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Changes Of CEA and CA15-3 Biomarkers in the Breast Cancer Patients following eight Weeks of Aerobic Exercise

Azar Esfahbodi[1], Mehrdad Fathi[*2], Gholam Rasul Mohammad Rahimi[3]

1. M.Sc graduated in Sports Physiology, Faculty of physical education and sport sciences, Islamic Azad University, Bojnord, Iran.
2. Associate Professor of Department of Sports Physiology, Faculty of physical education and sport sciences, Ferdowsi University of Mashhad, Mashhad, Iran.
3. Ph.D. Student in Sports Physiology, Faculty of physical education and sport sciences, Ferdowsi university of Mashhad, Mashhad, Iran.

***Corresponding Author:**
Mehrdad Fathi
Associate Professor of Department of Sports Physiology, Faculty of physical education and sport sciences, Ferdowsi University of Mashhad, Mashhad, Iran.
Tel: (+98)5138805413
Email address: mfathei@um.ac.ir

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ABSTRACT

Background: Exercise has positive effects on breast cancer evolution, including prevention, medical treatment, and aftercare clinical settings. Plus, elevated serum levels of CEA and CA15-3 as prognostic indicators were identified in patients with breast cancer. So, this study aimed to investigate the changes of CEA and CA15-3 biomarkers in the breast cancer patients following eight weeks of aerobic exercise.

Methods: In this quasi-experimental study, 15 females with breast cancer with mean age (44.46±17.15 years), weight (70.53±5.18 kg) and body mass index (27.58±2.18 kg/m2) were randomly selected and performed aerobic training (for 8 weeks,3 sessions per week, with an intensity of 30%-60% heart rate reserve). Before and after the intervention, while all patients were fasting for 12 hours, the levels of CEA and CA15-3 were measured. The data obtained were analyzed, using paired sample t-test at a significance level of $P<0.05$.

Results: Findings showed that the tumor marker (CA15-3) decreased following 8 weeks of aerobic exercise although it was not significant ($P=0.091$); CEA level did not change significantly after exercise, either ($P=0.542$), but a significant decrease was observed in body mass index, body fat percentage and weight values after exercise ($p=0.001$).

Conclusion: Elevated CA15-3 and CEA which are considered as the diagnosis of metastatic breast cancer was not observed in the study. Exercise could reduce CA15-3 insignificantly. Also, aerobic exercise for eight weeks improved body composition indices, without increasing the level of fatigue or stress values, which may contribute to the prevention of the cancer prevalence in middle-aged women.

Keywords: Exercise; Carcinoembryonic Antigen; Cancer Antigen 3-15; Women; Breast Cancer

INTRODUCTION:

The latest reports of Iranian Cancer Association show that 25% of all cancer manifestations in Iranian women are related to breast cancer[1]. The ever-increasing growth of breast cancer in recent decades and its harmful effects on physical and mental health as well as socioeconomic status have attracted experts` attention to this kind of disease more than ever, causing researchers to present it as the main hygienic problem of the current century[2]. According to deep research in the field of the biology of breast cancer, despite the increase in the occurrence of breast cancer in recent years, the survival rate has improved[3, 4]. Nevertheless, failure in disease treatment considerably affects the quality of life and survival rate in these patients. Therefore, it seems necessary that reliable predicting factors be determined to guide decision-making process during breast cancer treatment.

Over some decades, the clinical assessment of disease activity has been performed by means of blood tests, such as liver function tests, and imaging. However, these methods were not highly sensitive; so, measuring biomarkers presented in serum was taken into consideration. Biomarkers are diagnostic molecules in the blood of individuals with malignant tumors which can be used for immediate diagnosis, treatment control and the diagnosis of recurrence[5]. In most malignant tumors, measuring these biomarkers is an appropriate method for obtaining information on the natural history of the disease, and it can be used for planning the manner and duration of treatment. This method is fairly inexpensive, and it is performed with ease[6].

