review

Wien Klin Wochenschr (2013) 125:297–301
DOI 10.1007/s00508-013-0365-8

Wiener klinische Wochenschrift
The Central European Journal of Medicine

Exercise in the prevention and rehabilitation of breast cancer

Konstantinos A. Volaklis, Martin Halle, Savvas P. Tokmakidis

Received: 16 January 2013 / Accepted: 4 April 2013 / Published online: 8 May 2013
© Springer-Verlag Wien 2013

Summary Breast cancer is the most common type of cancer among women worldwide. Several epidemiological studies have shown an inverse relationship between the risk of breast cancer and physical activity levels, whereas exercise training has been recognized as a significant means in the rehabilitation process of breast cancer survivors. The relative risk reduction of breast cancer for women who engaged in moderate to vigorous physical activity for 3–5 days peek week ranged between 20–40 %. Furthermore, several studies demonstrated a 24–67 % reduction in the risk of total deaths and 50–53 % reduction in the risk of breast cancer deaths in women who are physically active after breast cancer diagnosis compared with sedentary women. Breast cancer survivors should be encouraged to participate in rehabilitation programs in order to obtain numerous physiological and psychological benefits. These include reductions in fatigue and improvements in immune function, physical functioning, body composition, and quality of life. Based on recent scientific evidence, a complete rehabilitation program for patients with breast cancer should combine both strength and aerobic exercise in order to maximize the expected benefits.

Keywords: Breast cancer, Exercise, Prevention, Rehabilitation

Dr. K. A. Volaklis, PhD (✉) · S. P. Tokmakidis, PhD
Department of Physical Education and Sport Science,
Democritus University of Thrace, 69100 Komotini, Greece
e-mail: kvolakli@phyed.duth.gr

Dr. K. A. Volaklis, PhD · M. Halle, MD
Department of Prevention and Sports Medicine,
Technische Universitaet Muenchen, Munich, Germany

M. Halle, MD
Munich Heart Alliance, Munich, Germany

Körperliches Training bei der Prävention und Rehabilitation von Brustkrebs

Zusammenfassung Brustkrebs ist weltweit die häufigste Krebserkrankung von Frauen. Verschiedene epidemiologische Studien haben eine inverse Korrelation zwischen dem Risiko an Brustkrebs zu erkranken und physischer Aktivität gezeigt. Körperliches Training wurde auch als ein signifikantes Mittel im Rehabilitationsprozess von Brustkrebs Überlebenden anerkannt.

Die Reduktion des relativen Risikos von Brustkrebs betrug bei Frauen, die moderates bis anstrengendes Training 3- bis maximal 5-Mal pro Woche betrieben, lag zwischen 20 und 40 %. Außerdem zeigten einige Studien eine 24–67 %ige Reduktion der Gesamtmortalität, beziehungsweise eine 50–53 %ige Reduktion des Risikos an Brustkrebs zu versterben bei physisch aktiven, an Brustkrebs erkrankten Frauen im Vergleich zu jenen, die keine physische Aktivität betrieben.

Brustkrebs Überlebende sollten motiviert werden, an Rehabilitationsprogrammen teilzunehmen, um von zahlreichen physischen und psychologischen Vorteilen zu profitieren. Diese Vorteile inkludieren eine Abnahme der Müdigkeit, sowie eine Besserung der Funktion des Immunsystems, des körperlichen Wohlbefindens und der Lebensqualität. Entsprechend rezenter wissenschaftlicher Evidenz sollte ein komplettes Rehabilitationsprogramm für Patienten mit Brustkrebs zur Maximierung des erwarteten Vorteils sowohl Kraft-Übungen als auch aerobe Übungen beinhalten.

Schlüsselwörter: Brustkrebs, Training, Prävention, Rehabilitation

Introduction

Breast cancer, as the most common kind of cancer, affects 1.1 million women all over the world, and about 58,000 new cases are diagnosed in Germany every year [1, 2]. Breast operation and postoperative chemotherapy/radiotherapy, as a regular treatment, has negative physiological and psychological effects on the patients; these side effects, however, could be counterbalanced by an increased level of physical fitness [3, 4]. Traditionally, clinicians advised cancer patients to rest and to avoid physical activity. During the last two decades, however, exercise training has been recognized as a significant means in the prevention and rehabilitation of breast cancer patients.

