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Aerobic Exercise, Estrogens, and Breast Cancer Risk

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With approximately 180,000 new cases reported in 2008, breast cancer continues to be the most frequently diagnosed cancer in American women and the second leading cause of death in this population. In recent systematic literature reviews, physical activity has been shown to be significantly associated with decreases in breast cancer risk. The goal of this training grant is to investigate changes in the hormonal profile of exercising women as one of the proposed mechanisms by which physical activity might lead to reductions in breast cancer risk. Specifically, this research project is a randomized clinical trial investigating the effects of a 16-week, aerobic exercise intervention on endogenous sex hormone levels and estrogen metabolism of sedentary, healthy, eumenorrheic, premenopausal women. Up-to-date highlights of this study include: 1) completion of recruitment and randomization efforts, 2) study completion by 290 women accounting for 90.6% of the total sample size, and 3) assay of more than half of total blood and urine samples. Participants in the last recruitment wave are expected to finish the study by the end of September 2009. Analyses of biological samples are scheduled to take place at the beginning of June 2009 and at the end of the study.
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INTRODUCTION

There is now high-quality epidemiological evidence to strongly suggest an inverse association between physical activity and breast cancer risk. The physiological mechanisms by which physical activity may help decrease breast cancer risk, however, are still not well understood. The goal of this training grant is to investigate how steady aerobic exercise may lead to changes in endogenous hormone levels and estrogen metabolism of young, sedentary, healthy women. Specifically, this study will measure plasma progesterone, estradiol, estrone sulfate, testosterone, and sex hormone binding globulin, as well as 12 urinary estrogen metabolites.

BODY

In terms of academic training, the PI has reached significant milestones toward the achievement of the doctorate degree in Nutrition at the University of Minnesota. For instance, both required preliminary written and oral exams have been successfully passed during the summer of 2008 and winter 2009, respectively. In addition, all required core and supporting courses (cumulative GPA 3.98) as well as teaching requirements have been completed. Efforts toward the completion of remaining graduating requirements (submission of doctoral dissertation and final oral defense) will begin immediately upon conclusion of this academic semester. On the other hand, clinical training has been enhanced through seminars offered by the University of Minnesota Cancer Research Center and the PI’s Food Science and Nutrition department. Lastly, the PI has been able to expand her training by attending scientific conferences such as the Transdisciplinary Research in Energetics and Cancer (TREC) this May, the American College of Sports Medicine (ACSM) at the end of May 2009, and the International Society for Behavioral Nutrition and Physical Activity (ISBNPA) in June 2009. The PI will be giving an oral presentation at the ACSM conference and a poster presentation at the ISBNPA conference.

In addition to academic accomplishments, significant research goals have been reached in terms of recruitment, retention, and subject completion for the Women In Steady Exercise Research (WISER) study. The PI will use data from the WISER study to write her doctoral dissertation. As of May 5 2009, 390 women have been recruited and randomized into the WISER study and 290 of them have completed the study. The final sample size, after accounting for a 20% dropout rate, is expected to include 320 women. Currently, 90.6% of this target sample size has been reached and the dropout rate in the exercise and control groups is 20% and 11%, respectively. The most recently randomized participants are expected to complete the study by the end of September 2009. Given the large amount of samples collected in the study, continuous efforts have been made to analyze blood and urine samples on a yearly basis. Specifically, sample analyses have been conducted during the summer when the PI can prepare, oversee and conduct the hormonal assays. Currently, 180 baseline/follow up blood samples have been assayed for estradiol, estrone sulfate,
progesterone, testosterone, and sex hormone binding globulin while 150 urine samples have been assayed for 12 urinary estrogen metabolites (estradiol, estrone, estriol, 16α-hydroxyestrone, 2- and 4- hydroxyestradiol and hydroxyestrone, and 2- and 4- methoxyestradiol and Methoxyestrone).

**KEY RESEARCH ACCOMPLISHMENTS**

- Recruitment and randomization of 390 participants
- Study completion by 290 women representing 90.6% of target sample size
- Assay of more than half (N=180) of total blood and urine samples

**REPORTABLE OUTCOMES**

Manuscripts based on main study outcomes are not expected to be written until the last participant completes the study, that is sometime in the early fall 2009. However, the writing of manuscripts describing the design and recruitment/retention details of the study have begun and these are expected to be submitted for publication at the end of 2009. One abstract has been accepted for an oral presentation at the annual ACSM conference in Seattle in May 2009 while another has been accepted for a poster presentation at the annual ISBNPA in June 2009. Please refer to the appendix for copies of the submitted abstracts.

Monies from this training grant have been allocated to cover the PI’s academic costs at the University of Minnesota, provide a stipend for living costs, and support the PI’s attendance to the ACSM annual conference.

