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DIET AND BREAST CANCER

HERMAN ADLERCREUTZ, YAGHOOB MOUSAVI and KRISTER HÖCKERSTEDT

It is a general opinion that the Western diet plays a significant role in increasing the risk of breast cancer in the Western World. Recently some likely mechanisms involved in increasing the risk have been disclosed. It has been found that a Western-type diet elevates plasma levels of sex hormones and decreases the sex hormone binding globulin concentration, increasing the availability of these steroids for peripheral tissues. The same diet results in low formation by intestinal bacteria of mammalian lignans and isoflavonoid phyotestrogens from plant precursors. These diphenolic compounds seem to affect hormone metabolism and production and cancer cell growth by many different mechanisms making them strong candidates for a role as cancer protective substances. The sex hormone pattern found in connection with a Western-type diet combined with low lignan and isoflavonoid excretion was found particularly in postmenopausal breast cancer patients and omnivores living in high-risk areas, and to a lesser degree in areas with less risk. However, the pattern observed was not entirely due to diet.

Key words: Breast cancer, diet, estrogens, androgens, lignans, isoflavonoids, isoflavones, genistein, daidzein, sex hormone binding globulin (SHBG).

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It has been suggested that a Western diet by some biochemical or other mechanisms may alter hormone production, metabolism or action at the cellular level increasing the risk of breast cancer (BC). Particularly in women, who have a much higher incidence of hormone-dependent cancer than men, diet has been suggested to be the main single determinant in the etiology of this type of cancer. Since it is not possible in this connection to discuss all aspects of the relationship between diet and BC, the following review will discuss this topic in light of our own results including epidemiological, metabolic and molecular biological studies on the connection between diet and BC (for additional references see (1)).

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Correspondence to: Prof. Herman Adlercreutz, Dept. of Clinical Chemistry, University of Helsinki, Meilahti Hospital, SF-00290 Helsinki, Finland.
Address: As above (H. Adlercreutz, Y. Mousavi) Dept. of Surgery, Helsinki University Hospital (K. Höckerstedt).

Nutrition and sex hormone metabolism

A high intake of fiber increases fecal wet and dry weight and the excretion of estrogens in feces (2). In postmenopausal American women we found positive associations between total and grain fiber intake, and fecal estrone (E1) and estradiol (E2) excretion (partly unpublished). Fat intake on the other hand seems to have a negative association with fecal excretion of estrogens (3) and in a recent study in Finnish women we found that the dietary fat/fiber ratio correlated negatively with fecal estrogen excretion (unpublished results). It was suggested (1) that the dietary fat/fiber ratio determines the degree of interruption of the enterohepatic circulation of steroids (4), but that the type of fiber also plays a significant role (1).

In premenopausal American women fecal weight and fecal estrogen excretion was found to correlate negatively with urinary estrogen excretion (2). In a study carried out in the Helsinki area in premenopausal women it was found that total fiber and grain fiber intake/kg body weight were negatively associated with the excretion of 10 urinary estrogens (5).

Fecal estrogen excretion showed a negative association with plasma E1 and E2 (2) and a negative correlation was also found between total fiber intake and plasma E1 and E2 (3). In young Finnish women plasma estrone sulfate (E1S) was negatively correlated with dietary total fiber intake (6). The reason for reduced intestinal reabsorption and increased elimination of estrogens by the fecal route in subjects consuming much fiber seems to be the larger fecal bulk and decreased concentration of intestinal β-glucuronidase (2). The latter phenomenon reduces hydrolysis of the biliary steroid conjugates, an event necessary for their reabsorption (4). Some fibers have also the property of binding sex hormones, particularly non-polar estrogens (7). Despite similar total fiber intake, fecal bulk in American women was found to be much lower than in Finnish women with lower BC risk, probably because the Finns consume much more grain fiber (partly unpublished).

Preliminary results in the large study in Helsinki, called the 'Finlandia study' revealed significant positive correlations between intake of total fiber, vegetable fiber and fiber from fruit and berries and plasma sex hormone binding globulin (SHBG), and negative associations between the intake of the same fibers and the concentration of free estradiol in plasma (% FE2). Furthermore, total fiber, grain fiber and vegetable fiber intake correlated negatively with free testosterone in plasma (% FT) (8, 9). The recent results obtained in postmenopausal Boston women agree well with those in the Finnish study in that significant negative correlations were found between intake of total fiber, grain fiber and nongrain fiber and plasma androstenedione (A), T, FT (10) and E1. In addition, intake of fruit and vegetable fiber and grain calories correlated negatively with plasma E1 (estrogen results unpublished, see (6)).