Exercise and breast cancer prevention

Several epidemiological studies have shown an inverse relationship between the risk of breast cancer and physical activity levels [5–9]. McTiernan et al. [5] prospectively examined the association between current and past recreational physical activity and incidence of breast cancer in postmenopausal women ($n=75{,}171$). Women who have been engaged in strenuous physical activity at least three times per week at age 35 years revealed a decreased risk of breast cancer by 14 % compared with women who did not exercise. In the same study, a greater amount of total (baseline) physical activity was associated with a lower risk of breast cancer. Compared with no current physical activity, risk was reduced by 18, 11, 17, and 22 % for women who exercised 5.1–10, 10.1–20, 20.1–40, and >40 metabolic equivalent task-hours/week (MET-h/wk). Eliassen et al. [8] conducted the largest prospective study in 95,396 postmenopausal women and documented 4,782 invasive breast cancer cases during a mean period of follow-up of 20 years. Compared with less than 3 MET-h/wk, women who were engaged in higher amounts of recent total physical activity (>27 MET-h/wk) had a lower breast cancer risk by 15 %.

On the basis of accumulated scientific evidence, the WHO, in its recent guidelines, recognized that the increased level of physical fitness may reduce breast cancer risk by 20–40 % [1]. Furthermore, Friedenreich et al. [10] stated that ca. 165,000–330,000 cases of the six major cancers (breast, colon, lung, prostate, endometrium, and ovarian) could have been prevented each year in Europe alone if the population had maintained sufficient levels of physical activity. The above data are very important because physical inactivity is a modifiable risk factor and women who improve their exercise habits may substantially reduce the morbidity and mortality risk of the disease.

Exercise and rehabilitation of breast cancer

In most women, the level of physical activity decreases after cancer diagnosis and remains low several months after the completion of the therapy. Breast cancer survivors, on average, decreased their total postdiagnosis physical activity levels by 2 h per week, compared with physical activity levels reported in the year before diagnosis [11]. Irwin et al. [12] reported that, compared with women who were inactive both before and after diagnosis, women who increased physical activity after diagnosis had a 45 % lower risk of death and women who decreased physical activity after diagnosis had a fourfold greater risk of death.

However, only 32 % of breast cancer survivors participated in recommended levels of physical activity defined as 150 min per week of moderate to vigorous intensity sports/recreational physical activity after completing treatment [13]. The majority of this population should follow systematic exercise in order to obtain numerous physiological and psychological benefits. These include reductions in fatigue and improvements in immune function, physical functioning, body composition, and quality of life [14–16].

Exercise and mortality risk

Several studies demonstrated that systematic exercise and increased levels of physical fitness after diagnosis are associated with a better prognosis (decreased risk of recurrence and mortality) [12, 17–20]. These studies have demonstrated a 24–67 % reduction in the risk of total deaths and 50–53 % reduction in the risk of breast cancer deaths in women who are physically active after breast cancer diagnosis compared with sedentary women.

In the Nurses' Health Study, compared with women who engaged in less than 3 MET-h/wk of physical activity, the adjusted relative risk of death from breast cancer was reduced by 20 % for 3–8.9 MET-h/wk, by 50 % for 9–14.9 MET-h/wk, by 44 % for 15–23.9 MET-h/wk, and by 40 % for ≥24 MET-h/wk ($p=0.004$) [17].

Peel et al. [20] examined the association between cardiorespiratory fitness and risk of death from breast cancer in 14,811 women, aged 20–83 years, from the Aerobics Center Longitudinal Study. After controlling for confounders, women with high and moderate physical fitness levels had reduced breast cancer mortality risk by 55 and 33 %, respectively, compared with those in the lowest tertile during a follow-up period of 16 years (Fig. 1).

Holick et al. [18] prospectively examined the relation between postdiagnosis recreational physical activity and risk of breast cancer death. Compared with women expending less than 2.8 MET-h/wk in physical activity, women who engaged in greater levels of activity had a significantly lower risk of dying from breast cancer (−35 % for 2.8–7.9 MET-h/wk, −41 % for 8.0–20.9 MET-h/wk, and −49 % to −0.89 for ≥21.0 MET-h/wk).

