Chapter 6

Flax and the Prevention of Cancer

A varied, healthy diet and physical activity are the cornerstones of cancer prevention. Cancer prevention should occur over the life course, beginning with the mother's diet during pregnancy and continuing through childhood and adolescence into adulthood (314). Flax contributes dietary fibre, omega-3 fat and lignans to a healthy diet. Its effects on cancer processes are reviewed in this chapter.

Overview of Cancer Processes

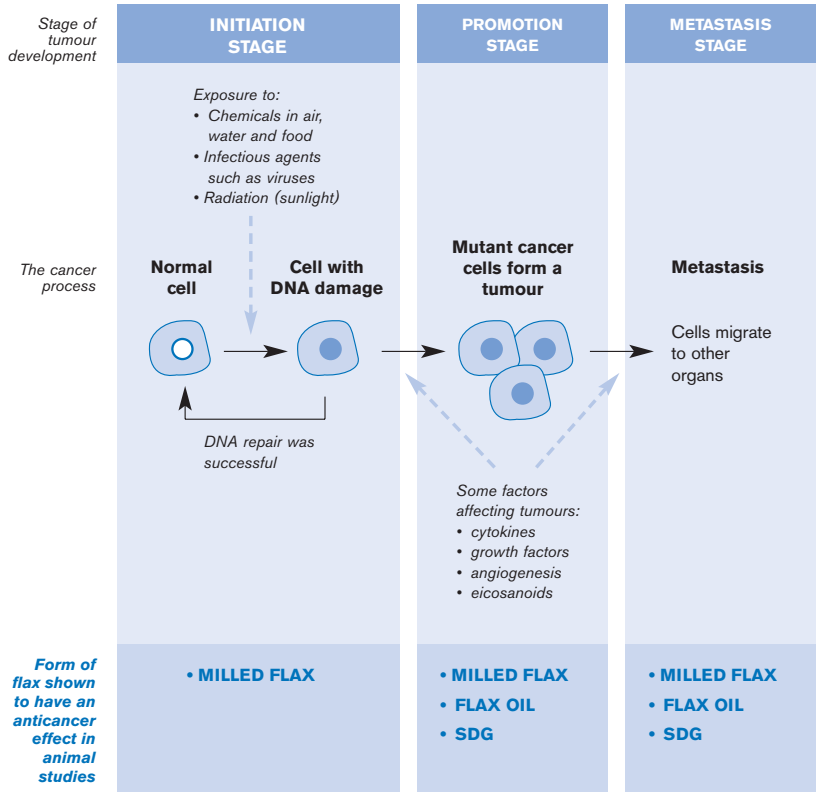
Cancer is a group of diseases characterized by the uncontrolled growth (proliferation) and spread (metastasis) of abnormal cells (315). Cancer develops along a complex path that involves many small, gradual changes in the behaviour of normal cells (316). A diagram of the cancer process is shown in the middle of **Figure 7**. The DNA of normal cells can become damaged when exposed to sunlight, tobacco smoke or industrial chemicals. Some internal factors like hormones and inherited damaged DNA (called genetic mutations) also contribute to cancer development (315). About 30-40% of cancer cases worldwide may be attributed to unhealthy diets and a sedentary lifestyle (317).

Cells have many methods for repairing DNA damage and restoring the cell to normal function. When the repair process fails, however, some cells undergo additional mutations (changes) and begin multiplying (proliferating) uncontrollably. This is the initiation stage of the cancer process (see the top of **Figure 7**). Many factors enhance the growth of these mutant cancer cells: cytokines, eicosanoids, hormones, and

nutrients like fatty acids. When the conditions are right, the mutant cells form a tumour that can develop a network of blood vessels to ensure a steady supply of oxygen and nutrients for growth, a process called angiogenesis. This is the promotion stage. Metastasis occurs when some tumour cells break away from the main tumour and travel to other tissues in the body. Fatty acids are involved both directly and indirectly in all of these processes (318-321). In animals, flax inhibits the initiation and promotion stages of tumour development and also metastasis, as shown at the bottom of **Figure 7**.

FIGURE 7

The effects of flax on the cancer process[a, b]



[a] Abbreviation = SDG, secoisolariciresinol diglucoside. DNA is the genetic material inside the cell nucleus.
[b] Adapted from Barnard (316).

Flax and Cancer Processes

Flax contains three nutritional components that may reduce the risk of developing some cancers: alpha-linolenic acid (ALA), the essential omega-3 fatty acid; lignans, which are phytoestrogens and antioxidants; and dietary fibre. The actions of ALA, lignans and dietary fibre may inhibit certain cancer processes, as described below.

- **ALA.** ALA alters the fatty acid composition of cell membranes in important ways and inhibits the release of pro-inflammatory eicosanoids, which are among the many factors that control the growth and invasiveness of tumour cells and modulate the cycle of cell death (called apoptosis) (322). In a study of liver cancer cells transplanted into male mice, ALA was as effective as eicosapentaenoic acid (EPA) in blocking the tumour's uptake of fatty acids from plasma and in preventing the conversion of linoleic acid (LA) to a tumour growth-promoting compound (323). In a human study – the Lyon Diet Heart Study, described in Chapter 5 – participants who ate a Mediterranean diet rich in ALA had a 61% reduction in cancer risk (324).
- **SDG.** The main flax lignan, secoisolariciresinol diglucoside (SDG), functions as a phytoestrogen and antioxidant (145,169). In a mouse model of melanoma (a darkly pigmented cancerous growth), SDG decreased the number of tumours, the size of tumours, and the rate or extent of metastasis (325,326).
- **FIBRE.** Foods rich in dietary fibre are sources of bioactive substances like antioxidants that may inhibit cancer processes. The greater fibre intake of Asian populations may contribute to their lower risk of cancer compared with Western populations (327). Vegetarians also have a lower risk of some types of cancer (328).

