Abstracts Flaxseed in Cancer

Nutr Cancer. 2018 Feb-Mar;70(2):306-315. doi: 10.1080/01635581.2018.1421677. Epub 2018 Jan 5.

Flaxseed Lignans Enhance the Cytotoxicity of Chemotherapeutic Agents against Breast Cancer Cell Lines MDA-MB-231 and SKBR3.

Di Y[1], De Silva F[1], Krol ES[1], Alcorn J[1].

Systemic cytotoxic chemotherapy remains the mainstay of metastatic breast cancer; however, prognosis and overall survival is unfavorable due to inadequate treatment response and/or unacceptable toxicity. Natural compounds and their active metabolites receive increasing attention as possible adjuvant therapy with cancer chemotherapeutics to improve treatment response, survival rates, and quality of life of breast cancer patients. This study investigated the combination of flaxseed lignans (Secoisolariciresinol and Enterolactone) with classic chemotherapeutic agents (Docetaxel, Doxorubicin, and Carboplatin) with different mechanisms of action to determine whether flaxseedlignans could enhance the cytotoxic effect of such drugs in the metastatic breast cancer cell lines, SKBR3 and MDA-MB-231. The experimental data suggests that flaxseed lignans significantly enhanced the ability of chemotherapeutic agents to cause cytotoxicity in SKBR3 and MDA-MB-231 breast cancer cells. A three compound combination study found that enterolactone and metformin together in combination with relatively low concentrations of chemotherapeutic drugs were able to significantly decrease cancer cell viability, compared to low concentrations of the individual chemotherapeutic drug alone. Our in vitro evaluation suggests a future direction in improving chemotherapeutic efficacy in breast cancer by adjuvant therapy with the flaxseed lignans.

Asian Pac J Cancer Prev. 2017 Apr 1;18(4):905-915.

Enterolactone Suppresses Proliferation, Migration and Metastasis of MDA-MB-231 Breast CancerCells Through Inhibition of uPA Induced Plasmin Activation and MMPs-Mediated ECM Remodeling

Mali AV[1,2], Joshi AA, Hegde MV, Kadam ShS.

BACKGROUND:

To enhance their own survival, tumor cells can manipulate their microenvironment through remodeling of the extra cellular matrix (ECM). The urokinase-type plasminogen activator (uPA) system catalyzes plasmin production which further mediates activation of matrix metalloproteinases (MMPs) and plays an important role in breast cancer invasion and

metastasis through ECM remodeling. This provides a potential target for therapeutic intervention of breast cancer treatment. Enterolactone (EL) is derived from dietary flax lignans in the human body and is known to have anti-breast cancer activity. We here investigated molecular and cellular mechanisms of EL action on the uPA-plasmin- MMPs system.

METHODS:

MTT and trypan blue dye exclusion assays, anchorage-dependent clonogenic assays and wound healing assays were carried out to study effects on cell proliferation and viability, clonogenicity and migration capacity, respectively. Real-time PCR was employed to study gene expression and gelatin zymography was used to assess MMP-2 and MMP-9 activities. All data were statistically analysed and presented as mean ± SEM values.

RESULTS:

All the findings collectively demonstrated anticancer and antimetastatic potential of EL with antiproliferative, antimigratory and anticlonogenic cellular mechanisms. EL was found to exhibit multiple control of plasmin activation by down-regulating uPA expression and also up-regulating its natural inhibitor, PAI-1, at the mRNA level. Further, EL was found to down-regulate expression of MMP-2 and MMP-9 genes, and up-regulate TIMP-1 and TIMP-2; natural inhibitors of MMP-2 and MMP-9, respectively. This may be as a consequence of inhibition of plasmin activation, resulting in robust control over migration and invasion of breast cancer cells during metastasis.

CONCLUSIONS:

EL suppresses proliferation, migration and metastasis of MDA-MB-231 breast cancer cells by inhibiting induced ECM remodeling by the 'uPA-plasmin-MMPs system'.

KEYWORDS: Enterolactone; breast cancer; Urokinase; type plasminogen activator; matrix metalloproteinases

Nutr Cancer. 2017 May-Jun;69(4):652-662. doi: 10.1080/01635581.2017.1296169. Epub 2017 Mar 21.

Enterolactone Induces G1-phase Cell Cycle Arrest in Nonsmall Cell Lung Cancer Cells by Downregulating Cyclins and Cyclin-dependent Kinases.

Chikara S[1], Lindsey K[1], Dhillon H[1], Mamidi S[2], Kittilson J[1], Christofidou-Solomidou M[3], Reindl KM[1].

Flaxseed is a rich source of the plant lignan secoisolariciresinol diglucoside (SDG), which is metabolized into mammalian lignans enterodiol (ED) and enterolactone (EL) in the digestive tract. The anticancer properties of these lignans have been demonstrated for

various cancertypes, but have not been studied for lung cancer. In this study, we investigated the anticancer effects of EL for several nonsmall cell lung cancer (NSCLC) cell lines of various genetic backgrounds. EL inhibited the growth of A549, H441, and H520 lung cancer cells in concentration- and time-dependent manners. The antiproliferative effects of EL for lung cancer cells were not due to enhanced cell death, but rather due to G_1-phase cell cycle arrest. Molecular studies revealed that EL decreased mRNA or protein expression levels of the G_1-phase promoters cyclin D1, cyclin E, cyclin-dependent kinases (CDK)-2, -4, and -6, and p-cdc25A; decreased phosphorylated retinoblastoma (p-pRb) protein levels; and simultaneously increased levels of $p21^{WAF1/CIP1}$, a negative regulator of the G_1 phase. The results suggest that EL inhibits the growth of NSCLC cell lines by downregulating G_1-phase cyclins and CDKs, and upregulating $p21^{WAF1/CIP1}$, which leads to G_1-phase cell cycle arrest. Therefore, EL may hold promise as an adjuvant treatment for lung cancer therapy.

BMC Complement Altern Med. 2017 Jan 9;17(1):30. doi: 10.1186/s12906-016-1512-3.

Enterolactone alters FAK-Src signaling and suppresses migration and invasion of lung cancercell lines.

Chikara S[1], Lindsey K[1], Borowicz P[1,2], Christofidou-Solomidou M[3], Reindl KM[4].

BACKGROUND:

Systemic toxicity of chemotherapeutic agents and the challenges associated with targeting metastatic tumors are limiting factors for current lung cancer therapeutic approaches. To address these issues, plant-derived bioactive components have been investigated for their anti-cancer properties because many of these agents are non-toxic to healthy tissues. Enterolactone (EL) is a flaxseed-derived mammalian lignan that has demonstrated anti-migratory properties for various cancers, but EL has not been investigated in the context of lung cancer, and its anticancer mechanisms are ill-defined. We hypothesized that EL could inhibit lung cancer cell motility by affecting the FAK-Src signaling pathway.

METHODS:

Non-toxic concentrations of EL were identified for A549 and H460 human lung cancer cells by conducting 3-(4, 5-Dimethylthiazol-2-yl)-2, 5-Dephenyltetrazolium Bromide (MTT) assays. The anti-migratory and anti-invasive potential of EL for lung cancer cell lines was determined by scratch wound healing and Matrigel® invasion assays. Changes in filamentous actin (F-actin) fiber density and length in EL-treated cells were determined using phalloidin-conjugated rhodamine dye and fluorescent microscopy. Vinculin expression in focal adhesions upon EL treatment was determined by immunocytochemistry. Gene and protein expression levels of

FAK-Src signaling molecules in EL-treated lung cancer cells were determined using PCR arrays, qRT-PCR, and western blotting.

