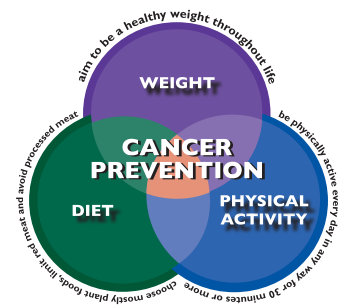


AICR InDepth



by Karen Collins, MS, RD, CDN

Flaxseed and Breast Cancer

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Flaxseed and Breast Cancer



The Take-Home

General Summary

- Because human studies are extremely limited, research does not provide a basis to recommend use of flaxseed for the explicit purpose of cancer protection at this time.
- For people who wish to consume flaxseed as a source of omega-3 fat or dietary fiber, studies do not support fears that flaxseed could increase incidence or recurrence of breast cancer.
- Because there are no studies regarding the effects of flaxseed in children or women who are pregnant or breastfeeding, researchers suggest caution.

Research Specifics

- Animal studies suggest that flaxseed may decrease growth of both estrogen receptor-negative and estrogen receptor-positive breast cancers.
- In animal studies, flaxseed did not interfere with tamoxifen's actions and may have enhanced effectiveness. However, with no results of clinical trials of flaxseed use during tamoxifen

or aromatase inhibitor treatment, decisions about flaxseed use should be discussed carefully with a patient's physician.

- Flaxseed's effects vary with individual differences including diet, hormones and genetics.
- In limited short-term human studies using 10 to 30 g flaxseed per day (corresponding to approximately 1 to 4 level tablespoons of ground flaxseed), consumption altered estrogen metabolism in ways that may protect against breast cancer.

Research Background

Most research in flaxseed and cancer has focused on flaxseed's relationship to breast cancer, though emerging research addresses its role in cancers of the prostate and colon. Research has primarily focused on the potential for flaxseed (also known as linseed) to reduce cancer risk through its lignan

compounds and its alpha-linolenic acid (ALA, an omega-3 fatty acid) content, and these will be the focus of this review, although its concentrated dietary fiber and other nutritional components may also influence cancer risk. The impact of flaxseed needs to be distinguished from that of flaxseed oil, which does not naturally contain lignans.

Few human intervention trials using flaxseed are available. Compared to a control group of postmenopausal women with newly diagnosed breast cancer, those who consumed 25 g ground flaxseed per day for approximately 32 days showed decreased tumor cell proliferation, decreased HER2 (c-erbB2) expression and increased apoptosis at the time of surgery. (HER2 leads to growth factor signaling pathways that play a role in cell proliferation, differentiation, apoptosis and metastasis.) Estrogen and progesterone levels and receptor activity did not change.¹

In early animal studies, flaxseed reduced tumor incidence, number and size when fed to carcinogen-treated rats at initiation, promotion or later stages of cancer development.^{2,3} More recently, diets with 5 percent or 10 percent flaxseed (comparable to 25 to 30 grams of flaxseed daily in humans) inhibited the growth of both estrogen receptor (ER)-positive^{4,5,6,7,8,9,10} and ER-negative^{11,12,13} human breast cancer cells injected in mice. It also reduced metastasis of ER-negative breast tumors.^{11,12,14} These studies maintained either high estrogen levels as a model for pre-menopausal breast cancer or low estrogen levels as a model of postmenopausal breast cancer. Decreased cell proliferation rates, decreased angiogenesis and increased apoptosis seem to account for the decreased tumor growth.