Flax and Breast Cancer

Breast cancer is the most frequently diagnosed cancer in women (315). It is a hormone-sensitive cancer, meaning that in the early stages of development, tumour growth is influenced by the sex hormones, particularly estrogen. (Other hormone-sensitive cancers include those of the endometrium and prostate.) Breast tumours that contain receptors for estrogen are called estrogen receptor positive (ER-positive or ER+); tumours without estrogen receptors are called ER negative (ER-negative or ER-). Women with ER+ tumours are more likely to respond to hormone therapy than women whose tumours are ER- (329). Both ER+ and ER- tumours have been studied in animals, as indicated below.

Animal studies

Milled flax, flax oil and SDG obtained from flax interfere with cancer processes in animals. Based on the findings of current studies, the initiation stage is affected by milled flax, as shown at the bottom of **Figure 7**, whereas the promotion stage and metastasis are affected by milled flax, flax oil and purified SDG.

Milled flax decreased tumour incidence, number and size when fed to carcinogen-treated rats at the initiation (330), promotion (331) and late stages of mammary cancer (332). In the cancer initiation stage, feeding milled flax or defatted flax meal to rats resulted in lower levels of cell proliferation and fewer nuclear aberrations in mammary gland tissue compared with the basal diet (330). Although not lethal events, nuclear aberrations are considered an early warning sign of cancer. In this rat study, the effects of flax on cell proliferation and nuclear aberrations were due to both its ALA and lignan content.

Feeding milled flax slowed the tumour growth rate in mice implanted with an ER- human breast cancer cell line (333) and decreased final tumour weight and volume in mice implanted with an ER+ human breast cancer cell line (334). Feeding rats milled flax at dietary levels of 2.5% and 5% decreased the volume of established mammary tumours by more than 70% (332).

Milled flax also enhanced the effects of tamoxifen in nude mice (334). This study is noteworthy because it was designed to compare the effects of milled flax and tamoxifen, alone and in combination, on the growth of mammary tumours in conditions of high versus low blood levels of estrogen. The study design mimicked the case of premenopausal women, who have high blood levels of estrogen, and postmenopausal women, who have low circulating estrogen. Tamoxifen has been the leading anticancer drug used in breast cancer treatment for women whose breast tumours are ER+ (335). In this mouse study, milled flax inhibited the growth of human ER+ breast cancer in mouse mammary glands. The combination of milled flax and tamoxifen had a greater inhibitory effect on tumour growth than tamoxifen treatment alone.

In a study comparing flax and soy in mice with low estrogen levels (336), long-term feeding (25 weeks) of milled flax did not stimulate the growth of ER+ human breast cancer cells (a positive finding), whereas long-term feeding of soy protein promoted tumour cell growth. Furthermore, feeding milled flax increased the proportion of non-growing and completely regressed tumours.

Finally, milled flax inhibited the growth and spontaneous metastasis of ER- human breast cancer cells in mice (333,337,338). In a study of metastasis and recurrence of tumours in mice, lung metastasis decreased significantly in the groups fed milled flax and flax oil + SDG (339).

Feeding flax oil to rats or mice slowed tumour growth (340), decreased the number of tumours (341), decreased tumour diameter and weight and increased survival time (342). In one rat study, the volume of established tumours decreased more than 50% from baseline (332). Feeding flax oil also decreased metastasis in nude mice (338,339). Metastasis to lung decreased by ~16%, to lymph nodes by ~52% and to other organs such as liver, bones and kidney by more than 90% (338). Flax oil decreased cell proliferation (measured by the Ki-67 labeling index) by 26.5% and increased cell apoptosis (cell death) by 60% compared with the basal diet in this study. These actions interfered with cancer processes.

SDG derived from flax has been shown to inhibit mammary tumour growth at the early promotion stage. For example, feeding rats purified SDG after treatment with a cancer-causing agent produced a 37% decrease in the number of tumours (343) and decreased new and total tumour volume but had no effect on the volume of established tumours (332). Thus, SDG may exert a stronger effect on new tumour development, whereas milled flax and flax oil appear to exert their effects at later stages of tumour development (343).

SDG inhibited metastasis in two studies of implanted ER- human breast cancer cells in nude mice (338,339). Feeding SDG decreased metastasis to lung, lymph nodes and other organs, but its effects were enhanced when it was combined with flax oil, where the combination significantly decreased total metastasis by ~43% (338). The researchers concluded that the inhibitory effects of milled flax were mediated by both the oil and lignan (SDG) components.