By altering the protein/carbohydrate ratio of the diet it was found that a high dietary protein/carbohydrate ratio decreased the plasma level of SHBG and that a low ratio had the opposite effect (11, 12). Furthermore, a high protein diet considerably diminished 4-ene-5α-reduction of T and enhanced 2-hydroxylation of E2 (13, 14). We could recently confirm that a high dietary protein/carbohydrate ratio is associated with a high urinary excretion of catecholestrogens (15). The dietary protein/carbohydrate ratio is also highly positively associated with the urinary 2-OH-E1/4-OH-E1 ratio. Furthermore, in young women the lowest mean ratios were found in Oriental migrants to Hawaii ($=2.0$) (16) and in Finnish vegetarians ($=3.6$), followed by the Finnish omnivores ($=4.3$) and the highest was found in the Finnish BC patients ($=7.1$), who had the highest dietary protein/carbohydrate ratio due to low grain intake (15).

Recently we found that postmenopausal women living in Boston showed significant negative associations between carbohydrate intake and plasma T, E1 and E2 (10) (estrogen data partly unpublished). Furthermore, in the same study the intake of grain calories showed negative correlations with plasma A, T, DHEAS, and E1. In the corresponding Finnish study in 33 premenopausal women including a group of subjects with BC (15), we found that urinary 2-hydroxyestrogens and 4-hydroxyestrone as well as the 2-OH-E1/4-OH-E1 ratio showed strong associations with diet (see details in section on 'Nutrition and breast cancer'). Urinary 4-hydroxyestrone excretion correlated positively with total and grain fiber intake and plasma SHBG, and negatively with % FE2 and FT. Starch intake was negatively associated with urinary E3-3-glucuronide, the specific marker of the enterohepatic circulation of estrogens (4), indicating partial interruption of this circulation (and higher fecal elimination of estrogens) in subjects with high starch intake. Carbohydrate intake was negatively associated with plasma E1S.

Oriental women living in East Asia and at low risk for BC consume a very low-fat diet (usually $<20\%$ of calories). Studies on the urinary excretion of E1, E2 and estriol (E3) have shown that these women excrete lower amounts of E1 and E2 and similar amounts of E3 compared to women in Western countries (3, 17, 18). Vegetarians living in Western societies show a trend towards lower urinary E1 and E2 values and similar or slightly higher E3 values than non-vegetarians (19, 20). The usually higher fecal excretion of E3 in vegetarians, however, reduces urinary E3 levels leading to varying quantitative results for E3 in urine, depending mainly on the nature of the fiber in the food and the quantity of both dietary fiber and fat. Simultaneously there seems to be a reduction in the relative concentration of 2-hydroxyestrogens in vegetarians, particularly in Oriental women and a relative increase in 4-hydroxylation (15, 16).

Women living in Africa consuming low-fat habitual diets (21) and Oriental migrants in Hawaii (3) have low plasma androgen levels compared with women on a Western diet. These observations are in agreement with the results obtained in postmenopausal omnivorous and vegetarian women and postmenopausal women with BC showing the lowest plasma A, T % FT and FE2 and DHEAS and highest SHBG (after correction for weight) in the vegetarian women, who had the lowest dietary fat/fiber ratio of the three groups (10). The lower DHEAS in these vegetarians is in agreement with recent results showing that plasma E1S levels are lower in women on a low-fat high-fiber diet compared to a typical Western diet (22) because the plasma levels of these sulfates show a significant association with each other ((6) and unpublished results). The higher levels of androgens in women consuming a Western diet and in some BC patients mean that higher levels of substrates are available in these women for aromatization to estrogens.

Lignans and isoflavonoid phytoestrogens

Since the detection and identification of mammalian and later also of plant lignans, and of isoflavonoid phytoestro-

gens in the animal and human organism, many studies on their biological role in health and disease have been carried out. Several reviews (1, 8, 23–26) on the topic have recently been published. These diphenolic compounds occurring in high amounts in the organism have numerous different biological activities of which many seem to make them candidates for a protective role with regard to cancer and particularly hormone-dependent cancers (6, 8, 24–28).