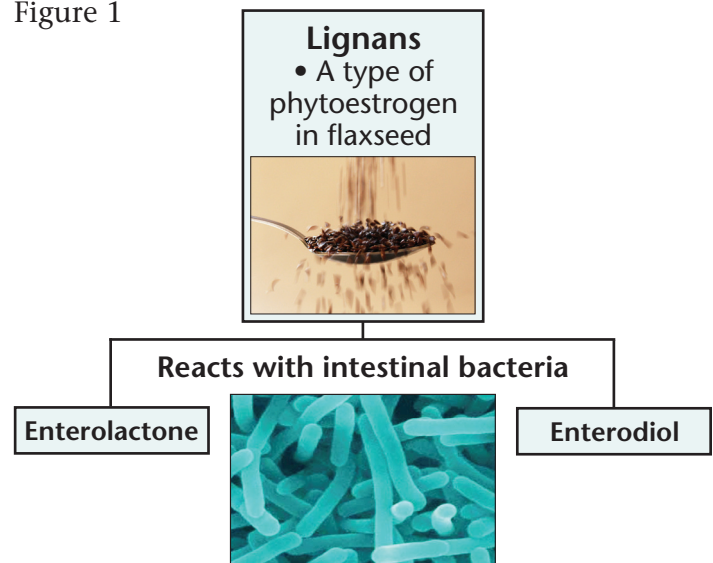
Lignans in Depth

Lignans occur in a number of plant foods, but flaxseed is a particularly rich source (lignans are not to be confused with lignins, a type of insoluble fiber). Lignans, along with isoflavones and coumestans, comprise the three major classes of phytoestrogens (plant estrogens). When plant lignans are consumed, intestinal bacteria convert some into two mammalian lignans, enterolactone and enterodiol. (Fig.1) These compounds are absorbed from the digestive tract, circulate and are excreted in the urine.

In some population studies, greater serum¹⁵ or urinary¹⁶ levels of enterolactone are associated with decreased breast cancer risk. In others, however, serum enterolactone showed no link to breast cancer risk,^{17, 18} and one nested case-control study showed a U-shaped relationship with increased risk at very low and very high levels of serum enterolactone.¹⁹

In a series of case-control studies, women with highest estimated lignan consumption showed 28 percent to 51 percent lower risk of breast cancer, though impact varied according to menopausal and estrogen receptor status,^{20, 21, 22} and was not seen in all such studies.^{23, 24} A meta-analysis of seven case-control and four cohort studies found no significant association of total lignan intake and overall breast cancer risk.²⁵ Separating analysis by menopausal status showed no significant link to premenopausal breast cancer, but a significant 15 percent lower risk of postmenopausal breast cancer in women with highest lignan consumption.

Figure 1



The breakdown of flaxseed lignans into mammalian lignans.

Another case-control study published since this meta-analysis showed highest estimated lignan consumption was associated with significantly lower postmenopausal breast cancer mortality, but showed no significant association with premenopausal breast cancer mortality.²⁶

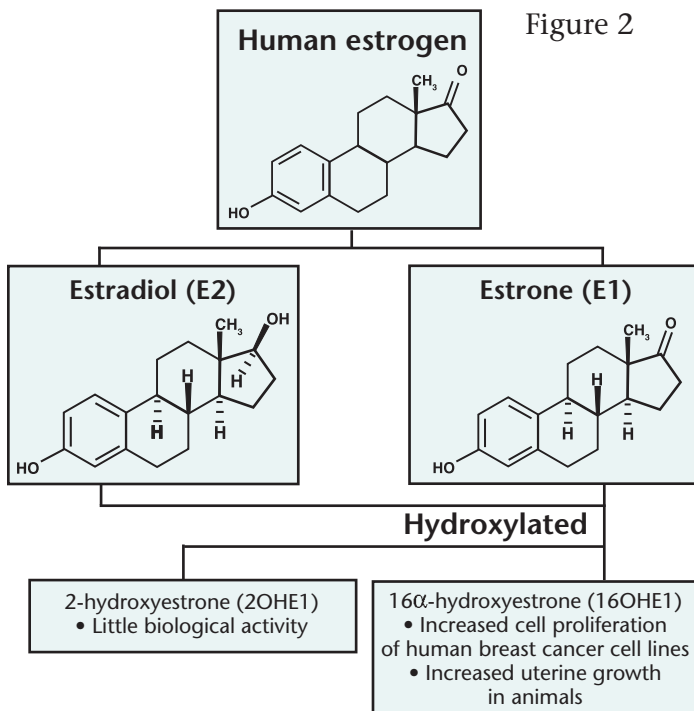
In studies such as these, it's important to note that dietary and body levels of lignans do not represent flaxseed consumption alone.

In studies such as these, it's important to note that dietary and body levels of lignans do not represent flaxseed consumption alone. In most Western diets, vegetables, grains, fruit, tea, coffee, legumes, nuts and seeds provide much larger amounts of lignans. Flaxseed is by far the most concentrated source of lignans, however, so including it in a diet changes lignan consumption dramatically.

The top quartile of lignan consumption in these studies is substantially lower than amounts provided by the two to four tablespoons of ground flaxseed per day typically used in human studies. So the effects, or lack of effects, of lignan consumption in these studies does not necessarily predict the effect of flaxseed consumption because flaxseed provides different types of lignans. In addition, the omega-3 fat in flaxseed is not likely obtained from other sources of lignans.

