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REVIEW

The Effects of Physical Activity on Breast Cancer Survivors after Diagnosis

Jeongseon Kim, Wook Jin Choi, Seung Hwa Jeong

Molecular Epidemiology Branch, Division of Cancer Epidemiology and Prevention, Research Institute, National Cancer Center, Goyang, Korea

Adverse health outcomes are often seen in breast cancer survivors due to prolonged treatment with side effects such as loss of energy and lack of physical strength. Physical activity (PA) has been proposed as an adequate intervention for women with breast cancer. Therefore, this review summarizes the effects of physical activity on breast cancer survivors after diagnosis. We searched electronic databases including PubMed, Medline, Embase, and Google Scholar for articles published between January 1980 and May 2013. We included a variety of studies such as randomized controlled trials, pilot studies, and clinical trials. We reviewed these studies for three major outcomes: changes in breast cancer mortality, physiological functions, and metabolic biomarkers. Of 127 studies, 33 studies were selected as eligible studies. These studies included physical activities of varying type, duration, frequency, and intensity (e.g., aerobic and resistance training) and examined changes in three major outcomes among breast cancer survivors. Many of the studies suggest that breast cancer survivors benefit from engaging in physical activity, but some studies were limited in their ability to provide adequate evidence due to relatively small sample sizes, short intervention periods, or high attrition. Based on epidemiological evidence, recent studies demonstrated that those breast cancer survivors who engaged in physical activity significantly lowered their risk of breast cancer mortality and improved their physiological and immune functions. Some studies demonstrated changes in metabolic biomarkers such as insulin and insulin-like growth factors. However, further investigation is required to support these findings because these results are not consistent. **(J Cancer Prev 2013;18:193-200)**

Key Words: Breast cancer, Physical activity, Mortality, Physiological function, Metabolic biomarker

INTRODUCTION

Breast cancer is the leading cause of death in females worldwide, accounting for 23% of total cancer cases and 14% of total deaths in 2008.[1] Approximately 89% of women with breast cancer survive at least 5 years after treatment, but side effects can persist for months to years.[2] Due to prolonged treatment, breast cancer survivors may experience loss of muscular strength in their cardiac and skeletal muscles and reduced mobility from abnormalities in their metabolic systems.[3] However, increasing muscular strength may prevent antioxidant loss and improve daily activity among cancer survivors.[4,5] In particular, the use of large skeletal muscle groups enhances oxidative capacity and improves oxygen uptake during aerobic exercise, while resistance exercise restores muscle mass and increases resting metabolic rate.[6,7]

A sedentary lifestyle may increase cancer risk through several mechanisms such as increased insulin-resistance and inflammation and decreased immune system functioning.[8] In particular, insulin and insulin-like growth factor-I (IGF-1) may play significant roles in the development of breast cancer.[9,10] Early-stage breast cancer survivors with elevated fasting insulin may be at increased risk of mortality due to poor prognosis.[11] Overall, physical activity (PA) may reduce the risk of breast cancer by

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Correspondence to: Jeongseon Kim
Molecular Epidemiology Branch, Division of Cancer Epidemiology and Prevention, Research Institute, National Cancer Center, 323 Ilsan-ro, Ilsandong-gu, Goyang 410-769, Korea
Tel: +82-31-920-2570, Fax: +82-31-920-2579, E-mail: jskim@ncc.re.kr

reducing metabolic hormones (e.g., insulin-resistance) and systemic inflammation (e.g., C-reactive protein) and increasing immune cell components (e.g., T-helper cells).[4,8,12] The purpose of this review is to provide useful information regarding the benefits of PA for breast cancer survivors in changing mortality, physiological functions, and metabolic biomarkers after diagnosis.

METHODS

1. Study selection

We searched PubMed, Medline, Embase, and Google Scholar for articles published between January 1980 and May 2013. The studies were independently reviewed by three investigators (JK, WJC, and SHJ) and included a variety of studies such as randomized controlled trials, pilot studies, and clinical trials. Our search terms included "breast cancer after diagnosis (title/abstract)," "physical activity (title/abstract)," and "aerobic or resistance training (abstract)." We searched for three major outcomes: (1) breast cancer mortality, (2) physiological function, and (3) metabolic biomarkers. The term "mortality" was also searched as "breast cancer death"; the second term "physiological functions" was also searched as "cardiorespiratory function and muscular strength"; and the third term "metabolic biomarkers" was also searched as "immune system," "metabolic hormones," and "blood pressure and heart rate."

