The Influence of Endurance training on serum Levels of IL-17 in mice with breast cancer

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ABSTRACT: The purpose of this study was to investigate the influence of endurance training on IL-17 levels in tumor as well as on tumor volume in female bulb/C mice with breast cancer. To do so, 20 bulb/C mice (4-5 weeks old with mean body mass of 17 grams) were randomly put into two groups of 10: one as Resting Tumor-Exercise (RTE) group and the other as the Resting –Tumor-Resting (RTR) group. After inducing a tumor within the breast texture, the influence of endurance training was investigated on IL-17 levels as well as on tumor volume. The endurance training was applied for 6 weeks with intensity of 55-70% VO₂max. Levels of IL-17 were measured through ELISA method at the end of protocol. The obtained data were then analyzed through SPSS 20 using independent t-test, partial correlation coefficient as well as Pearson correlation with a significance threshold of P≤0.05. Results of independent t-test showed that there is no significant difference between IL-17 levels in the RTR and RTE groups. The same test for the tumor volume, however, revealed that there is a significant difference (P=0.0001) between the tumor volume in two groups. Results of partial correlation coefficient and Pearson coefficient showed that there is no significant relationship between IL-17 textural levels and tumor volume among female bulb/C mice with breast cancer after a series of endurance training (P>0.05). Therefore, it seems that there are factors other than increased levels of interleukin 17 which plays different roles in decrease of tumor volume cancer index. Taking endurance training is, however, suggested as a non-risky adjuvant therapy in breast cancer.

Key words: Endurance training, interleukin 17 (IL-17), Breast cancer

INTRODUCTION

Breast cancer, the most common form of cancer among women, also has the second highest morbidity rate worldwide (10.9% of all cancers). With an estimated 1.38 million new cancer cases diagnosed in 2008, it is also the most common cancer in both developed and developing regions. About 69,000 new cases have been estimated in each of these regions (population ratio 1:4).

Statistical analysis suggests that _10% of patients with newly diagnosed breast cancer exhibit advanced or metastatic disease, whereas approximately 30% to 50% of patients who are diagnosed with this disease at an early stage are prone to progress to a metastatic stage despite administered treatment such as chemotherapy and/or adjuvant therapies (gupa et al 2009). This suggests that despite much advancement in breast cancer treatment over the years, relapse of this disease with time (approximately 40% of all patients with breast cancer experience relapsed disease, with 60%-70% cases of relapse having metastasis) serves as a major roadblock to complete cure of this disease. The only established reason behind this is the underlying presence of a small population of stem-like cells called cancer stem cells (CSCs), ie, breast cancer stem cells (BCSCs). A recent hypothesis states that these CSCs originate from normal tissue stem cells; adult stem cells serve as ideal targets for malignant transformation because of their lengthy lifespan, and they are normally under tight control within a niche. Also these CSCs share certain properties with normal stem cells (noteworthy ones being the self-renewal capability), which leads to the generation of more CSCs and the ability to differentiate to form a variety of differentiated cells that are found in malignancy (vermelen 2008) Additionally, CSCs pose a threat in the form of invasion that is resistant to current chemotherapy/radiotherapy, as well as distant metastasis.
Of course it is clear that bodily exercises have positive effects on prevention, control and betterment of diseases. Meanwhile resisting sports have also an inevitable role.

Most of researches about cancer show that sport exercises have a great role in betterment of life and reduction of mortality resulted from cancer. (Koist et al. 2006). By the way, such a role of physical training is not clear in breast cancer. Most of researches are only about the effects of physical training on betterment of life without any clear information about cellular metabolism. (Koma et al. 2006, Kornia et al. 2011).

Therefore if we could reduce the amounts of cytokine and angiogenesis factors as the major involved items in metastasis of tumors and increase the anti-inflammation cytokines such as IL-17 in prevention from tumor growth, it is possible to benefit from exercises as a cheap and useful guideline in betterment of breast cancer and prevention from cancer cells metastasis. But there are incomplete researches in this field. It is not specified whether pro-inflammatory cytokines have a double role in tumors (like IL17) accompanied with sport exercises or not.

Due to the lack of any researches about the effects of endurance training on levels of IL17 along with a relationship between training in tumor due to double role of cytokines, the real goal of this research is evaluation of any effects out of 6 weeks of endurance training on IL17 levels at tumor in any rats suffering from breast cancer.

Subjects
This research is an experimental & fundamental one made by a field and laboratory method. The statistical sample includes 20 bulb/C female Mice (4-5 weeks with an average weight of 17 g) purchased from Pasture Institute and transferred to animal home of Tarbiat Modares University. They were kept separately with limited number (10 mice in each cage). They were living in animal laboratory of Medical Tarbiat Modares University in a room with dimensions of 1.160 x 2.20m with light controlled conditions (12 hours day and 12 hours darkness, 6:00 am to 6:00 pm) and a temperature of 22-23° C and moisture of %45. Mice were put in cages made from Plexiglas with a network door and dimensions of 43x 27 x 25cm.

Their food was water and normal mice libitum foods available freely up to the end of protocol. All rats were familiar with running on a circulating tape and living at animal home within one week. Then we started our research protocol. For this purpose we divided them randomly into two groups of 10. There was a fixed hour for performing of exercises. Sport protocol includes Saturday, Sunday, Tuesday, Wednesday and Thursday from 9:00 am to 14:00 pm.

Portocal
Exercise protocol
Rest- Tumor- Exercise (RTE)

Upon purchase from Tehran Pasture Institute, this group were kept in animal home of Tarbiat Modares University for one week in order to be more familiar with environment. Then some cancer cells were injected to them. After that they relaxed for two weeks. After about two weeks from injection of cancer cells, they were familiar with treadmill. Then they performed six-weeks endurance training.

