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The Association Between Dietary Phytoestrogens and Endometriosis Development

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Abstract

Introduction: This study aims to investigate the relationship between phytoestrogens and endometriosis development. Endometriosis results from uterine-like endometrial and stromal cells growing outside the uterus [1]. People with endometriosis typically experience chronic inflammation, pelvic pain, and infertility resulting in lowered quality of life. Due to their structural similarities, phytoestrogens present in diets possess the ability to mimic the activity of estrogen and influence endometriosis development [3].

Methods: To better understand the role phytoestrogen plays in the development of endometriosis, a prospective clinical cohort study is proposed. The study will be conducted with a sample population of 196 participants lasting for six years [15]. Participants will be recruited if they are present with endometriosis on ultrasound and are confirmed through laparoscopy and excluded if they received a previous or current diagnosis of malignancy, current pregnancy, have been on a diet within the last year and utilized hormonal contraceptives within the last six months. Participants will be provided with a questionnaire describing the amount of phytoestrogen-containing food in their diets. This data will be compared against Agriculture-Agri-Food Canada to determine the relative concentration/amount of phytoestrogen in participants' diet foods.

The participants will be divided into groups, one group will receive high phytoestrogen-based foods(isoflavones:225 mg/day, lignans 100mg/day) to incorporate into their daily diet and the controls group (phytoestrogens free diet) [16]. Participants' diets will be analyzed every six months and lesion location, size and phenotype will be assessed via ultrasound.

Analysis of variance will be used to determine lesion size, location and phenotypes, paired t-test to determine inflammatory marker protein concentration and p-test to dictate statically significant results.

Anticipated Results: It is expected that participants with high amounts of phytoestrogen-containing foods in their diet will present a continual development of endometrial lesions while unexposed participants will present a stabilization in endometrial lesion development.

Conclusion: Based on the expected results, dietary phytoestrogen may lead to the development of endometriosis. As a result, women and dietitians should consider the effect of phytoestrogen-based foods when preparing diets. Future research should be conducted to assess phytoestrogen-containing foods to reap the nutritional benefits of these foods but also minimize endometrial lesions growth.

Keywords: endometriosis; estrogen; phytoestrogens; lesions; menstruation

Introduction

Endometriosis is one of the most prevalent gynecological diseases affecting 1 in 10 people with a uterus, leading to significant impairment of quality of life among those affected. Endometriosis results from uterine-like endometrial and stromal cells growing outside the uterus, leading to hormonal, neurogenic, and inflammatory milieu changes [3]. People with endometriosis typically experience severe chronic inflammation, pelvic pain, infertility, and complex, non-gynecological symptoms [3].

Endometriosis has been well characterized as an estrogen-dependent disease. Both autocrine and endocrine estrogen levels, including biosynthesis proteins and enzymes, are suspected of contributing to endometriosis pathogenesis significantly [1]. The relationship between estrogen and its respective receptors, estrogen receptors-α and β (ERα/β), have been well characterized in endometriosis etiology, development, and maintenance [1]. Despite our understanding of estrogen's role in endometriosis, with most treatments targeting the activity of the endogenous hormone to suppress menstruation, it is not fully understood if structurally similar molecules to estrogen affect endometriosis development [3]. One of the most common exposures of exogenous estrogen is through

diet. Phytoestrogens are structurally similar compounds to estrogen found in food such as tofu, grapes, soybean, grains, sprouts, and oilseed. Phytoestrogens can act as estrogen due to their structural similarities with the phenolic ring and the two hydroxyl groups allowing phytoestrogens to bind to the estrogen binding site with lower affinity than estrogen [6].