Of about 15 compounds identified (1, 8, 26) 7 can now be measured by isotope dilution mass spectrometry (24, 29). They are enterolactone (Enl), enterodiol (End), matairesinol (Mat), daidzein (Da), equol (Eq, *O*-desmethylangolensin (*O*-Dma), and genistein (Gen) (structures and systematic names in 26, 29). It was shown that Enl and a theoretical intermediate between Mat and Enl are moderate inhibitors of placental aromatase (1, 8). These diphenols are readily transferred from cell culture media into the cells and may inhibit cancer cell growth, since antiproliferative effects of some naturally occurring flavonoids (30) and of the lignans Enl and End and other lignans (28, 31, 32) with regard to certain estrogen sensitive BC cell lines have been reported. Genistein, recently identified and quantified by us in human urine (29, 33), is a specific inhibitor of several tyrosine-specific protein kinases (34–36) with the exception of the p40 protein-tyrosine kinase (37). It also inhibits the interleukin-1 stimulated production of prostaglandin E2 in mesangial cells (38). Furthermore, protein-tyrosine kinase activity has been found to be associated with cellular receptors for epidermal growth factor (EGF), insulin, insulin-like growth factor I (IGF-I), platelet-derived growth factor (PDGF), mononuclear phagocyte growth factor (CSF-1), and also with breast cancer oncogene expression (Härkönen, unpublished study), indicating that this enzyme plays an important role for cell proliferation and transformation.

In collaboration with Dr J. Clark we have found that several plant and mammalian lignans and isoflavonoids compete with E2 for the rat uterine nuclear estrogen type II binding site (39). These sites seem to constitute a component of the genome which regulates estrogen-stimulated uterine growth (40, 41). Originally it was observed that some flavonoids like luteolin, quercetin and pelargonin inhibit E2 binding to this receptor and in this way uterine cell growth. They also inhibited growth of MCF-7 cells in culture, and in vivo E2 stimulation of immature rat uterus (42). The structures of these flavonoids are very similar to those of the isoflavonoids (all are diphenols). Da and Eq also show relatively high affinity for binding to the bioflavonoid receptor, but also some lignans like Mat, isolariciresinol and Enl show competition (concentrations from 10 to 100 nmol/l). The possible growth-inhibiting and antiproliferative role of individual flavonoids and their metabolites with regard to hormone dependent cancer is a new interesting area of research.

Quantitative results indicate that lignans and isoflavonoid phytoestrogens are normal constituents of human urine and are excreted in large amounts particularly by vegetarians (both lignans and phytoestrogens) (8, 9, 24) by subjects consuming large amounts of certain whole-grain products, but also vegetables, fruits and berries, which are all associated with increased lignan excretion (8), and by the Japanese consuming traditional Japanese diet (mainly isoflavonoid phytoestrogens, due to intake of soy products) (8, 33, 43).

It has been demonstrated that the mammalian lignans Enl and End are formed from precursors, such as the plant lignans Mat and secoisolariciresinol, which are consumed and then structurally modified by intestinal bacteria (1, 8, 24–26). Eq and *O*-Dma are most likely formed by intestinal bacterial action from formononetin and Da present in food stuffs like soy products (26, 33, 43, 44). Because of the close association of lignan excretion with fiber intake (8, 9) and some other recent results we have obtained, it is likely, that the plant lignan precursors are localized in the aleuronic layer of the grain close to the fiber layer. This layer also contains phytic acid, polyphenols, enzyme inhibitors and other compounds usually regarded as antinutritional factors (45).

Recently, we suggested that the lignans and isoflavonoid phytoestrogens, which all are weak estrogenic diphenols, perhaps together with other similar compounds, stimulate SHBG synthesis in the liver and in this way reduce the biological effects of sex hormones (8, 9, 24). An increase in SHBG results in lowering of % FT and % FE2 and reduction of both the albumin bound and the free fraction of the sex hormones. This reduces the metabolic clearance rate (MCR) of the steroids and reduces in this way their uptake and biological activity in peripheral tissues.

In Finnish women total fiber intake, total fiber intake/kg body weight and grain fiber intake/kg body weight correlate positively and dietary fat/fiber ratio negatively with urinary excretion of total lignans and isoflavonoid phytoestrogens (1, 8, 9). The excretion of the two diphenolic groups of compounds and also of Enl alone in both pre- and postmenopausal Finnish women correlated positively with plasma SHBG and negatively with plasma % FE2 and % FT (1, 6, 8, 9).

Now it has been possible to demonstrate that Enl stimulates SHBG synthesis by human liver cancer cells (HepG2) in vitro in physiological concentrations (0.5 to 5 μmol/l) (39). The effect is synergistic with E2. Estradiol stimulates SHBG synthesis only in unphysiologically high concentrations (46) and the concentrations of Enl needed for a similar stimulation are only 5–10 times higher than those needed for E2. Enterolactone occurs in the organism in 100 to 10 000 times higher concentrations than E2, suggesting that Enl is a more physiological regulator of SHBG synthesis than E2.