RESULTS

A total of 127 studies were identified through electronic databases. Of these studies, 10 were excluded due to duplication of articles. Of the remaining 117 studies, 33 articles were excluded because they studied a (1) cancer-type other than breast cancer, or found a (2) lack of association between PA and breast cancer. Of the remaining 84 studies, 51 full-text articles were excluded due to study protocol, including (1) no PA intervention, (2) no control group, (3) lack of 3 major outcomes, or (4) subjects engaged in PA before diagnosis. After careful review, a total of 33 studies satisfied the selection criteria and were included in this review. These articles studied breast cancer mortality (n=8), physiological functions (n=15), and metabolic biomarkers (n=10). Fig. 1 describes the selection of eligible studies. The selected studies included PA interventions of varying duration, type, frequency, and intensity. The most common types of PA were aerobic exercise, resistance training, or combination of both exercises. Breast cancer mortality was measured by the multivariable hazard ratio (HR) or relative risk (RR) at a 95% confidence interval (95% CI). The amount of PA was expressed as metabolic equivalents (METs) (defined as 1 MET=3.5 ml $O_2 \cdot kg^{-1} \cdot min^{-1}$) and categorized into 3 types; low (<3 MET), moderate (3-6 MET), and vigorous intensity (>6 MET).[13] A p-value of <0.05 was considered to be a statistically significant change in mortality, physiological function, and metabolic biomarkers among the exercise group compared with the control group.

Table 1 describes the effects of PA on breast cancer

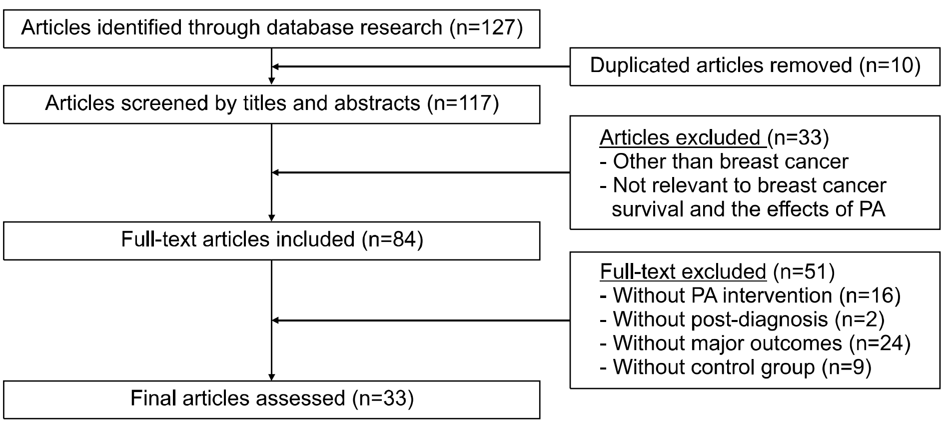

Fig. 1. Flow diagram for selection of eligible studies.

