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Nutritional Influences on Estrogen Metabolism

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ABSTRACT: *It is now well known that one of the most prominent causes of breast cancer, as well as many other hormone related health problems in both men and women, is excessive estrogen exposure from both endogenous and exogenous sources. Improving estrogen metabolism can be of benefit in women with various conditions and family histories, including a family history of breast, uterine, or ovarian cancer, and conditions such as endometriosis, premenstrual syndrome, uterine fibroid tumors, fibrocystic or painful breasts, cervical dysplasia, and systemic lupus erythematosis. Beneficial modulation of estrogen metabolism can be accomplished through dietary and lifestyle modifications such as increasing fiber and reducing fat, increasing phytoestrogen intake, losing weight, and increasing exercise. In addition, many nutrients effectively reduce estrogen load by supporting preferred pathways of estrogen metabolism and detoxification, including indole-3-carbinol, B vitamins, magnesium, limonene, calcium D-glucarate, and antioxidants. The influences of these nutrients on estrogen metabolism may have profound significance for diseases in which these hormones may play a role in clinical expression.*

ESTROGEN PRODUCTION

The term "estrogen" is used to collectively describe the female hormones, the most potent of which is estradiol. The other important—but less powerful—estrogens are *estrone* and *estriol*. Estrogens affect the growth, differentiation, and function of diverse target tissues—not only those involved in the reproductive process, but tissues throughout the body. Estrogens play an important role in bone formation and maintenance, exert cardioprotective effects, and influence behavior and mood. Although estrogen is best known for its critical role in female reproduction, less well known are the important actions of estrogen in male tissues, such as the prostate and testes.[1,2]

In women, estrogens are synthesized from cholesterol in the ovaries in response to pituitary hormones. In an adult woman with normal cycles, the ovarian follicle secretes 70 to 500 μg of estradiol per day, depending on the phase of the menstrual cycle. Estradiol can be converted to estrone and vice versa, and both can be converted to the major urinary metabolite, estriol. Estrogens are also produced by the aromatization of androgens in fat cells, skin, bone, and other tissues. After menopause, most endogenous estrogen is produced in the peripheral tissues by the conversion of androstenedione, which is secreted by the adrenal cortex, to estrone. In addition, some estrogen continues to be manufactured by aromatase in body fat, and the ovaries continue to produce small amounts of the male hormone testosterone, which is converted to estradiol. The total estrogen produced after menopause, however, is far less than that produced during a woman's reproductive years.[1,2]

Estradiol and other naturally occurring estrogens circulate in the body bound mainly to the sex hormone binding globulin (SHBG); however, only unbound estrogens can enter target-tissue cells and induce biological activity.[1,2] This is an important point, because it means that any change in the concentration of SHBG will alter estrogen metabolism by inducing changes in the availability of estrogen to the target cell.

ESTROGEN METABOLISM AND DETOXIFICATION

Metabolism of estrogen within the body is a complex and important subject (Figure 1). Estrone and estradiol are biochemically interconvertible and yield the same family of estrogen metabolites as shown for estrone in Figure 1. Because these metabolites vary greatly in biological activity, the ultimate biologic effect of estrogen depends on how it is metabolized. The metabolism of estrogen takes place primarily in the liver through Phase I (hydroxylation) and Phase II (methylation, glucuronidation, and sulfation) pathways with ultimate excretion in the urine and feces.[1]

- ***Hydroxylation***

Cytochrome P-450 enzymes mediate the hydroxylation of estradiol and estrone, which is the major Phase I metabolic pathway for endogenous estrogens. This takes place at two primary sites on the estrogen molecule, either at the 2 carbon (C-2) position yielding 2-hydroxyestrone (2-OH) or at the 16α carbon (C-16α) position yielding 16α-hydroxyestrone (16α-OH). A minor contribution is made from hydroxylation at the 4 carbon (C-4) position yielding 4-hydroxyestrone (4-OH).[3] The 2-OH metabolite confers very weak estrogenic activity, and is generally termed the "good" estrogen. In contrast, the 16α-OH and 4-OH metabolites show persistent estrogenic activity and promote tissue proliferation.[3-6] It is suggested that women who metabolize a larger proportion of their endogenous estrogen via the C-16α hydroxylation pathway may be at significantly elevated risk of breast cancer compared with women who metabolize

proportionally more estrogen via the C-2 pathway.[3-5,7-9] Furthermore, it is theorized that shifting estrogen balance toward a less estrogenic state through promotion of the C-2 pathway may prove beneficial for a variety of conditions related to estrogen dominance or imbalance.