In another study, compared with inactive women, the multivariable hazard ratios for total deaths for women expending at least 9 MET-h/wk (approximately 2–3 h/wk of brisk walking) were reduced by 31 % for those active in the year before diagnosis and by 67 % for those active

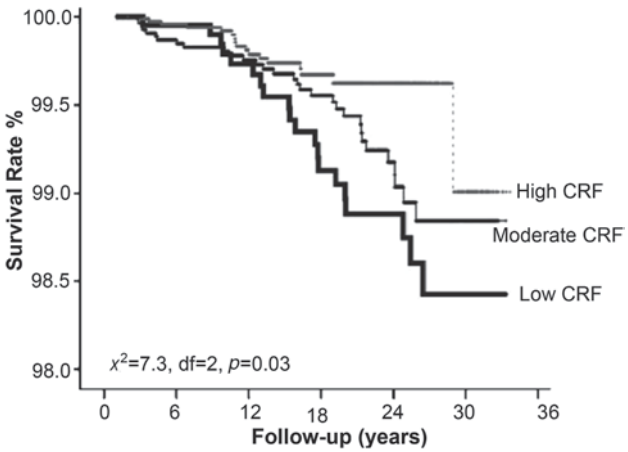

Fig. 1 Survival free of breast cancer according to the levels of cardiorespiratory fitness (*CRF*) of the patients [20]

2 years after diagnosis [12]. According to the relevant literature, the expected reduction in morbidity after exercise training was observed in pre- and postmenopausal women, overweight and normal weight women, and women with stage I–III of cancer.

Mechanisms of exercise

Exercise may influence breast cancer risk and recurrence of breast cancer through several mechanisms (Fig. 2). The most studied include sex steroid hormones (i.e., estrogens and androgens), insulin resistance, metabolic hormones (i.e., leptin, adipokines) and growth factors, inflammation markers (i.e., prostaglandin, C-reactive protein), immunological parameters (i.e., natural killer cells, leukocytes, T helper cells), and oxidative stress indexes (i.e., reactive oxygen species). Exercise training has the potential to positively affect all these biomarkers [4, 21–23], contributing significantly to the improved prognosis of the patients. However, there is a need to further examine whether exercise is equally beneficial in specific breast tumor types (invasive vs noninvasive or inflammatory breast cancer) or if the exercise-induced adaptations differ according to hormone receptor status, histology or tumor grade. For example, in the California Teachers Study [6], the researchers found a clear reduction of ER–/PR– (ER, estrogen receptor; PR, progesterone receptor) cancer risk but not of ER+/PR+ or ER+/PR– risk with increased levels of physical activity, whereas others found no reduction of ER+/PR – carcinoma risk in physically active women [24].

Furthermore, some studies provided evidence that exercise, in postdiagnosis animal models of carcinogenesis, is associated with inhibition of primary tumor growth and a decrease in metastatic dissemination [26, 27]. These findings have important implications and may allow for using exercise as a complement in order to improve the efficacy of conventional cancer therapies. However, the exact molecular pathways that could explain the beneficial effects of physical training in both prevention and rehabilitation of breast cancer must be further clarified.

Exercise and lymphedema

Arm lymphedema is a chronic complication that affects a significant number of women treated for breast cancer. Upper extremity exercise has been traditionally avoided for women who have undergone surgical resection of the

