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ORIGINAL ARTICLE

Effect of a 12-week walking exercise program on body composition and immune cell count in patients with breast cancer who are undergoing chemotherapy

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Ji Jeong Kim, Yun A Shin and Min Hwa Suk. Effect of a 12-week walking exercise program on body composition and immune cell count in patients with breast cancer who are undergoing chemotherapy. *JENB*., Vol. 19, No. 3, pp.255-262, 2015 **[Purpose]** The purpose of this study was to examine the effect of a 12-week walking exercise program on body composition and immune cell count in patients with breast cancer who are undergoing chemotherapy. **[Methods]** Twenty patients (age, 47.8 ± 3.12) participated in the study. Body composition (weight, body mass index, muscle weight, body fat mass, and percent body fat) and the cell counts for immune cells (white blood corpuscles, lymphocytes, helper T cells, cytotoxic T cells, natural killer cells, and natural killer T cells) were measured before and after the 12-week walking exercise program. SPSS 17.0 statistical software was used. The two-way repeated ANOVA with post hoc was used to determine the difference between time and interaction. **[Results]** There were significant reductions in the weight ($p < .05$), BMI ($p < .01$), and percent body fat ($p < .05$) after the 12-week walking exercise program. However, the immune cell counts did not change significantly. **[Conclusion]** These results indicated that the 12-week walking exercise program had an effect on the balances among weight, BMI and percent body fat in patients with breast cancer.
[Key words] walking exercise program, body composition, immune cell, breast cancer

INTRODUCTION

Based on the 2012 National Statistics of the Korean Ministry of Health and Welfare, malignant neoplasms ranked first among all causes of mortality, with 32.1% of all deaths resulting from cancer [1,2]. Among women specifically, breast cancer accounted for 25.5% of the total cancer incidence; it is the most prevalent type of cancer, followed by thyroid cancer. The increasing incidence rate of breast cancer has been attributed to multiple factors, including: younger age at menarche; older age at menopause, higher trend to unmarried or late marriage status, avoidance of breast feeding, adolescent obesity, adult obesity, stress, lack of exercise, and unhealthy eating habits [3]. Although the survival rate for breast cancer is very high compared to other cancers, breast cancer patients encounter many health-related difficulties associated to the various treatments implemented after diagnosis, including surgery, chemotherapy, radiotherapy, and hormone therapy [4]. In particular, chemotherapy and radiotherapy treatmentshave been associated with cardiopulmonary complications, ranging from heart palpitations and shortness of breath to general decreases in cardiorespiratory function, muscle strength and lung function, lower overall stamina, and pain which, together, often cause emotional stress and negative psychological effects [5,6]. Unlike other cancers, breast cancer has been associated with prevalence for weight gain due to an increase in fat retention [7-9]. The obesity resulting from this increased fat retention has been correlated to an accelerated recurrence of cancer and decreased survival rate [10], as well as being a risk factor for other comorbidities, including cardiovascular disease [11].

In addition to the negative effects of breast cancer and breast cancer treatment on physical status and body composition, impairment and damage to the immune defense mechanisms are also common outcomes of radiotherapy and chemotherapy [12,13]. Although decreased immune function in cancer patients may be due to the cancer itself, most commonly, leukopenia is a secondary outcome of radiotherapy and chemotherapy

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treatments that damage hematopoietic and secretory tissues. As a result, lymphocytic disorders, due to degeneration and death of lymphocytes, can occur over the course of treatment. Furthermore, although anticancer drug induce necrosis, as well as apoptosis, of tumor cells, these effects are non-specific in that these drugs attack not only quickly proliferating cancer cells but also active normal cells, such as follicular cells and epithelial cells or blood cells of intestinal membranes which, ultimately, rapidly decreasesimmune function as a main side effect [14].

Epidemiological studies have provided evidence of a preventative effect of exercise against certain cancers, as well as on ameliorating the outcomes of cancer therapy by reducing cancer-related side effects, such as loss of appetite, general fatigue, and lethargy, and improving therapeutic effects of drugs and, ultimately, survival rate [15,16]. In particular, studies have reported that treating obesity through regular physical activity lowers the risk for cancer, as well as lowering rates of cancer recurrence and cancer-related mortality [17-19]. Moreover, regular exercise of mild intensity has been shown to have a positive effect on the immune response [20,21] and to enhance adaptive immunity [22] through its promotion of cell-mediated immune responses [23] and antibody-mediated immune responses [24]. In animal models, exercise has been shown to stimulate activity of macrophage, natural killer (NK) cells, neutrophils, and cytokines, boosting the immune surveillance function of the body as a first-line host defense against cancer.

