Phytoestrogens: Epidemiology and a Possible Role in Cancer Protection

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Because many diseases of the Western Hemisphere are hormone-dependent cancers, we have postulated that the Western diet, compared to a vegetarian or semivegetarian diet, may alter hormone production, metabolism, or action at the cellular level by some biochemical mechanisms. Recently, our interest has been mainly focused on the cancer-protective role of some hormonelike diphenolic phytoestrogens of dietary origin, the lignans and the isoflavonoids. The precursors of the biologically active compounds originate in soybean products (mainly isoflavonoids), whole grain cereal food, seeds, and probably berries and nuts (mainly lignans). The plant lignan and isoflavonoid glycosides are converted by intestinal bacteria to hormonelike compounds with weak estrogenic but also antioxidative activity; they have now been shown to influence not only sex hormone metabolism and biological activity but also intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation, differentiation, and angiogenesis in a way that makes them strong candidates for a role as natural cancer-protective compounds. Epidemiologic investigations strongly support this hypothesis because the highest levels of these compounds in the diet are found in countries or regions with low cancer incidence. This report is a review on recent results suggesting that the diphenolic isoflavonoids and lignans are natural cancer-protective compounds. — Environ Health Perspect 103(Suppl 7):103–112 (1995)

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Introduction

Numerous epidemiologic and migrant studies support the view that the Western diet is one of the main factors causing the high incidence of the so-called Western diseases (*1–4*), among which we include the major hormone-dependent cancers, colon cancer, and coronary heart disease. Because all these diseases to various extents are related to sex hormones or sex hormone metabolism (*5–7*), we have postulated that the Western diet, compared to the vegetarian or semivegetarian diet in some developing and Asian countries, may alter hormone production, metabolism, or action at the cellular level by some biochemical mechanisms. Recently, our interest has been focused on the biological role of two groups of hormonelike diphenolic phytoestrogens of dietary origin, the lignans and the isoflavonoids; they have similar molecular weights and metabolism as the steroids, but partly with clearly different biological effects in the cells. These compounds, which mainly occur in soybean and whole-grain products, various seeds, and other similar food components, have now been shown to influence not only sex hormone metabolism and biological activity but also intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation, and angiogenesis in a way that makes them strong candidates for a role as cancer-protective compounds. This review discusses those compounds that are measurable in the mammalian organism.

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Abbreviations used: GC-MS, gas chromatography–mass spectrometry; SHBG, sex hormone-binding globulin; bFGF, basic fibroblast growth factor.

Lignans and Isoflavonoids in Foods

Since 1931 it has been well known that soybeans contain high amounts (up to 100–300 mg/100 g) of the glycosides of the two isoflavones daidzein and genistein (*8,9*). Much later, a third major compound, glycitein, was found also as a glycoside (*10*). Small amounts of these three compounds occur in the free form. Fermented soy may contain a catechol conversion product of glycitein, 6,7,4′-trihydroxyisoflavone (*11,12*). Furthermore, small amounts (about 5 μg/100 g) of the isoflavone coumestrol have been found (*13*). Soy sauce does not contain any isoflavones except the lignan precursor coniferyl alcohol (*14*). Recently, the content of daidzein and genistein glycosides in various soy bean products were determined (*15*).

We have developed new methodologies for the assay of phytoestrogens in meal, flour, and soy products using gas chromatography–mass spectrometry (GC-MS); the lignan secoisolariciresinol has been measured in soy meal, and the concentrations are relatively low.

The mammalian lignans seem to be mainly derived from grains and seeds and probably also berries and nuts. Our studies on fractionated meals of wheat and rye seem to indicate that the precursors matairesinol and secoisolariciresinol, both present in meal of these grains, are present in the aleurone layer of the grain. This cellular layer is tightly bound to the fiber layer, and the liberation of the precursors from these very resistant cells is difficult.

Phytoestrogens Identified in Man

When consumed, the plant isoflavonoids and lignans undergo many metabolic conversions in the gut, which results in the formation of hormonelike compounds with estrogen activity and the ability to bind weakly to estrogen receptors (*16*). About 15 years ago, two cyclically occurring unknown compounds, now called enterolactone and enterodiol, were detected in the

urine of the female vervet monkey and in women; these compounds were subsequently identified independently by two groups (*17,18*). Furthermore, small amounts of four plant lignans (matairesinol, lariciresinol, isolariciresinol, and secoisolariciresinol) have been identified in human urine (*19,20*); 7′-hydroxymatairesinol and 7′-hydroxyenterolactone were also tentatively identified in urine (*21*).

