The Positive Impact of Flaxseed (Linum Usitatissimum) on Breast Cancer

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Abstract

Breast cancer is a serious disease causing death for 13.7% of women. Hormones, persistently increased blood levels of estrogen are associated with an increased risk of breast cancer, as are increased levels of the androgens, androstenedione and testosterone. Patients who are currently undergoing treatment for breast cancer, or have been treated for breast cancer in the past, eating properly is particularly important. Fruit and vegetables, both contain high levels of nutrients with antioxidant properties, such as carotenoids and vitamins. We have made a multicentric study, there were involved 46 postmenopausal, under 70 years of age women. Our investigations have shown, but there is no absolute certainty about it, that flaxseeds eaten in a quantity of 40 g every day, may have a metabolic impact, which could reduce estrogen excess. This impact may be considered as favorable in the prevention and slowing down the evolution of breast cancer with positive hormonal receptors.

Keywords: breast cancer, flaxseed, nutrients, health

1. Introduction

Breast cancer is a type of cancer originating from breast tissue, most commonly from the inner lining of milk ducts or the lobules that supply the ducts with milk [1]. Worldwide, breast cancer comprises 22.9% of all cancers (excluding non-melanoma skin cancers) in women. In 2008, breast cancer caused 458,503 deaths worldwide (13.7% of cancer deaths in women) [2].

Breast cancer is more than 100 times more common in women than in men, although men tend to have poorer outcomes due to delays in diagnosis [2]. Prognosis and survival rates for breast cancer vary greatly depending on the cancer type, stage, treatment, and geographical location of the patient. Survival rates in the Western world are high [2]; for example, 84% of women in England diagnosed with breast cancer survive for at least 5 years [3].

The therapeutic objective in breast cancer is improving the quality of health care through standardized treatment and guidance for the physician in taking an optimal therapeutic decision, but also by providing access to all the potentially relevant information. The therapeutic algorithm starts with a description of the diagnostic and therapeutic work up in late-stage disease, as most cancers diagnosed in Romania are in a late stage. The therapeutic options for early breast cancer and tumors comparatively small to the breast size are more straightforward and involve either lumpectomy followed by radiotherapy or conservative mastectomy with breast reconstruction during the same surgical stage. Locally advanced breast cancer includes a heterogeneous group of tumors with various biologic properties, ranging from slowly growing and locally confined tumors to highly aggressive and rapidly fatal disease Cancer treatment strategies, in general – and for breast...
The aim of the following study is to determine if a diet of flaxseed to postmenopausal women aged under 70.

Risk factors of breast cancer:
Approximately 5% of new breast cancers are attributable to hereditary syndromes and well-established risk factors accounted for approximately 30% of cases [5]. One of the risk factor is age, the risk of getting breast cancer increases with it; sex, 99% of breast cancer cases are diagnosed in women [6] heredity, women who carry a harmful BRCA mutation have a 60% to 80% risk of developing breast cancer in their lifetimes [7]. Prior cancers, people who have previously been diagnosed with breast, ovarian, uterine, or bowel cancer have a higher risk of developing breast cancer in the future [6]; dietary factors: alcohol [8], phytoestrogens [10], iodine deficiency [14,15], obesity [16] environmental and racial factors [17,18]. Hormones, persistently increased blood levels of estrogen are associated with an increased risk of breast cancer, as are increased levels of the androgens androstenedione and testosterone (which can be directly converted by aromatase to the estrogens estrone and estradiol, respectively). Estradiol (E2) is the biologically active estrogen most often associated with mammary tumorigenesis. E2 is first oxidized in the liver to estrone (E1) [18]. Increased blood levels of progesterone are associated with a decreased risk of breast cancer in premenopausal women [19]. A number of circumstances which increase exposure to endogenous estrogens including not having children, delaying first childbirth, not breastfeeding, early menarche (the first menstrual period) and late menopause are suspected of increasing lifetime risk for developing breast cancer [20]. Tamoxifen is the usual endocrine (anti-estrogen) therapy for hormone receptor-positive breast cancer in pre-menopausal women. Tamoxifen is an antagonist of the estrogen receptor in breast tissue via its active metabolite, hydroxytamoxifen [21]. Tamoxifen is currently used for the treatment of both early and advanced ER+ (estrogen receptor positive) breast cancer in pre-menopausal women. Tamoxifen itself is a prodrug, having relatively little affinity for its target protein, the estrogen receptor. It is metabolized in the liver by the cytochrome P450 isofrom CYP2D6 and CYP3A4 into active metabolites such as 4-hydroxytamoxifen (afimoxifene) and N-desmethyl-4-hydroxytamoxifen (endoxifen) which have 30-100 times more affinity with the estrogen receptor than tamoxifen itself. These active metabolites compete with estrogen in the body for binding to the estrogen receptor. In breast tissue, 4-hydroxytamoxifen acts as an estrogen receptor antagonist so that transcription of estrogen-responsive genes is inhibited [22]. The ER/tamoxifen complex recruits intracellular proteins known as co-repressors to stop genes being switched on by estrogen [23].