Furthermore urinary Enl excretion in these Finnish women correlated negatively with plasma luteinizing hormone (LH) (1, 6) and recently a decrease in follicle stimulating hormone (FSH) and luteinizing hormone (LH) levels was found in women consuming soy bean products (47). It is therefore likely that the effect on sex hormone metabolism of these weakly estrogenic compounds is also mediated via an effect on the hypothalamic-hypophyseal endocrine system.

Nutrition and breast cancer

The main change in diet when subjects from developing countries migrate to Western countries is an increase in animal fat and protein and a decrease in intake of complex carbohydrates, particularly whole grain products (48); for Orientals, however, particularly rice and soy bean products. There has been a large debate about the role of dietary fat in BC and the opinions have been divergent (49–51). The main problem is that in some of the epidemiological studies the dietary differences with regard to fat intake have been comparatively small. In our own experience it needs at least a 15% difference in percentage fat calorie intake, from e.g. 35 to 20% fat calories of total calories, in order to be able to observe a significant difference in plasma estrogen levels (3).

A high fat intake is practically always associated with high protein and low complex carbohydrate and fiber intake. Since other dietary factors usually have received less interest we like in this connection to discuss mainly the significance in BC development of fiber-rich complex carbohydrates like whole grain and soy bean products and the possible role of lignans and isoflavonoid phytoestrogens.

High fiber, high carbohydrate or cereal product intake seem to decrease the risk of (BC) (52–55). The only significant difference we found between the diet of BC patients and omnivorous and vegetarian control women was a lower intake of grain products and grain fiber in the women with BC (10, 15). Finnish women with lower BC risk have significantly higher grain fiber intake than American women. This dietary difference causes the mean fecal weights to be higher in the Finnish compared to the Boston women, despite similar mean total fiber intake (partly unpublished results). The large fecal bulk affects the enterohepatic circulation of sex hormones and increases fecal excretion of steroids (2). The dietary fat to grain fiber ratio (g/g) was 16.4 in the old Boston BC women and only 10.2 in the young Finnish BC women and the corresponding values for the omnivores were 15.1 and 8.2 respectively. The Boston and Helsinki vegetarians had total fat/grain fiber ratios of 7.1 and 6.3 respectively. Very interesting are also the results of the protein/grain fiber (g/g) ratios in the 6 groups of women. The vegetarians, omnivores and BC patients in Boston (postmenopausal) and Helsinki (premenopausal) had the following ratios: 7.2, 15.2, 18.1, and 5.4, 7.2 and 8.8 respectively. This shows that these ratios are very high in the omnivorous women and the BC patients in Boston, and also higher in the BC group in Helsinki than in the other Finnish women. This was mainly due to differences in grain fiber intake.

There is a considerable difference in BC risk between USA and Finland and we have postulated that this is at least partly due to the great difference in intake of whole-grain fiber-rich food like rye bread and perhaps some other fiber-rich nutrients such as berries. Particularly these foodstuffs seem to increase the excretion of urinary lignans by the Finns and affect simultaneously also the intestinal milieu. This view was supported by the finding of very low urinary lignan excretion in the BC subjects living in Boston (27) and a tendency to lower excretion of total diphenols in the young BC women in Helsinki (9). However, in Helsinki the differences between the omnivorious, vegetarian and BC groups were relatively small, because the grain intake was comparably high in all groups. It should be mentioned that only grain products which have been made from milling of whole grain, without separating the different components and mixing them again (R. Korpela and H. Adlercreutz, to be published) seem to significantly increase lignan excretion. This is because during modern milling of the grain, with the aim to eliminate so-called antinutritional factors (45) in the aleuronic layer of the grain, simultaneously also the diphenolic plant lignans seem to be almost quantitatively removed.

Consequently, our hypothesis has been that high intake of whole-grain products (preferably in combination with reduced fat and moderate protein intake) reduces BC risk since such a diet increases fecal bulk, reduces intestinal β-glucuronidase activity and steroid enterohepatic circulation and results in increased lignan production (56). Later on we also included the isoflavonoids into the original theory (8, 25). This was due to the finding of a very high excretion of isoflavonoids in urine of Japanese women consuming a traditional diet and at very low risk of BC (33, 44), lower execretion in postmenopausal women of Eq in BC (not significant) (27) compared to omnivores and vegetarians and lower excretion of total diphenols in young premenopausal Finnish women with BC compared to omnivores (not significant) and lactovegetarians (9). In the Finnish women the significances of the positive correlation between the excretion of lignans and isoflavonoids in urine, and plasma SHBG, and the negative correlations with % FE2 and % FT are stronger than the separate correlations for each group of compounds (8, 9). Recently, our hypothesis with regard to the protective role of these compounds with regard to BC found support from studies showing that powdered soy bean chips, both before and after denaturation of protease inhibitors, decrease mammary tumor formation in a rat BC model (57). Furthermore it was shown that high intake of soya by young women in Singapore protected against BC (58).