Lignans & Estrogen

Human estrogen occurs in two major forms: estradiol (E2) and estrone (E1). Estradiol is oxidized in the liver to estrone, which can then be hydroxylated to one of several forms of widely differing estrogenic power. (Fig. 2) The two major forms are 2-hydroxyestrone (2OHE1), a relatively weak estrogen, and 16 α -hydroxyestrone (16OHE1), which increases cell proliferation of human breast cancer cell lines in vitro and increases uterine growth in animal studies. Research suggests that women with a low ratio of urinary 2OHE1 to 16OHE1 have an increased risk of both pre- and postmenopausal breast cancer.^{27,28, 29}



Estradiol is oxidized in the liver to Estrone.
Estrone is converted to the estrogen
2OHE1 and 16OHE1.

Among healthy postmenopausal women, ground flaxseed in amounts from 5 to 40 grams daily may³⁰ or may not³¹ reduce serum estrone and estradiol, but 5 to 25 grams of ground flaxseed per day has consistently shown a shift toward the weaker (2OHE1) form of estrogen.^{32, 33, 34} Flaxseed also showed a significant shift to the weaker estrogen (increased 2OHE1:16OHE1 ratio) in premenopausal women.³⁵

One trial that worked up to 15 grams of flaxseed per day suggests that flaxseed's impact on serum estrogens may be greater among overweight and obese postmenopausal women than those of normal weight;³⁶ these women generally have higher levels of circulating estrogen. The range in response to lignans may also reflect polymorphisms in genes related to hormone metabolism.³⁴

The range in response to lignans may
also reflect polymorphisms in genes
related to hormone metabolism

Another way lignans may alter estrogen metabolism in postmenopausal women is through decreasing estrogen levels by moderately inhibiting the aromatase enzyme responsible for the conversion of androstenedione to estrone in adipose tissue (the major source of estrogen after menopause). Some research suggests that lignans could also reduce bioavailable estrogen by increasing synthesis of sex hormone-binding globulin (SHBG), which binds androgens and estrogens, but results have not been consistent.

Lignans and Growth Factors

Lignans could influence ER-negative and ER-positive tumors by decreasing insulin-like growth factor-1 (IGF-1), epidermal growth factor receptor (EGFR), HER2 and the vascular endothelial growth factor (VEGF) which supports angiogenesis.^{12, 6, 5, 13, 9} Most of the studies showing effects on these growth factors involve xenografts of human breast cancer in mice. However, Thompson¹ also found decreased HER2 (c-erbB2) expression in breast tumor tissue at time of surgery compared with time of diagnosis in postmenopausal women given 25 grams of flaxseed daily for about 32 days.

Flaxseed as a Source of Omega-3 Fat

Flaxseed's omega-3 fat provides both hope for potential benefits and concerns of potential risks for some people. Alpha-linolenic acid (ALA, 18:3) comprises almost half of the fat in flaxseed. Each tablespoon of ground flaxseed provides 1.6 g ALA and each tablespoon of flaxseed oil has 7.3 g ALA, about four times the content of linoleic acid (LA, 18:2), an essential omega-6 fatty acid.

Role of ALA and LA in cancer cell growth

Humans can use ALA to synthesize eicosapentaenoic acid (EPA), the source of anti-inflammatory eicosanoids. Eicosanoids are signaling compounds involved in balancing and controlling inflammation and immunity. Emerging research suggests that EPA could influence cell-signaling pathways in ways that decrease cancer growth.³⁷ In contrast, LA leads to production of pro-inflammatory eicosanoids, which in vitro and animal studies suggest could increase cancer cell proliferation and angiogenesis.

Conversion of ALA to EPA and DHA

When considering omega-3 fat's impact on cancer, it's important to note that effects seen with a particular amount of EPA and DHA (another omega-3 fatty acid present in fish) should not be expected from an equal amount of ALA. Conversion of ALA to DHA is particularly inefficient, estimated at less than four percent in men and up to nine percent in women of reproductive age.^{38, 37} Estimates of ALA conversion to EPA, the source of anti-inflammatory and other potentially cancer-inhibiting compounds, range from 0.3 to 8 percent in men and up to 21 percent in women of childbearing age. Overall diet, including consumption of ALA, LA, DHA and EPA, affects rates of conversion as well.

