Original Article

The comparison of estrogen metabolites between active and inactive postmenopausal women

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Abstract:

Introduction:

Regular physical activity may alter estrogen metabolism. The aim of the present study was to compare estrogen metabolites between active and inactive postmenopausal women.

Materials and Methods:

75 postmenopausal women were asked to fill in the Beck questionnaire. Based on the questionnaire scales, they were divided into two groups: active and inactive. Blood samples were taken in fasting state from all subjects and serum concentration of 2-hydroxyestron and 16α-hydroxyestron metabolites and their ratios measured. Independent t-test was used for data analysis.

Results:

The results showed that 2-hydroxyestron metabolite level and 2-hydroxyestron/16α-hydroxyestron ratio were significantly higher among active postmenopausal women than inactive postmenopausal women but 16α-hydroxyestron metabolite level was significantly lower among active postmenopausal women than inactive postmenopausal women.

Conclusion:

It is concluded that long-term physical activity can reduce breast cancer risk in postmenopausal women through influencing the estrogen metabolites.

Keywords: Physical Activities, Estrogen, Postmenopause, Cancer

Introduction

Cancer is one of the common causes of death in the world that has an increasing prevalence (1). Cancer never occurs suddenly, but it is the inevitable outcome of causes which have not been eliminated for a long time (2). Breast cancer is one of the many various types of cancer. It is the most important threat to women's health and is the second most lethal cancer after lung cancer in Iran. Many factors including aging, menarche and menopause, pregnancy in older ages, abnormal cells in the breast, breastfeeding, taking oral contraceptives pills, hormone therapy, family history of breast cancer, obesity and overweight are involved in breast cancer(3-4). Few cancers occur before menopause. Researches highlight that occurrence of premenopausal breast cancer is associated with genetic factors while postmenopausal breast cancer may be associated with environmental factors such as the presence of estrogen (4-5).

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Prevention and early detection are two important strategies to reduce mortality from cancer (6). Considerable amount of researches are conducted with the aim to determine the causes of cancer and its prevention strategies. One of these research pathways is the role of physical activity in the primary prevention of cancer. Based on the evidence presented in more than 170 epidemiological observational study, a strong relationship between physical activity and breast and colon cancer risk in women, a possible relationship between physical activity and prostate cancer risk in men as well as a reasonable relationship between physical activity and endometrial and lung cancer has been observed. A relationship has been also reported between physical activity and other cancers such as ovarian cancer, kidney cancer, pancreas cancer, testis cancer, and thyroid cancer; however, little research has been conducted on this type of cancer and the evidence for this association is not enough to date (6). Research has shown that exercise reduces the risk of cancer, especially breast cancer (6-7). The biological mechanisms responsible for the relationship between physical activity and cancer risk reduction are still under investigation. Some proposed mechanisms include changes in sex steroid hormones, metabolic levels of developmental factors and possible changes in immune system function (6). A proposed biological mechanism for the relationship between physical activity and cancer risk is estrogen metabolism particularly 2-hydroxyestrone and 16 alpha- hydroxyestrone metabolism (8). Because the increase of cancer risk is associated with the years of estrogen exposure (9), it is expected that changes in lifestyle and physical activity potentially reduce estrogens. Majority of the estrogen produced by ovaries is 17 beta-estradiol. Enzymes in a number of tissues such as liver and breast turn estradiol to estrone. These hormones mainly become 2 and 16 alpha hdroxy positions by cytochrome P450 enzymes.

2-hydroxyestrone is considered a weak estrogen because of fast methylation, fast clearance, low affinity to estrogen receptors and antiproliferative effect on breast cells. In contrast, 16 alpha hydroxyestrone has estrogenic properties due to strong binding with estrogen receptors and stimulating breast cell proliferation (9-10).

The ratio of 2-hydroxyestrone to 16- alpha hydroxyestrone (2:16 ratio) is calculated in patients suffering from breast cancer due to the antagonistic function of these metabolites. Lower values of this ratio compared with healthy subjects that is due to high amount of estrogenic 16-alpha hydroxyestrone and low value of poor 2-hydroxyestrone are considered as breast cancer indicator in some studies (11-12). Modulating estradiol and 2 - hydroxyestrone and 16-alpha hydroxyestrone metabolites and the ratio of these two with factors related to diet, weight loss, physical activity, and smoking has been observed. The increase of 2-hydroxyestrone and the decrease of 16-alpha hydroxy estrone have been shown in women who smoke (10, 13, 18). There are few studies regarding the physical activity and estrogene metabolites and those are mostly about premenopausal women. Atkinson et al. and Campbell et al., in two separate studies showed that physical activity does not have any effect on 2 - hydroxyestrone to 16-alpha - hydroxyestrone ratio. In contrast, Rachel et al., Snow et al. and Bentz et al. showed a high proportion of 2 - hydroxyestrone to 16-alpha hydroxy estrone in female athletes compared to non-athletes (15,11,19-20,9).