Although several theories explain the disease's etiology, Sampson's theory of retrograde flow is the most recognized theory. The theory suggests that menstrual flow leads to the spillage of endometrial tissues into the peritoneal cavity, allowing for the implantation and development of endometrial cells [3]. However, due to the homogenous occurrence of retrograde flow among people with a uterus, the etiology of endometriosis is believed to be multi-dimensional, involving numerous factors that remain to be elucidated [1]. There are four phenotypes of endometriosis which vary depending on the location and level of infiltration within surrounding tissue, including superficial endometriosis (SE; non-infiltrative shallow growth along the peritoneum), endometriosis or ovarian endometriosis (OE; dark fluid-filled cysts on the ovaries), and deep endometriosis (DE; infiltrative growth, leading to significant perturbation of surrounding anatomy) [1].

Irrespective of disease phenotype, the estrogen-dependent nature of endometriosis has been heavily documented in past and current literature, with aberrant estrogen production suspected of playing a significant role in the pathogenesis of the disease. Smuc et al and Mori et al, suggest a significant amount of estrogen secreted during menstruation in women diagnosed with endometriosis compared to healthy controls from the disease. This was noted by the high amount of mRNA and steroidogenic acute regulatory (StAR) and aromatase, the rate-limiting enzyme that catalyzes the conversion of androstenedione and testosterone to estrone and β-estradiol [7]. Additionally, research done by Huhtinen et al shows that normal peritoneal tissue among people with endometriosis produces significantly higher amounts of estrogen relative to healthy controls [1]. Ectopic tissue has been shown to express a large amount of ERα and ERβ, the binding sites for estrogen within the endometrium, which play a vital role in endometrial development. Overexpression of ERβ results in the inhibition of tumor necrosis factor-alpha (TNF-α)-mediated apoptosis, suppressing the expression of ERα [1]. This causes an inflammatory response in endometrial tissue, which could account for pain and infertility among those affected by endometriosis [2]. The reliance on the hormonal milieu by endometriosis is an active research area and of high clinical interest, with current therapeutics targeting estrogen production and interactions to minimize disease growth and suppress menstruation.

Due to the prominent shift towards holistic treatment in modern medicine, there has been recent interest in the effects of diet and the expression of endocrine hormones. Phytoestrogens are estrogen-mimicking compounds found in some foods, including tofu, grapes, soybean, grains, sprouts, and oilseed. Phytoestrogens can be divided into four groups based on their chemical structure: flavonoids, isoflavonoids, stilbenes, and lignans [8]. Phytoestrogens can act similarly to estrogen due to their structural similarities, including phenolic rings and the two hydroxyl groups, allowing them to bind to the ERα and ERβ receptors [8]. These bind with low affinity to endogenous receptors, interfering with hormonal and molecular signaling and may prevent menopause symptoms, type 2 diabetes, cardiovascular disease, obesity, and cancer [5]. However, in high-estrogen environments, including those with endometriosis, phytoestrogen has an anti-estrogen activity [4]. Various studies have suggested an association between phytoestrogen concentration and endometriosis, but its relationship is quite inconsistent [8]. This study aims to improve our understanding of the relationship between phytoestrogens and endometriosis development.

Due to phytoestrogens' ubiquitous presentation in diets and the estrogen-dependent nature of endometriosis, this study aims to investigate the role of phytoestrogens in endometriosis tissue development. The findings of this proposed study will improve our understanding of endometriosis development through estrogen dependency and allow for the integration of holistic, multimodal management through diet.

Research Question and Hypothesis

Research Question:

Does dietary consumption of phytoestrogen affect the development of endometriosis?

Hypothesis

The increased consumption of dietary phytoestrogens will inhibit the binding of estrogen to endogenous receptors in high-estrogen environments, increasing the development of lesion growth.

Methodologies

Study Design

In order to gain a better understanding of the role phytoestrogen plays in the development of endometriosis, a prospective clinical cohort study is proposed. The following protocol will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

Setting

This research study aims to sample participants from a single tertiary Women's Health Clinic in Edmonton, Alberta, for six years.

Sample Size

Given the currently expected prevalence of endometriosis, with a confidence level and power of 95%, 98 participants will be recruited per group for a total sample population of n=196.