The isoflavonoid phytoestrogens are heterocyclic phenols with a close similarity in structure to estrogens and a diphenolic character similar to that of lignans. They occur in numerous plants, and many studies have shown that they have hormonal effects in animals (*22*), the most important being the clover disease. The following isoflavonoid phytoestrogens have been identified or detected in human urine in this laboratory: formononetin, methylequol, daidzein, dihydrodaidzein, *O*-demethylangolensin, genistein, and 3′,7-dihydroxyisoflavan. Equol was identified independently in two laboratories (*5,23*). Recently, glycitein was also identified in human urine, and five isoflavonoid metabolites (6′-hydroxy-*O*-demethylangolensin, dihydrogenistein, dehydro-*O*-demethylangolensin, and two isomers of tetrahydrodaidzein) were tentatively identified (Figure 1)(*24*).

Metabolism of Phytoestrogens in Man

The literature on the origin, formation, and metabolism of the phytoestrogens in animals (*22*) and in man (*16,21,25*) has been reviewed and therefore only a few points will be discussed here.

Equol and *O*-demethylangolensin are most likely formed, as in sheep, by intestinal bacterial action from formononetin and daidzein present in foodstuffs such as soy products. Some people are unable to produce equol or they excrete this isoflavane in very low amounts [H. Adlercreutz, unpublished results; (*16,26*)]. Of the isoflavonoids, we can now determine daidzein, *O*-demethylangolensin, equol, and genistein in plasma (*27*), urine (*28*), and feces (*29*) allowing studies on absorption and metabolism of these compounds.

The mammalian lignans enterolactone and enterodiol are formed from plant precursors by the action of intestinal bacteria. The lignan matairesinol is converted to enterolactone and secoisolariciresinol is converted to enterodiol; enterodiol may be oxidized to enterolactone (*16*). We have now established by gas chromatography–mass spectroscopy (GC-MS) techniques that the plant lignans are localized close to the outer fiber-containing layers of the grain called the aleurone layer, which contains phytin, polyphenols, enzyme inhibitors, and other compounds generally regarded as antinutritional factors. Modern milling techniques usually eliminate this fraction because it is tightly bound to the fiber layer, which does not occur in the products supplied to the market for consumption, with some exceptions. This occurs particularly in Western societies. It should be mentioned that administration of

