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Proper Exercise Decreases Plasma Carcinoembryonic Antigen Levels with the Improvement of Body Condition in Elderly Women

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Aging increases the risk of chronic diseases including cancers. Physical exercise has the beneficial effects for the elderly susceptible to the development of cancers, through maintaining a healthy body condition and improving the immune system. However, excessive or insufficient exercise might increase the risk for cancer. In the present study, we investigated what exercise frequency improves cancer-related biomarkers, such as carcinoembryonic antigen (CEA), alpha fetoprotein (AFP), red blood cell (RBC), and white blood cell (WBC), and the body composition of elderly women. Fifty-four females, aged 70 to 77 years, were divided into 4 groups: control, 1-day exercise (1E), 2-3-day exercise (2-3E), and 5-day exercise (5E) groups. The control group did not participate in any physical activity, while the subjects in the exercise groups underwent the exercise program for 12 weeks. As results, CEA was significantly decreased in the exercise groups, with the lowest values in 2-3E group. In contrast, AFP, RBC and WBC were not significantly changed. CEA is an oncofetal glycoprotein that is overexpressed in adenocarcinomas. Although the function of CEA has not been fully understood, CEA has been suggested to be involved in the release of pro-inflammatory cytokines via stimulating monocytes and macrophages. Moreover, body weight and body mass index were improved in the exercise groups, with the lowest levels in 5E group. Thus, we suggest that exercise for 2-3 days per week decreases the expression of CEA and improves body condition, without loading fatigue or stress, which may contribute to preventing cancer in the elderly women.

Keywords: alpha-fetoprotein; body weight; carcinoembryonic antigen; elderly; exercise
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Introduction

Aging increases the risk of chronic diseases, and can affect older peoples' independence, well being, and self-esteem. It is also the single huge risk factor for developing cancer. The International Agency for Research on Cancer estimates that 25% of cancer patients are caused by a sedentary lifestyle characterized by sitting or taking little exercise, as well as obesity (Campbell and McTiernan 2007). The overweight or obesity has been established as the epidemiological risk factor for many cancers, and its prevalence has risen constantly for the past several decades. The World Health Organization (2013) defines cancer as a generic term for a large group of diseases affecting any part of the body; however, one third of all cancer cases are preventable, such as quitting factors (smoking and alcohol use); avoiding factors (infectious agents, environmental pollution, occupational carcinogens, and ionizing radiation); and controlling factors (dietary modification and physical activity). In particular, it emphasizes that the body weight reduction from exercise will considerably reduce and prevent the cancer risk factors.

The physical activity for older people can help to maintain healthy body weight, enhance the muscle mass, and improve the immune system. According to the above theories, Rogers et al. (2008) and McTiernan (2008) showed that the modulation of energy balance by increasing physical activity has contributed to reduction of cancer risks through numerous epidemiological reviews. Friedenreich and Orenstein (2002) also suggested that

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active individuals have a relative low risk for colon cancer of ~ 0.5 to ~ 0.6, compared with sedentary persons. McTiernan et al. (2003) have shown that the cancer risk reduction via increased physical activity is the most effective in normal-weight people, compared with obese people.

When screening any cancer, the biomarkers in the blood that are widely investigated are carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) (Ganguly et al. 2003; Aarons et al. 2007; Ishizaka et al. 2008). CEA, an oncofetal glycoprotein, is overexpressed in adenocarcinomas, and thus it is widely used as a tumor marker (Hammarstrom 1999). Although the function of CEA has not been fully explained, CEA may be involved in the release of pro-inflammatory cytokines, probably by stimulating monocytes and macrophages (Ganguly et al. 2003) and in the release of endothelial adhesion molecules (Aarons et al. 2007). Thus, CEA may contribute to development of cancer. In addition, this action of CEA may also cause atherosclerosis and cardiovascular disease, as well as the metastasis of malignant cells (Piro et al. 2005; Steeg 2006). AFP is another tumor marker related to liver (Johnson 2001), and serum AFP levels were increased in all patients who had cancer cells (Stray-Pedersen et al. 2007). In addition, red blood cell (RBC) and white blood cell (WBC) may be considered to be cancer factors. Many researchers reported that lower levels of RBC are related to cancer, and estimated its level (Balducci 2003). Several prospective studies have also shown that increased WBC count within the clinically normal range is associated with increased risk of several chronic diseases, such as cardiovascular disease, diabetes mellitus, and cancer (Danesh et al. 1998; Schmidt et al. 1999; Erlinger et al. 2004).