- ***Methylation***

The 2-OH and 4-OH metabolites (catechol estrogens) are readily oxidized to quinones, which are highly reactive and can damage DNA and promote carcinogenesis directly or indirectly through the generation of reactive oxygen species. This harmful pathway can be minimized through preferential detoxification and excretion of the catechol estrogens via Phase II methylation by the catechol-*O*-methyltransferase (COMT) enzyme.[5,10,11] This methylation requires S-adenosylmethionine (SAM) and magnesium as cofactors.[11] COMT is present in most tissues and converts catechols into their corresponding methyl ester metabolites, which are more water soluble.[5,7] Recent data suggest that the methylation of 4-OH renders this harmful metabolite significantly less active, while 2-methoxyestrone may manifest beneficial properties by inhibiting breast cancer.[10,12] Therefore, supporting the methylation pathways promotes detoxification of estrogens and provides for more beneficial metabolites of estrogen.

- ***Glucuronidation***

Glucuronidation is one of the key Phase II liver detoxification pathways for estrogens and other toxins. Glucuronic acid is conjugated with the estrogen to facilitate its elimination from the body.[1] Unfortunately, some intestinal bacteria (mostly pathogenic) possess an enzyme, β-glucuronidase, that uncouples the bond between excreted estrogen and glucuronic acid in the large intestine, allowing the estrogen to reenter circulation (enterohepatic recirculation).[13] Not surprising is the finding that excess β-glucuronidase activity is associated with an increased cancer risk, including breast cancer.[14] The activity of β-glucuronidase is increased when the diet is high in fat and low in fiber, and can be reduced by establishing a proper bacterial flora by eating a diet high in plant foods and supplementing the diet with the "friendly bacteria" *Lactobacillus acidophilus* and *Bifidobacterium infantis*.[15]

ESTROGEN RECEPTORS

Estrogens, like all steroid hormones, have a wide range of actions and affect almost all systems in the body, yet act in a tissue-specific manner. Estrogens act by binding with high affinity to the estrogen receptor (ER) in target cells. Once bound by estrogens, the receptor undergoes a conformational change and binds to specific DNA sequences. This transcription complex regulates the expression of target genes within a cell.[16,17] Because the ER has a unique ability to bind with a wide variety of compounds with diverse structural features, many environmental toxins and plant compounds can bind to the ER with varying affinities and modulate estrogen activity.[17]

Two forms of the estrogen receptor, α and β, have been identified that differ in tissue distribution, binding affinity, and biological function.[16,17] Therefore, different target cells may respond differently to the same estrogenic stimulus depending on the ratio of expression of the two receptor subtypes in the cell.[16,17] This helps to explain how phytoestrogens and the new designer estrogen drugs such as tamoxifen and raloxifene—called selective estrogen receptor modulators (SERMs)—behave like estrogens in some tissues but block its action in others. Unraveling the detailed physiological role of each receptor subtype is needed to further elucidate the complex nature of estrogen's mechanisms of action.

ESTROGEN AND CANCER

Epidemiological and animal studies have identified estrogen exposure as a risk factor for several cancers, namely breast, endometrium, ovary, prostate, testis, and thyroid. Much of the evidence comes from the observation that cancer risk increases with increased exposure to endogenous or exogenous estrogens, and the positive relationship observed between blood levels of estrogens and cancer risk.[7,18-22] Prolonged estrogen exposure can cause direct genotoxic effects by inducing cell proliferation in estrogen-dependent target cells (increasing the opportunity for the accumulation of random genetic errors), affecting cellular differentiation, and altering gene expression. Additionally, there is increasing evidence for indirect genotoxic effects of estrogens as well. The relative importance of each mechanism is likely a function of the specific estrogen, as well as the exposed tissue or cell type and its metabolic state.[5,7]