Participants

Participants will be recruited within one year from a single tertiary gynecological clinic in Edmonton, Alberta. Participants will be excluded if they have received a previous or current diagnosis of malignancy, current pregnancy, have been on a diet within the last year and utilized hormonal contraceptives within the last six months. This was done to ensure there is no possible harm to participants and that all factors affecting the study results will be accounted for/anticipated.

Variables

The objective of the study proposed is to determine the effects of dietary phytoestrogens on endometriosis lesion development. The primary outcome measure is the change in endometriosis lesion development, including lesion size, location, amount, and phenotype, in response to phytoestrogen consumption relative to controls [10]. Although the mechanisms which contribute to lesion development remain to be elucidated, we speculate that phytoestrogens will affect lesion growth among those affected. However, several factors remain which may influence lesion development.

Participant demographics, including age and body mass index (BMI), may influence the kinetics of exogenous estrogen reaching distant locales, including the pelvic cavity, requiring adjustment for both variables [17]. Additionally, ethnicity and cultural factors may play a role in how phytoestrogens are metabolized among the participants, as household diets vary in their phytoestrogen levels.

Endometriosis characteristics may also vary at baseline, which may influence how phytoestrogens affect lesion growth. For instance, deep nodules may require significantly larger amounts of phytoestrogen intake relative to a superficial lesion. As such, endometriosis characteristics at baseline will be recorded and assessed relative to a standardized exposure corrected for age and BMI.

Data Sources/Measurement

Ultrasound and Laparoscopy

Exposed and unexposed participants will be given a transvaginal ultrasound (TVS) every 6 months to determine changes in disease growth relative to exposure to dietary phytoestrogens [14]. Upon initial exam, participants will be recruited if they are present with endometriosis on ultrasound and are confirmed through laparoscopy followed by histological confirmation. During laparoscopy, the size and location of the lesion will be recorded. The lesion's size, location, and phenotype will be characterized based on the internationally recognized European Society of Human Reproduction and Embryology (ESHRE 2022) guidelines.

Questionnaire

The participants will be given a questionnaire describing the amount of phytoestrogen-containing food in their current diet. Alongside dietary intake, demographics, including race, ethnicity, BMI, and age, will be collected. This data will be compared against Agriculture-Agri-Food Canada to determine the relative concentration/amount of phytoestrogen in participants' diet foods [16]. Throughout the study, the questionnaire will be given upon each visit to ensure dietary adherence.

Dietitian Visits

All participants will meet with a highly trained dietitian every six months before their routine ultrasound, who had previously reviewed the participant's questionnaire results. The visits will be composed of three sections: the initial, follow-up, and study completion. During the initial visit, both groups will be guided by the dietician on phytoestrogen-based diets, with the exposed group being provided with recommendations on high phytoestrogen-based foods to incorporate into their daily diet and the unexposed group foods to avoid [16]. Both groups will receive a digital log to document their daily food intake during this visit. The follow-up visits will encompass all visits between the initial and completion visit, where the digital log and repeated questionnaire data will be reviewed with the participant to ensure adherence. The completion visit will occur upon the completion of the study, where the relative exposures over the six years will be determined and reported.

Serum Collection

In order to determine whether endometriosis-associated inflammation, indicative of disease severity, has changed throughout the study due to phytoestrogen exposure, the serum will be collected every six months [10]. An immune-multiplex assay will be conducted to determine the expression of immune markers previously described in endometriosis, including C-reactive protein (CRP), interleukin (IL)-1, 8, 10, and TNF-α. It is expected there will be an increase in the level of immune markers due to increased endometrial lesion growth.

Potential bias

The participants are expected to record their dietary intake using an electronic log which may enable recall bias through improper reporting of dietary intake of phytoestrogens. The potential for recall bias will be minimized through periodic and consistent follow-up visits with dieticians to ensure adherence.