Although a physical exercise is beneficial for the old person to maintain a healthy body condition and improve the immune system, there is little research that explores the proper exercise time or frequency for the elderly to improve cancer-related biomarkers. Therefore, in the present study, we investigated what exercise frequency improves cancer-related biomarkers and the body composition of elderly women.

Methods

Subjects

The study sample consisted of 60 elderly women, who were living in the Seoul Seniors Tower, elderly nursing home, between January and December 2012. The experimental design and the assessment were carried out by the faculty of Exercise Physiology and Prescription in Hanseo University after obtaining agreement (IRB: SYUIRB2014-11) by the Sahmyook University Ethical Committee. The inclusion criteria were 70 to 77 years, and independent in the Barthel index (Mahoney and Barthel 1965) and Performance-Oriented Mobility Assessment (POMA) index (Tinetti 1986). Among 60 participants, we excluded 3 subjects having a history of cancer, or being current or former smokers. We also excluded 3 subjects belonging to one of the following exclusion criteria: history of chronic liver disease or abnormal liver function defined as serum aspartate aminotransferase or alanine aminotransferase > 100 IU/L, and history of chronic renal disease, or abnormal kidney function defined as a serum creatinine concentration > 1.4 mg/dl (Lee et al. 2011). The remaining 54 women were included in this study. The subjects were randomly divided into 4 groups: control (n = 15), 1-day exercise (1E, n = 15), 2-3-day exercise (2-3E, n = 11), and 5-day exercise (5E, n = 13) groups. The physical characteristics of subjects are provided in Table 1.

Experimental Design

Prior to this study, we explained study procedures to the subjects, and all of subjects voluntarily signed an informed consent form. During this study, all subjects agreed to keep their daily activity patterns unchanged, outside of their participation in the study, and to keep their dietary habits. They were also instructed by the hospital dietitian throughout the study periods. Later in the day, the subjects kept a fasting state for 12 hours, and came back to the laboratory for baseline measurements, including blood tests and body composition. The subjects in three exercise groups were instructed to take part in the exercise program, and they performed it, according to their group assignment, for 12 weeks. The follow up testing included the same measures, as in the baseline testing.

Measurement Methods

Blood test: Blood was collected using BD vacutainer tube (Becton Dickinson, NJ, USA) by a medical technologist for assessment of the complete blood count. The samples were taken to the laboratory for analysis. The plasma CEA and AFP were measured by the Sandwich principle of quantitative chemiluminescence assay, with a Roche E170 (Roche Diagnostics GmbH, Mannheim, Germany).

Table 1. Physical characteristics of the subjects.

Groups*	Control (n = 15)	1E (n = 15)	2-3E (n = 11)	5E (n = 13)	Chi-square** *(P)*
Age (years)	70.53 ± 5.86	72.13 ± 4.65	73.36 ± 5.72	76.08 ± 7.01	6.183 (0.103)
Height (cm)	161.80 ± 2.02	163.68 ± 3.12	159.75 ± 0.90	158.29 ± 1.16	4.698 (0.195)
Weight (kg)	68.20 ± 5.53	68.92 ± 5.67	69.35 ± 3.41	69.12 ± 4.77	3.068 (0.381)
BMI (kg/m^2)	27.19 ± 3.42	27.28 ± 2.65	28.46 ± 1.42	27.84 ± 1.25	1.760 (0.624)

All values are expressed as mean ± standard deviation.
*1E, 2-3E, and 5E represent 1-day exercise, 2-3-day exercise, and 5-day exercise groups, respectively.
**Results of Kruskal-Wallis test by non-parametric tests.