Direct Genotoxic Effects

Evidence is accumulating that some estrogen metabolites may be directly responsible for the initial genetic damage leading to tumors. 16α-OH and 4-OH are the primary estrogen metabolites that have been associated with direct genotoxic effects and carcinogenicity.[5,7] Some researchers believe increased levels of 16α-OH may increase the risk of breast cancer by increasing both cell proliferation and direct DNA damage; however, scientific consensus has not yet been reached.[5,7-9,23] Conversely, 2-OH may induce apoptosis and thereby inhibit cell proliferation, an important mechanism in the prevention of cancer.[12]

A recent 5-year prospective study of 10,786 women was conducted to investigate the role of estrogen metabolism as a predictor of breast cancer, specifically the ratio of 2-OH to 16α-OH.[4] The researchers found that premenopausal women who developed breast cancer had a decreased 2-OH:16α-OH ratio and a higher percentage of 16α-OH than 2-OH. Women with predominately 2-OH were 40% less likely to have developed breast cancer during the 5 years. Another recent case-control study that began in 1977 found that postmenopausal women who developed breast cancer had a 15% lower 2-OH:16α-OH ratio than control subjects.[8] Furthermore, those with the highest 2-OH:16α-OH ratios had about a 30% lower risk to breast cancer than women with lower ratios.

Diverse factors can add to the hormonal risk by decreasing the 2-OH:16α-OH ratio, including numerous pesticides and carcinogens, certain drugs such as cyclosporin and cimetidine (Tagamet), obesity, and genetic predisposition.[24-27] Dietary interventions such as increased consumption of cruciferous vegetables (e.g., broccoli and cabbage) and phytoestrogen-rich foods such as soy and flaxseeds can significantly promote C-2 hydroxylation and increase the 2-OH:16α-OH ratio.

Indirect Genotoxic Effects

Excessive production of reactive oxygen species has been reported in breast cancer tissue, and free-radical toxicity, which manifests as DNA single-strand breaks, lipid peroxidation, and chromosomal abnormalities, has been reported in hamsters treated with estradiol.[7] The oxidation of catechol estrogens (2-OH and 4-OH) yields reactive molecules called quinones. Quinones are thought to play a role in carcinogenesis by inducing DNA damage directly or as a result of redox cycling between the quinones and their semiquinone radicals, which generates reactive oxygen species including superoxide, hydrogen peroxide, and hydroxyl radicals.[5,7,10] Supplementation with antioxidant nutrients can reduce the oxidation of the catechols and promote greater excretion of these metabolites through the methylation pathway.

RISK FACTORS FOR INCREASED ESTROGEN EXPOSURE

There are many lifestyle factors that can influence the body's production of estrogen. Obesity increases endogenous estrogen production by fat tissue, where the enzyme aromatase converts adrenal hormones into estrogen.[18,28] Excess insulin in the bloodstream prompts the ovaries to secrete excess testosterone and reduces SHBG levels, thus increasing levels of free estrogen.[28] Alcohol consumption increases estrogen levels, and epidemiological studies suggest that moderate alcohol consumption increases the risk of breast cancer, an effect that may be synergistically enhanced when combined with estrogen replacement therapy.[29,30]

Two major sources of exogenous estrogens are oral contraceptives and hormone replacement therapy. Another major source is environmental toxins that are structurally similar to estrogen and have the ability to mimic harmful estrogens in the body.[17,31] These include aromatic hydrocarbons and organochlorines found in pesticides, herbicides, plastics, refrigerants, and industrial solvents. Furthermore, the hormones used to fatten livestock and promote milk production may be unknowingly ingested when consuming meat and milk products, thereby increasing one's exposure to environmental estrogens.[31]

While these lifestyle and environmental factors do influence the lifetime hormone burden of an individual, endogenous hormone levels also have a genetic basis that can be an important risk factor for hormone-dependent cancers and other conditions. Family history can be an important indicator of potential problems in this area.