Patients who are currently undergoing treatment for breast cancer, or have been treated for breast cancer in the past, eating properly is particularly important. Fruit and vegetables, both contain high levels of nutrients with antioxidant properties, such as carotenoids and vitamins. The association between fruit and vegetables and breast cancer is biologically plausible, because of their high contents of potentially anticarcinogenic compounds the literature on dietary patterns and breast cancer risk suggests that a diet characterized by food with high fat and high sugar content (western dietary pattern) is associated with an increased risk of breast cancer, whereas a diet characterized by vegetables, fruit, fish and white meat (prudent dietary pattern) is associated with a reduced risk.

Flax (Linum usitatissimum) is a member of the genus Linum in the family Linaceae. It is native to the region extending from the eastern Mediterranean to India and was probably first domesticated in the Fertile Crescent. It is known as Λινάρι (Linari) in Greek [24] Flax was extensively cultivated in ancient Ethiopia and ancient Egypt. In a prehistoric cave in the Republic of Georgia, dyed flax fibers have been found that date to 30,000 BC, implicating it as the first domesticated species in human history [25,26]. Flax seeds come in two basic varieties: brown and yellow or golden. Most types have similar nutritional characteristics and equal numbers of short-chain omega-3 fatty acids. The exception is a type of yellow flax called solin (trade name Linola), which has a completely different oil profile and is very low in omega-3 FAs. Although brown flax can be consumed as readily as yellow, and has been for thousands of years, it is better known as an ingredient in paints, fiber and cattle feed. Flax seeds produce a vegetable oil known as flaxseed or linseed oil, which is one of the oldest commercial
Flax seeds contain high levels of dietary fiber as well as lignans, an abundance of micronutrients and omega-3 fatty acids [27]. In addition to referring to the plant itself, the word "flax" may refer to the unspun fibres of the flax plant. The seeds contain nearly 25% of bulk materials (3–6% of mucilage, 4–7% of alimentary fibres), 30–45% fatty oil, 20–27% proteins, 3–5% minerals, vitamins, lignan precursors, linstatin, neolninustatin and linamarin, enzymes. The content of water is 5–14%. After swallowing the seeds arrived in the intestine are metabolized and eliminated. One part of the bulk materials in linseed is defaecated, the other part is fermented in the colon by bacteria. This process of fermentation can produce gas and lead to flatulence. The predominant products of fermentation are short chain fatty acids (SCFA), which are mainly resorbed. These acids can serve as nutrients for those cells forming the colonic mucosa. Beneficial properties of flaxseed are well known. Flax seeds may lower cholesterol levels, especially in women. Phytoestrogens, or dietary estrogens found in great quantities in flax seeds are classified into three major categories: isoflavones, resorcyclic acid lactones and coumestranes [28]. The major bioactive isoflavones are genistein and daidzein, which are derived from the precursors biochanin A and formononetin, respectively. Lignans are constituents of many plants and form the building blocks for the formation of lignin in the plant cell wall. They are more prevalent in the plant kingdom than are isoflavones. The two major lignans, enterolactone and enterodiol, are produced from matairesinol and secoisolariciresinol, respectively. Coumestrol is the most important form of coumestran consumed by humans [29]. B-glycoside forms of isoflavones are transformed into their active aglucone forms by bacterial enzymes in the intestine. Active forms of isoflavones reach concentrations in biological fluids surpassing that of the principal endogenous mammalian estrogens, estradiol or estrone [30]. Estradiol is the principle estrogen produced in human female ovaries [31,32]. Phytoestrogens, structurally similar to human estrogen, can act as estrogen mimics by exhibiting weak binding to estrogen receptors [33,34,35], or sometimes can act as antagonists of estrogen [36]. There are two variants of the estrogen receptor, alpha (ER-α) and beta (ER-β) and many phytoestrogens display somewhat higher affinity for ER-β compared to ER-α [37]. The phenolic ring that is indispensable for binding to estrogen receptor.

The phenolic ring of the phytoestrogen molecule mediates binding to estrogen receptors [38]. This involvement with estrogen receptors may initiate physiological changes to cells, tissues, or organs. Phytoestrogens like human estrogen have the potential to function as either estrogenic or antiestrogenic compounds depending on the amount that is ingested and absorbed by the body. A phytoestrogen's estrogenic or antiestrogenic activity is due to but not limited to "concentration dependency, receptor status, presence or absence of endogenous estrogens, and type of target organ or cell". The ability of a phytoestrogen to act as an estrogenic or antiestrogenic compound is an important factor in determining whether it would have a positive or negative impact on health. While phytoestrogens can display weak estrogen action, they can also act as an antiestrogen as shown by competitive binding with human estrogen at highly specific receptor sites.