Clinical studies

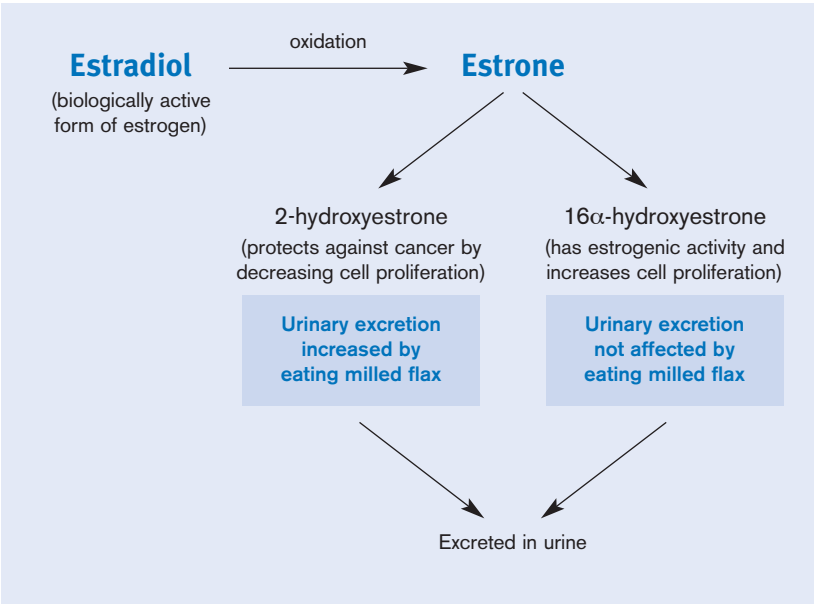
Several randomized, controlled clinical trials have investigated the effects of flax on factors related to breast cancer risk in postmenopausal women. The metabolism of estradiol, which is shown in **Figure 8**, has been studied because estradiol is the biologically active form of estrogen. Estradiol is oxidized to estrone, mainly in the liver. Estrone can be converted to 2-hydroxyestrone and 16α-hydroxyestrone. These two metabolites have different biological properties – the former has little biologic activity, whereas the latter enhances the actions of estrogen and increases cell proliferation (156). Individuals who produce more

16α-hydroxyestrone may have an increased risk of breast cancer (344).

In one study, the diet of 46 postmenopausal women was supplemented with a flax muffin (containing 25 g of milled flax), soy muffin (made with 25 g of soy flour) or a placebo muffin (made with whole wheat flour) for 16 weeks. Blood and urine samples were collected at baseline and at the end of the study. The urinary concentration of 2-hydroxyestrone increased significantly in the flax group, whereas the urinary concentration of 16α-hydroxyestrone did not. Urinary excretion of these two estrogen metabolites did not change in the placebo and soy groups (156). In a study of 28 postmenopausal women, consumption of 10 g (1+ tbsp) of milled flax daily for 7 weeks increased significantly the urinary excretion of 2-hydroxyestrone (345). In both studies, flax increased the ratio of 2-hydroxyestrone to 16α-hydroxyestrone. The finding that flax consumption shifted the balance toward more production of the relatively inactive 2-hydroxyestrone, without increasing 16α-hydroxyestrone production, provides support for a role for flax in breast cancer prevention.

FIGURE 8

Metabolism of estradiol and the effects of flax consumption on two estrogen metabolites



Another randomized, controlled clinical trial assessed the effects of flax on tumour biological markers in 32 postmenopausal women with newly diagnosed breast cancer (346). After confirmation by biopsy of breast cancer and before surgical excision, the women were randomized to eat daily either a flax muffin containing 25 g of milled flax or a placebo muffin made with whole wheat flour. The women consumed the muffins for between 32 and 39 days. Women who ate the flax muffin daily exhibited a significant reduction in cell proliferation (measured by the Ki-67 labeling index), increased cell apoptosis and decreased c-erbB2 expression. Expression of c-erbB2 is associated with aggressive types of breast cancer and a greater potential for metastasis. Although the study consisted of a small number of subjects, its findings suggest that flax has promise as an adjunct diet therapy in breast cancer treatment.

Epidemiologic studies

Whereas animal studies suggest anticancer effects of ALA found in milled flax and flax oil, the findings from human epidemiologic studies related to ALA are more complicated. Several case-control and cohort studies examined the relationship between ALA and breast cancer risk in women, as shown in **Table 15**.

TYPES OF LARGE-SCALE HUMAN (EPIDEMIOLOGIC) STUDIES

Case-control study – compares a group with a specific condition like breast or prostate cancer (the cases) with a group that is free of the condition (the controls).

Cohort study – follows a group of individuals (called a "cohort") over a period of time, often for several years. Any information about the cohort, including dietary intake and eating patterns, is gathered before the diagnosis of cancer is made. Individuals in the cohort who are later diagnosed with cancer are compared with those in the cohort who remained cancer-free.

The strongest findings come from two studies carried out in France (347,348). Both reported that the relative risk of breast cancer was lowest in women whose adipose breast tissue had the highest ALA content, suggesting a protective effect of ALA on breast cancer risk. Because breast cancer may take years, even decades, to develop, measuring the ALA content of adipose tissue provides a more reliable estimate of long-term dietary fatty acid intake than measuring the fatty acid content of blood lipids. This is especially true for ALA, which is obtained only from the diet and is not produced by the body (349). Thus, even though two case-control studies found no link between ALA and breast cancer risk based on measurements of the ALA content of serum fatty acids or red blood cells (350,351), it is not known whether blood levels of fatty acids correlate well with breast tumour fatty acid concentrations or risk of tumour development.