The postmenopausal BC patients in Boston had the lowest plasma SHBG and highest % FT and % FE2 (10). The Finnish premenopausal BC subjects had lower SHBG, higher % FT and % FE2 compared to the lactovegetarians (9). In many studies low SHBG has been associated with BC (10, 59).

Numerous studies of urinary and plasma estrogens in BC have shown inconsistent results. In very few studies simultaneous investigations of the diet of the subjects were carried out which with our present knowledge of dietary effects on sex hormones (60) seems mandatory. In a study measuring the estrogen profile in urine in young Finnish BC patients and omnivorous and lactovegetarian controls very small differences in pattern were observed and the total estrogen excretion was similar in the groups (15). The BC patients differed from the omnivorous and vegetarian controls by having a tendency to lower urinary 4-hydroxyestrone (significantly different from vegetarians, $p < 0.05$) and higher 2-hydroxyestrone/4-hydroxyestrone ratio in urine compared to both control groups (BC vs omnivores, $p < 0.02$; BC vs lactovegetarians $p < 0.005$) (15). The reason for this similarity of urinary estrogen profile was that the dietary composition was very similar in the different groups. The only difference between BC patients and the other two groups was a lower grain fiber intake in the BC group ($p < 0.01$) which is reflected in the lower lignan excretion observed. As mentioned above the 2-hydroxyestrone/4-hydroxyestrone ratio was found to be significantly associated with diet. Subjects with a high dietary protein/carbohydrate ratio had significantly higher excretion of 2-hydroxyestrogens ($p < 0.05$) and a higher 2-hydroxyestrone/4-hydroxyestrone ratio ($p < 0.025$). This ratio correlated significantly negatively with intake of carbohydrates ($p < 0.05$), starch ($p < 0.01$), total fiber ($p < 0.05$) and grain fiber ($p < 0.01$). Urinary 4-hydroxyestrone excretion correlated positively with total and grain fiber intake ($p < 0.05$) and plasma SHBG ($p < 0.01$) (15). It should be mentioned in this connection that Finnish postmenopausal BC patients had significantly higher plasma estrone sulfate levels than both omnivores and vegetarians (6) (main results unpublished).

The theory that high fat intake increases the BC risk by increasing 16α- and decreasing 2-hydroxylation of estrogens leading to biologically more active estrogens (61–63) was extensively discussed previously (1, 61) and will not be dealt with in this connection. However, it may be mentioned that a low-fat vegetarian diet leads to a relative increase in urinary 16-hydroxylated estrogens due to lower excretion of the 2-hydroxylated ones (for a review see (60)) despite the fact that the fecal excretion of estrogens in such subjects is much higher than in those on a Western diet (3, 16). Thus it is difficult to understand that increased 16-hydroxylation of estrogens should increase the BC risk. However, our recent observation showing a significant negative correlation between plasma SHBG levels and urinary excretion of 16α-hydroxyestrone ($p < 0.001$) and estriol ($p < 0.01$) in postmenopausal Finnish women (64) supports the view that SHBG is involved in liver cell uptake of estrogens (65) and may in this way affect 16α-hydroxylation of the estrogens in the liver. A low SHBG thus seems to increase 16α-hydroxylation of estrogens, which may be a secondary phenomenon to increased availability of E2 for liver cell uptake, the main site of 16α-hydroxylation in the organism.

In conclusion, a Western diet with high fat and protein intake and low intake of fiber, complex carbohydrates and whole-grain products is associated with high plasma sex hormone levels and low SHBG, high % FT and % FE2, high urinary relative to fecal excretion of estrogens, and low urinary excretion of lignans and isoflavonoid phytoestrogens. Furthermore, such a diet leads to high urinary 2-hydroxyestrogen and low 4-hydroxyestrone excretion and high 2-hydroxyestrone/4-hydroxyestrone ratio. Furthermore it seems that the frequently (but not always) low SHBG may result in increased 16α-hydroxylation of estrogens, which is regarded as a strong risk factor for BC (61–63). The hormonal pattern was particularly pronounced in American omnivorous postmenopausal women with or without BC and less in the omnivorous Finnish women with or without BC and was not entirely due to diet. The lignans and isoflavonoids apparently are protective with regard to cancer by many different mechanisms (1, 28). The above-mentioned studies showing very distinct associations between diet and sex hormones and SHBG fit rather well with the view of the epidemiologists, that Western diet is the main factor causing the high incidence of BC and other hormone-dependent cancers in the Western world.

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