RESULTS:

Non-toxic concentrations of EL inhibited lung cancer cell migration and invasion in a concentration- and time-dependent manner. EL treatment reduced the density and number of F-actin fibers in lung cancer cell lines, and reduced the number and size of focal adhesions. EL decreased phosphorylation of FAK and its downstream targets, Src, paxillin, and decreased mRNA expression of cell motility-related genes, RhoA, Rac1, and Cdc42 in lung cancer cells.

CONCLUSIONS:

Our data suggest that EL suppresses lung cancer cell motility and invasion by altering FAK activity and subsequent activation of downstream proteins needed for focal adhesion formation and cytoskeletal rearrangement. Therefore, administration of EL may serve as a safe and complementary approach for inhibiting lung tumor cell motility, invasion, and metastasis.

KEYWORDS:

Cell motility; Enterolactone; F-actin; Flaxseed; Focal adhesion; Lung cancer cells; Rho GTPases

Cancer Causes Control. 2015 Nov;26(11):1521-50. doi: 10.1007/s10552-015-0659-4. Epub 2015 Sep 9.

A systematic review of dietary, nutritional, and physical activity interventions for the prevention of prostate cancer progression and mortality.

Hackshaw-McGeagh LE[1,2], Perry RE[3], Leach VA[4,5], Qandil S[4], Jeffreys M[4], Martin RM[3,4], Lane JA[3,4].

PURPOSE:

Given the long-term, although potentially fatal, nature of prostate cancer, there is increasing observational evidence for the reduction in disease progression and mortality through changes in lifestyle factors.

METHODS:

We systematically reviewed dietary, nutritional, and physical activity randomized interventions aimed at modifying prostate cancerprogression and disease-specific mortality, including a detailed assessment of risk of bias and methodological quality.

RESULTS:

Forty-four randomized controlled trials of lifestyle interventions, with prostate cancer progression or mortality outcomes, were identified. Substantial heterogeneity of the data prevented a meta-analysis. The included trials involved 3,418 prostate cancer patients,

median 64 men per trial, from 13 countries. A trial of a nutritional supplement of pomegranate seed, green tea, broccoli, and turmeric; a trial comparing flaxseed, low-fat diet, flaxseed, and low-fat diet versus usual diet; and a trial supplementing soy, lycopene, selenium, and coenzyme Q10, all demonstrated beneficial effects. These trials were also assessed as having low risk of bias and high methodological quality (as were seven other trials with no evidence of benefit). The remaining trials were either underpowered, at high or unclear risk of bias, inadequately reported, of short duration or measured surrogate outcomes of unproven relationship to mortality or disease progression, which precluded any benefits reported being reliable.

CONCLUSION:

Large, well-designed randomized trials with clinical endpoints are recommended for lifestyle modification interventions.

KEYWORDS: *Diet; Nutrition; Physical activity; Prostate cancer; Randomized controlled trials; Systematic review*

Nutr Cancer. 2015;67(6):1001-9. doi: 10.1080/01635581.2015.1053496. Epub 2015 Jul 2.

α-Linolenic Acid Reduces Growth of Both Triple Negative and Luminal Breast Cancer Cells in High and Low Estrogen Environments.

Wiggins AK[1], Kharotia S, Mason JK, Thompson LU.

Flaxseed, rich in α-linolenic acid (ALA), is a complementary breast cancer (BC) therapy; however ALA effectiveness and mechanism are unclear. Variation in cellular expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and estrogen (E2) levels may alter ALA effectiveness. This research determined the effect of ALA on growth, apoptosis, and phospholipid fatty acids of 4 BC cell lines with varying receptor expression ± E2. MCF-7 (ER+/PR+/HER2-), BT-474 (ER+/PR+/HER2+), MDA-MB-231 (ER-/PR-/HER2-) and MDA-MB-468 (ER-/PR-/HER2-) cells were incubated with ALA (50-200 μM) ± 1 nM E2 for 48-72 h. ALA dose-dependently reduced growth, measured by trypan blue exclusion, of all cells (55-80% with 75 μM), and this effect was not altered by E2. ALA (75 μM)+E2 induced apoptosis, measured by flow cytometry (up to 111.2%). Decreased growth and increased apoptosis is related to increased cell phospholipid % ALA (up to 25.1%), measured by gas chromatography. ALA is shown for the first time to reduce cell growth and induce apoptosis regardless of receptor expression and E2 environment, by incorporating into BC phospholipids, supporting the use of ALA and ALA-rich foods as a safe, inexpensive complementary therapy for a wide range of BC.

Nutr Cancer. 2015;67(5):857-64. doi: 10.1080/01635581.2015.1042549. Epub 2015 May 26.

Effects of Flaxseed Lignan Secoisolariciresinol Diglucosideon Preneoplastic Biomarkers of Cancer Progression in a Model of Simultaneous Breast and Ovarian Cancer Development.

Delman DM[1], Fabian CJ, Kimler BF, Yeh H, Petroff BK.

Breast cancer prevention efforts are focused increasingly on potentially beneficial dietary modifications due to their ease of implementation and wide acceptance. Secoisolariciresinol diglucoside (SDG) is a lignan found in high concentration in flaxseed that may have selective estrogen receptor modulator-like effects resulting in antiestrogenic activity in a high estrogen environment. In parallel with a human phase II prevention trial, female ACI rats (n = 8-10/group) received 0, 10, or 100 ppm SDG in the feed. The 100 ppm SDG treatment produced similar blood lignan levels as those observed in our human pilot study. Mammary and ovarian cancer progression were induced using local ovarian DMBA treatment and subcutaneous sustained release 17β-estradiol administered starting at 7 weeks of age. Mammary gland and ovarian tissues were collected at 3 mo after initiation of treatment and examined for changes in epithelial cell proliferation (Ki-67, cell counts), histopathology, and dysplasia scores, as well as expression of selected genes involved in proliferation, estrogen signaling, and cell adhesion. Treatment with SDG normalized several biomarkers in mammary gland tissue (dysplasia, cell number, and expression of several genes) that had been altered by carcinogen. There is no indication that SDG promotes preneoplastic progression in the ovarian epithelium.

Curr Opin Urol. 2014 May;24(3):318-23. doi: 10.1097/MOU.0000000000000049.

What should we tell prostate cancer patients about (secondary) prevention?

Chan JM[1], Van Blarigan EL, Kenfield SA.

PURPOSE OF REVIEW:

To briefly summarize the epidemiologic findings of selected lifestyle factors for prostate cancer progression, metastasis, or death, with a focus on behaviors after diagnosis where possible. We conclude by providing guidance on the lifestyle practices that physicians may wish to prioritize for discussion with their patients.

RECENT FINDINGS:

Growing, but still limited, evidence suggests that lifestyle factors after prostate cancer diagnosis may impact prostate-cancer-specific and overall morality. In particular, smoking and obesity

may increase the risk of disease progression and mortality, whereas engaging in vigorous physical activity or brisk walking and consuming a diet rich in vegetables (particularly tomato sauce and cruciferous) and vegetable fats may lower the risk.

SUMMARY:

Patients should be counseled not to use tobacco products; to engage in daily physical activity; to minimize sedentary behavior; to consume plenty of healthy fats (i.e. fish, nuts, vegetable oils, soybeans, avocados, and flaxseed) and vegetables; to focus on getting nutrients from foods rather than supplements; and to limit refined grains, sugars, processed meat, and high-fat dairy.

J Pulm Respir Med. 2013 Aug 30;3(4):154.

Dietary Flaxseed in Non-Small Cell Lung Cancer Patients Receiving Chemoradiation.

Berman AT[1], Turowski J[2], Mick R[3], Cengel K[1], Farnese N[1], Basel-Brown L[1], Mesaros C[4], Blair I[4], Lawson J[4], Christofidou-Solomidou M[3], Lee J[3], Rengan R[1].