Of the two studies that measured ALA intake, one (352) reported that ALA intake was associated with increased risk of breast cancer, while the other (353) found that breast cancer risk decreased as ALA intake increased. These disparate findings may reflect differences in the study populations and methods of assessing dietary intake. The food frequency questionnaire (FFQ) used in The Netherlands study was a 150-item FFQ validated against a 9-day food record (353), which enhances confidence in its reliability and validity. The Uruguay study FFQ, by comparison, was a 64-item instrument that had been tested previously for reproducibility (352), thereby addressing its reliability but not its validity for assessing dietary fatty acid intakes. In other words, the Uruguay study FFQ may give reproducible but invalid or inaccurate results related to ALA intake.

TABLE 15

Case-control and cohort studies of ALA and breast cancer risk in women[a,b]

Study location	Study population	Main ALA outcome	Main finding
France [Klein] (347)	123 cases and 59 controls	ALA content of adipose breast tissue	ALA content of adipose breast tissue was inversely associated with breast cancer risk
France [Maillard] (348)	241 cases and 88 controls	ALA content of adipose breast tissue	Higher ALA content of adipose breast tissue was associated with lower breast cancer risk
New York state [Saadatian-Elahi] (350)	197 cases and 197 controls	Serum fatty acids, including ALA	ALA and other omega-3 fatty acids were not associated with breast cancer risk
China [Shannon] (351)	322 cases and 1030 controls	ALA content of red blood cells	ALA was not associated with breast cancer risk
Uruguay [De Stefani] (352)	365 cases and 397 controls	ALA intake	ALA intake was associated with an increased risk of breast cancer
The Netherlands [Voorips] (353)	Subcohort of 1812 women followed for about 16 years	ALA intake	Risk of breast cancer decreased as median ALA intake increased (ALA intake ranged from 0.6 to 1.7 g/day)

[a] Abbreviation = ALA, alpha-linolenic acid.
[b] The last name of the paper's first author is shown in brackets.

Regarding lignans and breast cancer, two reviews of epidemiologic studies published since 1997 (354,355) determined that most case-control studies found a protective effect of plant and mammalian lignans, although their anticancer effects may be limited to premenopausal women and differ by the type of estrogen receptor in breast tissue. One recent prospective cohort study (166) found that among 58,049 post-menopausal French women, those with the highest intake of lignans (>1395 µg/day) had a significantly reduced risk of breast cancer. When breast cancer risk was analyzed by receptor status, the inverse relationship between lignan intake and breast cancer risk was limited to breast cancers that were ER+ and progesterone-positive. These findings suggest that hormone receptors control the biologic effects of lignans.

Conclusions regarding flax and breast cancer

In the realm of breast cancer research, the animal data are strong, suggesting that flax and its main nutritional components interfere with tumour initiation, promotion and metastasis. One animal study found that flax and tamoxifen work synergistically to inhibit tumour growth (334). A test tube (*in vitro*) study found that the mammalian lignans, whether applied alone or combined with tamoxifen, inhibited metastasis in ER- human breast cancer cells; tamoxifen and the mammalian lignans together did not antagonize the effect of tamoxifen in ER- breast cancer cells (356). In clinical trials, flax favourably affected breast cancer risk factors by altering estrogen metabolism and decreasing cell proliferation (156,345,346,357,358). According to epidemiologic studies, diets high in lignans reduce breast cancer risk in premenopausal women and protect against ER+ breast cancer in postmenopausal women (354,355). The epidemiologic data regarding the benefits of ALA are less straightforward, but the two strongest studies – both case-control studies in which adipose tissue ALA was measured (347,348) – found a protective effect of ALA on breast cancer risk.

Flax and Prostate Cancer

Prostate cancer is the most frequently diagnosed cancer in men (315). Like breast cancer, it is hormone-sensitive and in the early stages of development, tumour growth is influenced by the sex hormones estrogen and testosterone and their active metabolites (327,359). The sections below review the studies of milled flax, dietary ALA and dietary lignans and prostate cancer risk.

Milled flax and prostate cancer risk

A small number of studies suggest a beneficial effect of milled flax on prostate cancer biology. The clinical findings are preliminary but promising.

ANIMAL STUDIES. Milled flax supplementation of the diet (5% by weight) appeared to block the progression of prostate cancer to a more advanced stage in a mouse model of prostate cancer. The mice fed milled flax in their rations experienced an increase in programmed cell death (apoptosis) and a decrease in cell proliferation (360).

CLINICAL STUDIES. In a pilot study, 25 men with prostate cancer who were awaiting surgery consumed 30 g (~3 3/4 tbsp) of milled flax daily for about a month as part of a low-fat diet. Prostate cancer cell proliferation decreased and apoptotic death of cancer cells increased among men who ate milled flax compared with a matched historic control group. Total serum prostate-specific antigen (PSA) levels did not change, although total testosterone and the free androgen index both decreased significantly between baseline and surgery (207). In a related pilot study, total serum PSA and the cell proliferation rate decreased significantly after 6 months of flax supplementation (30 g/day) in men scheduled for a repeat prostate biopsy (361). Although these findings suggest a beneficial effect of milled flax on prostate cancer biology, they are confounded by the low-fat background diet.