Results of these studies revealed that the athlete women compared to non-athlete women have more 2-hydroxyestrone at rest while 16-alpha hydroxyestrone amount remains unchanged (20). Accepting that physical activity might have a role in modulating estrogen

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metabolism to increase 2-hydroxyestrone value means that estrogen metabolism can be a mechanism to reduce breast cancer risk through physical activity (9, 21). Furthermore, the type, intensity and the duration that people do these exercises could influence these parameters.

Because aging and menopause occur along with changes in estrogen metabolites and the unidentified role of physical activity on these variables, 2 questions are raised (11, 16).

1) What changes do the primary levels of these variables have in healthy menopause people without breast cancer history? In other words, can menopause increase the value of 16-alpha hydroxyestrone and reduce the ratio of 2-hidroxyestrone to 16-alpha hidroxyestrone and increase the risk of breast cancer in menopause women? and 2) What is the impact of doing long term physical activity on these risk factors?

Answering these questions and knowing the role of physical activity in prevention of cancers especially breast cancer can make a strong motivation in women to extensively participate in regular exercise programs. The present research aimed to compare estrogen metabolites in active and inactive postmenopausal women.

Materials and Methods

Research method is causal comparative ex post facto. The population included all the postmenopausal women in Tehran with at least 5 years since their last menstrual period and age range of 50 to 65 years. Among these, 400 were selected on a voluntary basis, of whom 300 were eliminated from the study in the first phase of screening due to body mass index greater than 30 (20 cases), medical conditions (228 cases), age over 65 years (18 cases), smoking (12 cases), cancer history (10 cases) and no contact (12 cases). During the second screening phase, 20 people (7 people because of personal problems and 13 people due to lack of contact) were excluded and the remaining 80 people completed Beck's physical activity questionnaire. Then the participants were divided into two groups of active (41 cases) and inactive (39 case). Among these, 4 participants from the active group and 1 participant from the inactive group were excluded from the study due to lack of contact.

In order to perform this research, the authorities of the Elder's Cultural Center in Tehran were briefed on the subject, objectives and the methods. Then, the authorities helped us call the elderly for attending this research by posting announcements in different places such as sport venues, parks, cultural and art complexes and the cultural center itself. Then volunteers were briefed about the time, place and method of the test and filled out demographics and medical history questionnaire on certain days and at certain places.

Based on the questionnaire content, people with a history of diseases, suffering from cancer or hormone therapy and smoking were excluded from the study. After reviewing the questionnaires and the selection of eligible subjects and obtaining their written consent, the physical indicators such as height, weight, body fat percentage, body mass index, waist-to-hip ratio and aerobic fitness of all the participants were measured. Then the participants were divided into active and inactive groups based on the information on Beck's physical activity questionnaire which was presented to them. Active people were the ones who had at least one year history in regular physical activity and their Beck's physical activity questionnaire score was between 47.84 and 68.64. The inactive participants did not have any regular physical activity history and received a score between 31 and 47.84 in Beck's questionnaire (22).

Beck's physical activity questionnaire is used for determining people's routine physical activity. This questionnaire consists of sixteen questions which are classified into three sections such as

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occupational activities, sports activities and leisure time activities. Minimum and maximum individual's score of the questionnaire is between 17.60 to 89.36 points. In the present study, the minimum score was 31 and the maximum score was 68.64.In order to have two equal groups, the median of people was considered, so that people with scores above the median were allocated to active group and the scores below the median were allocated to inactive group. Blood sampling was performed after 10 to 12 hours of fasting between 8 to 10 am of the designated morning and in one session. The participants were asked not do any hard physical activity in two days prior to the test. Five milliliters of venous blood from each subject's left arm vein was taken in sitting position after five minutes of resting. After ten minutes of keeping blood samples at room temperature, they were centrifuged for ten minutes at 3500 rpm.
The resulting serum was kept frozen at -80°C for future use. Elisa was used to measure 2 - hydroxyestrone metabolite, using Estramet kit (Immunocare. U.S., sensitivity of 0.1 ng/ml, coefficient of variation of 4.5 percent) and 16-alpha hydroxyl estrone (coefficient of variation of 7.6 %). Body fat percentage was measured using caliper and skin thickness in subscapular and triceps were measured according to McArdle formula (23). Maximum oxygen consumption of individuals was calculated using physical activity rate and body fat percentage percentage (24).

Statistical Methods
The Kolmogrov-Smirnov was used to check normal distribution of variables, descriptive statistics were used for central tendency and dispersion and independent t-test was used to determine the differences between groups. Significance level of tests was considered < 0.05 and all tests were run in SPSS version 16.