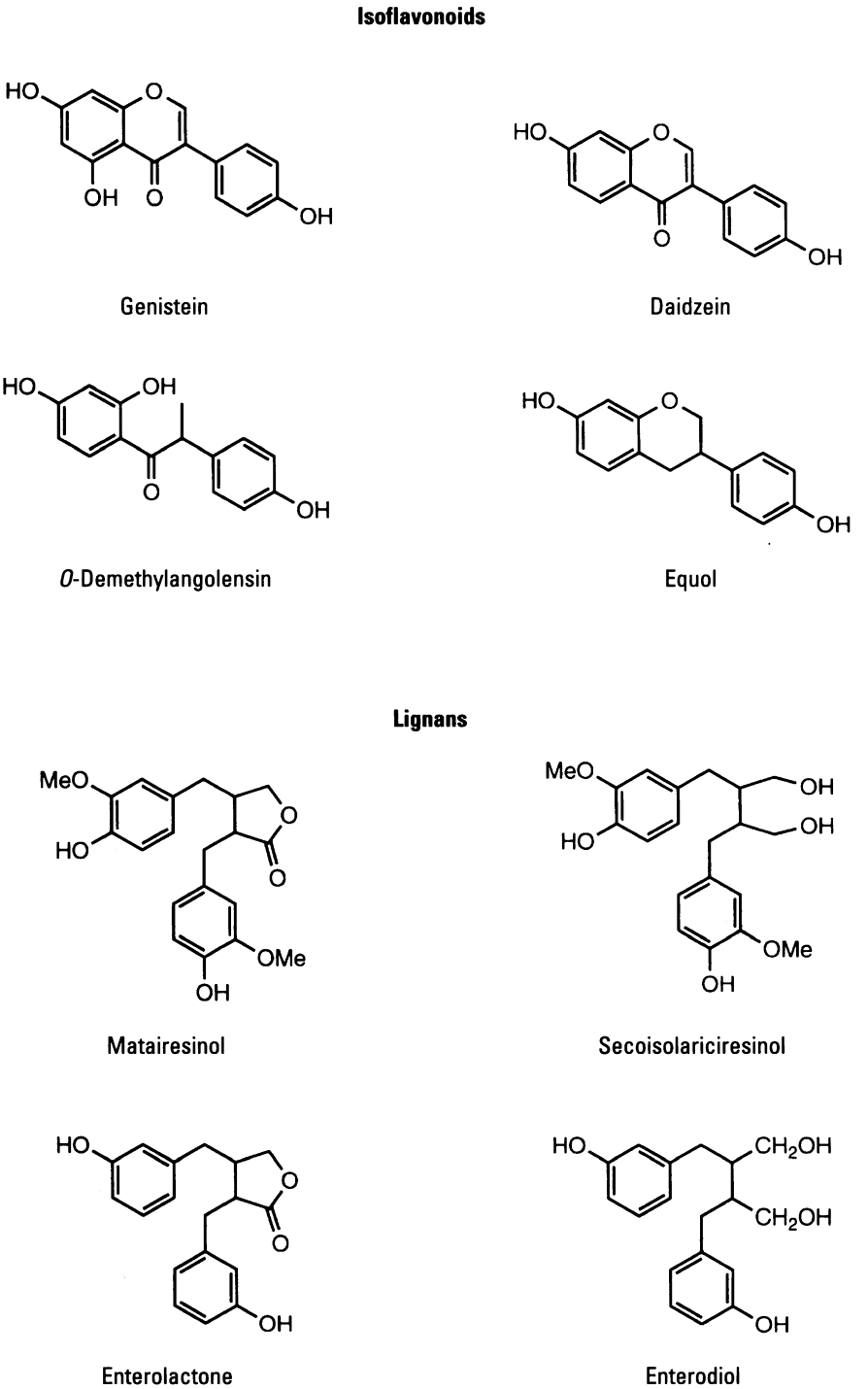

Figure 1. Structure of the most important isoflavonoids and lignans identified by human biological samples.

antibiotics almost completely eliminates the formation of enterolactone and enterodiol from plant precursors in the gut (*30,31*). Following further development of our methodology (*28*), we can now analyze matairesinol, secoisolariciresinol, enterodiol, and enterolactone in urine, plasma, and feces. Many of these compounds have also been identified and measured in cow's milk (*32*). Enterolactone concentration is high in human and bovine semen (*33*) and some lignans and isoflavonoids have been identified and measured by GC-MS in saliva, breast aspirate or cyst fluid, and prostatic fluid by GC-MS (*34*).

Phytoestrogen Levels in Various Populations

A summary of our results regarding urinary lignan and isoflavonoid excretion in various dietary groups of women and men, including two groups of breast cancer patients, has recently been presented (*35*). None of the subjects had been treated with antibiotics during the last 3 months.

With regard to lignans, the macrobiotic women living in Boston, Massachusetts, had the highest values, followed by the lactovegetarian women living in Boston and in Helsinki, Finland. The lowest lignan values were found among the breast cancer patients in Boston and in omnivorous women in both Boston and Helsinki. In our study of women in Hawaii that had recently immigrated from the Orient, even lower lignan values were found. These immigrants had similar isoflavonoid values as those consuming an omnivorous Western diet, showing that they had very rapidly left the soy products out of their diet. Leaving the soy from the diet and not consuming any whole-grain bread results in very low lignan and isoflavonoid values in urine, but the low-fat diet may still give some protection against breast cancer. Low lignan values were also found in the Japanese men and women, who had very high isoflavonoid values. Recent measurements of urinary and plasma phytoestrogens in Japanese and Finnish men revealed that despite low urinary lignan values in the Japanese men the values for the free + sulfate-conjugated lignans in plasma were as high as those in the Finnish men, but the glucuronide values for enterolactone were significantly lower ($p < 0.001$) (H Markkanen, unpublished results). In an earlier study we found that lignan excretion in Japanese subjects was related to the intake of whole soybeans (*26*), which agrees well with our recent detection of secoisolariciresinol in soybean meal.

