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**Research Article / Araştırma Makalesi**

# The effect of resistance exercise on quality of life and fatigue in patients with gynecological cancer

## *Jinekolojik kanserli hastalarda direnç egzersizinin yaşam kalitesi ve yorgunluk üzerine etkisi*

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**ABSTRACT**

**Objective**: It is known that the quality of life decreases and fatigue increases in cancer patients due to the disease and the effects of treatment. Regular exercise can significantly improve these complaints. The aim of this study is to investigate the effect of resistance exercises on quality of life and fatigue in patients with gynecological cancer.

**Materials and Methods:** Patients who completed gynecological cancer treatment were randomized to form the exercise group (n=80) and the control group (n=80). Quality of life and cancer-related fatigue were determined by means of Functional Assessment of Cancer Therapy-General and Functional Assessment of Chronic Illness Therapy-Fatigue, in order, as primary outcome measurements. Body mass index (BMI), body fat ratio, hand grip strength, hip and back extensor group muscle strength were determined as secondary outcome measurements.

**Results**: At the end of the study, significant improvements were observed in the quality of life ($p<0.001$) and fatigue ($p<0.001$), as well as body composition and strength values ($p<0.001$) in the exercise group compared to the control group. The levels of change in the values were more significant in the exercise group ($p<0.001$). A significant correlation was found between the changes in physical parameters (body fat ratio, BMI) and the changes in quality of life and fatigue levels ($p<0.001$).

**Conclusions:** It was revealed that resistance exercises could significantly reduce cancer-related fatigue and improve quality of life in patients with gynecological cancer. It can be concluded that resistance exercises can contribute to the treatment process and the patient's quality of life.

**Keywords:** *Gynecological cancer, fatigue, quality of life, resistance exercise, muscle strength*

**ÖZ**

**Amaç**: Kanserli hastalarda hastalığa ve medikal tedavinin etkilerine bağlı olarak yaşam kalitesinin düştüğü ve yorgunluğun arttığı bilinmektedir. Tedaviye düzenli egzersizin eklenmesiyle bu yakınmalarda anlamlı iyileşmeler olabilmektedir. Bu çalışmanın amacı jinekolojik kanserli hastalarda direnç egzersizlerinin yaşam kalitesi ve yorgunluk üzerindeki etkisini araştırmaktır.

**Gereç ve yöntemler:** Jinekolojik kanser tedavisini tamamlamış hastalar egzersiz grubu (n=80) ve kontrol grubu (n=80) oluşturacak şekilde randomize edildi. Toplam 12 hafta süren çalışmanın başında ve sonunda yaşam kalitesi (Functional Assessment of Cancer Therapy-General) ve kanser ilişkili yorgunluk (Functional Assessment of Chronic Illness Therapy-Fatigue) primer ölçümler olarak belirlendi. Vücut kütle indeksi (VKİ), vücut yağ oranı, el kavrama kuvveti, kalça ve sırt ekstensör grup kas kuvvetleri ise sekonder ölçümler olarak belirlendi.

**Bulgular:** Çalışma sonunda egzersiz grubunda yaşam kalitesi ($p<0.001$) ve yorgunluk ($p<0.001$) ile vücut kompozisyonu ve kuvvet değerlerinde kontrol grubuna göre anlamlı iyileşmeler gözlendi ($p<0.001$). Çalışma sonundaki ve başındaki değerlerin değişim düzeyleri egzersiz grubunda kontrol grubuna göre daha belirgindi ($p<0.001$). Fiziksel parametrelerdeki (vücut yağ oranı, VKİ) değişim ile yaşam kalitesi ve yorgunluk düzeylerindeki değişim arasında anlamlı düzeyde bir ilişki saptandı ($p<0.001$).

**Sonuçlar:** Bu çalışmanın sonunda jinekolojik kanserli hastalarda direnç egzersizleri ile kanser ilişkili yorgunlukta anlamlı azalma ve yaşam kalitesinde anlamlı iyileşmeler olabileceği ortaya kondu. Buradan yola çıkarak direnç egzersizlerinin jinekolojik kanseri olan kişilerde tedavinin bir parçası olması halinde tedavi sürecine ve hastaya katkı sağlayabileceğini söylenebilir.