PURPOSE:

The standard of care in Locally-Advanced Non-Small Cell Lung Cancer (LA-NSCLC) is chemotherapy and radiation; however, Radiation-Induced Lung Injury (RILI), which may be prevented by the anti-inflammatory and anti-oxidant properties of Flaxseed (FS), impedes its maximum benefit.

MATERIALS AND METHODS:

Patients with LA-NSCLC requiring definitive RT were randomized to one FS or control muffin daily from start to 2 weeks after RT. Blood and urine were collected to quantify plasma FS metabolites, Enterodione (ED) and Enterolactone (EL), and urinary oxidative stress biomarkers, 8, 12-iso-iPF2a-VI (isoprostane) and 8-oxo-7,8-dihydro-2'deoxyguanosine (8-oxo-dGuo). Tolerability was defined as consuming ≥ 75% of the intended muffins and no ≥ grade 3 gastrointestinal toxicities.

RESULTS:

Fourteen patients (control,7; FS,7) were enrolled. The tolerability rates were 42.9 versus 71.4% (p=0.59) for FS and control, respectively. Mean percentages of intended number of muffins consumed were 37% versus 73% (p=0.12). ED and EL increased at onset of FS and decreased with discontinuation, confirming bioavailability. Isoprostane and 8-oxo-dGuo were detectable. There was a trend towards decreased rates of pneumonitis in FS.

CONCLUSIONS:

This is the first study to report FS bioavailability and quantify oxidative stress markers in NSCLC patients. FS in the administered muffin formulation did not meet tolerability criteria. Given the promising mechanism of FS as a radioprotectant, further investigations should focus on the optimal method for administration of FS.

KEYWORDS:

8-oxo dGuo; Esophagitis; Fibrosis; Flaxseed; Isoprostane; Lignan; Non-small cell lung cancer; Pneumonitis; RILI; Radiation; Radiation induced lung injury

Gynecol Oncol. 2013 Sep;130(3):620-8. doi: 10.1016/j.ygyno.2013.05.018. Epub 2013 May 23.

Long term consumption of flaxseed enriched diet decreased ovarian cancer incidence and prostaglandin E_2in hens.

Eilati E[1], Bahr JM, Hales DB.

OBJECTIVE:

Ovarian cancer is the most lethal gynecological malignancy. Prevention may be the best approach to reduce ovarian cancer. Flaxseed is the richest vegetable source of omega-3 fatty acids which may be effective in the prevention of ovarian cancer. Prostaglandin E_2 (PGE_2) is the most pro-inflammatory ecoisanoid and one of the downstream products of two isoforms of cyclooxygenase (COX) enzymes: COX-1 and COX-2. Our objective was to determine if long-term consumption of a flaxseed enriched diet decreased ovarian cancer severity and incidence in the laying hen and to investigate its potential correlation with the expression of COX enzymes and PGE_2 concentration.

METHODS:

White Leghorn hens were fed 10% flaxseed-enriched or standard diet for 4years. The severity and incidence of ovarian cancerwere determined by gross pathology and histology. COX-1 and COX-2 protein and mRNA expression and PGE_2 concentrations in ovaries were measured by Western blot, quantitative real-time PCR and ELISA, respectively.

RESULTS:

The results demonstrated that there was a reduction in ovarian cancer severity and incidence in hens fed flaxseed diet. In correlation with decreased ovarian cancer severity and incidence, concentration of PGE_2 and expression of COX-2 were diminished in ovaries of hens fed flaxseed.

CONCLUSIONS:

Our findings suggest that the lower levels of COX-2 and PGE_2 are the main contributing factors in the chemo-suppressive role of long-term flaxseed consumption in ovarian cancer in laying hens.

These findings may provide the basis for clinical trials of dietary intervention targeting prostaglandin biosynthesis for the prevention and treatment of ovarian cancer.

KEYWORDS: Cyclooxygenase; Flaxseed; Inflammation; Laying hen; Ovarian cancer; Prostaglandin E(2)

J Med Food. 2013 Apr;16(4):357-60. doi: 10.1089/jmf.2012.0159.

Flaxseed-derived enterolactone is inversely associated with tumor cell proliferation in men with localized prostate cancer.

Azrad M[1], Vollmer RT, Madden J, Dewhirst M, Polascik TJ, Snyder DC, Ruffin MT, Moul JW, Brenner DE, Demark-Wahnefried W.

Enterolactone and enterodiol, mammalian lignans derived from dietary sources such as flaxseed, sesame seeds, kale, broccoli, and apricots, may impede tumor proliferation by inhibiting activation of nuclear factor kappa B (NFκB) and vascular endothelial growth factor (VEGF). We examined the associations between urinary enterolactone and enterodiol with prostatic tumor expression of NFκB, VEGF, and Ki67 among 147 patients with prostate cancer who participated in a presurgical trial of flaxseed supplementation (30 g/day) for ~30 days. Urinary enterolignans and tissue biomarkers were determined by high-performance liquid chromatography and immunohistochemistry, respectively. After supplementation, we observed significant correlations between intakes of plant lignan and urinary concentrations of total enterolignans (ρ=0.677, P<.0001), enterolactone (ρ=0.676, P<.0001), and enterodiol (ρ=0.628, P<.0001). Importantly, we observed that total urinary enterolignans and enterolactone were significantly and inversely correlated with Ki67 in the tumor tissue (ρ=-0.217, P=.011, and ρ=-0.230, P=.007, respectively), and a near-significant inverse association was observed for enterodiol (ρ=-0.159, P=.064). An inverse association was observed between enterolactone and VEGF (ρ=-0.143, P=.141), although this did not reach statistical significance. We did not observe an association between enterolignans and NFκB. In conclusion, flaxseed-derived enterolignans may hinder cancer cell proliferation via VEGF-associated pathways.

Indian J Cancer. 2012 Jan-Mar;49(1):181-7. doi: 10.4103/0019-509X.98948.

In vitro anti-metastatic activity of enterolactone, a mammalian lignan derived from flax lignan, and down-regulation of matrix metalloproteinases in MCF-7 and MDA MB 231 cell lines.

Mali AV[1], Wagh UV, Hegde MV, Chandorkar SS, Surve SV, Patole MV.

BACKGROUND:
Actin cytoskeleton is involved in actin-based cell adhesion, cell motility, and matrix metalloproteinases(MMPs) MMP2, MMP9, MMP11 and MMP14 are responsible for cell invasion in breast cancer metastasis. The dietary intake of lignan from flax seed gets converted to enterolactone (EL) and enterodiol in the human system. Here we show that the enterolactone has a very significant anti-metastatic activity as demonstrated by its ability to inhibit adhesion and invasion and migration in MCF-7 and MDA MB231 cell lines.

MATERIALS AND METHODS:
Migration inhibition assay, actin-based cell motility assay along with reverse transcriptase polymerase chain reaction (RT-PCR) for MMP2, MMP9, MMP11 and MMP14 genes were performed in MCF-7 and MDA MB 231 cell lines.

RESULTS:
Enterolactone seems to inhibit actin-based cell motility as evidenced by confocal imaging and photo documentation of cell migration assay. The results are supported by the observation that the enterolactone in vitro significantly down-regulates the metastasis-related metalloproteinases MMP2, MMP9 and MMP14 gene expressions. No significant alteration in the MMP11 gene expression was found.

CONCLUSIONS:
Therefore we suggest that the anti-metastatic activity of EL is attributed to its ability to inhibit cell adhesion, cell invasion and cell motility. EL affects normal filopodia and lamellipodia structures, polymerization of actin filaments at their leading edges and thereby inhibits actin-based cell adhesion and cell motility. The process involves multiple force-generating mechanisms of actin filaments i.e. protrusion, traction, deadhesion and tail-retraction. By down-regulating the metastasis-related MMP2, MMP9 and MMP14 gene expressions, EL may be responsible for cell invasion step of metastasis.