Biological Effects of Lignans and Isoflavonoids

In this connection only phytoestrogens that have been measured in the human organism will be considered. The lignans enterolactone and enterodiol bind weakly to rat uterine cytosol (JH Clark and H Adlercreutz, unpublished data) but have no detectable estrogenic activity *in vivo* in mice (*30*). However, in four sensitive assays of estrogen activity in tissue culture, including breast cancer cell lines, the lignans were stimulatory and the effect could be blocked by tamoxifen. No antiestrogenic properties could be observed (*36*). In another study enterolactone *in vivo* inhibited estrogen-stimulated RNA synthesis in rat uterine tissue when administered 22 hr before estradiol (*37*). The concentrations of enterolactone were very low, and it is doubtful whether this result can be repeated. We observed stimulatory effect of enterolactone on MCF-7 breast cancer cell growth in the absence of estradiol, but, at slightly stimulatory or nonstimulatory estradiol and physiological enterolactone concentrations, we observed no stimulation or a tendency to inhibition (*38*). Recently enterolactone, but not enterodiol, was shown to stimulate pS2 expression in MCF-7 cells (*39*). These diverging results are difficult to explain, but it has been suggested (*7,40*) that the effect of exogenous weak estrogens may be either agonistic or antagonistic depending on the level of endogenous estrogens; this has been experimentally confirmed with regard to coumestrol (*40*).

Many studies have shown that the isoflavonoid phytoestrogens bind to estrogen receptors and have weak estrogenic activity (*36,41,42*); they also have significant estrogenic effects in animals and in man (*40,43–46*). The most well-known estrogenic effect of phytoestrogens is the clover disease in Australian sheep (*22*). Furthermore, definite antiestrogenic effects have been observed *in vivo* because high levels of synthetic estrogens seem to be counteracted by administered isoflavonoids or their presence in the diet (*43,47,48*).

Several isoflavonoids and lignans compete with estradiol for the rat uterine nuclear type II estrogen binding sites (*49*). The highest affinity with regard to type II site binding of the diphenolic compounds that we found and measured in human urine is shown by the isoflavones daidzein and equol. Also, some lignans like matairesinol, isolariciresinol, and enterolactone show competition. These binding sites seem to constitute a component of the genome that regulates estrogen-stimulated growth (*50,51*). Thus the antiestrogenic effect of these compounds may be mediated via this binding site.

Many plant lignans have been shown to have anticarcinogenic, antiviral, bactericidic, and fungistatic activities (*16,52,53*). Enterolactone, the most abundant mammalian lignan, is a moderate inhibitor of placental aromatase and competes with the natural substrate androstenedione for the enzyme (*54*). Other experiments with a choriocarcinoma cell line (JEG-3) showed that enterolactone is very readily transferred from cell culture media into the cells (*54*). Flavonoids, occurring in very high amounts in the diet, are inhibitors of the aromatase enzyme (*55*). Studies in human preadipocytes show inhibition of the aromatase enzyme to various degrees by lignans, flavonoids, and isoflavonoids (*56,57*). Most of the lignans and flavonoids are only weak inhibitors. However, a diet rich in vegetables may, due to the abundance of these compounds in the diet, lead to sufficient concentrations (e.g., in fat cells) to reduce conversion of androstenedione to estrone, lowering risk for estrogen-dependent cancer (*58*).

Genistein, an isoflavone that we identified in human urine (*28*) and that occurs in large amounts both in urine and plasma of Japanese subjects consuming a traditional Japanese diet (*26,59*), is a specific inhibitor of tyrosine-specific protein kinases (except the p40 protein–tyrosine kinase), topoisomerase II (*7*), and protein histidine kinase (*60*). Protein–tyrosine kinase activity is associated with cellular receptors for epidermal growth factor, insulin, insulinlike growth factor I, platelet-derived growth factor, and mononuclear phagocyte growth factor. The tyrosine kinases seem to play an important role in cell proliferation and transformation. The enzyme has been associated with oncogene products of the retroviral *src* gene family and is correlated with the ability of retrovirus to transform cells (*61–64*). Tyrosine kinase activity is also associated with breast cancer oncogene expression (*65,66*).