The RBC and WBC counts were quantified by use of automated blood cell counter (ADVIA 120, Bayer, NY, USA).

Body composition: To measure body weight of the subjects, we used the bioelectrical impedance analysis (BIA) method with the InBody 320 Body Composition Analyzer (BioSpace, Seoul, Korea), and measured height by use of the BMS 330 anthropometer (BioSpace, Seoul, Korea). In this study, the electrodes used were made of stainless steel, and electrical interfaces were created as the subject stood upright, while gripping hand electrodes, and stepping onto foot electrodes. Then we calculated the body mass index, through the weight in kilograms, divided by the square of the height in meters.

Exercise program: Subjects in the control group participated only in the measurement procedures. They watched the health-related education video at the time when the subjects in the exercise group participated in the exercise program, and did not participate in any physical activity. The subjects involved in the 3 exercise groups took part in supervised progressive programs for 12 weeks (Table 2).

The exercise program consisted of three phases: first, the subjects began to warm up, with standing stretches for 10 min, throughout the 12-week program. In Table 2, standing stretches were performed before the workout phase, to protect the whole body joints. Second, the subjects performed a workout, including stationary cycling, treadmill walking, and then weight-bearing exercises. The aerobic exercise consisted of pedaling on a stationary bicycle, and walking on a treadmill. The subjects performed at 50% of heart rate reserve equation (0% grade) for 10 min, at first. Then, the aerobic exercise time increased 5 min every 4 weeks. The knee joint angle for pedaling of cycling was implemented at 120-150°, which was measured by a goniometer. The heart rates during exercising were continuously monitored, using Polar® heart rate monitors. The duration of each session was increased every 4 weeks as the exercise program progressed, according to the principle recommended by the American College of Sports Medicine (American College of Sports Medicine Position Stand 1998; American College of Sports Medicine 2006).

Prior to weight-bearing exercise, we checked the percentage of each subject's one repetition maximum or maximal voluntary contraction (MVC) for each exercise, which was used to determine the intensity. The exercise intensity of weight bearing was 60% MVC. The order of the weight bearing exercise was leg press, shoulder dumbbell, leg extension, leg curl, arm curl, back extension, abdominal flexion, and rotary torso, according to the recommendations of previous studies (American College of Sports Medicine Position Stand 1998; Vincent et al. 2002). The intensity and sets of weight-bearing exercise were not changed; but the number of repetitions performed for each exercise progressively increased by 2 repetitions per 4 weeks. Finally, subjects performed a cool down, with supine stretching for 10 min, throughout the 12-week.

Statistical analysis: Statistical analysis was conducted with SPSS software (ver 18.0; SPSS Inc., Chicago, IL). All data are reported as mean ± standard deviation. Before the comparison of measurements, including cancer-related biomarkers and body composition, the Kolmogorov-Smirnov test was performed to determine the normality of the distribution of the examined variables. The data from this study were not normally distributed, and thus, we analyzed the data using non-parametric tests. The detailed statistical methods were as follows: Firstly, the Kruskal-Wallis rank test was conducted, to identify differences among groups (i.e. control vs. 1E vs. 2-3E vs. 5E) at pre-time, and the delta values were analyzed to control the effects of pre-time on post-time score, using the formula: (variables at post time − variables at pre-time)/variables at pre-time × 100. The Kruskal-Wallis rank test was performed, to examine the differences among the 4 groups using the delta value, and then the Turkey test using ranks was conducted *post hoc*. The significance level for all analyses was set *a priori* at $P < 0.05$.

Results

Cancer-related biomakers

The data from 4 groups were analyzed for differences in pre- and post-exercise after 12 weeks (Table 3).