**Anahtar Sözcükler:** *Jinekolojik kanser, yorgunluk, yaşam kalitesi, direnç egzersizi, kas kuvveti*

## INTRODUCTION

Gynecological cancer is a term used to describe malignancies of the vulva, cervix, endometrium, tuba uterina, and ovaries and placenta, in the female urogenital system (1). Gynecological cancer diagnosis and treatment process may be associated with various physical, psychological and social difficulties (2). In recent years, in the light of promising developments in screening, early diagnosis and treatment of cancer, survival after diagnosis has been increasing (3). With increasing survival, the importance of both the effects of the primary disease and the side effects of treatment in

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cancer patients has begun to be emphasized more. Among these effects, anxiety, depression, sleep disorders, cancer-related fatigue, weight gain and low quality of life due to these factors, draw attention.

Cancer-related fatigue, which is frequently observed in patients; is defined as the subjective, physical, emotional and cognitive fatigue or feeling of exhaustion disproportionate to current physical activity, associated with cancer or cancer treatment, which can continue after treatment and affect the daily life of the person (4); which has been shown to be inversely related to quality of life (5).

Two pathological mechanisms are suggested for fatigue. While it has been suggested that there is a progressive failure in the transmission of motor neuron impulses in the central mechanism (6); contraction deterioration and decrease in muscle strength due to metabolic changes in the muscle are held responsible in the peripheral mechanism (7). Fatigue is also interrelated with low quality of life, low physical activity level, high body mass index (BMI) and other lifestyle factors (8). Today, the majority of patients diagnosed with endometrial and ovarian cancer lead a sedentary life without following physical activity and nutritional recommendations (9).

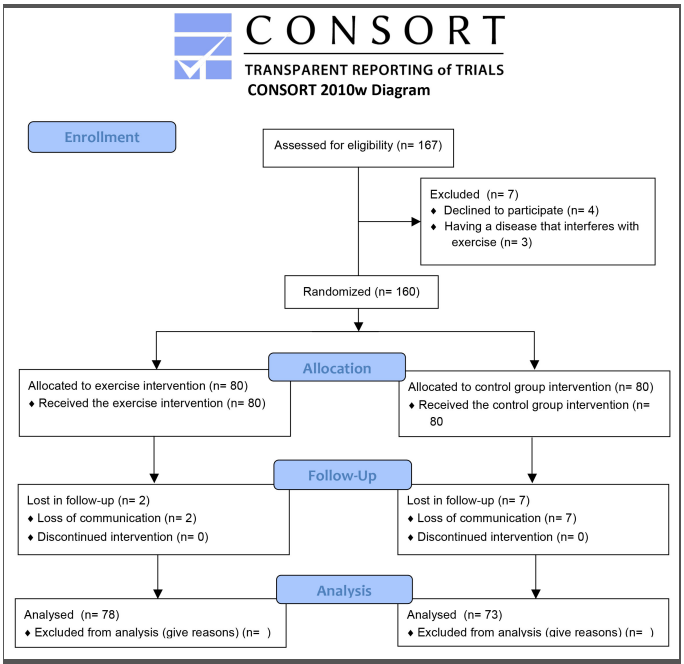



**Figure 1.** Trial steps

Many different approaches have been tried in patients receiving gynecological cancer treatment, including methods such as; dietary recommendations (10), isolated [aerobics only (11)] or combined exercise types [aerobic, resistance and flexibility exercises (12)], cognitive behavioral therapy (13), to increase the poor quality of life of cancer patients. In recent years, lifestyle changes and exercise therapy have been tried in different types of cancer in order to prevent comorbid diseases and improve the quality of life, and are recommended with varying levels of evidence (14). However, the evidence concerning the effect of lifestyle changes such as exercise, on the quality of life of patients with gynecological cancer is limited (15).

Our hypothesis is that regular resistance exercise group will benefit from the intervention in terms of muscle strength and body composition, and that these will translate to decreases in cancer-related fatigue and increases in quality of life.

## MATERIALS AND METHODS

### Study design

The study was designed as a single-centered, randomized controlled trial. Patients who applied to Ege University Gynecology and Obstetrics Clinic between 03/07/2017 and 03/07/2018 and who were within the three months of completion of cancer therapy were included in the study. A total of 12 weeks of intervention was applied. A total of 160 patients with endometrial, cervical or ovarian cancer participated in the study. Participants were divided into two groups as the exercise and control groups with 80 individuals in each. Two participants in the exercise group and seven in the control group were lost in the follow-up and were not included in the final analysis. At the end of the study, statistical analysis was performed with 151 patients (Figure 1). Participants in both groups were questioned in terms of whether they had additional diseases, and none of the patients had a contraindication for exercising and participating in the study.