Stimulation of the Synthesis of Sex Hormone-Binding Globulin

Lignans and isoflavonoids seem to stimulate sex hormone-binding globulin (SHBG) synthesis in the liver; in this way, they most

likely reduce the biological effects of sex hormones (*67,68*). An increase in SHBG results in lowering the percentages of free testosterone and free estradiol and in reducing both the albumin-bound and the free fraction of the sex hormones. This reduces the metabolic clearance rate of the steroids and, in this way, reduces their biological activity. In Finnish women total fiber intake, total fiber intake per kilogram body weight, and grain fiber intake per kilogram body weight correlate positively with urinary excretion of total lignans and isoflavonoids (*67,68*). The urinary excretion of the two groups of compounds and also enterolactone alone in both premenopausal and postmenopausal Finnish women correlate positively with plasma SHBG and negatively with plasma percentage free estradiol and percentage free testosterone [H Adlercreutz, unpublished results; (*67,68*)]. *In vitro* studies using HepG2 liver cancer cells showed that enterolactone (*49*), genistein (*69*), and daidzein (M Carson et al., unpublished data) stimulate SHBG synthesis. This seems to explain the higher SHBG values in vegetarians with normal weight (*68,70,71*).

Lignans, Isoflavonoids, and Cancer

Table 1 shows a number of studies related to possible anticancer effects of isoflavonoids and lignans detected in man. Studies have been mentioned if the pure compounds have been tested or lignans and/or isoflavonoids have been measured. Studies with soy products, with no mention or measurement of isoflavonoids, have not been included.

Subjects with breast cancer or at high risk of breast cancer excrete low amounts of lignans and isoflavonoids (*5,68*), but subjects living in areas with low risk of hormone-dependent cancers have higher levels (*26,31,59,67,68,109*). Finnish subjects with medium risk of breast and prostate cancer have relatively high lignan excretion but low isoflavonoid excretion. Japanese subjects at low risk have high isoflavonoid excretion. Interestingly, the biologically active free + sulfate fraction of the lignans is as high in Japanese men as in Finnish men (H Markkanen et al., unpublished results), despite low urinary lignan values and low lignan glucuronide values in plasma. Because in Boston and in Finland the lignan excretion is mainly associated with the intake of grain fiber or whole-grain products [H Adlercreutz, unpublished data; (*31,67*)], it seems that in the United States and Finland the risk may, to a relatively high degree, depend on the intake of such products. Higher mean values of lignan in women were observed in North Karelia compared to women in the Helsinki area, which also correlates with breast cancer risk (*31*). Intake of fruits and berries in Finnish women has a strong correlation with lignan excretion (*67*). Berries contain the seeds of the plant; these may be rich in lignan precursors.

In addition to possible inhibitory effects on cancer cell proliferation, on production of estrogens from androgens by inhibition of the aromatase enzyme, and on biological activity of sex hormones due to an effect on SHBG synthesis and clearance of these steroids from the circulation, there is evidence suggesting an effect of both lignans and isoflavonoids on the secretion of gonadotrophins and on the length of the menstrual cycle (*7,110–112*). It is therefore important for us to know which type of fiber and in which form it is consumed.

It is somewhat surprising that recent prospective epidemiological studies do not show any protective effect of fiber (*113*) with regard to breast cancer risk. However, in this case only the amount of total dietary fiber was determined. Total fiber intake in a subject tells us relatively little about lignan content of the diet and rather little about the effect on the enterohepatic circulation of estrogens affecting plasma estrogen levels (*7,114*). In agreement with the study of Pryor et al. (*115*), it has been observed that there is a correlation between fiber intake and menarcheal age in girls (*116,117*). This may be due to an effect on the enterohepatic circulation of estrogens reducing plasma estrogen levels, to a loss of energy by increased fecal excretion, or to hormonal effects of phytoestrogens associated with the fiber. In addition, the administration of bran to rats postpones menarche (*118*). Early menarche is associated with increased breast cancer risk (*119*). Results of studies in postmenopausal women in Boston (*71*) and in premenopausal women in Helsinki (*120*) show that the main and, in fact, the only significant difference between the diets of the breast cancer patients and the omnivorous and vegetarian control women was a lower intake of grain products in the breast cancer subjects. If we compare the diets of the Boston and Finnish women, the main difference between them is in the grain and grain-fiber intake, which is much higher in the Helsinki women and they have a lower risk of breast cancer than the Boston women. This disparity results in differences in lignan excretion. Further, the fat to grain fiber ratio (g/g) seems to be an important additional determinant of the enterohepatic circulation of estrogens (*7,114*).