AICR's second expert report notes biological plausibility of a relationship of omega-3 fat intake and reduced risk of breast and possibly other cancers, but found evidence was too limited to draw any conclusions.

Despite inefficient conversion, the 5.7 to 6.8 g of ALA in the approximately 25 to 30 gram daily doses of ground flaxseed generally used in studies of flaxseed and breast cancer-related biomarkers could increase circulating EPA levels significantly.³⁹ The effect on breast cancer incidence is unknown.

Animal and human studies and ALA

In a study of mice with xenografts of ER- human breast cancer, flaxseed oil alone decreased tumor cell proliferation and increased apoptosis, but best protection, including decreased overall metastasis, came from flaxseed or a combination of its lignans and its oil.¹¹ A prospective study of ALA consumption and breast cancer risk concluded that the effect of ALA or total omega-3 fat consumption depends on interactions among antioxidants, fatty acids and other components of the diet.⁴⁰

A review by the Natural Standard Research Collaboration concludes that evidence is not currently

adequate to support recommending alpha-linolenic acid as a way to reduce risk of breast or prostate cancer.⁴¹ *Food, Nutrition, Physical Activity and the Prevention of Cancer*, AICR's second expert report⁴² notes biological plausibility of a relationship of omega-3 fat intake and reduced risk of breast and possibly other cancers, but found evidence was too limited to draw any conclusions.

Flaxseed and Special Populations

People at Bleeding Risk

The ALA in flaxseed is converted to EPA, which forms compounds that decrease blood clotting and this raises questions about its safety for people at risk of bleeding. EPA and DHA in amounts less than 3 g per day are unlikely to increase bleeding tendencies.⁴³ Therefore, because of the inefficient conversion of ALA to EPA, flaxseed in typical amounts (two to four tablespoons of ground flaxseed or one tablespoon of flaxseed oil per day) poses little risk of bleeding in healthy people. People who take high-dose EPA and DHA supplements or medications with anticoagulant effects, such as aspirin, clopidogrel (Plavix), dipyridamole (Persantine), enoxaparin (Lovenox), heparin, ticlopidine (Ticlid), and warfarin (Coumadin), should talk with their doctor before beginning daily flaxseed use and have their coagulation status monitored.

Women on Adjuvant Breast Therapy

Tamoxifen is an adjuvant therapy for breast cancer that seems to work principally by competing with estrogen for binding to estrogen receptors. Health professionals often question whether the lignans in flaxseeds could interfere with tamoxifen. However, studies of mice injected with ER+ human breast cancer suggest that in both high- and low-estrogen conditions (modeling pre- and postmenopausal breast cancer), flaxseed either enhanced or maintained^{5, 6, 4, 8} the effectiveness of tamoxifen in decreasing tumor growth, decreasing cell proliferation and increasing apoptosis. However, no results of clinical trials of flaxseed use during tamoxifen treatment are currently available. Research is in progress regarding flaxseed use during treatment with aromatase inhibitors.

Interactions with Other Medications

Flaxseed may slow or decrease absorption of oral medications or nutrients, so it should be taken one hour before or two hours after any prescription or nonprescription medicine.

In addition to the interactions with anticoagulant medications above, the potential for glucose lowering due to flaxseed combined with antidiabetes medications increases the chances of hypoglycemia.⁴⁴

People who take high-dose EPA and DHA supplements or medications with anticoagulant effects should talk with their doctor before beginning daily flaxseed use.

Pregnancy, Breastfeeding, Children

Researchers have no conclusive data on the safety of flaxseed taken daily by children or by women who are pregnant or breastfeeding. The Natural Medicines Comprehensive Database says there is no reliable clinical evidence of safety during pregnancy or lactation. It lists flaxseed use during pregnancy as “possibly unsafe” and recommends avoidance during breastfeeding.

Questions That Need to Be Answered

What is the impact of regular long-term consumption of flaxseed on bone health?

Bone strength seems to be particularly increased by the 16OHE1 form of estrogen, so especially for cancer survivors who may be at increased risk of osteoporosis, it’s important to know whether changing the 2OHE1:16OHE1 ratio decreases bone mineral density. No significant effects – positive or negative – on biomarkers of bone health or bone mineral density were observed in postmenopausal women taking 25 g³² daily for sixteen weeks, 40 g flaxseed daily for three months,³¹ or 40 g flaxseed daily for one year.⁴⁵ It is however, an important issue to investigate and consider in the decision about regular use of flaxseed.