Table 1. The effects of physical activity on breast cancer mortality risk

Author (yr)	Study design (yr)	N	Follow-up (yr)	Age (mean)	PA type	MET (hr/wk)	Mortality (HR/RR; 95% CI)
Holmes et al.[14] (2005)	NHS (1984-1998)	2,987	8	42.5	•Choice of 8 Activities - Walking outdoors - Jogging (>10 min/mi) - Running (≤10 min/mi) - Bicycling (stationary) - Swimming laps - Tennis - Aerobics - Squash/racquetball	<3 (reference) a) 3-8.9 b) 9.0-14.9 c) 15.0-23.9 d) ≥24.0	RR (Ptrend<0.004) a) 0.80; 0.60-1.06 b) 0.50; 0.31-0.82 c) 0.56; 0.38-0.84 d) 0.60; 0.40-0.89
Holick et al.[15] (2008)	CWLS (1988-2001)	4,482	5.6	54	•Recreational PA - Walking outdoors - Running (≥10 min/mi) - Lap swimming - Sports - Calisthenics - Aerobic recreation	<2.8 (reference) a) 2.8-7.9 b) 8.0-20.9 c) ≥21.0	HR (Ptrend=0.050) a) 0.66; 0.39-1.13 b) 0.61; 0.36-1.05 c) 0.49; 0.27-0.89
Irwin et al.[16] (2008)	HEAL (1995-1998)	933	6	55	•All types of PA - Recreational - Occupational - Household	0 (reference) a) >0-8.9 b) ≥9	HR (Ptrend=0.460) a) 0.72; 0.28-1.85 b) 0.65; 0.23-1.87
Sternfeld et al.[20] (2009)	LACE (1997-2000)	1,970	7.25	48.5	•PA questionnaire - Occupational - Non-work routine - Recreational - Transportation	<29 (reference) a) 29≤44 b) 44≤62 c) ≥62	HR (Ptrend=0.410) a) 1.01; 0.57-1.78 b) 0.70; 0.38-1.29 c) 0.87; 0.48-1.59
Bertram et al.[18] (2011)	WHEL (1995-2000)	2,361	7.1	48	•Meeting PA guidelines	No→no (reference) a) No→yes b) Yes→no c) Yes→yes	HR a) 1.44; 1.02-2.03 (Ptrend=0.040) b) 1.22; 0.81-1.83 (Ptrend=0.340) c) 0.93; 0.70-1.24 (Ptrend=0.620)
Irwin et al.[17] (2011)	WHI (1993-1998)	4,643	3/6	63.6	•Walking •Recreational PA	0 (reference) a) >0-3 b) 3.1-8.9 c) 9+	HR (Ptrend=0.049) a) 0.30; 0.09-0.99 b) 0.77; 0.43-1.38 c) 0.61; 0.35-0.99
Chen et al.[21] (2011)	SBCSS (2002-2006)	4,826	4.3	53.5	•Walking (52%) •Gymnastics (14%) •Body building (7%) •Qigong/Tai Chi (5%)	0 (reference) a) 6 month (8.3 MET) b) 18 month (15.4 MET) c) 36 month (15.8 MET)	HR (Ptrend=0.050) a) 0.91; 0.75-1.11 b) 0.71; 0.57-0.90 c) 0.60; 0.47-0.76
Beasley et al.[19] (2012)	ABCPP (pooling project)	13,302	1.9	50	•2008 PA guidelines at least 2.5-h (10 MET-h/week)	<10 (reference) ≥10 MET	HR: 0.75; 0.65-0.85

NHS, the nurses' health study; CWLS, the collaborative women's longevity study; HEAL, the health, eating, activity, and lifestyle study; LACE, the life after cancer epidemiology study; WHEL, the women's healthy eating and living study; WHI, the women's health initiative; SBCSS, the shanghai breast cancer survival study; ABCPP, the after breast cancer pooling project.

mortality risk. The most common exercise was walking at moderate intensity, combined with occupational and recreational activities. The survivors who engaged in PA higher than 3 MET-h/week lowered their risk of breast cancer mortality by 26 to 40% and 35 to 49% compared with those engaged in PA less than 3 MET-h/week.[14,15] Those engaged in walking for 3 to 5 hrs per week at a moderate pace (2-2.9 mph) experienced the greatest