In the Finnish women, the significance of the positive correlation between the excretion of lignans and isoflavonoids in urine and plasma SHBG and the negative correlations with percentage free estradiol and percentage free testosterone are stronger than the separate correlations for each group of compounds (*67*). In two studies we found the lowest SHBG values in breast cancer patients compared to control omnivorous and vegetarian subjects (*68,71*). In the second part of the Finlandia project dealing with groups of postmenopausal women studied for 1 year, we again found the lowest SHBG values in the breast cancer groups and in omnivorous women and higher values in the vegetarians. There was a significant positive correlation between urinary total diphenol excretion and plasma SHBG ($R = 0.64$; $p < 0.001$) (*49*). Plasma SHBG levels are inversely correlated to plasma insulin (*121*) and androgens. Androgens tend to be high in breast cancer (*71*) and are likely to play a role in the pathogenesis of breast and prostate cancer.

Our hypothesis with regard to the protective role of phytoestrogens in breast cancer was supported by studies showing that powdered soy bean chips, both before and after denaturation of protease inhibitors, decrease mammary tumor formation in a rat breast cancer model (*77*). Furthermore, linseed, containing high amounts of lignans, inhibits mammary carcinogenesis in rats (*81,82*). Genistein, found in human, chimpanzee, and cow urine and in human plasma and feces, is anticarcinogenic, probably due to its inhibitory effect on protein tyrosine kinase (*61–64,122*) and angiogenesis (*98*) and perhaps due to its antioxidative properties (*97*). Genistein and other flavonoids have been shown to be antiproliferative with regard to breast cancer cells (Table 1)(*75,88*). When fed to rats, soy protein isolates (which in our experience always contain isoflavonoids) inhibit mammary tumor progression (*90*). Furthermore, epidemiological evidence obtained in Singapore indicates that soy intake protects women for breast cancer (*85*). Enterolactone alone (0.5–10 μM) stimulates the growth of MCF-7 cells; in the presence of estradiol, both in concentrations that slightly stimulate growth or in

Table 1. Some studies related to possible anticancer effects of isoflavonoids and lignans detected in man.[a]