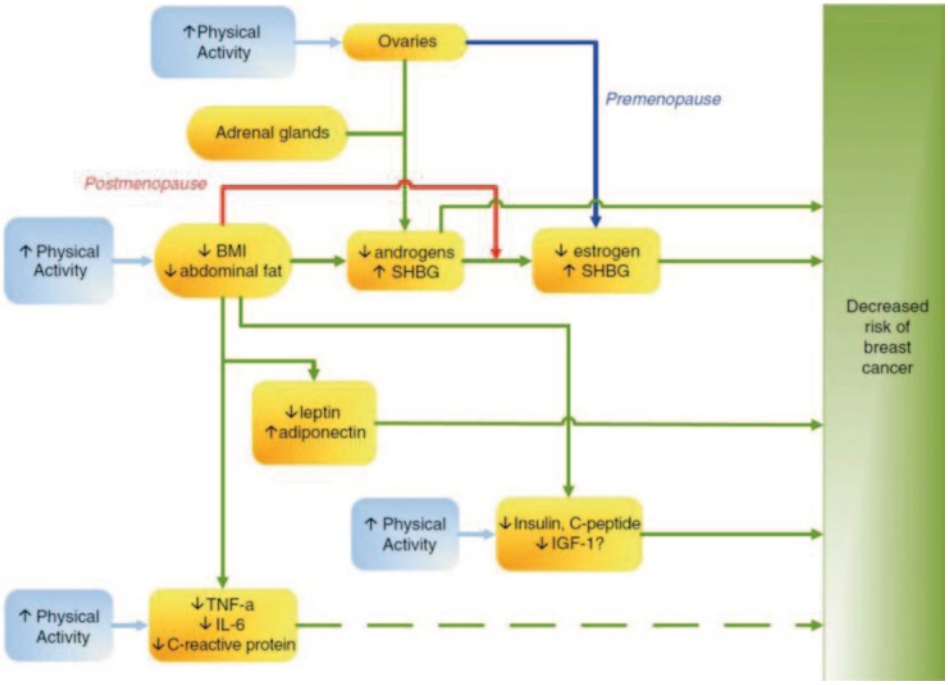

Fig. 2 Biological mechanisms showing how exercise reduces the risk of breast cancer. *BMI* body mass index, *SHBG* sex hormone-binding globulin, *TNF-a* tumor necrosis factor-alpha, *IL-6* interleukin 6, *IGF-1* insulin-like growth factor 1 [25]

axillary lymph nodes or radiation therapy. Recent studies, however, indicated that upper body exercise (aerobic and/or resistance training) does not contribute to the onset or worsening of lymphedema among breast cancer survivors [28–31]. In a recent, well-controlled study, Schmitz et al. [32] evaluated the onset of lymphedema after one year of progressive weight-lifting program in breast cancer survivors. Women in the intervention group experienced a relative risk reduction of 35 % in the incidence of lymphedema, whereas greater improvements (risk reduction of 70 %) were seen among women with five or more lymph nodes removed.

Resistance exercise for breast cancer survivors

Recently, resistance exercise has gained popularity in breast cancer patients because several studies have indicated that this type of training is safe and has positive effects on body composition, physical functions, psychological outcomes (depression, anxiety, and self-confidence), and quality of life. Furthermore, this type of training can provide significant protection against the two major side effects of cancer therapy: muscle wasting and chronic fatigue [33–36]. In these patients, fatigue is a cause as well as a consequence of skeletal muscle wasting leading to a vicious cycle (fatigue–limited physical activity–deconditioning–worsening of fatigue), which adversely affects the clinical status and the outcome. Throughout specific resistance programs, patients can regain their muscle strength, reduce fatigue symptoms, and by this way, improve the activities of daily living.

Training recommendations

In order to substantially reduce the risk of breast cancer, women must follow 150 min per week of moderate to vigorous intensity sports/recreational physical activity. When prescribing exercise training to breast cancer patients, caution should be given to the specific side effects of anticancer treatment (lymphedema, easy fatigue, anemia, etc.). For example, women with lymphedema should wear a compression garment during exercise, especially during upper body training. Intensity depends on the physical fitness and the clinical status of the patient and must be kept between 50 and 75 % of VO_{2peak} or 60 and 80 % of HR_{max}. The rate of perceived exertion should range from “fairly light” to “somewhat hard” on the Borg scale to fatigue (Table 1). With respect to the duration, the goal is to perform 30–45 min of continuous exercise; however, very few patients are able to achieve this target at the start of their rehabilitation program. For this reason, intermittent training has been used as a way to accumulating the appropriate exercise time, especially for the older and deconditioned patients. Regarding the modes of training, selection must be based on acute/chronic disease and treatment effects and participant preferences. Although walking and cycling are the most common modalities used in the literature, performing stretching and strengthening exercises can help patients to improve their flexibility and range of motion in the upper body [37, 38] (Table 1).

Table 1. Exercise recommendations to breast cancer patients [36, 37]

Intensity	50–75 % of VO_{2peak}, 60–80 % of HR_{max}, or RPE of 11–14
Duration	At least 20–30 min of continuous exercise; however, this may include several short bouts adding up to the goal time because the patient is deconditioned or because the patient is experiencing treatment-specific side effects
Frequency	At least 3–5 times a week, but daily exercise may be optimal for those who are deconditioned and require lower intensities and short durations of exercise
Mode	Aerobic and resistance exercises that include large muscle groups are appropriate; the optimal program should also include range of motion, flexibility, and coordination exercises

Conclusion

Accumulated evidence clearly suggested that a higher level of physical fitness is associated with a significantly lower risk of breast cancer. Furthermore, regular exercise following a breast cancer diagnosis may be associated with substantial reductions in cancer-specific and all-cause mortality. Breast cancer survivors should follow systematic exercise during their rehabilitation in order to achieve a better recovery and to improve their health status, quality of life, and prognosis. Based on recent scientific evidence, a complete rehabilitation program for patients with breast cancer should combine both strength and aerobic exercise in order to maximize the expected benefits.