All sources of estrogens—whether environmental, dietary, or endogenously produced—can affect ER function (Table 1). These substances can bind to estrogen α or β receptors with varying affinities and for varying lengths of time, producing a wide range of estrogen-related effects.[17]

Table 1. Sources of Estrogens

Environmental Estrogens[31]	Dietary Estrogens[32-35] ("Phytoestrogens")	Endogenous Estrogens
• Organochlorine chemicals such as vinyl chlorides, dioxins, PCBs, and perchloroethylene (~half of "endocrine disrupters" are in this class) • Non-organochlorine chemicals such as phthalates and phenols (plasticizers), aromatic hydrocarbons, and some surfactants • Medications such as hormone replacement, oral contraceptives, tamoxifen, and cimetidine • Agricultural hormones in animal products consumed by humans	• Isoflavones (e.g., genistein, daidzein, equol, puerarin, coumestrol, glycitein, biochanins) (from soy, beans, peas, clover, alfalfa, and kudzu) • Lignans (e.g., matairesinol, pinoresinol, secoisolariciresinol) (especially from flaxseed, rye, wheat, and sea vegetables) • Certain flavonoids (e.g., rutin, naringenin, luteolin, resveratrol, quercetin) (especially from citrus fruits and grapes)	• Estradiol • Estrone • Estriol • Hydroxylated estrogen metabolites • Methoxylated estrogen metabolites • Other estrogen metabolites

MANIFESTATIONS OF EXCESSIVE ESTROGEN EXPOSURE AND ESTROGEN DOMINANCE

An abundance of evidence makes it clear that excessive estrogen exposure from both endogenous and exogenous sources is a causal factor in the development of cancer in hormone-dependent tissues, such as the breast, endometrium, ovary, uterus, and prostate. Furthermore, hormonal imbalances between progesterone, testosterone, and estrogen can lead to symptoms and conditions of estrogen dominance. These include premenstrual syndrome (PMS), endometriosis, uterine fibroid tumors, fibrocystic or painful breasts, cervical dysplasia, and systemic lupus erythematosis.

Fortunately, beneficial modulation of estrogen metabolism can be accomplished through dietary modification and supplementation with select nutrients. A weight management program may also be very helpful in both reducing adipose aromatase activity and facilitating more desirable estrogen metabolism and excretion. The promotion of healthy estrogen metabolism in this way may have profound significance for diseases and conditions in which these hormones play a role.

NUTRITIONAL MODULATION OF ESTROGEN METABOLISM

Multiple dietary and nutritional factors have the ability to influence estrogen synthesis and receptor activity, as well as the detoxification pathways through which estrogens are metabolized (Table 2; Figure 1). Incorporating dietary changes with the use of select nutritional supplements can have profound effects in beneficially influencing estrogen balance and thus preventing estrogen-related diseases and conditions.

Dietary Fiber and Lignin

Insoluble dietary fibers such as lignin (found in flaxseeds and the bran layer of grains, beans, and seeds) can interrupt the enterohepatic circulation of estrogens in two ways, thus promoting their excretion and making them less available for reabsorption and further metabolism.[36] First, dietary fiber, especially lignin, can bind unconjugated estrogens in the digestive tract, which are then excreted in the feces. Second, dietary fiber can beneficially affect the composition of intestinal bacteria and reduce intestinal β-glucuronidase activity, resulting in a lowered deconjugation of estrogen and reduced reabsorption.[37] Dietary fiber intake also increases serum concentrations of SHBG, thus reducing levels of free estradiol.[38]

Carbohydrates

Complex carbohydrates, such as those found in vegetables and whole grains, are preferred over simple carbohydrates for optimizing estrogen metabolism. Excessive consumption of simple carbohydrates has detrimental effects by raising blood glucose levels and stimulating insulin release, resulting in secondary adverse influences on sex hormone balance. Conversely, the consumption of complex carbohydrates attenuates the glycemic and insulinemic responses.[28]

Fats

Balance among types and amounts of dietary fats may play a role in determining balance among estrogens in the body. In male chimpanzees fed a high-fat, low-carbohydrate, low-protein diet for 8 weeks, estradiol was metabolized primarily through C-16α hydroxylation, whereas it was metabolized primarily through C-2 hydroxylation in chimpanzees fed a normal diet.[39] Breast cancer cells exposed to eicosapentaenoic acid, an omega-3 fatty acid found in cold-water fish, showed increases in C-2 hydroxylation of estradiol and decreases in C-16α hydroxylation of estradiol.[24] Women with severe premenstrual breast symptomatology who reduced their intake of fat while increasing their consumption of complex carbohydrates experienced significant symptom reduction.[40]