Type of cancer	Compound or food	Species or cell type	Effect or result	Reference
Breast cancer	Genistein	MCF-7 cells	Competition with estradiol	(*42*)
Breast cancer	Diet and phytoestrogen excretion	Women	Low urinary excretion in women at higher risk	(*5*)
Breast cancer	Diet and phytoestrogen excretion	Women	Low urinary excretion in women at higher risk	(*31*)
Breast cancer	Diet and phytoestrogen excretion	Finnish, American, and Japanese women	Low urinary excretion in women at higher risk Correlation with plasma SHBG	(*67*)
(VAL 12)Ha-*ras*-transformed cells	Genistein	NIH 3T3 cells	Inhibition of proliferation	(*72*)
Breast cancer	Diet and phytoestrogen excretion	Women	Lowest urinary excretion in breast cancer	(*68*)
Prostate cancer	Soy products	Men of Japanese ancestry	Less risk	(*73*)
Mitogen-induced proliferation	Daidzein	Human lymphocytes	Inhibition of proliferation	(*74*)
Breast cancer	Daidzein	ZR-75-1 cells	Inhibition	(*75*)
Erythroleukemia	Genistein	Mouse MEL cells	Induction of differentiation	(*76*)
Breast cancer	Soy bean chips	Rat	Inhibition of tumor growth	(*77*)
Melanoma	Genistein	5 cell lines	Induction of differentiation	(*78*)
Myeloid leukemia	Genistein	Human K562 cells	Induction of differentiation	(*79*)
Breast cancer	Flaxseed	Rat	Protective	(*80,81*)
Colon cancer	Flaxseed	Rat	Protective	(*80,82,83*)
Leukemia	Genistein	Human HL-60, K562 cells	Induction of differentiation	(*84*)
Breast cancer	Soy food	Women in Singapore	High intake associated with low risk	(*85*).
Myeloid leukemia	Genistein	ML-1, HL-60 cells	Induction of differentiation	(*86*)
Myeloid leukemia	Genistein	MO7E cells	Inhibition of proliferation	(*87*)
Prostatic dysplasia	Soy food	Male mice	Inhibition	(*43*)
Breast cancer	Genistein, biochanin A	MCF-7 + other cells	Inhibition of proliferation	(*88*)
Embryonal carcinoma	Genistein	Mouse F9 cells	Induction of differentiation	(*89*)
Breast cancer	Heated soy bean protein isolate	Rat	Inhibition of tumor progression	(*90*)
Mitogen-induced proliferation	Plant lignans	Human lymphocytes	Inhibition of proliferation	(*91*)
Normal cells	Biochanin A	Embryonal hamster cells	Decreased the metabolism of benzo[*a*]pyrene	(*92*)
Breast cancer	Enterolactone	MCF-7 cells	Inhibition of proliferation in the presence of estradiol	(*38*)
Prostatitis	Soy food	Rat	Preventive effect	(*93*)
Leukemia	Genistein	MOLT-4, HL-60 human cells	Inhibits cell cycle, progression and growth	(*94*)
Breast cancer	Flaxseed	Rat	Inhibits promotional phase	(*82*)
Solid pediatric tumors	Genistein	Neuroblastoma, sarcoma	Inhibition of proliferation	(*95*)
Liver cancer	Enterolactone	HepG2 cells	Stimulation of SHBG synthesis	(*49*)
Non-P-glycoprotein-mediated multidrug-resistant cells	Genistein	K562/TPA	Reversal of resistance	(*96*)
Leukemia and TPA-stimulated PMN cells	Genistein	HL-60 and TPA-stimulated PMN cells	Inhibition of hydrogen peroxide formation	(*97*)
Placental microsomes	Lignans	Human	Inhibition of aromatase	(*54*)
Endothelial cells	Genistein	Many different endothelial cells	Inhibition of angiogenesis	(*98*)
Myeloid leukemia	Daidzein	HL-60 cells	Induction of differentiation	(*99*)
Non-P-glycoprotein-mediated multidrug-resistant cells	Genistein	Many different cell types	Modulation of decreased drug accumulation	(*100*)
Gastric cancer	Genistein	HGC-27 cells	Growth inhibition	(*101*)
Monoblastic leukemia	Genistein	U937 cells	Induction of differentiation	(*102*)
Liver cancer	Genistein	HepG2 cells	Inhibition of proliferation	(*69*)
Prostate cancer	Genistein	LNCaP, DU-145 cells	Inhibition of proliferation	(*103*)
Colon cancer	Soy intake	Japanese men, women	Reduced risk	(*104*)
Gastric, esophagus, colon cancer	Genistein, biochanin A	Many types of cells	Inhibition of proliferation	(*105*)
Preadipocytes	Biochanin A	Human	Inhibition of aromatase	(*56*)
TPA-mediated skin tumor	Genistein	Mouse	Inhibition	(*106*)
Monocytic leukemia	Genistein	Mouse cell line	Cytotoxicity	(*107*)
Lymphoma	Genistein	Rat Nb2 lymphoma cells	Growth inhibition	(*108*)

[a]Mainly studies that discuss the role of isoflavonoids in cancer or that use pure isoflavonoids have been included.

lower amounts, the growth was the same or less than the control (*38*). The mechanism of this phenomenon is unknown.