Table 2. The effects of physical activity on physiological functions

Author (yr)	Follow-up/ Total N	Age (Mean±SD)	Duration (wk)	Intervention (frequency/wk)	Key outcome (P<0.05)
Segal et al.[24] (2001)	99/123	50.9 (8.7)	26	•Self-directed/home-based (5×) •Supervised - Fitness center (3×) - Home-based (2×)	•No significant differences in aerobic capacity (VO_2 max)
Burnham et al.[5] (2002)	18/18	53.6 (8.6)	10	•Supervised (3×) - Treadmill walking - Stationary bicycles - Stair-climbing machines	•VO_2 max↑ (P<0.001) •Flexibility: Sit and reach (cm)↑ (P<0.002)
Courneya et al.[25] (2003)	50/53	59 (6)	15	•Cycle ergometers (3×)	•VO_2 peak↑ (P<0.001)
Pinto et al.[35] (2003)	21/24	52.5 (6.8)	12	•Supervised cardiovascular fitness (3×) - Treadmill walking - Arm and leg ergometers - Arm cycling - Stationary cycling - Rowing	•Peak SBP↓ (P≤0.050) •SBP, DBP, HR at 75 W↓ (P≤0.010; P<0.050; P<0.050)
Thorsen et al.[22] (2005)	111/139	39.1 (8.4)	14	•Supervised and home-based flexibility training - Walking - Muscle-strengthening (>2×; >30 min)	•VO_2 max↑ (P<0.010)
Sprod et al.[29] (2005)	8/12	54.7 (3.6)	8	•Supervised walking stick (2×; 1×20 min)	•Shoulder function↑ - Bench press↑ (P=0.046) - Lat pull down↑ (P=0.013)
Cho et al.[30] (2006)	55/65	49.1 (7.7)	10	•Group and home-based - Aerobic activity - Stretching (2×; 1×90 min)	•Shoulder of joint↑ - Extension↑ (P=0.000) - Abduction↑ (P=0.011) - External/internal rotation ↑ (P=0.006; P=0.000)
Kim et al.[26] (2006)	41/74	51.3 (6.7)	8	•Supervised (3×) - Walking - Cycling - Jogging - Treadmill running	•VO_2 peak↑ (P=0.000) •HRR↓ (P=0.030) •SBP resting↓ (P=0.040) •SBP maximum↓ (P=0.020)
Battaglini et al.[33] (2007)	20/20	57 (19.5)	21	•Supervised cardiovascular, resistance, flexibility training (2×; 1×<60 min)	•Overall muscle strength↑ (P=0.025)
Rogers et al.[27] (2009)	39/41	53 (9)	12	•The BEAT cancer program (1-3× supervised, 2, 3, or 5×home-based)	•Left-handed grip↑ (P=0.030) •Back/leg muscle extensor strength↑ (P=0.017)
Schmitz et al.[28] (2009)	139/141	56.5 (8.5)	48	•Weight lifting (2×; 1×90 min)	•Upper and lower-body strength↑ (P<0.001)
Twiss et al.[31] (2009)	209/223	58.7 (7.5)	96	•Weight training (2×; 30-45 min)	•Hip flexion↑ (P=0.011) •Hip extension↑ (P=0.000) •Knee flexion↑ (P<0.000) •Knee extension↑ (P=0.001) •Wrist flexion↑ (P=0.031) •Balance↑ (P=0.010)
LaStayo et al.[34] (2011)	40/49	74 (6)	12	•The RENEW exercise (3×) - Eccentric stepper	•Muscle size↑ (P=0.001)
Kalsatou et al.[32] (2011)	27/27	56.8 (4.2)	24	•Traditional Greek dance (3×; 1×60 min)	•Right and left handed-grip strength↑ (P=0.001) •Left-arm volume↓ (P=0.028)
Brdareski et al.[23] (2012)	18/18	52.1 (7.4)	3	•Bicycle ergometers (2×)	•VO_2 max↑ (P<0.002) •% VO_2 max↑ (P<0.002)

VO_2 max, maximum oxygen uptake; VO_2 peak, peak oxygen consumption; HR, heart rate; HRR, heart rate at resting; SBP, systolic blood pressure; DBP, diastolic blood pressure; BEAT, the better exercise adherence after treatment for cancer; RENEW, the resistance exercise via negative eccentrically-induced work.

health benefits.[14] Similarly, those engaged in PA higher than 9 MET-h/week for 2 years lowered their risk of mortality by 67% compared with women at 0 MET-h/week.[16] In the Women's Health Initiative study (WHI), survivors who engaged in walking at moderate to vigorous intensity (3 to 9+MET-h/week) lowered their risk of mortality by 39%.[17] Early-stage breast cancer survivors who engaged in PA for one year decreased their risk of mortality by 40%. Those who engaged in PA at least 10 MET-h/week for 18 to 48 months lowered mortality by 25% compared with those who did not meet this guideline.[18,19] Indeed, higher levels of PA at moderate intensity were associated with reduced breast cancer mortality.[20] This epidemiologic evidence suggests that survivors engaging in PA higher than 8.3 MET-h/week may experience health benefits that improve their chances of survival.[21] Overall, a significant dose-response relationship was found between breast cancer and mortality, exercise duration, and MET scores.[21]