Unlike for other cancers, inconsistent results regarding the benefits of exercise on outcomes have been reported in patients with breast cancer. Holick *et al*. [25] reported that weekly exercise of mild intensity (i.e., > 5 METs) reduced the mortality rate of breast cancer patients by 15%. Pierce *et al*. [26] also reported that continuous aerobic exercise lowered the mortality rate of breast cancer patients [26]. However, there have also been reports indicating no correlation between exercise and mortality rate of breast cancer patients, and even higher recurrence of breast cancer and mortality rate in patients who exercised [27,28]. Therefore, the effects of exercise specifically in patients with breast cancer are unclear.

Although various studieshave reported positive effectsof exercise for increasing the quality of life of breast cancer patients undergoing rehabilitation following surgery through improvements in body functions, cardiovascular endurance, stamina, and depression [25,26,29], the effects of exercise on the immune system of patients undergoing chemotherapy have yet to be clarified. Treatment, care, and exercise prescriptions vary depending on the stages of cancer [30] and, therefore,the effects of exercise are also predicted to vary with the stage of cancer, with most studies, to date, having been conducted on patients after the end of chemotherapy or in cancer stages 1 or 2. Therefore, this study aimed to identify the effects of regular exercise on changes in body composition and immune cells according to stages of breast cancer in patients during active chemotherapy treatment.

METHODS

Subjects

The participants were 20 breast cancer patients (mean age, 47.8 ± 6.77 years) who received radiotherapy and/or chemotherapy. The patients with histologically confirmed stage I to III breast cancer along with radiotherapy and/or chemotherapy were eligible for inclusion in this study. Participants were excluded if they had cardiac disease, uncontrolled hypertension, thyroid disease, lymphatic complications, diabetes mellitus, or mental illness. Breast cancer stage was TNM classified as follows [31] : stage I, tumor size < 2 cm; stage II, 2 cm ≤ tumor size < 5 cm and cancer spread only to the nearby lymph nodes; and stage III, tumor size ≥5 cm and cancer spread to the lymph nodes. All participants had a sedentary lifestyle and had not exercised regularly in the last 6 months.

Experiment design

The participants provided written consent after being informed about the purpose of the experiment and experimental procedures as well as possible discomfort, positive effects, and adverse effects of the study. All data were collected before and after the 12-week walking exercise program.

Body composition

Weight, fat free mass, and percentage fat were measured using the Inbody 3.0 system (Biospace, Seoul, Korea). Body mass index (BMI) was calculated by dividing the weight by the square of the height (kg/m^2). Participants were not permitted to consume food and to exercise for 6 h before the measurement of body composition parameters.

Blood collection

Blood samples were collected after a 6-h water and food fast with participants in the seated position. Blood samples were collected into ethylenediaminetetraacetic acid (EDTA)-

treated vacutainers on ice at Y hospital. Immunocyte (white blood cell [WBC], lymphocyte, helper T cell, cytotoxic T cell, natural killer cell, and natural killer T cell) counts were analyzed using flow cytometry (FACScan, Becton Dickinson, CA, USA). Two separate fluorescence immunocytochemistry analyses were performed with 2 different isotopic control reagents. Non-specific reaction markers of immunocytes were < 5%, and the cell count was determined.

Exercise program

The walking exercise program was performed 5 consecutive days per week for 12 weeks. An exercise intensity of 4-60% heart rate reserve (HRR) was recommended [32]. The exercise intensity was set at 40-60% HRR for this study: the exercise intensity for weeks 1-6 was 40–50% HRR, whereas that for weeks 7-12 was 50-60% HRR. The participants had a warm-up and cool-down period of 5-10 min and walked for 30-40 min. The exercise physiologist supervised the exercise sessions and monitored the rating perceived exertion (RPE) and heart rate using Polar (Sports Tester, Finland). The exercise program was performed in the presence of the exercise physiologist so that adverse effects of radiotherapy and/or chemotherapy, such as electrolyte imbalance, dizziness, and dehydration, can be appeared during exercise. So cancer patients were exercised with exercise physiologist.