Prostate Cancer

In Japan and some other Asian countries, despite the same incidence of latent and small or noninfiltrative prostatic carcinomas as in the Western countries, the mortality is low (*123–125*). In 1985 after having found very high urinary excretion of isoflavonoids in Japanese men (*126*), we suggested that this could be due to the effect of phytoestrogens, particularly isoflavonoids, inhibiting the growth of the latent cancers (*7,59*). In epidemiological studies, fat and meat show a positive association with prostate cancer mortality, and cereals show a negative association (*4*). Decreased prostate cancer risk has been found in Adventists men (*127*) that have a high consumption of beans, lentils, peas, and some dried fruits (all dietary sources of flavonoids) and in men of Japanese ancestry in Hawaii (*73*) who consume much rice and tofu, a soybean product containing isoflavonoids (*128,129*). We have measured isoflavonoids in 10 different tofu products by GC-MS (*130*), and the daidzein and genistein content varied from 220 to 460 and 580 to 1130 nmole/g, respectively. Mean consumption of soy products (except soy sauce) was 39.2 ± 36.4 g/day in Japanese men; the intake of various soy products in men and women showed a strong positive association with urinary excretion of isoflavonoids (*26*). Lignan excretion in Japanese subjects showed only a positive association with the intake of pulses, beans, and boiled unprocessed soybeans. Preparation of tofu products seems, therefore, to eliminate the lignan precursors from the beans.

Soy has been found to have a protective effect with regard to prostatitis in rats (*93*), but to my knowledge prostatitis has not been associated with prostate cancer. Recently it was found that soy is protective with regard to prostatic dysplasia in a mouse model (*43*). It was also reported that genistein and biochanin A, the precursor of genistein, inhibit the growth of both androgen-dependent and androgen-independent prostate cancer cells in cell cultures (*103*). The well-known therapeutic effect of estrogens in prostate cancer would suggest that phytoestrogens may inhibit prostate cancer-cell growth during the promotional phase of the disease or they may influence differentiation, as shown for genistein, with regard to different types of leukemia and other malignant cells (Table 1). Recently, an epidemiological study of Japanese subjects showed that environmental factors such as diet can substantially impact the likelihood of developing clinically detectable prostate cancer later in life (*131*).

Despite high fat intake, the prostate cancer incidence in Finland, particularly in northeast Finland (*132*), has been much lower than in the United States but higher than in Japan. The higher production of lignans in the gut due to relatively high intake of whole-grain products, particularly rye bread in the low-incidence rural areas in Finland, may perhaps explain this phenomenon. The lignans are weaker estrogens than the isoflavonoids, but a possible protective effect may well be independent from the estrogenic effect.

Thus, epidemiologic studies as well as cell culture and animal experiments provide evidence suggesting that isoflavonoids and perhaps other phytoestrogens like lignans are protective and can lower risk of prostate cancer during the promotional phase of the disease.

Colorectal and Other Cancers

In 1984 I suggested that the lignans may be protective with regard to both breast and colon cancer (*6*). We have observed a higher urinary lignan excretion in subjects consuming a diet that lowers the risk of colon cancer (*133*) or living in areas with low colon cancer risk (*30,132*). Some epidemiologic evidence obtained in Japan (*104*) points to lower colon cancer incidence in areas with high tofu consumption; this is now being further investigated. Five percent linseed (rich in lignans) in the diet of rats seems to protect against colon cancer, (*83*) and genistein and biochanin A inhibit the proliferation of gastric, esophagus, and colon cancer (*101,105*).

Extracts from human urine containing genistein and synthetic genistein have been shown to inhibit the growth of cells from solid pediatric tumors such as neuroblastomas (with both normal and enhanced MYCN oncogene expression), rhabdomyosarcomas, and Ewing's sarcomas (*95*). We showed that such extracts and synthesized genistein inhibited bFGF-stimulated endothelial cell (bovine brain-derived capillary endothelial cells) proliferation and *in vitro* angiogenesis (*98*). Genistein reduced the production of plasminogen activator and plasminogen activator inhibitor-1 (*98*) in cloned bovine microvascular endothelial cells from adrenal cortex.

Lignans and isoflavonoids of dietary origin seem to play a role in the prevention of several types of cancer. By inhibiting the effect of growth factors and angiogenesis, genistein may be more generally an inhibitor of cancer growth. Lignans and isoflavonoids may also be a preventive with regard to some other Western diseases, particularly cardiovascular diseases and osteoporosis, due to the estrogenic and antioxidative effects. The current evidence is not yet sufficient for any dietary recommendations, and further work is needed to establish the role of lignans and isoflavonoids in human health and disease.

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