Additionally, tumor size, histological grade (HG), and hormone receptors status are traditional prognostic factors, whereas axillary lymph node status has been the most important prognostic factor for primary breast cancer. Samy et al. (2010) suggested some other markers as biological prognostic indicators for breast cancer. They reported that preoperative serum levels of Her2/neu, BCL2, cancer antigen 15-3 (CA15-3) and carcinoembryonic antigen (CEA) in breast cancer patients were significantly higher compared with the levels of the control group; these markers have been observed to decrease significantly after the operation. Additionally, they were considerably associated with recurrence of disease[7].

Wang et al. (2017) suggested that serum CEA, CA19-9, CA125, CA15-3, and tissue polypeptide-specific antigen (TPS) can be used in the diagnosis of metastatic breast cancer; they pointed out that the highest sensitivity was seen in CEA and the highest specificity observed in CA125 for the diagnosis of metastatic breast cancer[8]. Shao et al. (2015) also declared that preoperative serum levels of CEA and CA15-3 are independent prognostic parameters for breast cancer. In their study, elevated serum levels of CEA and CA15-3 were observed in patients with breast cancer, and larger tumor size, as well as advanced axillary lymph nodal, exhibited a higher proportion of elevated CEA and CA15-3 levels in those patients. Also, patients with both elevated markers (CEA and CA15-3) presented the worst survival[9].

A large body of evidence indicates that exercise as a non-pharmacological and non-invasive method has positive effects on every aspect of breast cancer evolution, including prevention, medical treatment and aftercare clinical settings. Reduction of insulin resistance and improvement of immunity and cardiovascular function are some of the useful effects of exercise in people with breast cancer; Furthermore, acute and chronic symptoms of breast cancer, such as cachexia, muscle mass loss, fatigue, cardiotoxicity, weight gain, hormonal alterations, bone loss and psychological adverse effects may all be favorably influenced by regular training[10].

Cancer patients are under medical treatment but 60-70% of breast cancer survivors live with chronic adverse treatment-related side effects, such as upper-body symptoms, lymphedema, and fatigue. Younger women can even experience premature menopause, bone density loss, infertility and associated distress. Exercise is thought to reduce or also prevent these side effects[11]. Researchers believe that regular exercise in patients with a developed cancer augments the level of activity and energy expenditure without increasing the level of fatigue; exercise also causes hormonal variation through influencing body mass index and fat percentage levels[12,13]. On the one hand, CA15-3 is a protein made by a variety of cells, particularly breast cancer cells; on the other hand, exercise exerts favorable effects on tumor microenvironment by improving systemic pro-inflammatory profile and the serum concentrations of growth markers linked to tumorigenesis (Ramirez)[14]; finally, exercise is likely to reduce tumorigenesis and modify the production of cancer cells as CA15-3 and CEA which was investigated in the present study. In addition, we encountered some inconsistent and insufficient findings on the effects of exercise on biological prognostic indicators[15,16], that's why further investigation is necessary to establish the impact of exercise on CA15-3 and CEA. Considering the increasing number of women diagnosed with breast cancer each year, together with improving survival rates, the need to identify safe, effective, evidence-based strategies to improve quality of life in breast cancer patients seems essential; thus, changes in CEA and CA15-3 levels in the breast cancer patients following 8 weeks of aerobic exercise were investigated in the present study.

METHODS:

The method of implementing the present research was a quasi-experimental pretest-posttest design on an experimental group. The statistical population of this research consisted of middle-aged women with breast cancer in the 40-60 age range. After being invited for participation with the approval of specialists, 15 voluntary female patients were selected, using purposive sampling method, and they were considered as the experimental group on the basis of the output of a completed physical activity readiness questionnaire. The exclusion criteria of the research consisted of coronary artery disease, kidney failure, and Hypothyroidism.

In order to conform to the code of Ethics, prior to sampling, the patients were orally familiarized with the nature and the method of the experiment and its probable dangers and were reminded of major and necessary hints on diet, physical activity, disease and the use of medicines that they had to carefully follow. Afterward, the patients completed the written consent form of collaborating in the research and declared their readiness to participate in it. It should be mentioned that all of the patients were free to unconditionally withdraw from the research at any time.