Protein

Inadequate dietary protein may lead to decreases in overall cytochrome P450 activity, including cytochrome P450-1A2, which detoxifies estradiol.[41] Rice is a source of protein frequently used to nutritionally support hepatic detoxification function, because of its low allergy potential.[42] Lysine and threonine are limiting amino acids in the quality of rice protein. Fortifying rice protein with lysine and threonine resulted in better support of hepatic mitochondrial functions in rats fed a rice protein-based diet as compared to rats fed a casein protein-based diet or a rice protein-based diet without lysine and threonine supplementation.[43]

Phytoestrogens

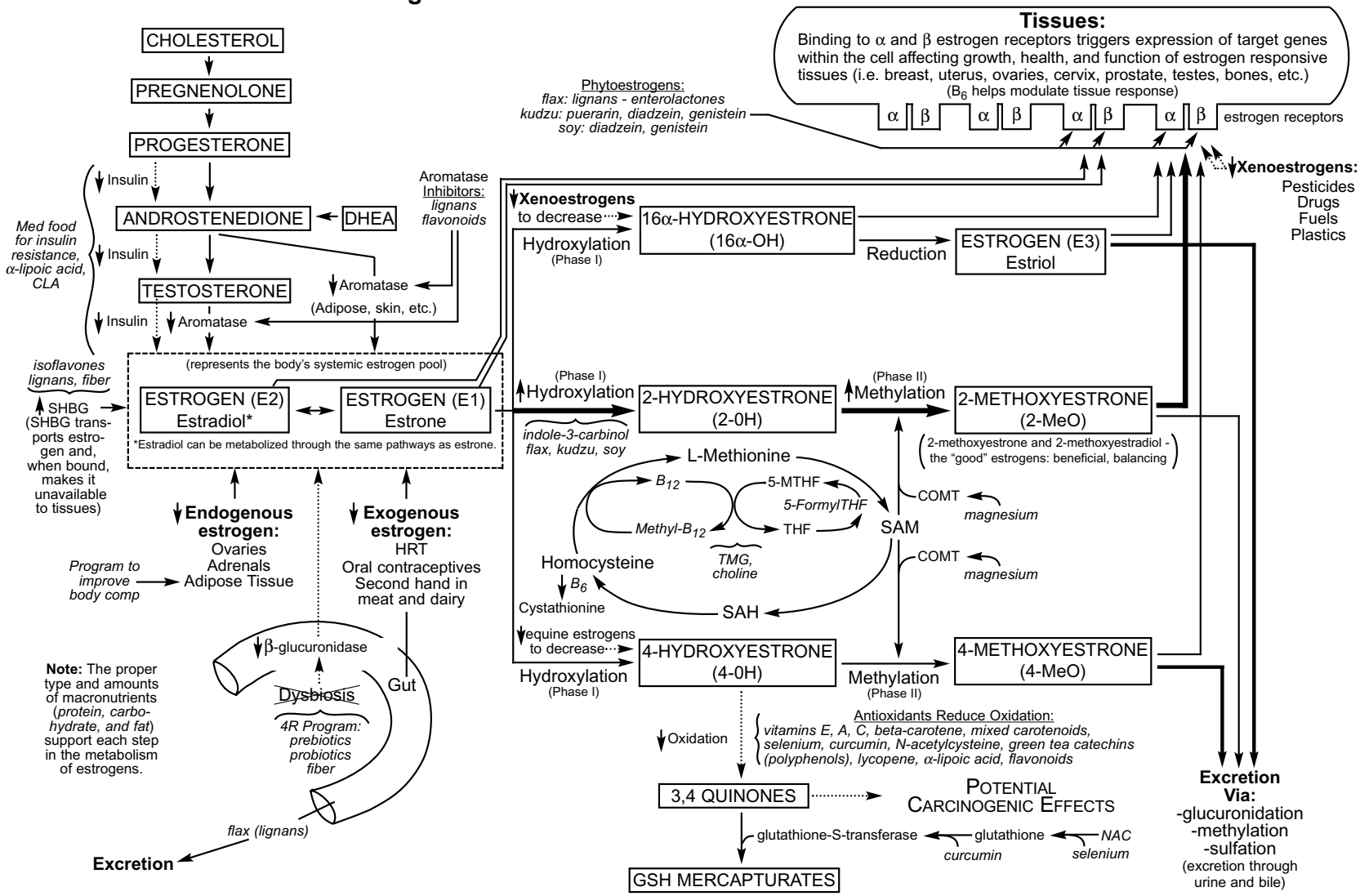
Phytoestrogens are plant compounds that have the capacity to bind to ERs and appear to have both estrogenic and anti-estrogenic effects, depending on the expression of ER subtypes in target cells and on the level of endogenous estrogen present.[16,17,44] Phytoestrogens are currently being extensively investigated as a potential alternative therapy for a range of conditions associated