By comparison, another study among 29 men diagnosed with prostate cancer and scheduled for surgery found no effect of consuming a bread made with soy grits + flax on PSA levels, free PSA, testosterone and sex-hormone-binding globulin compared with a bread containing only soy grits or a bread made with pearled wheat (362). Consumption of the soy grits + flax bread resulted in significant increases in the urinary excretion of soy isoflavones and the mammalian lignan enterolactone.

ALA and prostate cancer risk

ALA is an essential fatty acid in the human diet. All cells – including normal and cancerous cells (349) – need ALA and the other essential fatty acid, linoleic acid (LA), for growth and proper functioning. The findings of test tube (*in vitro*) and epidemiologic studies related to ALA and prostate cancer are reviewed below.

TEST TUBE STUDIES. One method of assessing the effects of fatty acids on tumour growth is to apply a pure form of the fatty acid to cells grown in test tubes. In one study where this method was used, ALA and EPA both stimulated the growth of human metastatic prostate cancer cells (363). However, in another type of cancer cell – a myeloma cell line called SP 2/0 Ag 14 – ALA and EPA inhibited the growth of SP 2/0 cells at all concentrations tested (364). ALA and EPA also inhibited the activities of certain enzymes bound to cell membranes, and they were more potent inhibitors of SP 2/0 cell growth than other fatty acids tested (365). In still another type of cancer cell, a mouse leukemia cancer cell called T27A, ALA and EPA were not effective killers of T27A cancer cells, whereas docosahexaenoic acid (DHA) was very cytotoxic (366).

What sense can be made of these findings? First, the human prostate cancer cell lines used in test tube studies are derived from metastatic tumours, and they are not likely to be affected by dietary interventions because they are drawn from a late stage in the disease process. Second, many factors affect the actions of fatty acids in cell cultures, including the amount of fatty acid added to the cell culture, the presence of other fatty acids in the growth medium and the cell type. It is not clear whether what is learned in test tube experiments applies to what happens in tumours that arise in animal and human tissues (367).

EPIDEMIOLOGIC STUDIES. Some – but not all – epidemiologic studies suggest that ALA is associated with an increased risk of prostate cancer. **Table 16** summarizes the findings of the few studies where the ALA content of prostate cancer tissues was analyzed, while **Tables 17** and **18** summarize the findings of studies that measured the fatty acid content of tissues (blood, adipose tissue) or diet and then correlated those figures with prostate cancer in a group of men with prostate cancer (the cases) versus a group without prostate cancer (the controls) or in a cohort of men followed for several years. The findings related to linoleic acid (LA) are included for comparison purposes.

Measurement of prostate cancer tissue samples

Three studies investigated the ALA content of samples of prostate cancer (**Table 16**). One study, conducted in Denmark, found more ALA in tissues taken from men with prostate cancer than in tissues taken from men with benign prostatic hyperplasia (BPH) (368), a non-cancerous enlargement of the prostate gland (369). Two studies carried out in the United States, however, found the opposite – ALA concentrations were lower in men with prostate cancer compared with controls, especially when the tumours were advanced (370). The most recent analysis found no correlation between ALA concentration in prostate tissue and locally advanced disease (371).

These conflicting study findings may be due to different population ages, sample sizes and methods for confirming and classifying prostate carcinoma. The study by Freeman and coworkers (371), for example, had a larger sample size (196 men with prostate cancer) and younger study volunteers (mean age = 62.2 years) than the study by Christensen et al. (20 men with prostate cancer, mean age = 70 years) (368). The Freeman et al. paper (371) provided considerably more information about how the prostate tissue was obtained and classified by grade and stage of disease, thus increasing confidence in the study findings.

TABLE 16

Studies investigating the ALA content of prostate cancer tissue samples[a]

Study[b]	Name of study or study location	Number of men in the study	Main study measure	Findings
Christensen (368)	Denmark	35 men with BPH and 20 men with prostate cancer	Fatty acid content of prostate tissue and white blood cells	ALA and EPA were higher in tissue from men with prostate cancer than in tissue from men with BPH. The ALA, but not EPA, content of prostate tissue increased as serum PSA levels increased.
Freeman (370)	Illinois, USA	49 men with prostate cancer	Fatty acid content of prostate tissue	ALA concentration was lower in PC cases than in controls, especially when the tumor extended to an anatomical or surgical margin.
Freeman (371)	Illinois, USA	196 men with prostate cancer	Fatty acid content of prostate tissue	ALA was not correlated with locally advanced disease.

[a] Abbreviations = ALA, alpha-linolenic acid; BPH, benign prostatic hyperplasia; EPA, eicosapentaenoic acid; PC, prostate cancer.
[b] The column shows the last name of the paper's first author.