What is the impact of flaxseed on risk of other cancers?

Prostate:

Limited studies have shown that flaxseed inhibits the growth and metastasis of prostate cancer in mice,⁴⁶ and lowers tumor biomarkers or pre-surgery cell proliferation rates in men with prostate cancer, with or without a low-fat diet.^{47, 48} Conflicting reports link ALA consumption with increased, decreased or unchanged prostate cancer risk, and impact likely varies with the food source of ALA and overall fatty acid composition of the diet.

Colon:

Laboratory studies suggest that flaxseed could protect against colon cancer through anti-inflammatory effects of its omega-3 fat, its lignans promotion of apoptosis and perhaps through its dietary fiber content,⁴⁹ but human studies are lacking.

Uterine:

Limited data does not suggest a protective role for flaxseed against uterine cancer. In an animal study, it did not seem to decrease estrogen-stimulated uterine growth⁶ and endometrial thickness (a measure of uterine cancer) did not change in postmenopausal women who took 25 g flaxseed for 3 months.⁵⁰ Some evidence suggests that flaxseed may, however, reduce uterine growth that can be promoted with tamoxifen use.⁴

How do the lignan phytoestrogens in flaxseed compare and interact with lignans from sesame seeds, grains and other foods, and with the isoflavone phytoestrogens in soybeans?

Preliminary evidence suggests that different lignans may have very different effects, and that flaxseed may interact in beneficial ways with soy.¹⁰



Talking with Patients about Flaxseed

Does flaxseed lower risk for cancer?

- Flaxseed may contribute to lower cancer risk, but research is too limited to recommend it for cancer protection.
- Flaxseed's effects vary depending on diet, hormones, genetics and more.
- 1 to 4 tablespoons of ground flaxseed per day appears to be safe and potentially protective against breast cancer based on studies using those amounts.

I heard that flaxseed might increase risk for getting breast cancer.

- Studies have not shown that flaxseed increases incidence or recurrence of breast cancer.

Is it safe to take flaxseed if I'm on tamoxifen or aromatase inhibitor treatment?

- Although in animal studies flaxseed did not interfere with tamoxifen's actions, there are no clinical study results available.
- Research with aromatase inhibitors is not yet available.
- It is best to discuss flaxseed use with your physician.

Does flaxseed interfere with any medications or supplements?

- Flaxseed may slow or decrease absorption of medications, so discuss with your doctor. (You may need to take it at different times than your prescription or nonprescription medicine.)
- It is also important to talk with your doctor before taking flaxseed if you take fish oil, EPA + DHA supplements or anticoagulant medications (aspirin or blood thinners such as clopidogrel (Plavix), heparin and warfarin (Coumadin)).

Can pregnant women and children take flaxseed?

- The effects of flaxseed supplements in pregnant and breastfeeding women and children are not known, so caution is advised. Talk with your doctor.

If I decide to take flaxseed, what's the best way to get started?

- Start with one tablespoon of ground flaxseed at a time; wait a few days to get used to the increased fiber before adding more.
- Use ground flaxseed ("flaxseed meal") so you'll absorb more omega-3 fats and the cancer-fighting lignans.
- Buy flaxseed pre-ground or grind the whole seeds in a coffee grinder or food processor.
- Drink at least 64 ounces of liquids daily to help move the fiber through your digestive system.
- Add to cereal, yogurt or salads. Include in baked muffins or quick breads as cooking does not change lignan content significantly.
- Bars and cereals with flaxseeds often contain small amounts of the omega-3 fats.
- Refrigerate in a closed container; it will stay fresh for three to four months.

What about taking flaxseed oil?

- Flaxseed oil provides omega-3 fat, but no fiber or lignans (unless they have been added to the oil), so effects may be different than those of ground flaxseed.
- The oil may be an attractive option if the fiber content of flaxseed causes discomfort for you, or if you are in one of the groups where research about safety of regular flaxseed is lacking (pregnant women and children).
- Flaxseed oil should not be used in cooking, but you could use about 1 tablespoon daily to be drizzled over vegetables after cooking or used in salad dressings. It is essential to store it in the refrigerator.

