash R, Gilliland FD, Baumgartner KB, Sorensen B, McTiernan A, Ulrich CM.** Correlates of circulating C-reactive protein and serum amyloid A concentrations in breast cancer survivors. Breast Cancer Res Treat. 2009;114:155-167. doi:10.1007/s10549-008-9985-5
23. **Schmitz KH, Ahmed RL, Hannan PJ, Yee D.** Safety and efficacy of weight training in recent breast cancer survivors to alter body composition, insulin, and insulin-like growth factor axis proteins. Cancer Epidemiol Biomarkers Prev. 2005;14:1672-1680. doi:10.1158/1055-9965.EPI-04-0736
24. **Schmitz KH, Courneya KS, Matthews C, Demark-Wahnefried W, Galvao DA, Pinto BM, Irwin ML, Wolin KY, Segal RJ, Lucia A, Schneider CM, von Gruenigen VE, Schwartz AL, and American College of Sports M:** 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
25. **Segal RJ, Reid RD, Courneya KS, Malone SC, Parliament MB, Scott CG, Venner PM, Quinney HA, Jones LW, D'Angelo ME, Wells GA.** Resistance exercise in men receiving androgen deprivation therapy for prostate cancer. J Clin Oncol. 2003;21:1653-1659. doi:10.1200/JCO.2003.09.534
26. **Segal RJ, Reid RD, Courneya KS, Sigal RJ, Kenny GP. Prud'Homme DG, Malone SC, Wells GA, Scott CG, and Slovinec D'Angelo ME:** Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. J Clin Oncol. 2009;27:344-351. doi:10.1200/JCO.2007.15.4963
27. **Tosti KP, Hackney AC, Battaglini CL, Evans ES, Groff D.** Exercise in patients with breast cancer and healthy controls: energy substrate oxidation and blood lactate responses. Integr Cancer Ther. 2011;10:6-15. doi:10.1177/1534735410387600
28. **Ulrich CM, Wiskemann J, Steindorf K.** Physiologic and molecular mechanisms linking physical activity to cancer risk and progression. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2012;55:3-9. doi:10.1007/s00103-011-1400-4
29. **Walsh NP, Gleeson M, Shephard RJ, Gleeson M, Woods JA, Bishop NC, Fleshner M, Green C, Pedersen BK, Hoffman-Goetz L, Rogers CJ, Northoff H, Abbasi A, Simon P.** Position statement. Part one: Immune function and exercise. Exerc Immunol Rev. 2011b;17:6-63.
30. **World Cancer Research Fund / American Institute for Cancer Research.** Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. WCRF/AICR. Printed Report (2007), Washington, D.C., and Continuous Update Project: http://www.wcrf.org/cancer_research/cup/
31. **Yuasa Y, Nagasaki H, Akiyama Y, Hashimoto Y, Takizawa T, Kojima K, Kawano T, Sugihara K, Imai K, Nakachi K.** DNA methylation status is inversely correlated with green tea intake and physical activity in gastric cancer patients. Int J Cancer. 2009;124:2677-2682. doi:10.1002/ijc.24231
32. **Zeng H, Irwin ML, Lu L, Risch H, Mayne S, Mu L, Deng Q, Scarampi L, Mitidieri M, Katsaros D, Yu H.** Physical activity and breast cancer survival: an epigenetic link through reduced methylation of a tumor suppressor gene L3MBTL1. Breast Cancer Res Treat. 2012;133:127-135. doi:10.1007/s10549-011-1716-7

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