In addition to interaction with ERs, phytoestrogens may also modulate the concentration of endogenous estrogens by binding or inactivating some enzymes, and may affect the bioavailability of sex hormones by binding or stimulating the synthesis of sex hormone binding globuline (SHBG) [39]. The antiestrogenic activity of phytoestrogens may contribute to a reduction of hormone-dependent cancers [40,41,42]. According to [43] selective phytoestrogens have an antiproliferative activity on breast cancer cells, as well as, an inhibitory effect on protein tyrosine kinase activity. Isoflavones are reported to have a number of disease-fighting properties; such as, an antitumoral effect in breast cancer [44] a protective role in hormone dependent cancers [41,42], an inhibition of cancer cell growth and angiogenesis, which is the development of bloodvessels around a tumor [45] and an effect on sex hormone metabolism. A phytoestrogen's estrogenic or antiestrogenic activity is due to but not limited to concentration dependency, receptor status, presence or absence of endogenous estrogens, and type of target organ or cell. Flaxseed is the richest source of mammalian lignan precursors. In vitro studies demonstrated that bacteria present in the colon convert these precursors into mammalian-lignans, which are resorbed subsequently. The lignans interfere with the metabolism and activity of oestrogens.
Experiments in pigs demonstrated the capacity of various fibres, including linseed, to bind oestrogens. Supplementation with flaxseed alters estrogen metabolism in postmenopausal women by increasing of urinary lignan excretion, without observing a negative effect on bone cell metabolism. In quantitative urine assays in 64 women studied 4 times during one year, a significant positive correlation could be shown between the intake of fibre (amounts not mentioned), lignan and phytooestrogen excretion and the concentration of plasma sex hormone-binding globulin (SHBG). In a study of ingestion of linseed powder on 18 normally cycling women the lutheal phase progesterone / estradiol was significantly higher during linseed cycles, this may conclude a significant specific role of lignans in the relation between diet and sex steroid action, and possibly between diet and the risk of breast and other hormonally dependent cancers. The linseed oil is exceptionally rich in alphalinolenic acid that may be associated with a preventive effect against cardiovascular diseases. Consumption of 40 g/d flaxseed for 3 months resulted in a significant decrease (6%) in both serum total and non-HDL cholesterol concentrations. Although flaxseed regimen reduced serum levels of LDL cholesterol by 4.7% and triglyceride by 12.8%, these decreases did not reach statistical significance. HDL-cholesterol concentrations were also somewhat lowered by flaxseed consumption. Apo A-1 and apo B concentrations were both significantly reduced as a result of flaxseed supplementation. Flax may also lessen the severity of diabetes by stabilizing blood-sugar levels. Since lignans and isoflavonoid phyto-oestrogens, produced from plant precursors by colonic bacteria, may be associated with protection against certain cancers, the effects of linseed...
ingestion on urinary lignans and isoflavonoids were investigated.

There is some support for the use of flax seed as a laxative due to its dietary fiber content. These effects are attributed to the bulk materials and in particular to the mucilage that binds with water and swells to form a demulcent gel in the intestine. Water is held back in the intestine due to the swelling of the mucilage. Faeces become softer. The volume of the intestinal content increases and causes a stretch stimulus, which results in a decrease in transit time. The swollen mass of mucilage forms a lubrication layer facilitating the transit of intestinal content [46]. Though excessive consumption without liquid can result in intestinal blockage. Broken seeds do not always cause a stretch stimulus because the increase of the volume may already start in the stomach. Consuming large amounts of flax seed may impair the effectiveness of certain oral medications, due to its fiber content, and may have adverse effects due to its content of neurotoxic cyanogen glycosides and immunosuppressive cyclic nonapeptides. The use as a poultice (symptomatic treatment of minor skin inflammations) can be attributed to the water-binding capacity of mucilages - physical action.

2. Materials and Method

We have made a multicentric study, in 2011, in 2 counties, Timis and Mehedinti, in 6 rural medical cabinets, there were involved in the study 46 postmenopausal under 70 years of age women. Study design, inclusion and exclusion criteria were the following.

Postmenopausal women, younger than 70 years old, who were not on hormone replacement therapy or any prescription medications known to influence estrogens, glucose, lipid, bowel movement or bone metabolism were recruited.

Women with cancer, liver disease, hypothyroidism or hyperthyroidism, gastrointestinal disorders, insulin-dependent diabetes mellitus, pelvic inflammatory disease, and endometrial polyps were excluded from the study.