Statistical analysis

Data were analyzed using SPSS version 17.0 for windows (SPSS Inc., Chicago, IL, USA), and they are presented as mean ± standard deviation. A two-way repeated ANOVA with post-hoc test was used for group comparisons after walking exercise. The statistical significance level was set at $p < 0.05$.

RESULTS

Changes in body composition parameters in breast cancer patients

Table 1. Walking exercise program

<table>
<tr><th>Stage</th><th>Exercise</th><th colspan="2">Intensity</th><th>Duration</th><th>Frequency</th></tr>
<tr><td>Warm-up</td><td>Stand Stretch</td><td colspan="2"></td><td>5~10min</td><td rowspan="4">5d/ week</td></tr>
<tr><td rowspan="2">Main Exercise</td><td rowspan="2">Walking</td><td>1-6 wks</td><td>40~50% HRR</td><td>30min</td></tr>
<tr><td>7-12 wks</td><td>50~60% HRR</td><td>40min</td></tr>
<tr><td>Cool-down</td><td>Stand Stretch</td><td colspan="2"></td><td>5~10min</td></tr>
</table>

Table 2. Changes of body composition in breast cancer

Values	Pre (n = 20)	Post (n = 20)	Δ%	*p*
Weight (kg)	57.02 ± 6.12	56.34 ± 5.63	-1.20	0.023*
BMI (kg/m^2)	22.84 ± 2.42	22.48 ± 2.26	-1.58	0.002**
Fat mass (kg)	16.50 ± 4.18	15.76 ± 3.72	-4.49	0.011*
%Fat (%)	28.61 ± 4.64	27.73 ± 4.12	-3.08	0.047*
Muscle (kg)	32.00 ± 7.80	32.42 ± 7.08	1.32	0.137

* $p < 0.05$.

Table 3. Changes of immunocyte in breast cancer

Values	Pre (n = 20)	Post (n = 20)	Δ%	*p*
WBC (103 µl)	4.89 ± 2.23	5.00 ± 1.64	2.25	0.805
Lymphocyte (103 µl)	1.31 ± 0.57	1.18 ± 0.41	-9.93	0.349
Helper T cell (%)	36.76 ± 13.90	40.36 ± 17.03	9.8	0.160
Cytotoxic T cell (%)	19.22 ± 8.27	22.22 ± 6.60	15.61	0.149
Natural Killer cell (%)	16.48 ± 8.23	15.82 ± 9.36	-4.01	0.729
Natural Killer T cell (%)	10.40 ± 6.03	8.21 ± 5.19	-21.06	0.118

* $p < 0.05$.

The changes in body composition parameters after the 12-week walking exercise program are shown in Table 2. Weight ($p < 0.05$), BMI ($p < 0.01$), fat mass ($p < 0.05$), and %fat ($p < 0.05$) significantly decreased after the exercise program.

Changes in immunocyte counts in breast cancer patients

Table 3 shows the changes in immunocyte counts after the 12-week walking exercise program. The immunocyte counts before and after the 12-week program did not differ significantly.

Changes in body composition parameters according to breast cancer stage

Table 4 shows the exercise-induced changes in body composition parameters according to breast cancer stage. Weight ($p < 0.05$), BMI ($p < 0.01$), and fat mass ($p < 0.05$) values before and after the 12-week program were significantly different. However, these values in patients with different breast cancer stages did not differ significantly.

Changes in immunocyte counts according to breast cancer stage

Table 5 shows the exercise-induced changes in immunocyte counts according to breast cancer stage. However, there was no significant difference between time and cancer stage after the 12-week walking exercise program.