Nutr Cancer. 2012;64(5):695-703. doi: 10.1080/01635581.2012.687426. Epub 2012 May 29.

Intake of phytoestrogen foods and supplements among women recently diagnosed with breast cancer in Ontario, Canada.

Boucher BA[1], Cotterchio M, Curca IA, Kreiger N, Harris SA, Kirsh VA, Goodwin PJ.

Phytoestrogens are found in foods such as soy (isoflavones) and flaxseed (lignans), and certain botanical supplements. Their role in estrogen receptor positive (ER+) breast cancer recurrence and treatment is controversial, and it is unknown how this affects intake among patients. The Ontario Cancer Registry was used to identify 417 population-based breast cancer cases (mean

time from diagnosis was 57 days). A questionnaire was mailed to determine intake of phytoestrogen foods and supplements in the last 2 mo, changes since diagnosis and differences by ER tumor status or hormonal treatment. Of 278 (67%) respondents, 56% consumed soy foods, 39% consumed isoflavone-rich foods (tofu, soybeans, soy milk, soy nuts), and 70% ate lignan-rich foods, including flaxseed (33%). Only soy milk, flaxseed, and flaxseed bread were commonly consumed more than once/wk. Few patients (4%) took isoflavone (soy, red clover, kudzu, licorice, isoflavones) or lignan/flaxseed supplements. Since diagnosis, 17% started or stopped soy foods (most stopped); this was more prevalent among those receiving hormonal treatment (20%; 95% confidence interval (CI): 14, 26) than not (6%; 95% CI: 1, 12). No other differences by ER status or hormonal treatment were observed. Research is needed to confirm this and to explore influencing factors.

Vopr Pitan. 2012;81(6):61-6.

[Phytoestrogenis properties of flaxseed lignans].

[Article in Russian]
Martinchik AN, Zubtsov VV.

The analysis of experimental, clinical and epidemiological data on the phytoestrogen properties of the components of flaxseed Linum Usitatissimum L., especially lignans and products of their biotransformation in humans and animals enterodiol (END) and enterolactone (ENL) are presented. Flaxseed is the richest in the vegetable world source of lignans (up to 0,7-1,5% of dry weight of seed), among which prevails secoisolariciresinol diglycoside (SIR-DG). Plant lignans are characterized as natural phytoestrogen that reduce the risk of hormonedependent cancers of breast, uterus and prostate. Anticancerogenic activity of flaxseed lignans due to antioxudant effect END and ENL in the human body. The antioxidant activity of SIR, END, ENL and SIR-DG is higher than that of vitamin E and the antioxidant activity of SIR, END and ENL higher than SIR-DG. On the basis of evidence-based biomedical researches on various models in experimental carcinogenesis, on the tumor cells in vitro, in clinical trials in patients with hormone-dependent tumors, and, finally, in epidemiological studies have proved the anticarcinogenic activity of the components of the flaxseed and validity of recommendations for preventive and curative use in hormone-dependent tumors.

J Med Food. 2010 Aug;13(4):834-41. doi: 10.1089/jmf.2009.0172.

Extraction of lignans from flaxseed and evaluation of their biological effects on breast cancerMCF-7 and MDA-MB-231 cell lines.

Lehraiki A[1], Attoumbré J, Bienaimé C, Matifat F, Bensaddek L, Nava-Saucedo E, Fliniaux MA, Ouadid-Ahidouch H, Baltora-Rosset S.

Over the last decade, there has been an increasing interest in using flaxseed (Linum usitatissimum) in diet in order to improve nutritional and health status. Lignans are major components of flaxseed. Therefore an extraction procedure for lignans from flaxseed has been optimized. The influence of some parameters was investigated: first the preliminary extraction step with alcoholic solvent, and then the solvent polarity and pH of the extract. All these conditions affected the total lignan content, but the most critical variables were preliminary extraction and solvent polarity. The optimized procedure, consisting of a direct hydrolysis in hydrochloric acid (1 M) at 100 degrees C for 1 hour followed by an extraction with a mixture of ethyl acetate/hexane (90:10 vol/vol), was applied to 340 g of defatted flaxseed and resulted in the isolation of secoisolariciresinol and anhydrosecoisolariciresinol with a purity of 97% and 98%, respectively, as determined by high-performance liquid chromatography. The ability of these two compounds and that of secoisolariciresinol diglucoside to modulate the growth of human breast cancer MCF-7 and MDA-MB-231 cell lines was assessed. Our results show that lignans modulate development of breast cancer cells. The most intense effect was observed for anhydrosecoisolariciresinol, which significantly decreased cell growth at 50 and 100 microM.

Nutrients. 2010 Feb;2(2):99-115. doi: 10.3390/nu2020099. Epub 2010 Jan 28.

Assessment of information to substantiate a health claim on the prevention of prostate cancer by lignans.

Saarinen NM[1], Tuominen J, Pylkkänen L, Santti R.

Lignans and their in vivo metabolites, especially enterolactone (ENL), have attracted substantial interest as potential chemopreventive agents for prostate cancer. Preclinical and clinical interventions performed with lignan-rich flaxseed that use surrogate biomarkers as endpoints suggest that lignans may attenuate prostate carcinogenesis in individuals with increased risk or with diagnosed cancer. No unequivocal prostate cancer risk reduction has been found for lignans in epidemiological studies, suggesting that lignan concentrations found in populations consuming a regular non-supplemented diet are not chemopreventive in prostate cancer. Presumably, the main obstacles in assessing the efficacy of food lignans is limited knowledge of the serum and tissue lignan concentrations required for the putative prevention. Further clinical studies performed with the purified compounds are required to substantiate a health claim.
KEYWORDS: diet; health claim; lignan; phytoestrogen; prostate cancer; surrogate biomarker

Avicenna J Phytomed. 2016 May-Jun;6(3):273-83.

Effects of flaxseed and Hypericum perforatum on hot flash, vaginal atrophy and estrogen-dependent cancers in menopausal women: a systematic review and meta-analysis.

Ghazanfarpour M[1], Sadeghi R[2], Latifnejad Roudsari R[3], Khadivzadeh T[3], Khorsand I[4], Afiat M[5], Esmaeilizadeh M[6].

OBJECTIVE:

In this study, we aimed at evaluation of the efficacy of Hypericum perforatum and flaxseed on hot flash, vaginal atrophy and estrogen-dependent cancers in menopausal women.

MATERIALS AND METHODS:

We searched MEDLINE, Scopus, and the Cochrane Central Register of Controlled Trials (RCT) to explore trials that assessed the effectiveness of H. perforatum and flaxseed on hot flash, vaginal atrophy and estrogen-dependent cancers. In this regard, the following terms were used "menopause AND H. perforatum OR flaxseed OR Linum usitatissimum. Only randomized controlled trials were included in the study.

RESULTS:

Nine RCTs were included in this systematic review. Based on the literature, flaxseed showed beneficial effect on hot flash frequency and intensity, which was not statistically significant. According to two trials, flaxseed showed estrogenic effects; however, no conclusion regarding cancer promoting or protecting effects can be made. The evidence of the efficacy of the flaxseed on alleviating vaginal atrophy was also limited due to inconsistent findings in this regard. One trial declared that Vitex agnus-castus and H. perforatum showed comparable decrease in the frequency of hot flashes.

CONCLUSION:

The results of our systematic review suggest beneficial effect on vasomotor symptom with both of flaxseed and H. perforatum. Consistent conclusion regarding estrogen-dependent cancers and maturation value is limited due to small number of trials related to flaxseed. Further trials are still needed to confirm the results of our systematic review.