Measurement of adipose tissue and blood samples

In case-control studies summarized in **Table 17**, ALA was associated with increased prostate cancer risk in three studies (372-374), but not in two others (375,376). A 1994 analysis of samples from men participating in the Physicians Health Study (377) found an association between ALA and increased prostate cancer risk, whereas a 2007 analysis (378), in which tumours were classified according to their aggressiveness, found no association between ALA and prostate cancer risk. The most reliable finding is that of Godley and coworkers (375), who measured the fatty acid content of adipose tissue and found no correlation between prostate cancer risk and the ALA content of adipose tissue. The concentration of fatty acids in adipose tissue provides the best estimate of long-term fatty acid intake, particularly of fatty acids like ALA which are obtained from diet and not synthesized within the body (349,379).

Red blood cell membranes provide a good estimate of fatty acid intake over the previous month or so because their half-life is about 120 days (349). In the two studies that measured ALA content of red blood cell membranes, ALA was associated with increased prostate cancer risk in one study (373) but not in the other (375).

Compared with adipose tissue, measurements of blood phospholipids, serum cholesterol esters, serum fatty acids or red blood cells are considered short-term markers of fat intake – that is, they reflect dietary fat intakes over the previous few days or months before the blood sample was drawn (349). Because the fatty acid pools in the bloodstream are in constant flux between tissues, measuring these blood lipids or cells does not reflect the long-term ALA intake. This is a significant limitation, because prostate cancer develops over a period of several years. If ALA affects the development and progression of prostate cancer in any way, it is likely to do so over a period of many years, not a few days or months. In the final analysis, the relationship between the ALA content of healthy or cancerous prostate tissue and ALA levels in the diet, blood lipids and red blood cells has not been established (380).

TABLE 17

ALA and linoleic acid in blood or adipose tissue and risk of prostate cancer[a]

Study[b]	Name of study or study location	Blood fatty acids or tissue studied	ALA associated with increased risk of prostate cancer?	LA associated with increased risk of prostate cancer?
Case-control studies of the fatty acid content of blood or adipose tissue				
Gann (377), Chavarro (378)	Physicians Health Study, USA	Plasma phospholipids (377),whole blood fatty acids (378))	Yes (377) No (378)	No (377) No[c**] (378)
Godley (375)	North Carolina, USA	Adipose tissue and red blood cell membranes	No	Yes
Harvei (372)	Norway	Serum fatty acids	Yes	No
Männistö (376)	Finland	Serum cholesterol esters	No	No[d]
Newcomer (373)	Washington state, USA	Red blood cell membranes	Yes	Yes
Yang (374)	Korea	Serum fatty acids	Yes	No

[a] Abbreviations = ALA, alpha-linolenic acid; LA, linoleic acid.
[b] The column shows the last name of the paper's first author.
[c] ** Denotes an inverse relationship between the fatty acid and risk of prostate cancer.
[d] For linoleic acid, risk of prostate cancer differed by vitamin E (α-tocopherol) status – a high proportion of linoleic acid in serum cholesterol esters decreased prostate cancer risk in those who received vitamin E, but not in those subjects who did not receive vitamin E.

Measurement of dietary ALA intake

Five case-control and five prospective cohort studies (see **Table 18**) examined the relationship between dietary ALA intake and risk of prostate cancer. Three of the case-control studies (381-383) found no evidence of an association between dietary ALA and prostate cancer risk, while two (384,385) reported that ALA intake was associated with increased prostate cancer risk. These studies were conducted in Canada, Italy, Spain, Sweden and Uruguay.

Among the cohort studies, two found no association (386,387) and one found an inverse relationship (388) between ALA intake and prostate cancer risk. Three analyses of data from the Health Professionals Follow-up Study (389-391) found a positive association between dietary ALA and risk of advanced prostate cancer. These studies were conducted in Finland, The Netherlands and the United States. All cohorts consisted of thousands of men – between 29,592 (386) and 58,279 (388) – who were originally free of prostate cancer at the time of the initial screening many years ago.

Perhaps the most striking findings are those of the Health Professionals Follow-up Study (389-391), which consistently reported a link between ALA intake and risk of advanced prostate cancer, and those of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, which found no association between ALA or any individual food source of ALA and overall prostate cancer risk or risk of advanced disease (386). These two studies were carried out by leading researchers at respected institutions, consisted of a fairly homogenous group of American men, and appeared to employ the highest standards of research design, including strict selection of eligible study participants, identification and classification of prostate cancer tissue and rigorous attention to diet assessment. Yet, their findings are completely different! Indeed, their findings are so disparate as to cast doubt on the reliability of most epidemiologic studies of diet and prostate cancer risk.

The only logical explanation for the stark difference in the findings of these two studies is the nature of the food frequency questionnaire (FFQ) administered to study participants and the nutrient databases on which they are based. By virtue of its FFQ, one of these studies may provide a more accurate estimate of the relation between dietary ALA and prostate cancer risk – but which one? FFQ methodology is convenient for evaluating dietary intake in large studies, but FFQ

TABLE 18

Studies investigating the dietary intakes of ALA and linoleic acid and risk of prostate cancer[a,b]