**CONCLUSION**

Given premenopausal women have been largely underrepresented in breast cancer research and that physiological changes leading to the initiation and development of breast cancer are likely to occur over a long period of time, it is of outmost importance to conduct studies on environmental exposures and social behaviors in women at a younger age. The WISER study is a randomized, clinical trial seeking to understand the endocrine changes associated with a 16-week, aerobic exercise intervention in young, sedentary, healthy, premenopausal women. To date, this will be the largest human study measuring changes in endogenous sex hormone levels and estrogen metabolism in young women as a result of a structured exercise regimen. Results from this study will allow us to determine whether physical activity is really capable of inducing changes in the hormonal profile of women. This investigation is important because endocrine changes are one of the factors thought to be associated with breast cancer risk.

**REFERENCES**
3. E. M. Monninkhof et al., Epidemiology 18, 137 (2007).

APPENDIX 1
Oral presentation for ACSM annual conference, May 27-30, 2009 in Seattle, WA.

Aerobic Exercise, Estrogens and Breast Cancer Risk in Premenopausal Women

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PURPOSE: Currently known risk factors for breast cancer are difficult to control and modify and therefore, there is a need to identify alternative risk factors that are more suitable for intervention, especially among young women. The WISER study, Women in Steady Exercise Research, and the pilot study that preceded it investigate the effect of aerobic exercise on sex hormone levels in healthy premenopausal women.

METHODS: The WISER study is a randomized, exercise-controlled clinical trial that is randomizing 320 sedentary, healthy (BMI 18-40kg/m²), eumenorrheic, premenopausal women aged 18 to 30 years old into an exercise or no-exercise control group. Intervention subjects exercise aerobically for 30 minutes, 5 times a week during 4 menstrual cycles in which the workout intensity increases every four weeks by 5% of their age-predicted maximal heart rate until it reaches 80%-85%. The effect of aerobic exercise on blood sex hormones, urinary estrogen metabolites, menstrual cycle characteristics, ovulation status, measures of fitness (time to 85% max heart rate, MET-h/week), and body composition are being measured at baseline and follow-up. The study design for the completed pilot study in 15 women was identical, except for the lack of a comparison group.

RESULTS: In the WISER pilot study, after 15 weeks of aerobic exercise, there were significant reductions in body weight (-1.7 %, p <0.007), BMI (-2.4%, p< 0.01), and fat mass (-6.5%, p<0.04). In contrast, a significant 10.6% increase in submaximal fitnesss (p< 0.004) was attained through the intervention. No significant changes in endogenous estrogens were observed, though the pattern of changes was consistent with a reduction of cancer risk. Levels of estrone, 16-α-hydroxyestrone, estriol, 4-hydroxyestrogens, and the ratio of 2-to-4 hydroxyestrogens were reduced while that of 2-hydroxyestrogens and the ratio of 2-to-16-α-hydroxyestrone increased.

CONCLUSIONS: Results from the pilot study showed that aerobic exercise training at the dose currently recommended for health promotion and disease prevention results in significant reductions in body fat in young eumenorrheic women. Changes in estrogens were in the expected direction, though not significant. The larger, ongoing WISER trial was designed to further investigate the effects of aerobic exercise training on endogenous sex hormones and other breast cancer biomarkers. The WISER study will contribute to a better understanding of the effect of aerobic exercise on the hormonal and physiological profiles of healthy, sedentary, young women and help determine the efficacy of such an intervention on breast cancer risk prevention.

APPENDIX 2
Is Body Mass Index (BMI) A Good Indicator of Health and Healthy Behavior in Young, Sedentary Women?

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Purpose: Body mass index (BMI) is extensively used as a convenient and fairly accurate surrogate measure of body composition and health. Its use as an indicator of health behavior, however, has not been thoroughly explored in young, sedentary women. The objective of this study was to examine whether BMI is associated with measures of health and healthy behaviors in this population.

Methods: Baseline data was collected from 246 premenopausal women enrolled in an exercise intervention on bone mineral content and percent body fat from dual energy x-ray absorptiometry (DXA). Three-day food records were used to assess intake of dietary fiber, calcium, saturated fat and trans fat. Total physical activity and aerobic fitness were measured by the modifiable physical activity questionnaire and a sub-maximal treadmill fitness test, respectively. Women were divided into healthy and overweight BMI (≥ 25) categories. Associations were adjusted for age, race and education level.

Findings: BMI was significantly associated with increasing percent body fat and bone mineral content. BMI was inversely associated with measured aerobic fitness but not with self-reported physical activity. The only eating behavior to be significantly associated with increasing BMI levels was decreased dietary fiber intake.

Conclusions: In this study, BMI was significantly associated not only with body composition measures but also aerobic fitness and fiber intake. Differences in self-reported physical activity, however, were not significantly explained by differences in BMI. Therefore, BMI seems to be a good indicator of objective measures of fitness and healthy eating behaviors in young, sedentary women.