Statistical Methods and Analysis

The primary outcome of this study is to identify the changes in endometriosis lesion development relative to dietary phytoestrogen exposure. The ultrasound and laparoscopy findings, particularly the size and number of lesions, will be collected numerically by amount and volume (length x width x height; mm^2) [14]. The location and phenotype of the lesion will be described categorically, which will be converted into numerical data. As the

ultrasound will be performed periodically, the lesion's size, amount, location, and phenotype will be compared using a repeated measures analysis of variance (ANOVA) relative to baseline [10].

Laboratory analysis of serum for inflammatory markers will be quantified based on mean absorbance against the protein concentration (pg/ml) numerically per marker [10]. Similarly, the protein concentration will be assessed through paired t-tests relative to the participant's baseline concentration.

The pre-exposure questionnaire will illuminate whether pre-exposures to phytoestrogens through their typical diet influence disease development upon higher or lower exposure relative to group allocation. Similarly, we expect every participant to have various base diets, which will be modified to increase or decrease phytoestrogen intake. Both pre-exposure and base and all demographics collected will be evaluated using multivariate analysis to determine their influence on endometriosis development.

All data will be cleaned and analyzed using IBM SPSS (V29). A statistically significant result will be dictated using a confidence interval of 95%, $\alpha = 0.05$, and a p-value equal to or less than 0.05 [12].

Discussion

This research study intends to explore endometrial lesion development changes relative to phytoestrogen consumption. It is hypothesized that consumption of phytoestrogen leads to endometrial lesion growth. The analysis will be conducted through lesion size/number and location measured periodically through the study. Also, serum analysis will be used to identify concentration of endometriosis markers throughout the study.

The study is conducted with participants with differing baseline diets which are adjusted by increasing or decreasing their phytoestrogen consumption. Based on the hypothesis, there is a positive correlation between lesion development and phytoestrogen consumption. It is expected that there will be an increase in lesion growth during the study with an increased consumption of phytoestrogen [9]. Due to structural similarity to estrogen, phytoestrogen mimics estrogenic activity and increases endometrial lesion growth [5]. Also, there will be an increase in the amount and volume of endometrial lesion observed after each testing which show continual lesion growth throughout the study rather than initial lesion growth compared to baseline that remains constant for the duration of the study. This determines that phytoestrogen consumption can cause extreme lesion development compared to other factors that can cause the development of endometriosis. Additionally, there will be lesion growth in locations different from those observed at baseline. This will support Sampson's theory of retrograde flow, which states that menstrual flow leads to the spillage of endometrial tissues into the peritoneal cavity, allowing for the implantation and development of endometrial cells [3].

Also, the study also examines the presence of endometrial marker proteins in serum collected throughout the study. It is anticipated that as phytoestrogen consumption increases, there will be a corresponding increase in protein markers observed throughout the study. Increased concentration of endometriosis protein markers would indicate that phytoestrogen does not only influence lesion development but can also contribute to overall pathogenesis of endometriosis [10]. This further supports the hypothesis that phytoestrogen consumption plays a role in development and consumption of endometriosis.

The findings from this study poses significant implications for the understanding of the role dietary phytoestrogen consumption plays in endometriosis development. The analysis of the size, volume and location of endometrial lesions will provide a proper understanding of phytoestrogen in the growth and spreading of endometrial lesions [10]. Also, the examination of endometriosis marker protein in serum will provide insight into the pathological development of endometriosis in relation to phytoestrogen consumption [10]. Endometriosis is an estrogen-dependent condition and its progression is also attributed to hormonal imbalance [3]. Because through their structural similarity, phytoestrogen has the ability to mimic estrogen [3]. The results from this experiment will impact our understanding of how dietary factors can cause hormonal modulation that may influence endometriosis development [4]. Also, Phytoestrogens have been added to diets for their therapeutic effect due to its anti-inflammatory properties. Understanding its role in endometriosis development will provide vital information on how it should be included in dietary preparation and proven recommendation to manage endometriosis.