In this research, before and after implementing the physical exercise program, a blood sample of 10 cc was taken from the biceps vein of the patients. Prior to collecting the blood samples, all the patients were fasting for 12 hours and did not have any vigorous physical activity for 24 hours. In both of the pre-intervention and the post-intervention phase, blood sampling was performed between 8 and 9 am. The blood samples were centrifuged for 10-15 minutes at 2700 rpm to detach the serum. The serum level of CEA and CA 15-3 was measured by the electrochemiluminescence immunoassay method (Roche's technology, Germany). The study selection process is described in **Figure 1**.

The aerobic training protocol was performed for eight weeks, three sessions per week and 40 to 60 minutes in every session. Exercise consisted of general warm-up exercises (walking, jogging, and stretching and flexibility exercises), main exercise, and 10-minute cool-down ones. The intensity of aerobic training was progressively increased (30-60% heart rate reserve (HRR))[17]. The intensity of the exercise was calculated via Karvonen formula for each patient, and during the exercise it was controlled, using Polar Heart Rate Monitor manufactured in Finland.

HRR = [(220 – Age) – Resting Heart Rate) × Target percentage] + Resting Heart Rate

The results were expressed as the mean ± SD (standard deviation) as applicable. The Shapiro-Wilk test was applied to test the sample distribution and homogeneity of the variance method. Paired t-test was used to examine the differences in the baseline and after intervention in variables within the group. A significance level of 5% was accepted. The statistical analyses were performed, using SPSS 16.0 software (Chicago, IL, USA).

RESULTS:

Findings showed that the tumor marker (CA15-3) decreased following eight weeks of aerobic exercise although it was not significant (P=0.091); CEA level did not change significantly after exercise, either (P=0.542). In addition, a significant decrease was observed in body mass index, body fat percentage and

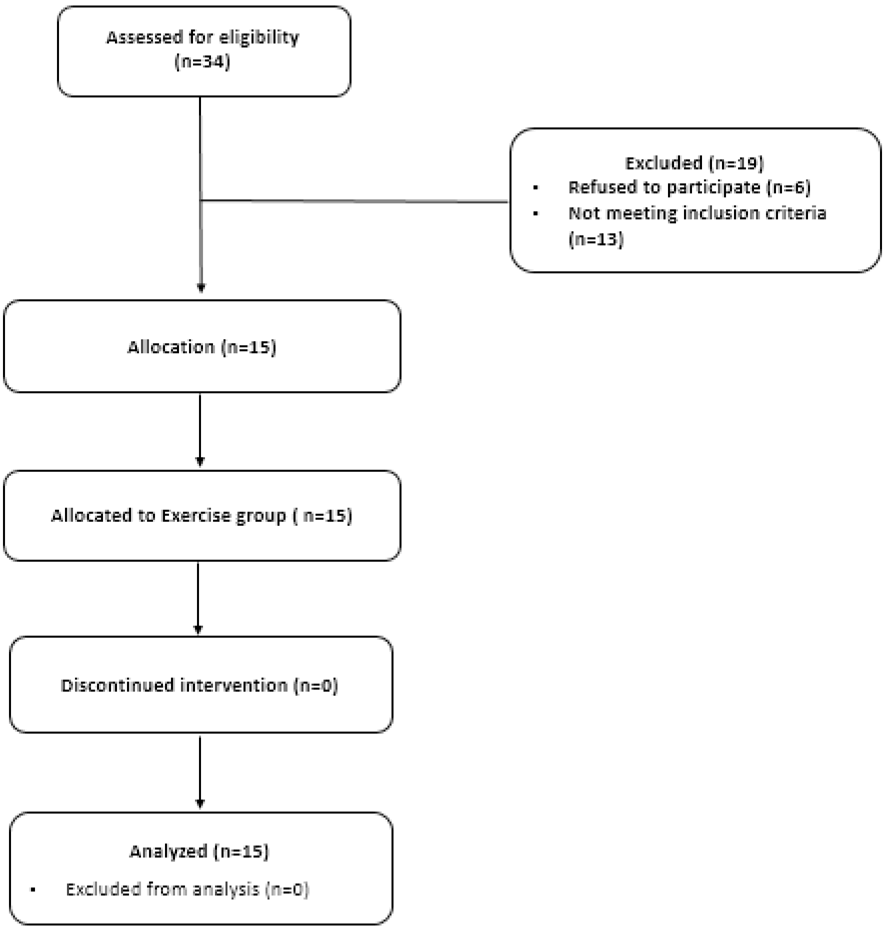

Figure 1. Flow chart of the study.