Table 2 describes the effects of PA on physiological functions. The studies found major changes in cardio-respiratory functions such as increased oxygen uptake and decreased blood pressure in the exercise group. Three studies reported significant increases in maximum oxygen uptake (VO_2 max), including an increase of 18.6, 23, and 11.8% from aerobic training.[5,22,23] However, Segal et al.[24] (2001) found no significant improvement in oxygen uptake from self-directed or supervised exercise training. Two studies reported a significant increase of peak oxygen consumption (VO_2 peak) by 17.4% and 8.3% from aerobic training.[25,26] The studies observed major changes in muscular strength, including increases in upper-lower body strength, hand grip, and flexibility. Two studies reported significant increases in upper-lower body strength (e.g., bench and leg press) due to weight training.[27,28] Two studies reported significant increases in shoulder function following cancer treatment.[29,30] For example, using a walking stick for 8 weeks significantly increased muscular endurance and upper-body strength.[29] Early-stage breast cancer survivors with rehabilitation significantly increased the range of motion (ROM) in their shoulder joints by 11.5%.[30] Two studies reported significant increases in lower-body flexibility (e.g., sit and reach).[5,31] In particular, survivors who engaged in weight training for 24 months significantly increased hip flexibility and extension by 9.5% and 28.5%, wrist flexibility by 50.0% and 19.4%, and knee flexibility by 21.1% and 11.6%.[31] Two studies reported significant increases in right or left- handed grip strength.[27,32] Survivors who engaged in traditional Greek dance significantly increased both right and left-handed grip.[32] One study reported significant increases in overall muscle strength from combined aerobic and resistance training.[33] Older cancer survivors who engaged in resistance training significantly increased muscle size by 4%.[34] The major changes in blood systems were decreases in heart rate and blood pressure. Two studies reported a significant decrease in resting systolic blood pressure due to aerobic training.[26,35]

Table 3 describes the effects of PA on metabolic biomarkers. In the immune system, natural killer cells (NKCA), the composition of leucocyte sub-populations (e.g., granulocytes, phagocytosis activity, and spontaneous [^{3}H] thymidine), and T-helper lymphocytes (e.g., $CD4^+CD9^+$) were significantly increased through aerobic training (e.g., cycle ergometers).[36-38] However, Nieman et al.[39] (1995) found no significant improvement in NKCA from supervised exercise for 8 weeks possibly due to the study's relatively small sample size and its short intervention period. In addition to the changes in immune functions, several studies reported changes in insulin-like growth factors. Fairey et al.[40] (2003) found a significant decrease of IGF-I and an increase of IGFBP-3 in the exercise group (e.g., cycle ergometers), while Irwin et al.[41] (2009) found significant decreases in both IGF-1 and IGFBP-3 in the exercise group (e.g., brisk walking). Only Schmitz et al.[42] (2005) found a decrease of IGF-II among survivors who participated in weight training for 6 months. At the same time, changes in insulin levels were not statistically significant among survivors who engaged in either aerobic or weight training.[11,40-42] Chinese traditional exercise, known as Tai Chi Chuan (TCC), may result in changes of metabolic biomarkers. The changes between IGF-I and IGFBP-I were inversely correlated in the TCC group; as IGF-1 decreased, IGFBP-1 increased, while IGF-1 and IFN-γ were positively correlated; as IGF-1 increased, IFN-γ increased.[43] Furthermore, the decrease of C-reac-