Table 3 displays the changes observed in the CEA and AFP of the 4 groups. The AFP values of the delta percent were not significantly different among the 4 groups. However, the CEA values of the delta percent were significantly different among the 4 groups ($\chi^2 = 8.204$; $P = 0.042$). In particular, the CEA concentrations were decreased in the 3 exercise groups, in which the CEA level of 2-3E group was lower than the other 2 exercise groups, in the *post hoc* results.

Blood corpuscles

The data from 4 groups were analyzed for differences before and after exercise, after 12 weeks (Table 4). Although the changes were observed in the WBC and RBC of the 4 groups after the experiment, the values of those delta percent were not significantly different among the 4 groups.

Body weight and body mass index

The data from 4 groups were analyzed for differences

Table 2. Exercise program for three exercise groups.

Items	Exercise modes	Exercise periods		
		1 ~ 4 weeks	5 ~ 8 weeks	9 ~ 12 weeks
Warm up	Standing stretch	10 min	10 min	10 min
Work out	Cycling	10 min	15 min	20 min
	Treadmill walking	10 min	15 min	20 min
	Weight bearing	10 reps × 2 sets	12 reps × 2 sets	15 reps × 2 sets
Cool down	Supine stretch	10 min	10 min	10 min

Table 3. Changes of CEA and AFP between pre and post among 4 groups.

Groups*	CEA (ng/ml)			AFP (ng/ml)		
	Pre	Post	Δ%	Pre	Post	Δ%
Control	2.06 ± 0.85	2.49 ± 1.48	20.88 ± 3.58[a]	2.69 ± 1.37	3.35 ± 1.87	24.54 ± 4.01
1E	2.68 ± 1.74	1.25 ± 0.50	−53.36 ± 4.62[b]	2.30 ± 0.61	2.73 ± 0.85	18.70 ± 5.35
2-3E	4.98 ± 1.06	2.03 ± 1.23	−59.24 ± 5.06[c]	2.98 ± 0.36	3.00 ± 1.79	0.68 ± 4.82
5E	2.78 ± 1.45	1.45 ± 1.03	−47.85 ± 4.78[b]	3.41 ± 0.91	3.25 ± 1.23	−2.70 ± 3.69
Chi-square**	7.020		8.204	4.154		4.779
P	0.071		0.042	0.103		0.189

All values are expressed as mean ± standard deviation.
*1E, 2-3E, and 5E represent 1-day exercise, 2-3-day exercise, and 5-day exercise groups, respectively.
**Results of Kruskal-Wallis test by non-parametric tests.
a,b, and c mean symbols of *post hoc* results.

Table 4. Changes of WBC and RBC between pre and post among 4 groups.

Groups*	WBC ($10^3/\mu l$)			RBC ($10^6/\mu l$)		
	Pre	Post	Δ%	Pre	Post	Δ%
Control	6.20 ± 0.27	6.51 ± 0.23	5.00 ± 0.88	4.89 ± 0.72	4.05 ± 0.09	−17.18 ± 0.42
1E	6.64 ± 0.41	6.75 ± 0.46	1.66 ± 0.65	4.02 ± 0.09	4.06 ± 0.07	1.00 ± 0.84
2-3E	7.57 ± 0.53	7.35 ± 0.24	−2.91 ± 0.21	3.98 ± 0.13	4.05 ± 0.12	1.76 ± 0.68
5E	6.47 ± 0.51	6.59 ± 0.56	1.86 ± 1.08	4.25 ± 0.12	4.56 ± 0.13	7.30 ± 1.87
Chi-square**	4.907		0.379	3.501		7.181
P	0.179		0.945	0.321		0.066

All values are expressed as mean ± standard deviation.
*1E, 2-3E, and 5E represent 1-day exercise, 2-3-day exercise, and 5-day exercise groups, respectively.
**Results of Kruskal-Wallis test by non-parametric tests.

Table 5. Changes of body weight and body mass index between pre and post among 4 groups.