KEYWORDS: *Cancers; Hot flash; Menopause; Systematic review; Vaginal atrophy*

Exp Cell Res. 2015 Apr 10;333(1):147-54. doi: 10.1016/j.yexcr.2015.02.020. Epub 2015 Mar 2.

Growth and gene expression differ over time in alpha-linolenic acid treated breast cancer cells.

Wiggins AK[1], Mason JK[1], Thompson LU[2].

SCOPE:

Heterogeneity of breast cancer (BC) subtypes makes BC treatment difficult. α-linolenic acid (ALA), rich in flaxseed oil, has been shown to reduce growth and increase apoptosis in several BC cell lines, but the mechanism of action needs further understanding.

METHODS AND RESULTS:

Four BC cell lines (MCF-7, BT-474, MDA-MB-231 and MDA-MB-468) were incubated with 75 μM ALA+1 nM 17-β estradiol (E2) or 1 nM E2 only (control) for 24 h. MDA-MB-231 cells were additionally incubated at 6 and 12 h. Viable cell number was measured, and expression of genes related to BC (signaling pathways, cell cycle, apoptosis) was quantified by real-time PCR array. There was a reduction in growth of all ALA treated cell lines after 24 h, and in MDA-MB-231 cells this was time-dependent. Many genes were altered after 24 h, and these differed between cell lines. In MDA-MB-231 cells, several gene expression changes were time-dependent.

CONCLUSIONS:

ALA reduces growth of BC cell lines, by modifying signaling pathways, which differ between BC molecular subtypes. The ALA effect on gene expression is dynamic and changes over time, indicating the significance of incubation period in detecting gene changes.

KEYWORDS: Alpha-linolenic acid; Breast cancer; Gene expression; Molecular subtype; Time effect; n-3 PUFA

J Nutr Biochem. 2015 Jan;26(1):16-23. doi: 10.1016/j.jnutbio.2014.08.001. Epub 2014 Sep 22.

Flaxseed oil enhances the effectiveness of trastuzumab in reducing the growth of HER2-overexpressing human breast tumors (BT-474).

Mason JK[1], Fu M[1], Chen J[1], Thompson LU[2].

Flaxseed oil (FSO) reduces breast tumorigenesis and HER2 expression in animal models of luminal breast cancer. The primary treatment for HER2-overexpressing tumors is trastuzumab (TRAS). We aimed to determine the effect of 4% FSO alone and combined with TRAS on HER2-overexpressing tumor (BT-474) growth and to explore potential mechanisms with a specific focus on HER2, mitogen-activated protein kinase (MAPK) and Akt signaling and fatty acid profile. Athymic mice with established tumors were fed the basal diet (control) or 4% FSO diet, with or without TRAS (1 or 2.5 mg/kg) treatment for 4 weeks. Tumor growth, HER2 signaling biomarkers (mRNA and protein) and fatty acid profile were measured. Tumors treated with FSO alone showed no difference in tumor growth compared to control; however, compared to TRAS2.5 and other groups, FSO+TRAS2.5 caused significantly lower tumor growth and cell proliferation and higher apoptosis and the greatest lowering of signaling biomarker expressions

(MAPK2, HER2 mRNA; pHER2 protein). Both TRAS and FSO had main effects of reducing the phosphorylated/total expression of Akt and MAPK protein expression. Dietary FSO altered the tumor fatty acid profile. In conclusion, 4% dietary FSO alone does not affect BT-474 tumor growth but enhances the tumor-reducing effect of TRAS (2.5 mg/kg). FSO×TRAS interactive effect may be modulated by their combined reductions of HER2 signaling through the Akt and MAPK pathways leading to reduced cell proliferation and increased apoptosis. FSO alters tumor fatty acid profile that likely contributes to effects on signaling pathways. This supports FSO as a complementary treatment for HER2+ breast cancer treated with TRAS.

KEYWORDS: Breast cancer; Drug–diet interaction; Flaxseed oil; HER2; Trastuzumab; α-Linolenic acid

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Flaxseed and its lignan and oil components: can they play a role in reducing the risk of and improving the treatment of breast cancer?

Mason JK[1], Thompson LU.

Flaxseed (FS), rich in the phytoestrogen lignans and α-linolenic acid-rich oil, has been suggested to have an anticancer effect. Questions remain whether FS and its lignan and oil components are effective in reducing breast cancer risk and tumour growth, and can interact beneficially with breast cancer drugs. To find answers, in vitro, animal, observational, and clinical studies on FS and its lignan and oil components were reviewed. The majority of studies in various rodent models show that 2.5%-10% FS diet or the equivalent amount of lignan or oil reduces tumour growth. Ten percent FS and equivalent lignans do not interfere with but rather increase the effectiveness of tamoxifen (80 mg/day) while the 4% FS oil increases trastuzumab/Herceptin (2.5 mg/kg) effectiveness. Observational studies show that FS and lignan intake, urinary excretion, or serum levels are associated with reduced risk, particularly in postmenopausal women. Lignans reduce breast cancer and all-cause mortality by 33%-70% and 40%-53%, respectively, without reducing tamoxifen effectiveness. Clinical trials show that FS (25 g/day with 50 mg lignans; 32 days) reduces tumour growth in breast cancer patients and lignans (50 mg/day; 1 year) reduces risk in premenopausal women. Mechanisms include decreased cell proliferation and angiogenesis and increased apoptosis through modulation of estrogen metabolism and estrogen receptor and growth factor receptor signalling pathways. More clinical trials are needed but current overall evidence indicates that FS and its components are effective in the risk reduction and treatment of breast cancer and safe for consumption by breast cancer patients.

KEYWORDS: acide α-linolénique; breast cancer; cancer du sein; chemoprevention; chimioprévention; drug–diet interaction; flaxseed; flaxseed oil; graine de lin; huile de graine de lin; interaction médicament-aliment; lignan; lignanes; α-linolenic acid

Integr Cancer Ther. 2014 May;13(3):181-92. doi: 10.1177/1534735413502076. Epub 2013 Sep 8.

Flax and Breast Cancer: A Systematic Review.

Flower G[1], Fritz H[2], Balneaves LG[3], Verma S[4], Skidmore B[2], Fernandes R[5], Kennedy D[5], Cooley K[5], Wong R[6], Sagar S[6], Fergusson D[7], Seely D[8].

BACKGROUND:

Flax is a food and dietary supplement commonly used for menopausal symptoms. Flax is known for its lignan, α-linolenic acid, and fiber content, components that may possess phytogestrogenic, anti-inflammatory, and hormone modulating effects, respectively. We conducted a systematic review of flax for efficacy in improving menopausal symptoms in women living with breast cancer and for potential impact on risk of breast cancer incidence or recurrence.

METHODS:

We searched MEDLINE, Embase, the Cochrane Library, and AMED from inception to January 2013 for human interventional or observational data pertaining to flax and breast cancer.

RESULTS:

Of 1892 records, we included a total of 10 studies: 2 randomized controlled trials, 2 uncontrolled trials, 1 biomarker study, and 5 observational studies. Nonsignificant (NS) decreases in hot flash symptomatology were seen with flax ingestion (7.5 g/d). Flax (25 g/d) increased tumor apoptotic index ($P < .05$) and decreased HER2 expression ($P < .05$) and cell proliferation (Ki-67 index; NS) among newly diagnosed breast cancer patients when compared with placebo. Uncontrolled and biomarker studies suggest beneficial effects on hot flashes, cell proliferation, atypical cytomorphology, and mammographic density, as well as possible anti-angiogenic activity at doses of 25 g ground flax or 50 mg secoisolariciresinol diglycoside daily. Observational data suggests associations between flax and decreased risk of primary breast cancer (adjusted odds ratio [AOR] = 0.82; 95% confidence interval [CI] = 0.69-0.97), better mental health (AOR = 1.76; 95% CI = 1.05-2.94), and lower mortality (multivariate hazard ratio = 0.69; 95% CI = 0.50-0.95) among breast cancer patients.