Anthropometric measurements of the patients (height, weight, BMI, body fat analysis) were performed at the first admission. Then, grip strength of both hands, hip extensor muscle strength and back extensor muscle strength were measured with a spring dynamometer. Patients were asked to complete the Functional Assessment of Cancer Therapy-General (FACT-G), a questionnaire on health-related quality of life, and the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), a questionnaire for cancer-related fatigue. All measurements on patients and surveys were repeated after 12 weeks of intervention.

Written informed consent to participate in the study, was obtained from all participants and this permission was approved by the Ege University Clinical Research Ethics Committee (Decision no. 17-5.2/8, dated: 03/07/2017).

### Eligibility criteria

Patients who were diagnosed with endometrial, cervical or ovarian cancer, and had no barrier for participating in the

study and volunteered to participate after being informed about the study, were included.

Presence of severe cognitive impairment that may impair cooperation; presence of vascular, degenerative, inflammatory or traumatic diseases of the CNS; having other metabolic system diseases preventing exercise, such as diabetes mellitus, thyroid disorders that are not under control; presence of second primary malignancy, radiculopathy, mononeuropathy, plexopathy, and/or polyneuropathy; cardiac arrhythmia, ischemic heart disease; the presence of a chronic disease related to the respiratory system and an orthopedic disorder that prevents exercise were defined as exclusion criteria. In addition, patients who wanted to withdraw from the study at any stage of the study, and who could not participate regularly in the recommended exercises were excluded from the study. In addition, patients who wanted to withdraw from the study at any stage of the study, and who could not participate regularly in the recommended exercises were excluded from the study.

### Measurements

Body mass index (BMI) was calculated by measuring the height and weight in addition to the determination of the cancer type (endometrial, cervical or ovarian) and its stage, at the first visit of each patient. Then, body fat analysis was performed with the bioimpedance method (Tanita TBF-300). The maximal isometric grip strength of both hands was measured with a spring hand dynamometer (16). Maximal isometric hip extensor and trunk extensor muscle strength were measured using a portable spring dynamometer, and were recorded (17). Verbal motivation was provided at each maximal strength measurement, and the best of three trials was recorded. The quality of life of the patients was evaluated with the FACT-G questionnaire, and the fatigue with the FACIT-F questionnaire.

*FACT-G:* It is a measurement tool consisting of four subunits as physical, social/familial, emotional and functional well-being and a total of 27 questions, and its validity and reliability in Turkish in cancer patients has been demonstrated in previous studies (18). Each question is scored using a Likert scale from 0 (not at all) to 4 (very much). A higher FACT-G score is indicative of better quality of life.

*FACIT-F:* It is a 13-item scale, covering the seven days before the application date, in which the complaint of fatigue is questioned in detail, and its validity and reliability in Turkish has been demonstrated previously (19). Higher scores for the FACIT-F indicate that the person's energy level is better.

*Outcome measures:* Quality of life assessed by FACT-G and cancer-related fatigue status assessed by FACIT-F were determined as primary outcome measures for this study. BMI, body fat ratio, hand grip strength, hip extensor muscle strength and back extensor muscle strength were considered as secondary outcome measures for this study.

### Intervention

The control group patients consisted of the participants who were diagnosed with gynecological cancer and whose usual oncological care were continued. Considering the recommendations of the American College of Sports Medicine (ACSM) for patients with cancer, who do not have an obstacle for exercise, exercises using resistance bands and training especially large muscle groups, were recommended (20). Resistance exercises are recommended in the range of 1-2 sets x 8-12 repetitions for 2 days/week. Exercises for the upper extremity are as follows:

- Abduction, extension, and external rotation of the shoulder against resistance,
- Horizontal adduction and protraction against resistance,
- Flexion of the elbow against resistance.

Exercises for the lower extremity are as follows:

- Flexion-extension of the hip against resistance,
- Abduction and adduction of the hip against resistance,
- Flexion and extension of the knee against resistance,
- Flexion and extension of the ankle against resistance.

Flexibility exercises are recommended as 2-4 reps x 10-30 seconds for 2-3 sessions per week. These should include large muscle groups as shown in the clinical visit, and performed at the level of tension without any pain.

The exercises were individually explained and demonstrated to each patient at the beginning of the study by the principal investigator with emphasis on breathing and proper technique. The patients were also provided with a brochure with images of resistance exercises and their simplified variations.