Groups*	Body weight (kg)			Body mass index (kg/m^2)		
	Pre	Post	Δ%	Pre	Post	Δ%
Control	68.20 ± 5.53	69.72 ± 2.42	2.71 ± 3.01[a]	27.19 ± 3.42	28.30 ± 2.18	2.76 ± 1.58[a]
1E	68.92 ± 5.67	67.68 ± 3.59	−1.93 ± 2.71[b]	27.28 ± 2.65	26.30 ± 2.49	−1.94 ± 2.11[b]
2-3E	69.35 ± 3.41	66.55 ± 3.83	−4.74 ± 2.64[c]	28.46 ± 1.42	27.61 ± 2.60	−4.87 ± 2.09[c]
5E	69.12 ± 4.77	63.92 ± 2.41	−8.80 ± 1.48[d]	27.84 ± 1.25	25.77 ± 2.68	−9.29 ± 2.72[d]
Chi-square**	3.068		8.827	1.760		9.698
P	0.381		0.032	0.624		0.021

All values are expressed as mean ± standard deviation.
*1E, 2-3E, and 5E represent 1-day exercise, 2-3-day exercise, and 5-day exercise groups, respectively.
**Results of Kruskal-Wallis test by non-parametric tests.
a, b, c, and d mean symbols of *post hoc* results.

in pre- and post-exercise after 12 weeks (Table 5). The baseline characteristics of the subjects with full data at baseline and follow-up examinations are summarized in Table 1. No differences were observed in the baseline characteristics among groups, indicating homogeneity in anthropometric characteristics.

Table 5 displays the changes observed in the body weight of the 4 groups. The body weight values of the delta percent were significantly different among the 4 groups ($\chi^2 = 8.827$; $P = 0.032$). In particular, the body weights were decreased in the 3 exercise groups, in which the body weight level of 5E group was lower than the other 2 exercise groups, in the *post hoc* results. Similar to the changes of body weight, the values of body mass index were significantly decreased after 12 weeks ($\chi^2 = 9.698$; $P = 0.021$).

Discussion

In the present study, we evaluated the effect of 12-week exercise program on the expression of cancer-related biomarkers and body composition in elderly women. The main finding of this study is that exercise for 12 weeks significantly decreased the CEA level, body weight and body mass index in elderly women. Moreover, 2-3 days of exercise allowed elderly women to reach a lower level than the other exercise groups. However, the body composition was conspicuously decreased in 5E group, after the experiment.

As shown in many previous researches including our results, a physical exercise has the beneficial effects for prevention of cancer and a healthy body condition. However, a threshold of activity was necessary because lower amounts of exercise were of no benefit (Lee et al. 1992). Kobayashi et al. (2013) suggested the high levels of moderate and vigorous physical activity during adolescence might be protective from breast cancer risk in both premenopausal and postmenopausal women. Other prospective studies have examined exercise levels and cancer. In an attempt to determine the amount of exercise that will reduce cancer incidence, an investigation by questionnaire of Harvard alumni suggested that more than 40,000 kcal of weekly energy expenditure were necessary to decrease the development of prostate cancer (Lee et al. 1992). This level of exercise would be comparable to walking or jogging more than 5.5 miles each day. Lauffer (1991) directly determined fitness levels by treadmill testing. Subjects were separated into five levels of fitness. Those in the lowest quintile of fitness had higher mortality rates due to cardiovascular disease and cancer, than individuals who were more fit, after an average 8-year follow-up. Thus, an emerging body of evidence suggests a strong inverse association between higher levels of fitness, or greater amounts of exercise, and cancer occurrence, or mortality (Winningham 1994). However, there are some discrepancies regarding exercise volume (intensity, time, frequency) for prevention of cancer. Many studies reported that exercise could inhibit cancer develop through enhancement of immunity, or promote cancer through suppression of immunity (Shephard et al. 1991; Newsholme and Parry-Billings 1994; Westerlind 2003).