There are numerous strengths that were derived from this study. This is a prospective clinical cohort study that is designed for an extended six year period of data collection. According to previous literature, a common challenge encountered in endometriosis experiments is inadequate time for proper observation of lesion growth as observed in cross-sectional and retrospective studies [3]. The duration of this study provides the necessary time for reliable and vigorous data collection [9]. Lesion growth was confirmed through ultrasound and laparoscopy which provide accurate diagnosis reducing potential risks [14]. Also, six-month analysis of participant's diets provide valuable insight into progression of endometriosis development. The size and volume of endometrial lesions was run through the proper statistical test such as analysis of variance, paired t-test and p-test provided grounds for proper analysis and interpretation of endometriosis development [12]. On the other hand, there were various limitations encountered. Firstly, the study requires participants to follow specific diets which contain large amounts of phytoestrogen and due to its potential risk factors poses ethical questions [9]. The study is carried with participants already diagnosed with endometriosis. This offers a limited population which may

introduce selection bias and limit the proper representation of the broad population [13]. Also, the questionnaire section relies on participants to recall and report their phytoestrogen-containing foods in their diets. This introduces recall bias that may affect the accuracy and reliability of the study [13]. The study requires participants to follow a diet provided by the dietitian. It is difficult to ensure participants comply with the recommended diet over the six year duration and any variation may introduce confounding variables and affect the validity of the results [6]. Also, the study establishes a causal relationship between phytoestrogen consumption and endometriosis development. This relationship is difficult to establish due to external factors such as genetic predisposition, lifestyle and environmental factors [1].

This research plan is highly feasible but there are factors such as time, funding, access to participants, equipment and specialized facilities that should be held in close consideration for the study to be successful. The duration of the proposed study is six years. This is substantial time to observe changes and gather data but it is important to have the necessary resources required for the duration of the study [3]. Conducting a six-year clinical cohort study requires considerable funding. It will be necessary to seek grants, sponsorships and partnership to cover expenses for resources such as participants, data collection, laboratory analysis and compensation for participants and other involved personnels [17]. The study requires a sample size of 196 participants who are diagnosed with endometriosis. It might be challenging to recruit these participants needed for the study [3]. Collaboration with multiple healthcare facilities or endometriosis clinics would help to provide the pool of participants needed for the study. The study involves processes that require specialized equipment such for ultrasound, laparoscopy and analysis of dietary data and trained personnels to operate these equipment. The study also requires a team of researchers, clinicians and supporting staff for data collection and statistical analysis all with expertise in endometriosis [3].

This plan research proposal should provide a better understanding of the role of phytoestrogen in endometriosis development. If there is a significant association, it could highlight the importance of dietary factors in the management and treatment of endometriosis [8]. Also, the findings from the study could have future implications into endometriosis research [9]. Future research could focus on the mechanism into which phytoestrogen influences endometriosis development and progression. These involve exploring molecular mechanisms, hormonal interaction and immune system modulation related to phytoestrogen and endometriosis [8].

Conclusion

Phytoestrogen does influence the development of endometriosis. The mechanism of endometriosis is inconsistent and this study seeks to understand how phytoestrogen affects endometriosis development. The study excluded any participants on oral hormonal contraceptives, future research should investigate how hormonal contraceptives influence the role of phytoestrogens in endometriosis development and also how to maximize from the nutritional benefits of phytoestrogens while reducing lesions growth.

Conflict of Interest

The author(s) declare that they have no conflicts of interest.

Ethics approval and Participant's Consent

The participants recruited for this study will be diagnosed with endometriosis or present lesions growth via ultrasound. The participants will be told that the role of phytoestrogen in the development of endometriosis is not fully understood and consumption may lead to further lesion growth or reduction in lesion growth. Also, participants will be informed about the new diets that will be prescribed and guaranteed that they will be customized to fit their regular diet as best as possible.

Authors' Contribution

NJM: contributed to the introduction, study design and planning, statistical method analysis of data, interpretation and gave final approval of the version to be published.
MP: contributed to the introduction, study design and planning, statistical method analysis of data, interpretation and gave final approval of the version to be published.

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