Results
Physical and physiological characteristics of active and inactive postmenopausal women are presented in Table 1. It can be seen that active and inactive postmenopausal women do not have any significant differences in terms of variables such as age (p=0.3), height (p=0.74), weight (p=0.1), BMI (p=0.07), body fat percentage (p=0.53) and the menopause duration (p=0.32). Moreover, the index of maximum aerobic power in active post-menopausal women was significantly more than that in inactive postmenopausal women (p=0.001). Waist to hip ratio was also significantly less in active post-menopausal women in comparison with inactive postmenopausal women.

According to table 2, it is clear that there is a significant difference between active and inactive postmenopausal women regarding the three indicators in that the 2-hydroxyestrone metabolite value and the ratio of 2-hydroxyestrone to 16-alpha hydroxyestrone were significantly higher and 16-alpha hydroxyestrone metabolite value is lower in active menopausal women.

Discussion
This study attempted to show the effects of physical activity independent of changes in weight and body fat percentage. Evidence shows that 2-hydroxyestrone increase is inversely associated with body mass index and the improved ratio of 2 - hydroxy estrone to 16-alpha hydroxyestrone is associated with reduced weight and body fat (7, 12, 18). Moreover, it was shown that body weight can influence the level of estrogen metabolites by the increase in aromatization of androgens to estrogen in adipose tissue (18). In this regard, Coker et al. reported that obese women may have lower amounts of 2-hydroxyestrone to 16-alpha hydroxyestrone compared with non-obese women (25).

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Table 1: Physical and physiological properties of active and inactive postmenopausal women

Variables	Active postmenopause (37 people)	Inactive postmenopause (38 people)	Significance level
Age(years)	55.89±4.38	57±4.80	0.33
Postmenopausal duration (year)	5.27±3.55	6.08±3.44	0.32
height (centimeter)	156.93±0.05	156.95±0.052	0.74
Weight (kilogram)	63.18±6.50	65.93±7.67	0.1
Body fat percentage	26.25±6.29	27.07±6.44	0.531
Body mass index(kilogram per square meter)	25.79±2.37	26.69±1.95	0.078
Waist to hip ratio(meter)	0.85±0.087	0.89±0.08	0.04*
Maximum oxygen uptake (ml /kg/min)	34.02±5.08	24.21±2.10	0.001*

*p<0.05 Significant difference level

Table 2: Comparison of estrogen metabolites and their ratio in active and inactive postmenopausal women

Variables	Active postmenopause	Inactive postmenopause	Significance level
2- hydroxy estron(ng/ml)	2.094±0.61	0.927±0.36	0.001*
16-alpha hydroxy estrone(ng/ml)	20.37±0.81	2.95±1.02	0.001*
ratio of 2 - hydroxy estrone to 16-alpha hydroxy estrone	1.09±0.35	0.341±0.14	0.001*

*p<0.05 Significant difference level

Based on the main findings of the present study, 2-hydroxyestrone level and 2-hydroxy estrone to 16-alpha hydroxyestrone ratios in active postmenopausal women are significantly higher than those in the inactive postmenopausal women. Higher 2-hydroxy estrone concentration in active postmenopausal women in response to physical activity is in line with the findings of De Cree et al., Russell et al., snow et al, Matthews et al. and Bentz et al. studies which were performed on postmenopausal women (26-27, 19-20, 16, 28,9).

These researchers indicated the 2-hydroxy estrone increase in aerobic performers and active people and expressed that this increase is related to reduced body fat percentage. Observational studies of Snow et al. indicated the increase of 2-hydroxyestrone level only in athletes with irregular menstrual cycles with low fat percentage (20). Farish et al. also showed a high concentration of 2-hydroxyestrone in athletes compared with the control group and expressed that its amount has a reverse relationship with body fat percentage (29). Moreover, Bentz et al. also observed a high concentration of 2-hydroxyestrone in women with high levels of physical activity, based on Matt hours per day (15 to 30 minute walk) (9). This amount of physical activity changes body composition and consequently body fat percentage. These results showed that reduction in body fat percentage while doing physical activity would be somewhat beneficial for 2-hydroxy estrone metabolite. However, Snow et al. did not observe any significant relationship between 16-alpha hydroxy estrone concentration and physical activity in athletes having amenorrhea, irregular menstruation and the control group (20). On the other hand, the concentration of estrogen metabolites in postmenopausal women in the present study contradicts

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with previous studies that did not observe a change in the mentioned index.