Table 1. Difference within groups of CEA and CA 15-3 values before and after the intervention. †P≤0.05 vs before

variable	significance level	t	Changes (%)	Phases	
				pretest (M±SD)	posttest (M±SD)
CEA (ng/mL)	0.542	-0.62	9.67±0.18	0.62±0.68	0.68±0.50
CA15-3 (U/ml)	0.091	1.82	-9.01±0.47	37.95±23.10	34.53±22.63

weight values after exercise (p=0.001) (**Table 1** and **2**). **Figure 1** and **2** also show the serum changes in CEA and CA 15-3 in the middle-aged women following eight weeks of aerobic exercise.

DISCUSSION:

This study revealed that tumor marker (CA15-3) decreased insignificantly following 8 weeks of aerobic exercise, CEA level did not change significantly after exercise, too. These results are supported by findings of Kheyrdeh et al. (2014), indicating that eight weeks of aerobic training had no significant effect on CA 15-3 in women with breast cancer. In contrast, the findings of Ko et al. (2014) do not confirm ours; they have reported a decrease of CEA in elderly women after 12 weeks of aerobic training[15,16].

These contradictions possibly originate from the different training programs (various intensity, duration, volume and rest periods of the training), and also diverse individual characteristics like fitness level and genetic

Table 2. Difference within groups of weight, body mass index, waist-hip ratio, and body fat percentage before and after the intervention. †P≤0.05 vs before

variable	significance level	t	Changes (%)	Phases	
				pretest (M±SD)	posttest (M±SD)
weight (kg)	0.001†	6.36	-5.43±0.09	71.40±6.85	67.52±6.76
body mass index (kg/m2)	0.001†	6.00	-5.16±0.10	31.00±2.05	29.40±1.95
waist-hip ratio	0.235	1.27	-3.01±0.02	0.994±0.04	0.964±0.06
body fat percentage	0.001†	5.05	-4.03±0.22	37.92±4.71	36.39±4.93

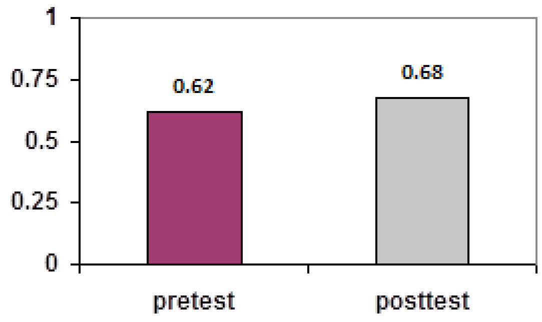

Figure 2. CEA value before and after the intervention in the middle-aged women with breast cancer

variation or heredity, the difference in the method of analysis, the age of patients, the state of menstruation, the use of chemotherapeutic drugs and hormonal treatment method can also influence the blood levels of these biomarkers[18,19].

Overall, exercise can modify the risk factors in chronic diseases and promote health, and as a behavioral intervention and a complement to treatment, it can play an essential role in improving quality of life in cancer patients20. A considerable body of evidence indicates that exercise has positive effects on breast cancer evolution as prevention, medical treatment and aftercare clinical settings[10]. However, the beneficial effects of exercise are not confirmed in all studies: Dethlefsen et al (2016) showed that a 6-month training intervention had no effect on breast cancer cell viability in vitro, while exercise increased VO2peak and muscle strength and reduced resting levels of plasma cholesterol and inflammatory cytokines. Conroy et al. (2016) found that aerobic exercise (225 min/week) failed to change