Table 2. Mechanisms through which dietary and nutritional factors may influence estrogen metabolism

Mechanism of Action	Nutrient
Promote C-2 hydroxylation over C-4 and/or C-16α hydroxylation of estrogens	Cruciferous vegetables, indole-3-carbinol, isoflavones (soy, kudzu)
Reduce the oxidation of catechol estrogens (2-OH and 4-OH)	Vitamins A, E, & C, N-acetylcysteine, turmeric, green tea, lycopene, α-lipoic acid, flavonoids
Promote the methylation of catechol estrogens (2-OH and 4-OH)	Folate, vitamins B_2, B_6, & B_{12}, trimethylglycine, magnesium
Increase circulating concentrations of sex hormone binding globulin (SHBG), thus reducing levels of unbound, active estrogens	Fiber, lignans (flaxseed), isoflavones (soy, kudzu)
Inhibit the activity of aromatase, which converts testosterone and androstenedione into estradiol and estrone, respectively	Lignans (flaxseed), flavonoids
Promote the detoxification of estrogens by upregulating Phase I and Phase II enzymes	Turmeric (curcumin), D-limonene, magnesium, vitamins B_2, B_6, & B_{12}, flavonoids
Inhibit the activity of β-glucuronidase, which deconjugates estrogens in the large intestine, allowing them to be reabsorbed and re-metabolized	Fiber, probiotics (acidophilus, bifidobacteria), calcium D-glucarate
Modify estrogen receptor activity	Isoflavones (soy, kudzu), lignans (flaxseed), indole-3-carbinol

Figure 1.

Nutritional Influences on Estrogen Metabolism



Acronym Key: *CLA*: conjugated linoleic acid, COMT: catechol-*O*-methyltransferase, DHEA: dehydroepiandrosterone, *5-FormylTHF*: 5-formyltetrahydrofolate, HRT: hormone replacement therapy, *5-MTHF*: 5-methyltetrahydrofolate, *NAC*: N-acetylcysteine, SAM: S-adenosylmethionine, SAH: S-adenosylhomocysteine, SHBG: sex hormone binding globulin, THF: tetrahydrofolate, *TMG*: trimethylglycine

with estrogen imbalance including menopausal symptoms, premenstrual syndrome (PMS), endometriosis, prevention of breast and prostate cancer, and protection against cardiovascular disease and osteoporosis.[17,44-46] The two main classes of phytoestrogens are the isoflavones and lignans.

Many of the benefits of increased intakes of dietary phytoestrogens are due to their ability to beneficially influence estrogen synthesis and metabolism through a variety of mechanisms:1.) they have a similar structure to estradiol and can bind to the ER,[16,17,45] 2.) they increase plasma SHBG levels,[47] 3.) they decrease aromatase activity,[48] and 4.) they shift estrogen metabolism away from the C-16α pathway to the C-2 pathway.[49,50]

Therefore, it may be possible to demonstrate significant hormonal effects through dietary modification. For example, a recent study found that a low-fat vegetarian diet was associated with a 19% increase in mean serum SHBG levels, as well as reductions in weight, body mass index, and symptoms of dysmenorrhea and PMS.[51] Two other recent studies found that increased isoflavone consumption decreased urinary excretion of the genotoxic estrogen metabolites 16α-OH and 4-OH, indicative of their decreased formation, and significantly increased the 2-OH:16α-OH ratio in both pre- and postmenopausal women.[49,50]

***Isoflavones*—**Soy is perhaps the most common food source of isoflavones, but others include legumes, alfalfa, clover, licorice root, and kudzu root. Biologically active isoflavones include genistein, daidzein, equol, and puerarin, and some of their plant precursors include formononetin, biochanins, genistin, and daidzin. Soy isoflavones consist primarily of genistin and daidzin, while kudzu isoflavones consist primarily of puerarin and daidzin. Higher intakes of soy products and isoflavones, such as consumed in traditional Japanese diets, are associated with low rates of hormone-dependent cancers.[52] The average daily isoflavone intake of Japanese women is 20 to 80 mg, while that of American women is 1 to 3 mg.[53]