Study[c]	Name of study or study location	ALA associated with with increased risk of prostate cancer?	LA associated with increased risk of prostate cancer?
Case-control and prospective cohort studies of dietary intake			
Andersson (381)	Sweden	No	No
Bairati (382)	Quebec, Canada	No	No[d**]
Bidoli (383)	Italy	No**	No**
De Stefani (384)	Uruguay	Yes	No
Giovannucci (389,390)	Health Professionals Follow-up Study, USA	Yes	No (389)[e]
Koralek (386)	Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, USA	No	------
Laaksonen (387)	Kuopio Ischaemic Heart Disease Risk Factor Study, Finland	No	No**
Leitzmann (391)	Health Professionals Follow-up Study, USA	No, for total PC risk Yes, for advanced PC risk	No
Ramon (385)	Spain	Yes	------
Schuurman (388)	The Netherlands Cohort Study	No**	No**

[a] Abbreviations = ALA, alpha-linolenic acid; LA, linoleic acid; PC, prostate cancer.
[b] A food frequency questionnaire was used to assess the dietary intakes of ALA and LA in all but two studies (382, 387).
[c] The column shows the last name of the paper's first author.
[d] ** Denotes an inverse relationship between the fatty acid and risk of prostate cancer.
[e] The relationship of linoleic acid intake to prostate cancer risk was not evaluated in the 2007 analysis of data from this study.

instruments can differ in terms of how foods are grouped together (meat may mean red meat and poultry on one FFQ and red meat, poultry and fish on another), how serving sizes are estimated by researchers and interpreted by participants, which foods are included on the FFQ, how complete the nutrient database is, and how decisions are made about incomplete questionnaires (392).

In the end, the validity and reliability of FFQs and other diet instruments must be improved before we can be confident about the findings of diet studies in this area. There is a need for a validated questionnaire that reliably estimates ALA intake from commonly eaten foods and dietary supplements, as has been done with the long-chain omega-3 fatty acids (393) and with lignans in flax and other foods (168).

Lignans and prostate cancer risk

Plant and mammalian lignans appear to have beneficial anticancer effects in test tube studies (that is, *in vitro*). Only a handful of prostate cancer studies have been conducted in animals, but the general finding is that lignans decrease tumour mass and increase cell apoptosis (327). The findings of human studies are mixed, with three studies reporting beneficial results in men who consumed a lignan-rich diet (207,361,394), one study finding no effect of soy and flax taken together in bread on prostate cancer biomarkers (362), and two studies finding no link between serum enterolactone concentrations and prostate cancer risk (395,396). The latter studies suffer from the same limitation as those in which blood measurements of fatty acids like ALA are correlated with prostate cancer risk – serum enterolactone levels are not a valid measurement of long-term lignan intake and prostate cancer risk, especially as the prostate gland can achieve much higher concentrations of lignans than can blood (327).

A recent case-control study conducted among 1499 Swedish men with prostate cancer and 1130 controls found that a high intake of foods rich in phytoestrogens, including lignans, was associated with a decreased risk of prostate cancer (168). This may be the first large-scale population study in which the diet assessment instrument – a 261-item FFQ – asked specifically about the consumption of phytoestrogen-rich foods like flax, berries, nuts, peanuts, beans, sunflower seeds and soy as part of a typical diet. The FFQ's ability to estimate dietary phytoestrogen intake was validated against serum levels of enterolactone in this study.

Conclusions regarding diet and prostate cancer

Three conclusions can be drawn from studies related to diet and prostate cancer risk.

First, the exact cause of prostate cancer is not known, but the most consistent risk factors for its development are advancing age, family history and race (359,369). Diet is believed to contribute to the pathology of prostate cancer, based on differences between its incidence in Eastern and Western populations whose diets differ in the intakes of fats, cereals, fruits and vegetables (327). Environmental factors such as infectious agents, chemicals and diet may contribute to prostate cancer by triggering inflammatory reactions. Roughly 20% of all human cancers are caused by chronic infection or inflammation (369).

Second, no consistent dietary effect has emerged from the human cohort and case-control studies. Two dietary factors are the most likely contributors to prostate cancer development – excess calories and total fat (322,397,398). The dietary ratio of omega-6 to omega-3 fatty acids may also be important (399). In the Physicians' Health Study (377) and the Health Professionals Follow-up Study (389), eating red meat emerged as a risk factor for prostate cancer. Even though meat contains only small amounts of ALA, it is a leading source of ALA in some people's diets, making it a marker for a diet rich in animal fat and meat (134). Indeed, Australian men who ate a high-meat diet had significantly higher intakes of ALA than men who ate a moderate-meat diet or who were ovolactovegetarians or vegans (400). Thus, ALA may be guilty by association in some studies because it was linked with red meat, which is itself associated with increased prostate cancer risk.

Otherwise, there are too many inconsistencies among the research findings to be confident that any one fatty acid contributes to cancer development in humans (401). These inconsistencies apply to most fatty acids, not just ALA. For instance, among the studies summarized in **Tables 17** and **18**, LA was associated with an increase in prostate cancer risk in 2 studies (373,375), had no association with prostate cancer in 7 studies (372,374,376,377,381,384,389,391) and had an inverse relationship with prostate cancer in 5 studies (378,382,383,387,388).

Third, there is no conclusive evidence of a dose-response relationship between the dietary intake of ALA and prostate cancer risk (399). In other words, if ALA is associated with tumour development, then the risk of prostate cancer should increase steadily as ALA intake

increases. The Uruguay study (384) reported evidence of such a dose-response relationship. However, men in the PLCO study, which found no evidence of a link between ALA intake and prostate cancer risk (386), had higher ALA intakes than men in the Health Professionals Follow-up Study (389,390), which reported that ALA intake was associated with increased risk of prostate cancer. If a dose-response relationship exists, one would expect men in the PLCO study to exhibit a greater risk of prostate cancer due to their higher ALA intakes.