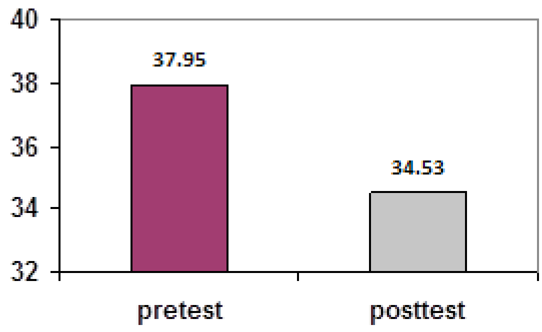

Figure 3. CA 15-3 value before and after the intervention in the middle-aged women with breast cancer

the levels of IL-4 and IL-10 in a manner consistent with chronic disease and cancer prevention. Carmen Sáez et al. (2007) also suggested that intense training significantly increased the tumor growth rate through the involvement of adrenaline and prolactin[21-23].

To justify such a contradiction, it can be said that depending on the type, duration and intensity of exercise, multiple influences on breast cancer risk can occur 10; for example, exercise with low volume and low intensity has no effect on breast cancer risk[24,25]; Kobayashi et al. (2013) suggested that physical activity with moderate-to-vigorous intensity attenuated the risk of pre- and post-menopausal breast cancer[26].

As it was discussed before, serum levels of CEA and CA15-3 in patients with breast cancer are higher than the healthy control group. In the present study, the authors observed an insignificant decrease in CA15-3 following eight weeks of aerobic exercise. CEA level did not change significantly after exercise, either. Considering findings of some studies, it seems that in this study the training protocol was not sufficiently intensive although eight weeks of aerobic training improved body composition indices in women with breast cancer; and it may lead to better results if the duration of training lasts longer and the intensity of exercise is higher.

Nowadays, the biomarkers CEA and CA 15-3 are referred to as the most practical indices in the prevention, diagnosis, and treatment of breast cancer[27]. In fact, CEA is a molecule that is expressed by blood cells or cancer-related tissues, so its measurement is extensively used for the diagnosis and management of disease[28]. Moreover, increase of CEA and CA 15-3 is related to various critical conditions[29,30]. There is a correlation between increased CEA and breast cancer recurrence[31]. In particular, aging is one of the important factors in the increase of CEA value. Recently, Lee et al. (2011) have reported that the concentration of CEA is related to metabolic disorders, cardiovascular diseases, and also various cancers. They also observed a positive relationship between the serum level of CEA and metabolic syndrome prevalence[25]. Additionally, high level of CA 15-3 and a hormonal imbalance have been considered as the main factors in breast cancer development. A concentration of 5 to 10 times more than its natural range can be a sign of danger[32].

It has been reported that there is a competition between active muscles and tumor tissue for blood and nutrients supply; during exercise, the blood flow is directed towards active muscles, and tumor tissue probably undergoes higher necrotic and apoptotic stress by receiving less blood flow and nutrients, while nutrients and tropic factors are consumed by active muscles[33]. Exercise is likely to reduce tumorigenesis and modify the production of cancer cells like CA15-3 and CEA. On the other hand, it has been suggested that CEA affects the release of pro-inflammatory cytokines through stimulation of monocytes and macrophages[34]. Although aerobic training failed to change the CEA levels in the present study, the useful effect of regular exercise on inflammatory conditions in patients with breast cancer has been confirmed in some studies[10,11]. The anti-inflammatory effects of regular exercise may be mediated via a reduction in visceral fat mass as well as the induction of an anti-inflammatory environment by decrease of CRP, IL-2, IL-6 and TNF-α and an increase in the circulating numbers Treg cells and the anti-inflammatory cytokines IL-10 and IL-1 receptor antagonist (IL-1RA)[35].