A total of five different levels of resistance bands were used. The patients were asked to choose the resistance band in such a way that they would perform the last repetitions with a compelling effort. The participants were guided to switch to the next level of difficulty if the last reps were performed with little effort.

The patients in the exercise group were instructed to adjust the intensity of sessions according to the validated OMNI-RES (OMNI-Perceived Exertion Scale for Resistance) exerci–

se (21), and they were asked to keep the intensity between somewhat easy (3/10) and somewhat hard (6/10).

The patients in the exercise group were informed about the benefits of regular exercise and healthy nutrition in cancer treatment. In order to provide objective documentation of compliance with the recommended exercise program and to maintain a high participation in the program, case follow-up forms covering 12 weeks were given to the patients, and they were asked to note the exercise volume and intensity they did on the relevant days. Exercise records were queried during weekly calls, and patients were counselled as much as they needed. In the weekly calls, information was obtained from the patients about the feasibility of the exercises and the perceived degree of difficulty. In addition, activity modification (switching to a milder resistance, short rest when necessary) was applied to the patients in order to maintain high compliance to the program. Patients are instructed to inform the researchers in case of any adverse events.

### Statistical analysis

Firstly, residuals of error estimates were obtained by applying Analysis of Variance for Repeated Measures to numerical variables. The compliance of the residuals obtained from these analyzes with the normal distribution was examined with the Kolmogorov-Smirnov test, and it was observed that they did not fit the normal distribution. The analyses mentioned above were performed using IBM SPSS Statistics for Windows, version 25.0. (IBM Corp. Released 2017, Armonk, NY) package program. Since the parametric analysis method assumptions were not fulfilled, the analyzes were continued with appropriate non-parametric methods.

Checking the significance of intergroup difference (independent factor), pre- and post-exercise difference (repeat factor), and interaction terms were performed through application of the Brunner-Langer model F1-LD- F1 using R 3.5.2 software (R software, version 3.5.2, package: nparLD, R Foundation for Statistical Computing, Vienna, Austria; http://r-project.org) (22). Since the interactions between factors were significant in this analysis, baseline values and (pre-post) differences were compared between the two groups with the Mann-Whitney U Test. Differences between the two measurements within the group were examined with the Wilcoxon Signed Rank test. The existence of linear relationship between numerical variables was evaluated with Spearman correlation analysis. Pearson Chi-Square analysis method was used to evaluate the differences between categorical variables. Non-parametric Spearman correlation analysis test was performed to examine whether there was a relationship between the parameters. The level $p<0.05$ was considered as statistically significant throughout the entire study.

## RESULTS

Although they did not constitute an obstacle to exercise, 50% (n=40) of the exercise group and 55% (n=44) of the control group patients had comorbidities such as diabetes mellitus, hypertension, hyperthyroidism, cardiovascular disease and osteoarthritis.

Except for the FACT-G ($p=0.001$) and FACIT-F scores ($p=0.026$), along with the body fat ratio ($p=0.007$) and back muscle strength ($p<0.001$), there was no statistically significant difference regarding the baseline measurements between groups ($p>0.05$).

While 22 (28.2%) of the patients in the exercise group were Grade I and 56 (71.8%) were Grade II, 21 (28.8%) of the patients in the control group were Grade I and 52 (71.2%) of them were Grade II. The groups were similar in terms of disease stages ($p=0.939$).

When the participants were examined in terms of cancer types; 31 patients (39.7%) in the exercise group were diagnosed with endometrial cancer, 29 patients (37.2%) with cervical cancer, and 18 patients (23.1%) with ovarian cancer. In the control group, 28 (38.4%) patients had endometrial cancer, 23 (31.5%) cervical cancer and 22 (30.1%) ovarian cancer diagnosis. There was no difference between the groups in terms of cancer types ($p=0.583$).

***FACT-G:*** Significant improvements were determined in the FACT-G score at the end of the study, both in the control group ($p=0.013$) and the exercise group ($p<0.001$). Considering the difference between the groups after the study, the increase in the quality of life scale was significantly higher in the exercise group, comparing to the control group ($p<0.001$) (Table 1).

***FACIT-F:*** While a significant improvement in fatigue was observed in the exercise group, regression was observed in the control group at the end of the study ($p<0.001$) (Table 1).

***Anthropometric measurements:*** After the study, body weight was decreased in the control group but it was not statistically significant ($p=0.147$), while a statistically significant decrease was observed in the exercise group ($p<0.001$). At the end of the study, while there was no significant difference in the control group, a statistically significant decrease was observed in the exercise group ($p<0.001$). There was a statistically significant decrease in body fat ratio in both groups ($p<0.001$) (Table 1).