CONCLUSIONS:

Current evidence suggests that flax may be associated with decreased risk of breast cancer. Flax demonstrates antiproliferative effects in breast tissue of women at risk of

breast cancer and may protect against primary breast cancer. Mortality risk may also be reduced among those living with breast cancer.

KEYWORDS: *Linum usitatissimum; breast cancer; breast neoplasm; complementary and alternative medicine (CAM); flax; hot flashes; integrative oncology; menopause; phytoestrogen; systematic review*

Cancer Causes Control. 2013 Apr;24(4):813-6. doi: 10.1007/s10552-013-0155-7. Epub 2013 Jan 25.

Consumption of flaxseed, a rich source of lignans, is associated with reduced breast cancer risk.

Lowcock EC[1], Cotterchio M, Boucher BA.

PURPOSE:

To investigate the association between intake of flaxseed-the richest source of dietary lignans (a class of phytoestrogens)-and breast cancer risk.

METHODS:

A food frequency questionnaire was used to measure the consumption of flaxseed and flax bread by 2,999 women with breast cancer and 3,370 healthy control women who participated in the Ontario Women's Diet and Health Study (2002-2003). Logistic regression was used to investigate associations between consumption of flaxseed and flax bread and breast cancer risk. Confounding by established and suspected breast cancer risk factors, as well as dietary factors, was assessed.

RESULTS:

Flaxseed or flax bread was consumed at least weekly by 21 % of control women. None of the 19 variables assessed were identified as confounders of the associations between flaxseed or flax bread and breast cancer risk. Consumption of flaxseed was associated with a significant reduction in breast cancer risk (odds ratio (OR) = 0.82, 95 % confidence interval (CI) 0.69-0.97), as was consumption of flaxbread (OR = 0.77, 95 % CI 0.67-0.89).

CONCLUSIONS:

This Canadian study is, to our knowledge, the first to report on the association between flaxseed alone and breast cancerrisk and has found that flaxseed intake is associated with a reduction in breast cancer risk. As dietary intake of flaxseed is modifiable, this finding may be of public health importance with respect to breast cancer prevention.

In Vitro Cell Dev Biol Anim. 2012 Apr;48(4):244-50. doi: 10.1007/s11626-012-9492-1. Epub 2012 Mar 22.

Flaxseed sprouts induce apoptosis and inhibit growth in MCF-7 and MDA-MB-231 human breast cancer cells.

Lee J[1], Cho K.

Flaxseeds have been shown to play a role in the prevention of cancer and heart disease, and it is believed that their more favorable fatty acid composition is responsible. Sprouting is a natural method to modify nutritional components and to decrease cyanide poisoning of raw flaxseeds. Here, we investigated the in vitro effects of flaxseed sprouts on cell growth and apoptosis of human breast cancer cells. In a series of in vitro experiments, estrogen-receptor-positive (MCF-7) and estrogen-receptor-negative (MDA-MB-231) cells were cultured and treated with flaxseed sprouts, and then cell proliferation, apoptosis, and gene expression were measured. Flaxseed sprouts significantly reduced the growth of both of MCF-7 and MDA-MB-231 cells and also increased apoptosis. However, flaxseed sprouts did not affect the growth of MCF-10A mammary epithelial cells. In gene transcription analysis using quantitative real-time polymerase chain reaction, flaxseed sprout treatment significantly upregulated p53 mRNA in both cell cancer lines. These results suggest that flaxseed sprouts induce apoptosis and inhibit cancercell growth, thereby demonstrating their anti-proliferative effects in breast cancer cells. This study may provide important information for devising dietary strategies to reduce breast cancer risk.

PLoS One. 2011;6(9):e25720. doi: 10.1371/journal.pone.0025720. Epub 2011 Sep 30.

Tamoxifen and flaxseed alter angiogenesis regulators in normal human breast tissue in vivo.

Åberg UW[1], Saarinen N, Abrahamsson A, Nurmi T, Engblom S, Dabrosin C.

The incidence of breast cancer is increasing in the Western world and there is an urgent need for studies of the mechanisms of sex steroids in order to develop novel preventive strategies. Diet modifications may be among the means for breast cancer prevention. Angiogenesis, key in tumor progression, is regulated by the balance between pro- and anti-angiogenic factors, which are controlled in the extracellular space. Sampling of these molecules at their bioactive compartment is therefore needed. The aims of this study were to explore if tamoxifen, one of the most used anti-estrogen treatments for breast cancer affected some of the most important endogenous angiogenesis regulators, vascular endothelial growth factor (VEGF), angiogenin, and endostatin in normal breast tissue in vivo and if a diet supplementation with flaxseed had

similar effects as tamoxifen in the breast. Microdialysis was used for in situ sampling of extracellular proteins in normal breast tissue of women before and after six weeks of tamoxifen treatment or before and after addition of 25 g/day of ground flaxseed to the diet or in control women. We show significant correlations between estradiol and levels of VEGF, angiogenin, and endostatin in vivo, which was verified in ex vivo breast tissue culture. Moreover, tamoxifen decreased the levels of VEGF and angiogenin in the breast whereas endostatin increased significantly. Flaxseed did not alter VEGF or angiogenin levels but similar to tamoxifen the levels of endostatin increased significantly. We conclude that one of the mechanisms of tamoxifen in normal breast tissue include tipping of the angiogenic balance into an anti-angiogenic state and that flaxseed has limited effects on the pro-angiogenic factors whereas the anti-angiogenic endostatin may be modified by diet. Further studies of diet modifications for breast cancer prevention are warranted.

Cancer Res. 2011 Jan 1;71(1):51-60. doi: 10.1158/0008-5472.CAN-10-2289. Epub 2010 Nov 19.

Tamoxifen, flaxseed, and the lignan enterolactone increase stroma- and cancer cell-derived IL-1Ra and decrease tumor angiogenesis in estrogen-dependent breast cancer.

Lindahl G[1], Saarinen N, Abrahamsson A, Dabrosin C.

The proinflammatory cytokines IL-1α and IL-1β promote tumor angiogenesis that might be counteracted by the IL-1 receptor antagonist (IL-1Ra), anakinra, a clinically approved agent. A diet with high amounts of phytoestrogens, such as flaxseed (Flax), genistein (GEN), and the mammalian lignan enterolactone (ENL), may affect breast cancer progression in a similar fashion as the antiestrogen tamoxifen. Both cancer cells and tumor stroma may be targets for cancer therapy. By using microdialysis in a model of human breast cancers in nude mice, we could perform species-specific analyses of released proteins in the microenvironment. We show that tumors treated with tamoxifen and fed Flax or ENL exhibited decreased in vivo release of IL-1β derived from the murine stroma and decreased microvessel density whereas dietary GEN had no effects. Cancer cell-released IL-1Ra were approximately 5 times higher than stroma-derived IL-1Ra. Tamoxifen, Flax, and ENL increased IL-1Ra levels significantly whereas GEN did not. The tumor stroma contained macrophages, which expressed the estrogen receptor. In vitro, estradiol decreased IL-1Ra released from breast cancer cells and from cultured macrophages. IL-1Ra decreased endothelial cell proliferation significantly in vitro whereas breast cancer cell proliferation was unaffected in presence of estradiol. Finally, IL-1Ra therapy of tumor-bearing mice opposed estrogen-dependent breast cancer growth and decreased angiogenesis. We conclude that the release of IL-1s both by cancer cells and the stroma, where macrophages are a

key component, may offer feasible targets for antiestrogen therapy and dietary interventions against breast cancer.

Nutr Cancer. 2005;52(2):156-65.