Conclusions regarding flax and prostate cancer

There is no evidence that flax contributes to prostate cancer. Indeed, flax may reduce prostate cancer risk by dampening inflammatory reactions (98,99,219,263). Inflammation is a hallmark of early premalignant lesions in the prostate gland (359,369).

Questions about the potential adverse effects of ALA in prostate cancer development deserve to be addressed through well-designed animal and human studies that use appropriate tissue biomarkers and measures of dietary ALA intake (402). Even though a meta-analysis reported a concern about ALA and prostate cancer risk (310), the role of ALA in the metabolism of the healthy prostate is not understood. Likewise, the extent to which diet influences prostate fatty acid metabolism is not known. Vegetarian men, for instance, have low incidences of invasive prostate cancer (327) and yet have a significantly greater concentration of ALA in plasma phospholipids compared with omnivorous men (400).

Perhaps the most important unanswered question is whether a high ALA content in prostate tissue signals an increased risk of prostate cancer and, if so, why this pattern differs from that of breast cancer, especially as the two types of cancer are strikingly similar in pathology, hormone metabolism and extent of inflammation (359). In two human studies (347,348), the relative risk of breast cancer was lowest in women whose adipose breast tissue had the highest content of ALA, suggesting a protective effect of ALA on breast cancer risk. These discrepancies between breast tissue and prostate tissue have not been explained.

A dietary strategy for health

In the absence of consistent research findings about diet and prostate cancer, what should men do? The best dietary strategy is one linked with the lowest overall risk of chronic diseases such as cancer, heart disease and stroke: Eat a diet high in dietary fibre and low in fat, particularly saturated fat, and eat several servings every day of fruit, vegetables, whole grains and cereals (403). Considering that a single nutrient or food is not likely to account for increased risk of aggressive prostate cancer (404), benefits may be derived from incorporating into the daily diet a modest amount (1-2 tbsp) of milled flax, which provides lignans, dietary fibre, antioxidants, vitamins, minerals and omega-3 fat.

The notion that flax oil should be avoided has arisen only because it is a rich source of ALA. There is no evidence that flax oil contributes to prostate cancer risk, and flax oil is not a major source of ALA in the North American diet. In the United States, meat, poultry, fish and mixtures of these foods contribute 26-29% of the total 18:3n-3 intake; grain products contribute ~20%; and fats, vegetable oils and salad dressings, ~18-20%. Furthermore, consumption of flax oil on a population basis is miniscule relative to that of other ALA-containing oils like soybean oil, which is the predominant oil in the U.S. food supply (135). Where dietary ALA is concerned, the individual's overall diet pattern and genetic makeup are important considerations (404).

Flax and Colon Cancer

A role for flax in the prevention of colon cancer is plausible because the colon is the region where mammalian lignans are produced from plant lignans. A study in rats treated with a cancer-causing chemical showed that rats fed diets supplemented with either 5% or 10% milled flax or defatted milled flax for 4 weeks had a significantly lower number of aberrant crypts and less cell proliferation in the colon compared with control rats (405). In another rat study, feeding flax oil and flax meal reduced the number of aberrant crypts in the distal colon by 88% and 77%, respectively (406). Aberrant crypts are considered early markers of colon cancer risk. The mammalian lignans derived from flax have also been shown to inhibit the growth of human colon cancer cells grown in test tubes. Enterolactone was more than twice as effective as enterodiol in reducing the growth of human colon cancer cells in test tubes (407).

Anticancer Mechanisms of Flax

The anticancer effects of flax derive from its hormone and non-hormone-related actions. Flax lignans exert hormone-related actions by competing with estrogen for binding to the estrogen receptor and by inhibiting the enzyme aromatase, which converts androgens into estrogen (408,409). Mammalian lignans derived from flax inhibit aromatase in human breast cancer cell lines (156).

Non-hormone-related actions include decreasing nuclear aberrations and genetic damage (330,410); cell proliferation (330,334); the production of prostaglandin E_2 (PGE_2), an eicosanoid that enhances cell proliferation and metastasis (342); the production of growth factors like vascular endothelial growth factor (VEGF) that promote the building of new capillaries to supply the tumour (a process called angiogenesis) (333); and the production of insulin-like growth factor 1 (IGF-1), which promotes tumour growth (337). Flax also increases cell apoptosis (334), which inhibits cell proliferation and tumour growth. Flax lignans have antioxidant effects (169,172).

Flax in the Cancer Prevention Diet

Although the data set is small, there is evidence, mainly from animal studies, that flax has anticancer effects. Given the strong evidence that diet and physical activity are determinants of cancer risk (314), a common sense approach to cancer prevention includes the following timeless strategies: Be physically active; maintain a healthy weight; and eat a variety of foods in a balanced diet plan, including ample amounts of whole grains, cereals, fruits, vegetables and healthy fats and oils, in moderation (403). Adding a little flax to the daily diet contributes omega-3 fat, lignans and dietary fibre and may help reduce cancer risk.