Subjects signed a consent form after being provided with oral and written descriptions of the study. A complete medical history was obtained from all subjects before initiating the treatments.

The dietary regimen consisted of 40 g of ground whole flaxseed to be consumed daily, 10g/breakfast; 20g/lunch;10g/supper, for 2 months. Phisical exam was performed at the beginning and at the end of the study. Their estrogen level was monitored at baseline and monthly.

They have also completed a QoL SF 32 questionnaire and have been determined the next parameters: Body Weight, Sistolic and Diastolic Blood Pressure, Fasting Blood Glucose and Cholesterol level, also at baseline, after a month and 2 month. Subjects lived at home, consumed their habitual diet, and maintained their usual physical activity.

Subjects were asked to return any unusual symptom to monitor treatment compliance. Anthropometric data were collected at the beginning and the end of the study by a single trained staff member. Physical examinations were repeated at the end of the study. Estrogen (Estradiol and Estrone), Cholesterol, Glucose, Triglycerides, Lipoproteins levels were collected to all women at the beginning and at the end of the study.

3. Results and Discussion

From the 46 women only 38 completed the study (two because of medical problem, one suffered farming accident, other had surgery (haemorhoidectomy); other 2 because of lack of compliance of the dietary regimen, 2 were lost of follow up.

From the 38 women left, 19 were given flax seeds.

There were no significant differences in the baseline and final values of body weight and body mass index (BMI) among the subjects. The flaxseed regimen had serum level of LDL-Cholesterol reduced by 4.2%, and Triglyceride by 7.6%. The fasting blood glucose (FBS) was reduced by 7%, the 2 hour postprandial blood sugar (PPBS) was reduced by 18%.

Estrogen levels: Estradiol was 7.2% lowered with a peak of 11.4 and Estrone was 7.8% with a peak of 15.1% decreased more pronounced for overweight / obese women and more for estrone level.

Safety Endpoints: Patients, with an allergic history, have not been considered in our study. The laxative side effect of flaxseeds is insignificant, due to their grinding, they are ground and turned into powder, which is mixed with water.
Efficacy Endpoints: Our investigations have shown, but there is no absolute certainty about it, that flaxseeds eaten in a quantity of 40 g every day, may have a metabolic impact which could reduce estrogen excess. This impact may be considered as favorable in the prevention and slowing down the evolution of breast cancer with positive hormonal receptors. In this study, we have shown that supplementation of flaxseed to the diets of postmenopausal women can lower serum concentrations of total cholesterol and non-HDL cholesterol. This finding is in conformity with literature findings for the whole ground flaxseed.

We obtained a percentage of Triglyceride decreasing level of 7,6%, a significant value, dates in the international finding being ambiguous, some studies had no effects on Triglycerides, some had up to 17,5%. The mechanism might be that fibres from flaxseed mixes with fats and stops reabsorbing them in the colon as well as fastening the stools with a decreasing of its time passage, and so a smaller contact in time with the absorbing mucosa.

The findings of fasting blood glucose of a medium decrease of 7%, a max of 11,2% to a patient with an initial blood glucose of 108mg/dl might be due to the flaxseed capacity of being a rich source of both soluble and insoluble fiber. Probable due to insoluble fiber found in flaxseed that helps to slow the release of sugar into the bloodstream, preventing spikes in blood glucose levels and hence could decrease blood glucose levels. Similar results has also been reported on other studies.

Estrogen levels has been reduced too, similar to other studies (estradiol by 7,2% and estrone by 7,8%) probably due to the high mass of phytoestrogens contained in the seeds. The ability of a phytoestrogen to act as an estrogenic or antiestrogenic compound is an important factor in determining whether it would have a positive or negative impact on health. While phytoestrogens can display weak estrogen action, they can also act as an antiestrogen as shown by competitive binding with human estrogen at highly specific receptor sites.

This study has certain limitations. The patients population includes both prospective patients with a high risk of developing breast cancer, as well as retrospective patients with previously diagnosed breast cancer. These results need to be validated in prospective clinical trials.

For its number of medicinal uses, flaxseed has achieved recognition in complementary and alternative medicine for ages. Through its action on the cholesterol and triglyceride metabolism it is a good cardiovascular digestive adjuvant, especially for obese patients, for it’s glucose lowering capacity might be useful in diabetes mellitus patients and diabetes mellitus predisposed individuals, and a very important role that requires further investigations is the estrogene-antiestrogen capacity of its high levels of phytoestrogens, that may be applied for treatment and predisposing of hormonal malignant tumors as breast, prostate, colon cancers.

4. Conclusion

As a conclusion, eating flaxseeds is trustworthy and we highly recommend it, since it has lowering effect of estrogen in the blood and consequently slowing down the evolution of breast cancer with positive hormonal receptors.

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