Whole sesame seed is as rich a source of mammalian lignan precursors as whole flaxseed.

Coulman KD[1], Liu Z, Hum WQ, Michaelides J, Thompson LU.

The mammalian lignans enterolactone and enterodiol, which are produced by the microflora in the colon of humans and animals from precursors in foods, have been suggested to have potential anticancer effects. This study determined the production of mammalian lignans from precursors in food bars containing 25 g unground whole flaxseed (FB), sesame seed (SB), or their combination (FSB; 12.5 g each). In a randomized crossover study, healthy postmenopausal women supplemented their diets with the bars for 4 wk each separated by 4-wk washout periods, and urinary mammalian lignan excretion was measured at baseline and after 4 wk as a marker of mammalian lignan production. Results showed an increase with all treatments (65.1-81.0 mumol/day; $P < 0.0001$), which did not differ among treatments. Lignan excretion with the whole flaxseed was similar to results of other studies using ground flaxseed. An unidentified lignan metabolite was detected after consumption of SB and FSB but not of FB. Thus, we demonstrated for the first time that 1) precursors from unground whole flaxseed and sesame seed are converted by the bacterial flora in the colon to mammalian lignans and 2) sesame seed, alone and in combination with flaxseed, produces mammalian lignans equivalent to those obtained from flaxseed alone.

Anticancer Res. 2005 May-Jun;25(3A):1817-22.

Flax-seed extracts with phytoestrogenic effects on a hormone receptor-positive tumour cell line.

Waldschläger J[1], Bergemann C, Ruth W, Effmert U, Jeschke U, Richter DU, Kragl U, Piechulla B, Briese V.

The higher soy intake in the Asian population compared to Europeans is believed to be an essential factor for the lower incidence of hormone-dependent tumours in Asia. It has already been shown that soya beans, with their ingredients genistein and daidzein from the isoflavonoid group, have protective effects on hormone-caused diseases. Lignans are another, less

investigated, group of phytoestrogens. The aim of this study was to investigate the effects of flax-seed, which is typically found in Northern European diets, on the proliferation and hormone production of an estrogen receptor (ER)-positive trophoblast tumour cell line.

MATERIALS AND METHODS:

Trophoblast tumour cells of the cell line Jeg3 were incubated with 2 different concentrations of the isolated crude extract of flax-seed and 7 chemically partitioned extract fractions. Untreated cells were used as controls. After 48 h of stimulation, cell proliferation was measured using the BrdU method. The concentrations of hCG and progesterone produced by the trophoblast tumour cells were measured 48 h after stimulation. Extract fractions with antiproliferative effects in the BrdU- test were analysed by HPLC-MS.

RESULTS:

Our study showed an inhibitory influence of some of the isolated flax-seed fractions on the Jeg3 tumour cells. Proliferation of the Jeg3 cells was decreased by flax-seed fractions I, V, VI and VII in a dose-dependent manner. Inhibition of hCG production by flax-seedextracts III, V, VI and VII was also dose-dependent. Extract fractions V and VI decreased the production of progesterone by 58% to 86%. Some extract fractions showed a stimulating effect on hormone production and cell proliferation. HPLC-MS analysis showed the presence of matairesinol and biochanin A in flax-seed fraction VI.

DISCUSSION:

Flax-seed seems to have similar inhibitory effects to soya on hormone production and proliferation of hormone-sensitive tumour cells. Our results showed a dose-dependent inhibition by isolated flax-seed extracts on the Jeg3 cell line. Matairesinol and biochanin A seem to be useful candidates for extended tests on other tumour cell lines and normal tissues to evaluate the potential benefit of a lignan-containing therapy in hormone-dependent diseases.

Nutr J. 2004 Oct 20;3:19.

Nutrition and cancer: a review of the evidence for an anti-cancer diet.

Donaldson MS[1].

It has been estimated that 30-40 percent of all cancers can be prevented by lifestyle and dietary measures alone. Obesity, nutrient sparse foods such as concentrated sugars and refined flour products that contribute to impaired glucose metabolism (which leads to diabetes), low fiber intake, consumption of red meat, and imbalance of omega 3 and omega 6 fats all contribute to excess cancer risk. Intake of flax seed, especially its lignan fraction, and abundant portions of fruits and vegetables will lower cancer risk. Allium and cruciferous vegetables are especially

beneficial, with broccoli sprouts being the densest source of sulforophane. Protective elements in a cancer prevention diet include selenium, folic acid, vitamin B-12, vitamin D, chlorophyll, and antioxidants such as the carotenoids (alpha-carotene, beta-carotene, lycopene, lutein, cryptoxanthin). Ascorbic acid has limited benefits orally, but could be very beneficial intravenously. Supplementary use of oral digestive enzymes and probiotics also has merit as anticancer dietary measures. When a diet is compiled according to the guidelines here it is likely that there would be at least a 60-70 percent decrease in breast, colorectal, and prostate cancers, and even a 40-50 percent decrease in lung cancer, along with similar reductions in cancers at other sites. Such a diet would be conducive to preventing cancer and would favor recovery from cancer as well.

J Agric Food Chem. 2003 Feb 26;51(5):1181-8.

Identification and stereochemical characterization of lignans in flaxseed and pumpkin seeds.

Sicilia T[1], Niemeyer HB, Honig DM, Metzler M.

Phytoestrogens of the lignan type are widely distributed in plant-derived food items and are believed to protect against hormone-dependent cancer. The richest known dietary source of lignans is flaxseed. Flaxseed has been reported to contain glycosides of secoisolariciresinol as the major lignan, together with small amounts of matairesinol, isolariciresinol, and pinoresinol. Secoisolariciresinol, but none of the other lignans, has so far been identified in pumpkin seeds. In the present study, two different methods for the hydrolysis of lignan glycosides are compared. Artifact formation and loss of lignans under acidic conditions were observed. Lariciresinol was identified by GC-MS analysis in two different types of flaxseed (Linum usitatissimum L. and Linum flavum L.) and in pumpkin seeds (Cucurbita pepo L.) for the first time. Likewise, the novel lignan demethoxy-secoisolariciresinol was tentatively identified in the flaxseed samples. Stereochemical analysis by chiral HPLC of several lignans isolated from flaxseed showed that secoisolariciresinol, matairesinol, and lariciresinol consisted predominantly of one enantiomer.

Cancer Lett. 2002 Nov 8;185(1):31-7.

Flaxseed inhibits metastasis and decreases extracellular vascular endothelial growth factor in human breast cancer xenografts.

Dabrosin C[1], Chen J, Wang L, Thompson LU.

Angiogenesis is important in tumor growth, progression and metastatic dissemination. Vascular endothelial growth factor (VEGF) is one key factor in promotion of breast cancer angiogenesis. VEGFs are bioactive in the extracellular space where they become available to the endothelial cells. Phytoestrogens such as lignans have been shown to alter breast cancer incidence and be cancer-protective in rats. We show that supplementation of 10% flaxseed, the richest source of mammalian lignans, to nude mice with established human breast tumors reduced tumor growth and metastasis. Moreover, flaxseed decreased extracellular levels of VEGF, which may be one mechanistic explanation to the decreased tumor growth and metastasis.

Nutr Cancer. 2010;62(2):175-80. doi: 10.1080/01635580903305342.

Effect of flaxseed consumption on urinary levels of estrogen metabolites in postmenopausal women.

Sturgeon SR[1], Volpe SL, Puleo E, Bertone-Johnson ER, Heersink J, Sabelawski S, Wahala K, Bigelow C, Kurzer MS.