Conflict of interest

The authors declare that there are no actual or potential conflicts of interest in relation to this article.

References

1. www.who.int
2. www.cancer.org
3. Dimeo FC, Stieglitz RD, Novelli-Fischer U, Fetscher S, Keul J. Effects of physical activity on the fatigue and psychologic status of cancer patients during chemotherapy. Cancer. 1999;85(10):2273–7.
4. McTiernan A. Mechanisms linking physical activity with cancer. Nat Rev Cancer. 2008;8(3):205–11.
5. McTiernan A, Kooperberg C, White E, Wilcox S, Coates R, Adams-Campbell LL, Woods N, Ockene J. Recreational physical activity and the risk of breast cancer in postmenopausal women. The women’s health initiative cohort study. JAMA. 2003;290(10):1331–6.
6. Dallal CM, Sullivan-Halley J, Ross RK, Wang Y, Deapen D, Horn-Ross PL, Reynolds P, Stram DO, Clarke CA, Anton-Culver H, Ziogas A, Peel D, West DW, Wright W, Bernstein L. Long-term recreational physical activity and risk of invasive and in situ breast cancer: the California teachers study. Arch Intern Med. 2007;167(4):408–15.

7. 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(8):636–47.
8. Eliassen AH, Hankinson SE, Rosner B, Holmes MD, Willett WC. Physical activity and risk of breast cancer among postmenompausal women. Arch Intern Med. 2010;170(19):1758–64.
9. Pronk A, Shu XO, Ji BT, Chow WH, Xue S, Yang G, Li HL, Rothman N, Gao YT, Zheng W, Matthews CE. Physical activity and breast cancer risk in Chinese women. Br J Cancer. 2011;106(9):1443–50.
10. Friedenreich CM, Neilson HK, Lynch BM. State of the epidemiological evidence on physical activity and cancer prevention. Eur J Cancer. 2010;46(14):2593–604.
11. Irwin ML, Crumley D, McTiernan A, Bernstein L, Baumgartner R, Gilliland FD, Kriska A, Ballard-Barbash R. Physical activity levels before and after a diagnosis of breast carcinoma: the Health, Eating, Activity, and Lifestyle (HEAL) study. Cancer. 2003;97(7):1746–57.
12. Irwin ML, Smith AW, McTiernan A, Ballard-Barbash R, Cronin K, Gilliland FD, Baumgartner RN, Baumgartner KB, Bernstein L. Influence of pre- and postdiagnosis physical activity on mortality in breast cancer survivors: the health, eating, activity and lifestyle study. J Clin Oncol. 2008;26(24):3958–64.
13. Irwin ML, McTiernan A, Bernstein L, Gilliland FD, Baumgartner R, Baumgartner K, Ballard-Barbash R. Physical activity levels among breast cancer survivors. Med Sci Sports Exerc. 2004;36(9):1484–91.
14. Fairey AS, Courneya KS, Field CJ, Mackey JR. Physical exercise and immune system function in cancer survivors. Cancer. 2002;94(2):539–51.
15. Courneya KS, Mackey JR, Bell GJ, Jones LW, Field CJ, Fairey AS. J Clin Oncol. 2003;21(9):1660–8.
16. Jones L, Demark-Wahnfried D. Diet, exercise and complementary therapies after primary treatment for cancer. Lancet Oncol. 2006;7(12):1017–26.
17. Holmes MD, Chen WY, Feskanich D, Kroenke CH, Colditz GA. Physical activity and survival after breast cancer diagnosis. JAMA. 2005;293(20):2479–86.
18. Holick C, Newcomb P, 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(2):379–86.
19. Friedenreich CM, Gregory J, Kopciuk KA, Mackey JR, Courneya KS. Prospective cohort study of lifetime physical activity and breast cancer survival. Int J Cancer. 2009;124(8):1954–62.
20. Peel JB, Sui X, Adams SA, Hebert JR, Hardin JW, Blair SN. A prospective study of cardiorespiratory fitness and breast cancer mortality. Med Sci Sports Exerc. 2009;41(4):742–8.