***Strength values:*** Right hand grip strength decreased in the control group, while a statistically significant increase was

observed in the exercise group (p<0.001). While the left hand grip strength did not change in the control group, a statistically significant increase was observed in the exercise group (p<0.001). A statistically significant increase in leg extensor muscle strength was found only in the exercise group (p<0.001). An increase in back extensor muscle strength was statistically significant only in the exercise group (p<0.001) (Table 1).

**Table 1.** Anthropometric characteristics, strength values, quality of life and fatigue levels of the participants at the beginning (pre-) and the end (post-) of the study

| Parameters | Exercise Group pre- | Exercise Group post- | Control Group pre- | Control Group post- | Exercise pre-Control pre- |
|---|---|---|---|---|---|
| **Weight** (kg) | 75.9 (54.0-110.7) | 72.1** (55.2-108.0) | 78.0 (58.9-108.5) | 76.3 (61.5-103.4) | p=0.174 |
| **Height** (cm) | 163 (150-175) | 163 (150-175) | 165 (155-174) | 165 (155-174) | p=0.916 |
| **BMI** (kg/m²) | 28.4 (19.9-43.2) | 27.4** (21.0-42.1) | 28.9 (20.8-40.0) | 28.5 (21.7-38.8) | p=0.820 |
| **BFR** (%) | 32.5 (19.9-45.1) | 30.2** (17.3-41.8) | 30.6 (19.6-43.2) | 30.1** (18.7-41.9) | p=0.007** |
| **FACT-G** (Life quality) | 80 (51-106) | 88** (71-103) | 74 (64-87) | 76* (62-90) | p<0.001** |
| **FACIT-F** (Fatigue) | 38 (24-51) | 45** (35-52) | 37 (26-47) | 36** (26-46) | p=0.026* |
| **Hand Grip (R)** (kgf) | 34 (6-59) | 41** (11-70) | 37 (11-58) | 34 (10-60) | p=0.297 |
| **Hand Grip (L)** (kgf) | 29 (9-51) | 37** (12-70) | 29 (10-54) | 29 (10-60) | p=0.694 |
| **Leg Strength** (kgf) | 50 (21-88) | 62.5** (30-99) | 52 (16-80) | 53 (15-80) | p=0.749 |
| **Back Strength** (kgf) | 52.5 (30-78) | 66.5** (38-90) | 43 (17-60) | 43 (17-60) | p<0.001** |

BMI: body mass index; BFR: body fat ratio. Values as median (min-max); Pre-post comparisons through Mann-Whitney U: *: p<0.05, **: p<0.001. Group level of change comparisons (Mann-Whitney U): p<0.001 for all parameters except height (p>0.05).

***Between groups comparisons:*** The comparison of the levels of change between the last and the first measurement between the groups are shown in Table 1. At the end of the study, an interaction was found between the exercise group and time-dependent change. The levels of change in the examined parameters were more significant in the exercise group (p<0.001).

***Correlations between parameters:*** At the end of the study, there was a significant correlation between the change in physical parameters and the change in quality of life (FACT-G), and fatigue (FACIT-F) levels (p<0.001) (Table 2).

**Table 2.** Correlations between the changes in physical parameters, and quality of life (FACT-G) and fatigue (FACIT-F).

| Parameters | Fact-G (Life quality) | Facit-F (Fatigue) |
|---|---|---|
| **Body weight** (kg) | *r=-0.324; p<0.001* | *r=-0.431; p<0.001* |
| **BMI** (kg/m²) | *r=-0.326; p<0.001* | *r=-0.432; p<0.001* |
| **Body fat ratio** (%) | *r=-0.598; p<0.001* | *r=-0.672; p<0.001* |
| **FACT-G** (Life quality) | - | *r= 0.877; p<0.001* |
| **FACIT-F** (Fatigue) | *r=0.877; p<0.001* | - |
| **Grip (R) strength** (kgf) | *r=0.624; p<0.001* | *r=0.653; p<0.001* |
| **Grip (L) strength** (kgf) | *r=0.617; p<0.001* | *r=0.646; p<0.001* |
| **Leg strength** (kgf) | *r=0.682; p<0.001* | *r=0.703; p<0.001* |
| **Back strength** (kgf) | *r=0.806:p<0.001* | *r=0.803; p<0.001* |

*BMI: body mass index; R: right, L:.left.*

## DISCUSSION

As an outcome of this study, significant improvements in quality of life and cancer-related fatigue were revealed with regular resistance exercise in patients with gynecological cancer. Significant improvements were observed in body composition and maximal strength values in the exercise group. In parallel, a significant correlation was found for the change in each physical parameter (weight, BMI, body fat ratio) with quality of life (FACT-G) and cancer-related fatigue (FACIT-F).