The present results show that exercise program is associated with CEA and body composition. In fact, CEA is a molecule expressed in blood cells or tissues associated with cancer, and thus measurement of CEA is widely used in patient diagnosis or clinical management (Hammarstrom 1999). It is related to several degenerative conditions (Ruibal Morell 1992; Fukuda et al. 1998). Elevated CEA levels are associated with an increased risk of disease relapse (Carriquiry and Pineyro 1999). In particular, aging is a major factor in increasing the CEA level. Similarly, in this study, the levels of CEA and AFP, another tumor marker, in control group showed the tendency to increase after 12 weeks. On the other hand, the CEA in elderly women was significantly reduced by the exercise program after a 12-week period. Gerhardsson et al. (1988) suggested that greater exercise reduces stool transit time by decreasing local contact between colonic mucosa and fecal carcinogens in patients with colorectal carcinoma. They also reported that people with low physical activity levels during occupational and recreational periods had the greatest risk of colon cancer (Gerhardsson et al. 1988). Recently, Lee et al. (2011) reported that CEA concentration could be associated with metabolic disturbances and cardiovascular disease, as well as cancer. Moreover, they found a positive association between serum CEA and the prevalence of metabolic syndrome in a dose-response manner.

Aging may also be associated with the increased risk of cancer through decreasing immune function (Mazzeo 1994). In particular, aging-related decrease in immune function occurs in cellular immunity, such as decreased T-cells or interleukin-2 proteins derived from WBC. Actually, the elderly exercising regularly significantly improved T-cell function in comparison with sedentary control groups (Mazzeo 1994). From these studies, it can be speculated that the decrease in cancer risk via greater physical activity may be accomplished by attenuating immune senescence normally occurring with aging (Westerlind 2003). Recently, Hu and Lin (2012) suggested that exercise training can increase total hemoglobin and RBC mass, enhancing oxygen-carrying capacity. They suggested that exercise training improved the hematopoietic microenvironment. Similar to RBC, WBC is also associated with cancer (Erlinger et al. 2004). In particular, age-related immune decline has been observed to decrease WBC or RBC. Therefore, the maintenance of normal levels of WBC and RBC in the elderly is very important for a healthy life. In the present study, the exercise program did not significantly change the WBC and RBC in elderly women. However, the levels of RBC in elderly women of exercise groups remained stationary, whereas the level of RBC in control group showed the tendency to decrease.

With reduction of CEA, the 12-week exercise significantly decreased body weight and body mass index in elderly women. However, unlike the CEA, body weight and body mass index in 5E group were significantly lower than those in other groups. In other word, the 5-day exercise was more effective in decreasing body weight and body mass index, but the 2-3-day exercise was more effective in decreasing the plasma CEA. These results mean that a 5-day exercise per week regime was effective in reducing body weight and body mass index, but accumulated exercise-induced fatigue or stress in the elderly women. CEA is associated with exercise-induced fatigue or stress, to some extent. Leutholtz and Ripoll (1999) reported that the elderly recovered more slowly from working out than the young, and they had a slow rate of recovery. Namely, excessive training for old people destroyed their immune function (Nieman 1994; Westerlind 2003); finally, cancer-related factors could not be improved. Karacabey (2005) has suggested that the natural defense system of the organism needs to be strengthened to decrease the risk of disease, and to maintain good health, and that the increased body resistance to disease through the strengthening of the immune system could decrease the convalescence time, increase work efficiency, and improve sportive performance. Seruga et al. (2008) reported that the systemic effects of pro-inflammatory cytokines are associated with fatigue, depression and cognitive impairment, but physical activity decrease fatigue in patients with cancer by altering cytokine levels. From these studies, it can be inferred that the proper exercise without loading fatigue or stress can contribute to prevention of cancer in elderly women.

In conclusion, the 2-3-day exercise per week, combined with proper rest in the middle of the week, most effectively suppressed the expression of CEA, highly expressed in patients with cancer. In addition, the 2-3-day exercise significantly improved body weight and body mass index, though the 5-day exercise was most effective in improving body weight and body mass index. From these results, we suggest that the exercise program of 2-3 days per week is of more benefit to elderly women.

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Conflict of Interest

The authors declare no conflict of interest.

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