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ABSTRACT

Epidemiological and animal studies associate high levels of dietary fat with increased risk of sex hormone mediated cancer, such as breast cancer. A high intake of total fat and omega-6 fatty acids increases risk while omega-3 (n3) fatty acids are associated with risk reduction. Our proposal is testing the effect of dietary fat and fatty acids on sex hormone concentrations in post-menopausal women. The objectives are to evaluate 1) the effects of total fat and n3 intake on plasma and urinary sex hormone levels, 2) the relationship between plasma fatty acids and plasma and urinary sex hormones, and 3) the effects of total fat and n3 on the association between sex hormone concentrations and urinary prostaglandin E₂ (PGE₂). We are performing a randomized, Latin square-designed controlled feeding study testing High Fat, Low Fat, and Low Fat + n3 diets, each of 8 week duration. In order to determine the estrogenic effects of the diets, sex hormone endpoints will be measured reflecting availability, metabolism, and action. Plasma fatty acids fractions and urinary PGE₂ will be measured to evaluate mechanistic effects. At present 139 women have been screened by telephone, 24 have been screened in the clinic, 24 have been enrolled in the trial. Sixteen subjects have completed all aspects of the trial. Preliminary data of the sex hormone samples for the first 10 subjects has resulted in 2 abstracts for presentation at the DOD 2008 Era of Hope meeting. No manuscripts have yet been generated.

SUBJECT TERMS

dietary fat, omega-3 fatty acids, eicosanoids, sex hormones

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Introduction

Our project addresses important questions about the effects of dietary total fat and fatty acids on sex hormone concentrations in postmenopausal women. The study is being conducted at the General Clinical Research Center of the University of Minnesota. Our guiding hypothesis is that dietary total fat and fatty acid content affect sex hormone concentrations in a manner associated with sex hormone mediated cancer risk. The specific objectives are 1) to evaluate the effects of total fat and omega-3 fatty acid intake on plasma and urinary sex hormone levels in postmenopausal women, 2) to evaluate the relationship between plasma concentrations of specific fatty acids and concentrations of plasma and urinary sex hormones, and 3) to evaluate the effects of total fat and omega-3 fatty acids on the association between sex hormone concentrations and urinary prostaglandin E₂ and thromboxane B₂ concentrations.

We are conducting a well controlled feeding study to evaluate the role of fat and fatty acids in 24 healthy, postmenopausal women. The diets being tested include a "high risk" American diet (40% fat), a low fat diet (20% fat) and a low fat diet with supplemental omega-3 fatty acids (23% fat). Endpoints are being measured to assess availability, metabolism, and action of sex hormones in response to the diets. Plasma fatty acids fractions and urinary prostaglandin E₂ is being measured to evaluate mechanistic effects of dietary fat.

Increased understanding of the mechanisms by which dietary fat affect sex hormone action may provide critical information for the development of cancer-preventative dietary recommendations. Nutrition information provided as focused guidelines regarding fat intake can be developed for public use that indicate which types of foods to include in the daily diet and which to avoid.

Body

Study Progress:

The project is proceeding along the time line as defined in our statement of work. We received final approval to initiate the project from the University of Minnesota Human Subject Protection Program/Internal Review Board on 10/29/2004. A second no-cost extension has been granted for 1 year through 4/30/09.

Extensive recruitment efforts are ongoing. We advertise throughout the medical campus and surrounding campus buildings and through a text ad in the Fairview University Medical Center staff and patient flier. To date 139 subjects have been screened by telephone, 24 subjects have been screened at the research center and 24 subjects have been enrolled in the feeding trial. Of these subjects, 16 have completed all aspects of the study. We anticipate that the final subject will complete the feeding portion of the trial by January 09 and data analysis will be completed by Feb 09.

Personnel:

The following personnel are presently supported on this grant
Susan Raatz PhD RD, Principle Investigator (5% effort)
Mindy Kurzer PhD, Co-investigator (5% effort)
J Bruce Redmon MD, Co-investigator (5% effort)
Michael Walcher, Senior Scientist (25% effort)
Natalie Hansen, Student Food Service Worker (75% effort)

Lindsay Orr BA, Graduate Research Assistant – Currently funded on a DOD Predoctoral Fellowship based on this project

Key Research Accomplishments

Preliminary analysis for the first 10 subjects has been completed. These preliminary data showed that within subjects, 8 weeks consumption of a LF ω 3 significantly decreased plasma E₂ concentrations in postmenopausal women. Compared to HF, consumption of the LF ω 3 significantly decreased E₂ concentrations between groups at 8 weeks.

Reportable Outcomes

Training:

Lindsay Orr, BA, a graduate student in Human Nutrition, received a DOD Breast Cancer Research Program predoctoral traineeship award (Award #W81XWH-06-1-0778) in August of 2006 based on this study. This grant will fund Ms. Orr to work on this project as part of her predoctoral training and includes yearly travel from Sept 2006 through October 2009.

Data Presentation:

Two abstracts were accepted for presentation at the 2008 Era of Hope meeting as both posters and platform presentation. See Appendix 1 for the abstracts.

Conclusions

The study is progressing as projected on the “Statement of Work”. Given the nature of a long term feeding trial, no reportable data has yet been obtained. The study progress is as expected with recruitment of participants proceeding smoothly. The test diets are well accepted by the participants, all endpoint visits have gone well.