Table 4. Changes of body composition in breast cancer stage (mean ± SD)

Variables	Group	Pre	Post	F-values		
				G	T	G × T
Weight (kg)	stage 1 (n = 6)	55.17 ± 3.46	53.83 ± 2.18			
	stage 2 (n = 7)	57.83 ± 6.93	57.60 ± 6.47	.590	5.556*	1.747
	stage 3 (n = 7)	57.79 ± 7.47	57.49 ± 6.76			
BMI (kg/m^2)	stage 1 (n = 6)	22.74 ± 1.30	22.12 ± 1.05			
	stage 2 (n = 7)	23.24 ± 2.86	23.09 ± 2.73	.214	13.118**	2.263
	stage 3 (n = 7)	22.52 ± 2.93	22.29 ± 2.70			
Fat mass (kg)	stage 1 (n = 6)	15.57 ± 2.82	14.72 ± 1.77			
	stage 2 (n = 7)	16.41 ± 4.70	15.50 ± 4.79	.311	7.663*	.004
	stage 3 (n = 7)	17.36 ± 4.99	16.50 ± 4.29			
%Fat (%)	stage 1 (n = 6)	28.12 ± 4.25	27.27 ± 2.81			
	stage 2 (n = 7)	28.06 ± 5.40	27.67 ± 6.34	.163	1.473	.128
	stage 3 (n = 7)	29.59 ± 4.72	28.40 ± 4.00			
Muscle (kg)	stage 1 (n = 6)	34.02 ± 6.64	33.28 ± 5.37			
	stage 2 (n = 7)	29.40 ± 9.32	28.94 ± 9.77	.674	.552	2.955
	stage 3 (n = 7)	32.86 ± 7.51	33.50 ± 6.83			

G, group; T, time; G*T, group*time; * $p < .05$; ** $p < .01$ F-values in two-way repeated ANOVA, No marking means no significance.

Table 5. Changes of immunocyte in breast cancer stage (mean ± SD)

Variables	Group	Pre	Post	F-values		
				Groups (G)	Times (T)	G × T
WBC (10^3 µl)	stage 1 (n = 6)	5.25 ± 1.56	5.93 ± 1.43			
	stage 2 (n = 7)	4.53 ± 2.12	4.91 ± 2.01	.644	.093	.861
	stage 3 (n = 7)	4.91 ± 2.97	4.24 ± 1.09			
Lymphocyte (10^3 µl)	stage 1 (n = 6)	1.23 ± 0.42	1.08 ± 0.64			
	stage 2 (n = 7)	1.39 ± 0.31	1.36 ± 0.29	.611	.628	.092
	stage 3 (n = 7)	1.26 ± 0.85	1.10 ± 0.22			
Helper T cell (%)	stage 1 (n = 6)	35.82 ± 17.76	43.45 ± 16.99			
	stage 2 (n = 7)	35.83 ± 16.45	37.86 ± 20.79	.060	2.281	.552
	stage 3 (n = 7)	38.07 ± 8.20	39.81 ± 15.31			
Cytotoxic T cell (%)	stage 1 (n = 6)	18.85 ± 8.35	24.35 ± 9.44			
	stage 2 (n = 7)	17.53 ± 9.74	19.99 ± 6.11	.483	2.175	.355
	stage 3 (n = 7)	20.96 ± 7.75	22.20 ± 3.35			
Natural Killer cell (%)	stage 1 (n = 6)	19.28 ± 9.46	20.95 ± 9.84			
	stage 2 (n = 7)	16.54 ± 9.85	18.23 ± 8.49	.825	.042	.164
	stage 3 (n = 7)	13.86 ± 5.37	13.54 ± 8.59			
Natural Killer T cell (%)	stage 1 (n = 6)	13.27 ± 8.40	8.87 ± 5.85			
	stage 2 (n = 7)	9.41 ± 4.42	9.50 ± 6.49	.912	3.366	.981
	stage 3 (n = 7)	9.03 ± 4.90	5.94 ± 2.82			

F-values in two-way repeated ANOVA, No marking means no significance.

DISCUSSION

Loss of appetite is a common side effect of cancer treatments, such as surgery, chemotherapy and radiotherapy, which generally results in loss of weight in cancer patients after diagnosis. However, cancer of the female reproductive system has been strongly correlated to an increase in fatretention due to the effects of cancer on hormone regulation [9,33,34]. In cancer treatment, weight gain or loss is a factor that affects the prognosis, the quality of life [35,36] and, ultimately, the survival [37] of patients undergoing chemotherapy. As well, as weight control influences the risk for cancer development and recurrence, maintaining an appropriate body weight should be regarded as a preventative strategy for cancer and cancer recurrence [38,39].