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REFERENCES:

1. Guarneri V, Conte P. The curability of breast cancer and the treatment of advanced disease. Eur J Nucl Med Mol Imaging. 2004; 31:149-56.
2. Taleghani F, Yekta ZP, Nasrabadi AN. Coping with breast cancer in newly diagnosed Iranian women. J Adv Nurs. 2006; 54:265-72.
3. Lonning PE. Breast cancer prognostication and prediction: are we making progress? Ann Oncol. 2007; 18: 3–7.
4. Reis-Filho JS, Pusztai L. Gene expression profiling in breast cancer: classification, prognostication, and prediction. Lancet. 2011; 37:1812–1823.
5. Valenzuela P. The contribution of CEA marker to CA15-3 in the follow up of breast cancer. Eur J Gynaecol Oncol. 2003; 24: 60-62.
6. Hashemi E, Montazeri A, Akbari ME, Njafi M, Haghighi SH, Kaviani A. Role of tumor markers in breast cancer recurrence. J Guilan University Med Sci. 2014; 14: 28-32.
7. Samy N, Ragab H.M, Maksoud E, Abd N, Shaalan M. Prognostic significance of serum Her2/neu, BCL2, CA15-3 and CEA in breast cancer patients: a short follow-up. Cancer Biomarkers. 2010; 6(2): 63-72.
8. Wang W, Xu X, Tian B, Wang Y, Du L,Sun T, Jing J. The diagnostic value of serum tumor markers CEA, CA19-9, CA125, CA15-3, and TPS in metastatic breast cancer. Clinica Chimica Acta. 2017; 470, 51-55.
9. Shao Y, Sun X, He Y, Liu C, Liu H. Elevated levels of serum tumor markers CEA and CA15-3 are prognostic parameters for different molecular subtypes of breast cancer. PloS one. 2015; 10(7): e0133830.
10. Adraskela K, Veisaki E, Koutsilieris M, Philippou A. Physical Exercise Positively Influences Breast Cancer Evolution. Clin Breast Cancer. 2017; 17(6):408-17.
11. Gordon LG, DiSipio T, Battistutta D, Yates P, Bashford J, Pyke C, Eakin E, Hayes SC. Cost-effectiveness of a pragmatic exercise intervention for women with breast cancer: results from a randomized controlled trial. Psycho-oncology. 2017; 26(5):649-55.
12. Esfahbodi A, Fathie M, Moazami M, Mohammad Rahimi GH R. The Effect of Aerobic Training on the Level of Growth Hormone and 17-beta Estradiol Middle-aged Women with Breast Cancer. Armaghane-danesh. 2016; 21: 563-75.
13. Fathi M, Moazami M, Esfahbodi A, Mohammad Rahimi G. Effects of an Eight-Week Aerobic Training Program on Anthropometric Indices and Cardiorespiratory Fitness of Middle-Aged Women with Breast Cancer. Journal of Ergonomics. 2016; 3:49-56.
14. Velez RR, Meneses-Echávez J, Jímenez EG, Río-Valle J, Correa-Bautista J. Influence of exercise training on markers of tumor microenvironment in breast cancer: a comprehensive meta-analysis from 15 trials. The FASEB Journal. 2015; 29(1):916-1.
15. Kheyrdeh M, Daryanoosh F, Sadeghi Poor H.R, Khoshneshin Ghashghayi Z, Salesi M. Effects of an Eight-Week Aerobic Training on CA15-3 Marker,Growth Hormon and Insulin of Middle-Aged Women with Breast Cancer. Journal of Research in Exercise Biologycal Sciences. 2014; 3: 88-96.
16. Il-Gyu Ko, Eung-Mi Park, Hye-Jung Choi, Jaehyun Yoo, Jong-Kyun Lee and Yong-Seok Jee. Proper Exercise Decreases Plasma Carcinoembryonic Antigen Levels with the Improvement of Body Condition in Elderly Women. Tohoku J. Exp. Med.2014; 233: 17-23.
17. Segal R, Evans W, Johnson D, Smith J, Colletta S, Gayton J, et al. Structured exercise improves physical functioning in women with stages I and II breast cancer: results of a randomized controlled trial. J Clin Oncol. 2001; 19(3): 657-65.
18. Kurebayashi J, Nishimura R, Tanaka K, et al. Significance of serum tumor markers in monitoring advanced breast cancer patients treated with systemic therapy: a prospective study. Breast Cancer. 2004; 11: 389-95.
19. Cengiz B, Atabekoglu C, Cetinkaya E and Cengiz SD. Effect of hormone replacement therapy on serum levels of tumor markers in healthy postmenopausal women. Maturitas. 2003; 46: 301-06.
20. Kolden GG, Strauman TJ, Ward A, Kuta J, Woods TE, Schneider KL, et al. A pilot study of group exercise training (GET) for women with primary breast cancer: feasibility and health benefits. Psychooncology.2002; 11: 447-56.
21. Dethlefsen C, Lillelund C, Midtgaard J, Andersen C, Pedersen BK, Christensen JF, Hojman P. Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses. Breast Cancer Res Treat. 2016; 159(3):469-79.
22. Conroy SM, Courneya KS, Brenner DR, Shaw E, O'Reilly R, Yasui Y, Woolcott CG, Friedenreich CM. Impact of aerobic exercise on levels of IL-4 and IL-10: results from two randomized intervention trials. Cancer Med. 2016;