Campbell et al. did not observe any significant difference between the aerobic fitness and 2 - hydroxyestrone and 16 alpha – hydroxyesterone concentration and the ratio between them during twelve weeks program of diet and exercise intervention in premenopausal women between 20 to 24 years old, with normal menstrual cycles, high and medium aerobic fitness and body mass index between 18 to 24 kg per square meter (11). Mc Tiernan et al. investigation on the effect of exercise on serum estrogens in postmenopausal women over 12 months showed that exercise reduces estrogen and estradiol, and increases the globulin-binding sex hormone (30). On the other hand, Atkinson et al. in a separate study on postmenopausal women showed that 12 months of moderate-intensity exercise intervention does not bring any changes on 2 - hydroxyestrone and 16- alpha hydroxyesterone and their ratio (15). In this study, a weak relationship was found between body mass index and increase in 2-hydroxyestrone in the case and a weak inverse relationship between body fat percentage and 2-hydroxyestrone in the control group. These researchers attributed ineffectiveness of exercising on those indexes to the following:

A) The difference in age and menstruation status (Given the fact that age, especially reproductive age affects estrogen metabolism pattersn);

B) The difference in time of measuring estrogen metabolism during menstrual cycle (the amount of estrogen is different at follicular and luteal phases);

(C) The time interval between exercise stopping and blood sampling and the existence of exercise threshold at this time;

D) Workout intensity and duration (10, 11, 16).

The reasons for the difference of the present research finding with the previous research findings can be due to obesity and body composition that are effective in the amount of produced estrogen. The estrogen production in premenopausal women is mostly through ovaries and less estrogen comes from peripheral tissues, but in postmenopausal women estrogen is produced through androgen conversion instead of follicular production in ovaries which have stopped due to ovarian shrinkage and the loss of follicles. This causes more access to estrogen due to reducing the amount of globulin-binding sex hormone (10). In the present study, the subjects were homogeneous and had the same body fat percentage. However, if more precise methods such as dual energy absorption spectroscopy, MRI, etc were used to measure body fat percentage, the differences between the two groups might be discoverable.

Table 1 shows that hip to waist index that indirectly shows the abdominal obesity is higher in inactive women compared to active women (31-32).Thus, since abdominal fat tissue is an important source of estrogen production in postmenopausal women, so it can be said that the increase in adipose tissue increases the conversion of androgens to estrogen and this increase cause more estrogen access due to the reduction in amount of sex hormone binding globulin (10). In the present study, the decrease in waist to hip ratio in active women is 0.04 percent, increase in 2-hydroxyestrone equals 125%, and 2-hydroxyestrone ratio to 16-alpha hydroxyestrone equals 225%, so it is expected that other factors in addition to the reduction of abdominal fat result in this findings. For instance, differences in exercise parameters can affect the amount of estrogen production. In one study, the intensity of physical activity showed a positive relationship with serum levels of 2-hydroxyestrone in postmenopausal women (33). On the other hand, in Atkinson's study, the exercise intensity was moderate (15). However, the effect of high intensity workout on changes in estrogen metabolism, body composition and body fat percentage cannot be ignored

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but its effects on the amount of 2-hydroxyestrone and 16-alpha hydroxyestrone are not fully explained. De Cree et al. conducting a series of acute and short-term exercises, observed the lack of change in 2-hydroxyestrone and its increase (34, 26-27). These studies stressed the importance of controlling the intensity of physical activity over the course of the study. The intensity of physical activity can also increase the concentration of globulin binding sex hormone. This increase causes the estrogen decrease in blood circulation (33). Vistisen et al. also reported that intense workout results in 70% increase in cytochrome P450 enzyme and hepatic CYP1A2 gene in response to 8 to 11 hours of practice per day, over a 30-day program (35). CYP1A2 gene production would lead to an increase in the amount of 2-hydroxyestrone. Duration of physical activity can also be one of the factors that make a difference in the findings. The active participants in the present research, based on the contents of the questionnaire, had more than a year of physical activity. This long period of physical activity probably could have favorable effects on estrogen metabolites and improve the 2-hydroxyestrone indicators and 2-hydroxyestrone to16- alpha hydroxyestrone.

On the other hand, other possibilities including the lack of diet control in the present study cannot be ignored. Since the diet containing vegetables, fiber and fat could influence estrogen metabolites, it is likely that the active group in this research have used these materials more in their diets (18). However, to achieve more conclusive results, other researches with more controls are essential. In addition, smoking and use of hormones can also affect the estrogen metabolites.

Because the above mentioned items are controlled through the questionnaire, it is likely that people did not answer the questionnaire with complete honesty. Finally, because physical activity can cause various physiological and metabolic changes in people, it is likely that physical activity have affected the estrogen metabolism through other unknown mechanisms. In this regard, Campbell et al. stated that aerobic fitness is not the only influential path on estrogen metabolism. They observed that doing aerobic exercises do not make any significant changes in their aerobic fitness despite improving the estrogen metabolites in premenopausal women (11).

Conclusion

In sum, it can be stated that doing long term physical reduce the breast cancer risk in postmenopausal women activities by affecting estrogen metabolites.

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Conflict of interest

The authors declare no conflicts of interest.

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