21. 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(4):1534–40.
22. 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(6):907–12.
23. Lira FS, Rosa JC, Yamashita AS, Koyama CH, Batista ML Jr, Seelaender M. Regulation of inflammation in the adipose tissue in cancer cachexia: effect of exercise. Cell Biochem Funct. 2009;27:71–5.
24. Schmidt ME, Steindorf K, Mutschelknauss E, Slanger T, Kropp S, Obi N, Flesch-Janys D, Chang-Claude J. Physical activity and postmenopausal breast cancer: effect modification by breast cancer subtypes and effective periods in life. Cancer Epidemiol Biomarkers Prev. 2008;17(12):3402–10.
25. Neilson HK, Friedenreich CM, Brockton NT, Millikan RC. Physical activity and postmenopausal breast cancer: proposed biologic mechanisms and areas for future research. Cancer Epidemiol Biomarkers Prev. 2009;18(1):11–27.
26. Zielinski MR, Muenchow M, Wallig MA, Horn PL, Woods JA. Exercise delays allogeneic tumor growth and reduces intratumoral inflammation and vascularization. J Appl Physiol. 2004;96(6):2249–56.
27. Jones LW, Viglianti BJ, Tashjian JA, Kothadia SM, Keir ST, Freedland SJ, Potter MQ, Moon EJ, Schroeder T, Herndon JE, Dewhirst MW. Effect of aerobic exercise on tumor physiology in an animal model of human breast cancer. J Appl Physiol. 2010;108(2):343–8.
28. Harris SR, Niesen-Vertommen SL. Challenging the myth of exercise-induced lymphedema following breast cancer: a series of case reports. J Surg Oncol. 2000;74(2):95–8.
29. McKenzie DC, Kalda AL. The effect of upper extremity exercise on secondary lymphedema in breast cancer patients: a pilot study. J Clin Oncol. 2003;21(3):463–6.
30. Hayes SC, Reul-Hirche H, Turner J. Exercise and secondary lymphedema: safety, potential benefits and research issues. Med Sci Sports Exerc. 2009;41(3):483–9.
31. Schmitz KH, Ahmed RL, Troxel A, Cheville A, Smith R, Lewis-Grant L, Bryan CJ, Williams-Smith CT, Greene QP. Weight lifting in women with breast-cancer-related lymphedema. N Engl J Med. 2009;361(7):664–73.
32. Schmitz KH, Ahmed RL, Troxel AB, Cheville A, Lewis-Grant L, Smith R, Bryan CJ, Williams-Smith CT, Chittams J. Weight lifting for women at risk for breast cancer related lymphedema. JAMA. 2010;304(24):2699–705.
33. Ohira T, Schmitz KH, Ahmed RL, Yee D. Effects of weight training on quality of life in recent breast cancer survivors: the weight training for breast cancer survivors (WTBS) study. Cancer. 2006;106(9):2076–83.
34. Courneya KS, Segal RJ, Mackey JR, Gelmon K, Reid RD, Friedenreich CM, Ladha AB, Proulx C, Vallance J, Lane K, Yasui Y, McKenzie D. Effects of aerobic and resistance exercise in breast cancer patients receiving adjuvant chemotherapy: a multicenter randomized controlled trial. J Clin Oncol. 2007;25:4396–404.
35. De Backer IC, Vreugdenhil G, Nijziel MR, Kester AD, van Breda E, Schep G. Long-term follow-up after cancer rehabilitation using high-intensity resistance training: persistent improvement of physical performance and quality of life. Br J Cancer. 2008;99(1):30–6.
36. DeBacker IC, Schep G, Backx FJ, Vreugdenhil G, Kuipers H. Resistance training in cancer survivors: a systematic review. Int J Sports Med. 2009;30(10):703–12.
37. Courneya KS, Mackey JR, McKenzie DC. Exercise for breast cancer survivors: research evidence and clinical guidelines. Phys Sportsmed. 2002;30(8):33–42.
38. 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. Roundtable on exercise guidelines for cancer survivors. Med Sci Sports Exerc. 2010;42(7):1409–26.