Flaxseed is a rich source of dietary lignans. It has been hypothesized that lignans may decrease breast cancer risk through modulation of endogenous hormone levels. The aim of this study was to determine the effect of flaxseed supplementation on urinary levels of estrogen metabolites that may be involved in the development of breast cancer. Forty-three postmenopausal women participated in this 12-wk preintervention-postintervention study. Participants consumed 7.5 g/day of ground flaxseed for 6 wk, followed by 15 g/day for an additional 6 wk. The mean urinary level of 16alpha -hydroxyestrone (16alpha -OHE1) was higher at the end of 12 wk compared to baseline (change of 1.32 ug/day, P = 0.02). There was no significant change in 2-OHE1 excretion. The mean urinary level of the 2-OHE1/16alpha -OHE1 ratio was lower at the end of 12 wk compared to baseline (change of -1.1, P = 0.02). Mean urinary excretion of 2-methoxyestradiol was also lower at 12 wk than at baseline (P = 0.03). Based on the current paradigm of the effects of estrogen metabolism on breast cancer risk, the regimen of dietary flaxseed intake used in this study did not appear to favorably alter breast cancer risk through shifts in estrogen metabolism pathways in postmenopausal women.

Nutr Cancer. 2008;60(5):612-8. doi: 10.1080/01635580801971864.

Effect of dietary flaxseed on serum levels of estrogens and androgens in postmenopausal women.

Sturgeon SR[1], Heersink JL, Volpe SL, Bertone-Johnson ER, Puleo E, Stanczyk FZ, Sabelawski S, Wahala K, Kurzer MS, Bigelow C.

Flaxseed is a rich source of dietary lignans. Experimental studies suggest lignans may exert breast cancer preventive effects through hormonal mechanisms. Our aim was to study the effects of flaxseed on serum sex hormones implicated in the development of breast cancer. Forty-eight postmenopausal women participated in a 12-wk preintervention-postintervention study. Participants consumed 7.5 g/day of ground flaxseed for the first 6 wk and 15.0 grams/day for an additional 6 wk. Nonsignificant declines were noted over the 12 wk (95% confidence intervals) for estradiol (pg/ml), estrone (pg/ml), and testosterone (pg/ml): -4.4 (-12.6 to 3.9), -3.3 (-7.7 to 1.2), -4.7 (-17.8 to 8.5), respectively. Changes tended to be more pronounced in overweight/obese women, particularly for estrone (-6.5, -11.9 to -1.2; P = .02). Our results suggest that dietary flaxseed may modestly lower serum levels of sex steroid hormones, especially in overweight/obese women.

Clin Cancer Res. 2007 Feb 1;13(3):1061-7.

Flaxseed and its lignans inhibit estradiol-induced growth, angiogenesis, and secretion of vascular endothelial growth factor in human breast cancer xenografts in vivo.

Bergman Jungeström M[1], Thompson LU, Dabrosin C.

PURPOSE:

Vascular endothelial growth factor (VEGF) is a potent stimulator of angiogenesis, which is crucial in cancer progression. We have previously shown that estradiol (E2) increases VEGF in breast cancer. Phytoestrogens are potential compounds in breast cancer prevention and treatment by poorly understood mechanisms. The main phytoestrogens in Western diet are lignans, and flaxseed is a rich source of the mammalian lignans enterodiol and enterolactone.

EXPERIMENTAL DESIGN:

In the present study, ovariectomized mice were treated with continuous release of E2. MCF-7 tumors were established and mice were fed with basal diet or 10% flaxseed, and two groups that were fed basal diet received daily injections with enterodiol or enterolactone (15 mg/kg body weight).

RESULTS:

We show that flaxseed, enterodiol, and enterolactone counteracted E2-induced growth and angiogenesis in solid tumors. Extracellular VEGF in vivo, sampled using microdialysis, in all intervention groups was significantly decreased compared with tumors in the basal diet group.

Our in vivo findings were confirmed in vitro. By adding enterodiol or enterolactone, E2-induced VEGF secretion in MCF-7 cells decreased significantly without agonistic effects. The increased VEGF secretion by E2 in MCF-7 cells increased the expression of VEGF receptor-2 in umbilical vein endothelial cells, suggesting a proangiogenic effect by E2 by two different mechanisms, both of which were inhibited by the addition of lignans.

CONCLUSIONS:

Our results suggest that flaxseed and its lignans have potent antiestrogenic effects on estrogen receptor-positive breast cancer and may prove to be beneficial in breast cancer prevention strategies in the future.

Urology. 2004 Sep;64(3):510-5.

Effects of a diet rich in phytoestrogens on prostate-specific antigen and sex hormones in men diagnosed with prostate cancer.

Dalais FS[1], Meliala A, Wattanapenpaiboon N, Frydenberg M, Suter DA, Thomson WK, Wahlqvist ML.

Author information

Abstract

OBJECTIVES:

To determine the effects of diets rich in soy and linseed compared with a control diet on biochemical markers of prostate cancer in men diagnosed with prostate cancer.

METHODS:

Twenty-nine men diagnosed with prostate cancer and scheduled to undergo a radical prostatectomy were randomized to one of three groups: soy (high phytoestrogen), soy and linseed (high phytoestrogen), or wheat (low phytoestrogen). A bread was specially manufactured to incorporate 50 g of heat-treated (HT) soy grits or 50 g of HT soy grits and 20 g of linseed as part of the study participant's daily diet. Baseline and preoperative levels of prostate-specific antigen (PSA), free PSA, testosterone, sex hormone-binding globulin, free androgen index, and dihydrotestosterone were measured.

RESULTS:

Statistically significant differences were detected between the HT soy grits group and the control wheat group for the percentage of change in total PSA (-12.7% versus 40%, P = 0.02) and the percentage of change in free/total PSA ratio (27.4% versus -15.6%, P = 0.01); and between the HT soy grits group and the HT soy grits and linseed group for the percentage of change in free androgen index (16.4% versus -15.5%, P = 0.04) and the percentage of change in free/total PSA ratio (27.4% versus -10%, P = 0.007).

CONCLUSIONS:

The data from this study indicate that a daily diet containing four slices of a bread rich in HT soy grits favorably influences the PSA level and the free/total PSA ratio in patients with prostate cancer. This work provides some evidence to support epidemiologic studies claiming that male populations who consume high phytoestrogen diets have a reduced risk of prostate cancer development and progression.

Nutr Cancer. 1999;33(2):188-95.

Effect of flaxseed consumption on urinary estrogen metabolites in postmenopausal women.

Haggans CJ[1], Hutchins AM, Olson BA, Thomas W, Martini MC, Slavin JL.

Flaxseed, the richest known source of plant lignans, has been shown to have chemoprotective effects in animal and cell studies. Some of its effects may be mediated through its influence on endogenous hormone production and metabolism. Two competing pathways in estrogen metabolism involve production of the 2-hydroxylated and 16 alpha-hydroxylated metabolites. Because of the proposed differences in biological activities of these metabolites, the balance of the two pathways has been used as a biomarker for breast cancer risk. We examined the effects of flaxseed consumption on urinary estrogen metabolite excretion in postmenopausal women. Twenty-eight postmenopausal women were studied for three seven-week feeding periods in a randomized crossover design. During the feeding periods, subjects consumed their usual diets plus ground flaxseed (0, 5, or 10 g/day). Urinary excretion of the estrogen metabolites 2-hydroxyestrogen (2-OHEstrogen) and 16 alpha-hydroxyestrone (16 alpha-OHE1) as well as their ratio, 2/16 alpha-OHE1, was measured by enzyme immunoassay. Flaxseed supplementation significantly increased urinary 2-OHEstrogen excretion ($p < 0.0005$) and the urinary 2/16 alpha-OHE1 ratio ($p < 0.05$) in a linear, dose-response fashion. There were no significant differences in urinary 16 alpha-OHE1 excretion. These results suggest that flaxseed may have chemoprotective effects in postmenopausal women.