In our study, weight, BMI, and fat mass were significantly reduced after a 12-week program of walking exercise. When we consider previous reports of either low weight loss [40] or weight gain [41,42] in breast cancer patients during chemotherapy, as well as the association between increased body weight and obesity on the incidence and recurrence of breast cancer [10], our findings provide clinically meaningful evidence for a positive effect of exercise training in breast cancer patients, even during chemotherapy.

Physiological indicators of immune function in cancer patients include neutrophil count, NK cell number, T-lymphocyte count, and cytokines regulator [43]. The prognosis of immune function in cancer patients can be predicted by histopathological findings of the stages of cancer [44,45]. Impairments in immune function of patients with advanced cancer have been shown to be related to decreases in the activity of T-lymphocyte and NK cells, and increased proliferation of subtype distribution within the venous blood of cancer tissues [46,47]. The interdependency between cancer stage and immune function has been well-described in studies evaluating changes in lymphocyte count and function at different stages of gastric cancer [48,49]. Although there were no discernable effects of stage 1 cancer on immune function, there was a gradual decline subsequently in stages 2 through 4, with a decrease in T-lymphocyte function in stage 2, in T- and B-lymphocyte function in stage 3, and an additional decrease in NK cell function in stage 4. Levels of lymphocyte and WBCs in patients with malignant tumors are predictive of outcomes, with high risk for recurrence and very low survival rate when levels fall below the normal range [50-52]. Chemotherapy and radiotherapy can further decrease immune function through their targeted effect on T- and B-lymphocyte cells, which play an important role in acquired immunity. Choi [53] reported a reduction in CD4 T cells during cancer treatment which made patients' recovery difficult. Furthermore, these treatment-related effects on the immune system reduced the ability of the body to fight against tumor cells, as well as viruses, by depleting NK cells which play an important role in the body's initial immune response [54]. Therefore, suppressing inflammation and/or improving immune function is a main objective of cancer treatment [28,55].

There has been increasing interest in exercise intervention to improve immune function in breast cancer patients [56,57]. The optimal timing of exercise has been reported to be 6 months post-mastectomy [58]. However, considering the possible benefits of exercise in ameliorating short-term complications post-mastectomy, including pain, swelling, fatigue, and reduced upper limb range of motion, beginning of exercise as early as possible post-mastectomy has been recommended to shorten the length of rehabilitation. Moreover, Zimmer *et al*. [59] have provided evidence that exercise started 24 hours after surgery can restore B-and T-lymphocyte cell counts to pre-operative values. McNeely *et al*. [60] have recommended that exercise be initiated 1 to 2 days post-surgery to maximize positive effect on the recovery of physiological functions. In our study protocol, the walking exercise program was implemented 1-week post-surgery, and we demonstrated improved outcomes on WBC, cytoxic T-cell (T8) and NK cell counts at the end of the 12-week program in patients with stage 1 and 2 breast cancer, although these positive effects on immune function did not reach statistical significance. Previous studies evaluating the effects of exercise on immune function in cancer patients have also reported equivocal results. Febbraio [61] reported that aerobic exercise, performed on a regular basis, improved immune function by activating lymphocyte and NK cells. Fairey *et al*. [28] reported that a 15-week exercise program significantly increased NK cells in patients with breast cancer. Conversely, Nieman *et al*. [62] did not identify any significant changes in the activity of immune T-lymphocyte cells with an 8-week exercise program. As well, Ladha *et al*. [63] and Galvao *et al*. [64] reported a decrease in lymphocyte count in breast cancer patients after exercise. Research by Feuerer *et al*. [65] also reported changes in immune cell count to vary depending on treatment methods, with an increase in immune cell count for patients who did not undergo chemotherapy whereas immune cell count decreased slightly for those undergoing chemotherapy. In our study, our 12-week program of exercise did not increase immune cell count and, in fact, T-lymphocyte and NK cell count decreased slightly. Although it is not possible to discern from our data if these effects can be attributed to chemotherapy, the fact that immune cell counts did not significantly decrease over the course of chemotherapy and radiotherapy treatment is indicative of a positive effect of our 12-week walking program.

We do propose that the absence of significant effects of exercise on the immune system may be due to the small size of our study group, with few patients in each stage of cancer. Therefore, further studies that compare the difference in the immune function by stages of breast cancer, using a larger sample size,are needed.

CONFLICTS OF INTEREST

The authors declare no potential conflicts of interest.

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