We expect to generate 3 primary papers from this project:

1. Primary results – Effect of fat modified diets on plasma sex hormone concentrations
2. Secondary results - Effect of fat modified diets on urinary sex hormone metabolite concentrations
3. Secondary results - Effect of fat modified diets on urinary eicosanoids and plasma fatty acids

References

None

Appendix 1: Women's Health Seminar Poster Presentation (abstract)

Breast cancer risk reduction: Effect of dietary fat and fatty acids on plasma estrogen and testosterone indices in postmenopausal women SK Raatz^{1,2},

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Breast cancer, a sex hormone mediated cancer, presents a significant problem in the United States. It is important to develop safe and effective preventative strategies for this disease. Epidemiological evidence and animal studies show that dietary fat is associated with risk of development of sex hormone mediated cancer. Specifically that a high intake of omega-6 fatty acids increases risk while omega-3 fatty acids are associated with risk reduction. Although the associations between dietary fat and sex hormone mediated cancers is unclear, it is likely due to mechanisms of endocrine balance.

The primary objective of this investigation was to determine whether diets of varied fat and fatty acid content would favorably affect sex hormone distribution in postmenopausal women in a direction associated with reduced risk of sex hormone-mediated cancer development. The specific aims of this study are to evaluate the effects of total fat and omega-3 fatty acid intake on androgen and estrogen indices.

In order to evaluate these relationships we are conducting a well-controlled feeding study to evaluate dietary fat and fatty acid effects. The diets being tested in 8 week feeding periods include a "high risk" American diet (40% fat; HF), a low fat diet (20% fat; LF) and a low fat diet with supplemental omega-3 fatty acids (23% fat; ω 3). Endpoint measures of plasma sex hormones were obtained at baseline (BL), 4, and 8 weeks of each dietary treatment. Plasma estradiol (E_2), testosterone (T) and sex hormone binding globulin (SHBG) were analyzed by radio-immunoassay for 10 participants. The Estrogen and Androgen Indices (EI, AI) were calculated as the ratio of E_2 :SHBG and T:SHBG, respectively.

A trend for decreased concentrations from baseline to 8 weeks was detected for E_2 with the LF and ω 3 diets. Consumption of the ω 3 increased SHBG concentrations significantly from baseline to 8 weeks ($p = 0.04$). The EI showed a trend for increase from baseline to 8 weeks in the HF compared to the ω 3 diet at week 8 ($p = .08$). The AI was significantly reduced following the HF compared to LF and ω 3 ($p = .006$ and $.002$, respectively).

Preliminary data shows that within subjects, 8 weeks consumption of a ω 3 diet significantly decreased plasma E_2 and increased SHBG concentrations in postmenopausal women. Compared to HF, consumption of the ω 3 and LF diets significantly decreased E_2 concentrations between groups at 8 weeks. The HF diet resulted in a decreased AI and increased EI. The LF and ω 3 diets are associated with reduced free estrogen levels which may reduce risk for breast cancer.

Effect of High Omega-3 Fatty Acid Diet on Markers of Breast Cancer Risk in Postmenopausal Women Orr L.R.², Redmon J.B.¹, Kurzer M.S.², Raatz S.K.¹

Departments of ¹Medicine and ²Food Science and Nutrition, University of Minnesota, Minneapolis, MN

Sex hormone mediated cancers, such as breast cancer, present a significant problem in the United States. It is important to develop safe and effective preventative strategies for these diseases. Epidemiological evidence and animal studies show that dietary fat is associated with risk of development of sex hormone mediated cancer. Specifically that a high intake of omega-6 fatty acids increases risk while omega-3 fatty acids are associated with risk reduction. Although the associations between dietary fat and sex hormone mediated cancers is unclear, it is likely due to mechanisms of endocrine balance, eicosanoid production, or immune function.

The primary objective of this investigation is to determine whether diets designed to increase plasma omega-3 fatty acid concentrations (a low fat diet, with or without omega-3 fatty acid enrichment), will favorably affect sex hormone distribution in postmenopausal women in a direction associated with reduced risk of sex hormone-mediated cancer development. The specific aims of this study are to evaluate the effects of total fat and omega-3 fatty acid intake on plasma sex hormone levels in postmenopausal women.

In order to evaluate these relationships we are conducting a well-controlled feeding study to evaluate dietary fat and fatty acid effects. The diets being tested in 8 week feeding periods include a "high risk" American diet (40% fat; HF), a low fat diet (20% fat; LF) and a low fat diet with supplemental omega-3 fatty acids (23% fat; LFn3). Endpoint measures of plasma sex hormones were obtained at baseline and 8 weeks of each dietary treatment.

Plasma estradiol (E_2), estrone (E_1), estrone sulfate (E_1 -S), testosterone (T), androstenedione (AS), sex hormone binding globulin (SHBG), follicle stimulating hormone (FSH), dehydroepiandrosterone (DHEA), and dehydroepiandrosterone sulfate (DHEAS) were analyzed by radio-immunoassay for 10 participants. SHBG levels were significantly increased at 8 weeks with LFn3 compared to LF ($p < 0.05$), and there was a trend for decreased DHEAS level at 8 weeks with LFn3 compared to LF ($p < 0.15$). A trend for increased E_2 was observed with HF compared to both LF and LFn3 at 8 weeks ($p < 0.15$). A trend for decreased E_1 and FSH was observed from baseline to 8 weeks with LFn3 ($p < 0.15$). No statistically significant differences were observed between treatments for A, T, E_1 -S, or DHEA.

Preliminary results suggest that LFn3 alters estrogen metabolism in a direction associated with reducing breast cancer risk in postmenopausal women. LFn3 significantly increased plasma SHBG and decreased DHEAS concentrations in postmenopausal women compared to LF at 8 weeks. Within the LFn3 group, trends were observed for decreased E_1 and FSH from baseline to 8 weeks. A trend for elevated E_2 level was observed with HF relative to LF and LFn3 at 8 weeks. The full effects of the three diets on plasma sex hormone profile will be further elucidated as more subjects complete the study.