Rest- Tumor- Rest (RTR)

This group had also their normal life like RTE one after purchasing from Pasture Institute for one week at animal home of Tarbiat Modares University. Then we injected cancer cells to them. After about two weeks of recovery, they were familiar with treadmill and continued their natural life without any exercises. They were killed after about six weeks. (The process of familiarization with treadmill in RTR group is due to probable effects of one-
week familiarity with effective factors. This is because the real goal of this research is only study the effects of six-week endurance training.

**Manner of making a tumor**

Tumor is rat adenocarcinoma type which was made by injection cancer cells model mc4 below the skin.

**Measuring of tumor**

Volume of tumor was measured in two dimensions. The greatest dimension of tumor was its length (L) and the other was width (W) (with 90 degree). After injection of cancer cells and creation of tumor up to the end of sixth week, we measured both the length and width of tumor by a digital caliper.

We could calculate volume of tumor by the following formula (Jones et al. 2010) in both groups:

\[ V = \frac{1}{2} (l^2 \times w) \]

**RESULTS**

**Findings**

**Testing of first theory**

Endurance training have no more effects on IL-17 in rats with breast cancer.

<table>
<thead>
<tr>
<th>Variant</th>
<th>Group</th>
<th>Mean &amp; Standard violation</th>
<th>t value</th>
<th>Freedom degree</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-17</td>
<td>Rest-Tumor-Exercise</td>
<td>21.93±154.46</td>
<td>4.126</td>
<td>8.9</td>
<td>0.003</td>
</tr>
<tr>
<td>(pg /ml)</td>
<td>Rest-Tumor-Rest</td>
<td>25.54±1.23</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

The results of independent t-test for comparing IL-17 in research groups, it is obvious that there is not a significant difference between IL-17 levels in both research groups. (P<0.05).

**Testing of second theory**

**Endurance training have no more effects on tumor volume in rats with breast cancer**

The results of independent t-test for comparing volume of tumor in research groups, it is obvious that there is a significant difference between volumes of tumor in both research groups. (P=0.0001).

According to the results of partial modified correlation coefficient test and Pearson correlation coefficient between IL17 levels and volume of tumor after one term of endurance training with separation of research groups, there is a significant relationship between IL-17 levels and volume of tumor in female mic of bulb/C with breast cancer after one term of endurance training. (P=0.0001).
DISCUSSION AND CONCLUSION

Most of researches have involved with any effects of sports on life quality, power and muscular strength with patients suffering from cancer. There is a little number of studies about cellular & molecular metabolisms of sports on inflammation and metastasis of tumors. Some of the researchers show that sports are able to slowdown any development and growth of tumors. (Agha Ali Nejad et al. 2008, Haffman-Goetz et al. 1994, Lee et al. 2005, Zeelinski et al. 2004). As a result, if sporting has such a potential but its molecular and cellular mechanism are not clear. Likely, it is possible that endurance training to decrease pro-inflammation cytokine, especially IL17 as one of the major factors in reduction of tumor inflammation, probably it is possible to benefit from endurance activities for reduction of tumor inflammation and even reducing of tumor volume. Therefore endurance training are considered as some adjuvant therapy besides other treatments. On the other hand, it is a long time that assumed IL17 as a potential tool in treatment of cancer and most of study reported the positive effect of IL17 in treatment of most types of cancers. But there are some discrepancies in obtained results, without a good conclusion. Of course IL17 has a major role in inflammation of breast cancer. Furthermore with regard to key role of IL17 increases of inflammation and of tumor growth and any probable effects of sports on its rate, it is necessary to evaluate any effects of endurance training IL17 at tumor. Also six weeks endurance training may cause a reduction in tumor volume with female rats. Finally it seems that there is a relationship between different levels of IL-17 protein of serum and tumor volume. There are lots of researches about physical training and cancer. Meanwhile there is great number of studies about breast cancer among other types of it. According to some epidemiologic studies, there are valuable evidences that physical training not only will prevent from promotion of disease but also reduce any dangers of breast cancer after menopause (%20). (Spack et al. 2010). Today physical training is an auxiliary factor in increase of life quality of patients suffering from breast cancer. (American Cancer Association, 2007). The role of physical activity in increase of different types of cancer is a subject of recent decades for most researchers. For this purpose they most of researches as well. The primary researches in this field are about any relation between physical activity and dangerous factors in various common types of cancer (Jones et al. 2010). There is some evidence that physical activity intervention may result in beneficial changes in inflammatory biomarkers included IL-17 in breast cancer survivors. However, available studies to-date are generally small, and the evidence is not consistent. Therefore, further physical activity and biomarkers in breast cancer survivors are warrants (Marie et al, 2012).

Totally we can say this study was for evaluating any effects of endurance training on IL-17 levels and volume of tumor in female mice of bulb/C with breast cancer. The most important finding of this research was an decrease in content of IL-17 in train group. It was significant from statistical viewpoint but its increase was considerable. Furthermore the volume of tumor had a significant difference in research groups. (P=0.0001). Therefore if we could decrease the quantities of cytokines of tumor especially IL-17 through endurance training as the most effective factor in prevention and reduction of tumor growth, probably we can benefit from endurance activities for reducing of tumor inflammation and even tumor volume along with introducing it as a cheap and auxiliary guideline in increase of breast cancer and prevention from metastasis of cancer cells besides all other therapeutic methods. As a result, it is recommended to perform physical training besides another therapeutic methods for treatment of breast cancer.

REFERENCES

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