Table 3. The effects of physical activity on metabolic biomarkers

Author (yr)	Follow-up/ Total N	Age (Mean±SD)	Duration (wk)	Intervention (Frequency/wk)	Key outcome (P<0.05)
Nieman et al.[39] (1995)	12/16	53.5 (-)	8	•Supervised aerobic and weight training (3×; 1×60 min)	•No significant changes in NKCA
Peters et al.[36] (1995)	24/24	49.3 (6.4)	28	•Bicycle training (5×; 1×30−40 min)	•% of lymphocytes↓ (P<0.050) •% granulocytes↑ (P<0.050) •Resting level of monocytes↓ (P<0.050) •Phagocytosis (%, PI) vs. RDSE↑ (P<0.050)
Fairey et al.[40] (2003)	52/53	59 (6)	15	•Cycle ergometers (3×)	•IGF-1↓ (P=0.045) •IGFBP-3↑ (P=0.021)
Fairey et al.[37] (2005)	52/53	59 (6)	15	•Cycle ergometers (3×)	•NKCA↑ - Total lytic units (P=0.035) •Lymphocyte proliferation↑ (Spontaneous [^{3}H]thymidine) (P=0.007)
Fairey et al.[44] (2005)	52/53	59 (6)	15	•Cycle ergometers (3×)	•No significant changes in CRP (P=0.060)
Hutnick et al.[38] (2005)	36/49	48.5 (10.6)	24	•Trainer with 1:1 session - Aerobic activity - Stretching (3×; 1×40−90 min)	•% $CD4^+CD69^+$↑ (P=0.050) •Level of tritiated thymidine↑ (counts/min P=0.050)
Schmitz et al.[42] (2005)	69/85	53 (8.1)	24	•Weight training (2×)	•IGF-II↓ (P=0.020)
Ligibel et al.[11] (2008)	82/101	52.5 (9)	16	•Strength training (2×; 1×50 min) •Home-based (1×90 min)	•Insulin-resistance↑ (P=0.050) •Insulin↓ (P=0.070) •Glucose↔ (P=0.470) •HOMA↓ (P=0.090)
Irwin et al.[41] (2009)	68/75	56 (8.6)	24	•Supervised aerobic training at local health club (3×) •Home-based (2×)	•Insulin↔ (P=0.089) •IGF-1↓ (P=0.026) •IGFBP-3↓ (P=0.006)
Janelsins et al.[43] (2011)	19/31	53 (8.6)	12	•TCC (3×; 1×60 min)	•IGF-1 (−) IGFBP-1 (P=0.001) •IGF-1 (+) IFN-γ (P=0.024) •IFN-γ (+) Insulin (P=0.055)

NKCA, NK cell cytotoxic activity; PI, phagocytotic index; RDSE, receptor destroying enzyme-treated sheep erythrocytes; IGF-1, IGF-II, insulin-like growth factor-I, II; IGFBP-1, 3, insulin-like growth factor biding protein-1, 3; CRP, C-reactive protein; HOMA, the homeostatic assessment model; TCC, Tai Chi Chuan; IFN-γ, Interferon-gamma; ↔, no changes; (−), negative/inverse correlation; (+), positive correlation.

tive protein (CRP) was greater in exercise group compared with control group, but the changes were not statistically significant. [44]

DISCUSSION

Engaging in PA among breast cancer survivors was significantly associated with decreased mortality, increased physiological functions, and changes in metabolic biomarkers. The major health outcomes were the increased cardiorespiratory functions, muscular strength, and immune cell components. In particular, aerobic training was significantly associated with increasing cardiorespiratory functions such as improvement in maximum and peak oxygen uptake and decreased blood pressure. Resistance training was significantly associated with increasing muscular strength such as the increase of upper-lower body strength, hand grip, and flexibility. Moreover, the immune system was enhanced by the increase of NKCA and lymphocytes, but changes in metabolic biomarkers such as insulin-like growth factors were not clearly proven or consistent in previous studies. The differences in age or health status among survivors could explain these inconsistencies, but an additional research is necessary to find comprehensive mechanisms to explain about changes in metabolic biomarkers.

These studies found some limitations such as relatively small sample sizes, short intervention periods, and high attrition. To increase statistical power, future studies should utilize larger sample sizes and longer intervention periods to examine greater health outcomes among survivors. During interventions, high attrition induced by recurrence of cancer, side-effects of treatment, or sudden death should be minimized to increase study quality. In addition, the intensity of PA may play a significant role in study designs, but the level of intensity was not consistently reported. Many studies recommended moderate intensity PA, while several studies recommended vigorous intensity PA. Thus, current studies do not provide conclusive evidence about which PA intensity is more beneficial to survivors.

Only a few studies have conducted research on the effects of PA on other cancer types such as prostate and colorectal cancer.[45-47] Similarly, these studies also demonstrated that PA is associated with reducing mortality and recurrence of cancer and improving overall health outcomes among survivors, but further investigation is necessary to compare these results with breast cancer studies.

Overall, survivors who engaged in higher amounts of PA (e.g., METs) had greater health benefits compared with those who were not engaged in PA. The studies suggested that survivors may have the greatest health benefits from walking at moderate intensity compared with other types of PA (e.g., recreational, sports, or occupational activities). The increased breast cancer mortality risk was higher among survivors with sedentary life-style compared with those who were physically active. Therefore, the studies encouraged survivors to engage in PA to reduce possible side-effects or poor prognosis of breast cancer after diagnosis.

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