Exercise interventions are often recommended to eliminate high BMI (23) and low physical activity levels, which are modifiable risk factors in poor quality of life. Programs recommended for this purpose are generally a combination of aerobic, resistance and flexibility exercises. An increase in bone density (24) and muscle strength (25), and functional improvements in cardiovascular health (26) can be achieved with resistance exercises.

According to a recent systematic review investigating the effect of exercise on fatigue in patients with gynecological cancer; although a decrease in cancer-related fatigue and an increase in quality of life were reported in some studies (23), no significant improvement in quality of life was ob–

served in others (27). Many features such as physical characteristics and medical conditions of patients, disease stage, differences in diagnosis and treatment, and differences in the content and duration of interventions may vary between studies in the literature. In a study by Donnelly et al., examining the effects of combined exercise (aerobic and resistance) in 33 patients, no significant difference was reported between the groups in quality of life at the end of three months (28).

Factors such as the different size of patient populations, the inclusion of different types of cancer (only ovarian or cervix, ovary, endometrium), and the fact that patients who received interventions were at different stages of cancer treatment may explain the inconsistencies in the gynecological cancer literature. In a single-armed study conducted by Basen-Engquist et al. in 100 patients with endometrial cancer, significant changes in the quality of life were reported in the aerobic exercise group at the end of the six-month intervention (11). In a controlled study conducted by Hwang et al. on 40 patients with ovarian cancer, significant improvements were reported in cardiopulmonary capacity, quality of life, and muscle strength in the exercise group compared with the control group (12). In our study, an improvement in the quality of life was observed in the exercise group, in line with the general exercise interventions. The correlation of this improvement with the increase in strength values suggests that the increase in strength helps to improve the quality of life.

Most patients with cancer describe fatigue as the most disturbing symptom that affects their quality of life (29). According to a current systematic review, exercise has moderate-to-large scale positive effects on muscle strength, and small-scale positive effects on cancer-related fatigue (25). The increase in muscle protein synthesis (30) and endurance may be a factor here. Resistance exercises may have increased the energy level of patients through the central mechanism by improving neuro-motor control and cytokine response (31). In the peripheral mechanism; replacement of energy sources such as ATP-creatine phosphate in the muscle, improvement of oxidative metabolism (7) and increasing strength may have been effective. Resistance exercises also improve the mechanical functions of the musculoskeletal system, thereby improving functional performance in sports and daily life activities (30). In our study, significant improvements were observed in maximal strength measurements in the exercise group, and these improvements were associated with improvements in cancer-related fatigue and in quality of life.

The strengths of the study include a well-defined and large sample size, randomized controlled design, increased participation and compliance with weekly calls and consultations, and minimal loss in follow-ups. The inclusion of individual exercises instead of group activities, their implementation without supervision, the lack of comparison with different types of exercise (aerobics), and the failure to evaluate long-term effects may be considered among the limitations.

As a conclusion, significant reductions in cancer-related fatigue, and significant improvements in body composition, maximal strength and global quality of life were revealed with resistance exercises in patients with gynecological cancer, at the end of the study. In line with these findings; we can say that performing regular exercise is important to increase the quality of life and to reduce fatigue in cancer patients, and that it is a supportive method that should be considered in the treatment process. In order to investigate the effects of physical activity on survival and prognosis in cancer, studies with larger populations are needed, where the effects of exercise and lifestyle interventions are observed for a longer period of time, comparing different types of exercise (aerobics, resistance, group activities).

***Ethics Committee Approval / Etik Komite Onayı***

The approval for this study was obtained from Ege University Clinical Research Ethics Committee (Decision no. 17-5.2/8, Date: 03.07.2017).

***Conflict of Interest / Çıkar Çatışması***

The authors declared no conflicts of interest with respect to authorship and/or publication of the article.

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***Author Contributions / Yazar Katkıları***

Concept All authors; Design All authors; Supervision All authors; Materials All authors; Data Collection and/or Processing AB. Analysis and Interpretation All authors; Literature Review All authors; Writing Manuscript All authors; Critical Reviews All authors

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