5(9):2385-97.

23. del Carmen Sáez M, Barriga C, Jos J, Rodríguez AB, Ortega E. Exercise-induced stress enhances mammary tumor growth in rats: beneficial effect of the hormone melatonin. Mol and cell bioch. 2007; 294(1-2):19-24.
24. Lee, I.M., Paffenbarger, R.S. Jr. & Hsieh, C.C. Physical activity and risk of prostatic cancer among college alumni. Am. J. Epidemio, .1992;135: 169-79.
25. Lee, J.W., Park, K.D., Im, J.A., Hwang, H.J. & Kim, S.H. Serum carcinoembryonic antigen is associated with metabolic syndrome in female Korean non-smokers. Clin. Chim. Acta .2011; 412: 527-30.
26. Kobayashi, L.C., Janssen, I., Richardson, H., Lai, A.S., Spinelli, J.J. & Aronson, K.J. Moderate-to-vigorous intensity physical activity across the life course and risk of pre- and post-menopausal breast cancer. Breast Cancer Res. Treat. 2013; 139: 851-61.
27. Omidvari SH, Moslemi D, Larizadeh MH, Mosalaei A Mohamadian Panah M, Ah,adloo N. Sesitivy and specificity of CA15-3 in detection of breast cancer recurrence. Journal of Kerman University of Medical Sciences.2005; 12: 181-87.28.
28. Hammarstrom, S. The carcinoembryonic antigen (CEA) family: structures, suggested functions and expression in normal and malignant tissues. Semin. Cancer Biol, 1999; 9: 67-81.
29. Fukuda, I., Yamakado, M. & Kiyose, H. Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. J. Med. Syst. 1998; 22: 89-93.
30. Ruibal Morell, A. CEA serum levels in non-neoplastic disease. Int. J. Biol. Markers. 1992;7: 160-66.
31. Carriquiry, L.A. & Pineyro, A. Should carcinoembryonic antigen be used in the management of patients with colorectal cancer? Dis. Colon Rectum. 1999; 42: 921-29.
32. Bast R C, Bates S, Bredt A B. Clinical practice guidelines for the use of tumor markers in breast and colorectal cancer. J Clin Oncol. 1996;14:2843–77.
33. Shalamzari SA, Agha-Alinejad H, Alizadeh S, Shahbazi S, Khatib ZK, Kazemi A, Saei MA, Minayi N. The effect of exercise training on the level of tissue IL-6 and vascular endothelial growth factor in breast cancer bearing mice. Iran J Basic Med Sci. 2014; 17(4):231.
34. Ganguly, A., Yeltsin, E. & Robbins, J. Identification of a carcinoembryonic antigen binding protein on monocytes. Biochem. Biophys. Res. Commun.2003; 311: 319-23.
35. de Boer MC, Wörner EA, Verlaan D, van Leeuwen PA. The mechanisms and effects of physical activity on breast cancer. Clin Breast Cancer. 2017; 17(4):272-8.