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Glossary

Alpha-linolenic acid (ALA)

An essential fatty acid. ALA is an omega-3 fatty acid that serves as the parent compound in the synthesis of other omega-3 fatty acids in the body.

Androstenedione

An adrenal steroid that is a precursor to testosterone and other androgens.

Angiogenesis

Blood vessel formation. Tumor angiogenesis is the growth of new blood vessels that tumors need to grow. This is caused by the release of chemicals by the tumor.

Apoptosis

A type of cell death in which a series of molecular steps in a cell leads to its death. This is the body's normal way of getting rid of unneeded or abnormal cells. The process of apoptosis may be blocked in cancer cells. Also called programmed cell death.

Case-Control study

A study that compares two groups of people: those with the disease or condition under study (cases) and a very similar group of people who do not have the disease or condition (controls). Researchers study the medical and lifestyle histories of the people in each group to learn what factors may be associated with the disease or condition. For example, one group may have been exposed to a particular substance that the other was not. Also called retrospective study.

Docosahexaenoic acid (DHA)

An omega-3, polyunsaturated, 22-carbon fatty acid found almost exclusively in fish and marine animal oils.

Eicosapentaenoic acid (EPA)

An omega-3, polyunsaturated, 20-carbon fatty acid found almost exclusively in fish and marine animal oils.

Epidermal growth factor receptor (EGFR)

The protein found on the surface of some cells and to which epidermal growth factor binds, causing the cells to divide. It is found at abnormally high levels on the surface of many types of cancer cells, so these cells may divide excessively in the presence of epidermal growth factor. Also called EGFR, ErbB1 and HER1.

Estrogen receptor-negative (ER-)

Describes cells that do not have a protein to which the hormone estrogen will bind. Cancer cells that are estrogen receptor negative do not need estrogen to grow and usually do not stop growing when treated with hormones that block estrogen from binding. Also called ER-.

Estrogen receptor-positive (ER+)

Describes cells that have a receptor protein that binds the hormone estrogen. Cancer cells that are estrogen receptor positive may need estrogen to grow and may stop growing or die when treated with substances that block the binding and actions of estrogen. Also called ER+.

HER2/c-erbB2

A protein involved in normal cell growth. It is found on some types of cancer cells, including breast and ovarian. Cancer cells removed from the body may be tested for the presence of HER2/neu to help decide the best type of treatment. Also called c-erbB-2, human EGF receptor 2 and human epidermal growth factor receptor 2.

Insulin-like growth factor-1 (IGF-1)

A protein made by the body that stimulates the growth of many types of cells. Insulin-like growth factor is similar to insulin (a hormone made in the pancreas). There are two forms of insulin-like growth factor called IGF-1 and IGF-2. Higher than normal levels of IGF-1 may increase the risk of several types of cancer. Insulin-like growth factor is a type of growth factor and a type of cytokine. Also called IGF and somatomedin.

Lignan

A member of a group of substances found in plants that have shown estrogenic and anticancer effects. Lignans have been used in some cultures to treat certain medical problems.

Lignin

An insoluble polysaccharide that with cellulose and hemicellulose forms the chief part of the skeletal substances of the cell walls of plants. It provides bulk in the diet necessary for proper GI functioning.

Linoleic acid (LA)

An essential fatty acid. Linoleic acid is an omega-6 fatty acid that serves as the parent compound in the synthesis of other omega-6 fatty acids such as arachidonic acid.

Meta-analysis

A quantitative statistical analysis that is applied to separate but similar experiments of different and usually independent researchers and that involves pooling the data and using the pooled data to test the effectiveness of the result.

Nested case-control study

In a nested case-control study, cases of a disease that occur in a defined cohort are identified and, for each, a specified number of matched controls is selected from among those in the cohort who have not developed the disease by the time of disease occurrence in the case.

Population study

A study of a group of individuals taken from the general population who share a common characteristic, such as age, gender or health condition. This group may be studied for different reasons, such as their response to a drug or risk of getting a disease.

Sex hormone-binding globulin (SHBG)

A glycoprotein that binds to sex hormones, specifically testosterone and estradiol.

Vascular endothelial growth factor (VEGF)

A substance made by cells that stimulates new blood vessel formation.

Xenografts

Tissue or organs from an individual of one species transplanted into or grafted onto an organism of another species, genus or family.

Sources:

<http://www.cancer.gov/dictionary/>

<http://www.nlm.nih.gov/medlineplus/mplusdictionary.html>