Women given 45 mg of isoflavones daily for one month experienced longer menstrual cycles (increased number of days between menstruation) and lower luteinizing hormone and follicle-stimulating hormone surges.[54] Young women consuming 36 ounces of soymilk daily for one month also experienced longer menstrual cycles (28.3 +/- 1.9 days before soymilk feeding, increasing to 31.8 +/- 5.1 days during the month of soymilk feeding) and lower serum estradiol levels, both effects which persisted for two to six menstrual cycles after discontinuation of the soymilk.[55] In women with low levels of SHBG, consumption of a soymilk powder providing about 69 mg of isoflavones daily substantially increased their SHBG concentrations, an effect not observed in women with higher initial SHBG levels.[47]

***Lignans*—**These compounds are found in fiber-rich foods and, through intestinal fermentation, are converted into mammalian lignans with greater biological activity, such as enterolactone and enterodiol. Primary dietary sources of plant lignans are flaxseed and other oil seeds, whole grains, legumes, and vegetables.[56,57] Lignans stimulate the production of SHBG in the liver, and therefore reduce the levels of free estrogen in circulation. Enterolactone inhibits aromatase activity, and may thereby decrease the conversion of testosterone and androstenedione into estrogens in fat and breast cells.[38,48,58] Lignans also have been shown to inhibit estrogen-sensitive breast cancer cell proliferation.[59] Women consuming 10g of flaxseed per day experienced longer menstrual cycle length, increased progesterone-to-estrogen ratios, and fewer anovulatory cycles, all of which were considered to reflect improved ovarian function.[60] Through their detrimental effects on intestinal flora, antibiotics may reduce the formation of mammalian lignans.

Vitamin E

Low serum vitamin E is associated with elevated estrogen levels, and women with PMS experienced symptomatic improvements when given supplemental α-tocopherol.[61] Vitamin E inhibits *in vivo* and *in vitro* growth of breast cancer cells, possibly by inhibiting the expression of vascular endothelial growth factor, which encourages angiogenesis.[62] Furthermore, vitamin E deficiency may negatively affect cytochrome P450 function, thus impacting estrogen detoxification.

Magnesium

Magnesium is an essential cofactor for the COMT enzyme, and therefore optimizes the methylation and excretion of catechol estrogens.[7] Magnesium also promotes estrogen detoxification by directly increasing the activity of glucuronyl transferase, an enzyme involved in hepatic glucuronidation. Ovarian hormones influence magnesium levels, triggering decreases at certain times during the menstrual cycle as well as altering the calcium to magnesium ratio. These cyclical changes can produce many of the well-known symptoms of PMS in women who are deficient in magnesium and/or calcium.[63]

Indole-3-Carbinol (I3C)

I3C is a naturally occurring compound derived from cruciferous vegetables such as broccoli, Brussels sprouts, and cabbage that actively promotes the breakdown of estrogen to the beneficial metabolite, 2-OH. However, modern diets are often deficient in these vegetables. Fortunately, research shows that supplementation with isolated, concentrated I3C promotes 2-hydroxlation of estrogen.[64] Therefore, I3C is protective to estrogen-sensitive tissues and may be beneficial to those with health issues related to estrogen dominance.

The mechanism by which I3C promotes 2-OH formation involves the selective induction of Phase 1 metabolizing cytochrome P450 enzymes (P450-1A1 and P450-1A2), which facilitate the 2-hydroxylation of estrogen.[64,65] Through this metabolic role, I3C promotes an increased ratio of 2-OH to 16α-OH and may improve estrogen metabolism in women with poor diets or impaired detoxification.[3,64,66] I3C may also reduce the activity of the enzyme required for the 4-hydroxylation of estrogen, thereby decreasing carcinogenic 4-OH formation.[67]

According to a recent human study in both men and women, supplementation with 500 mg and 400 mg of I3C, respectively, resulted in significantly increased urinary excretion of 2-OH, while that of nearly all other metabolites including estradiol and 16α-OH was lower—indicative of their decreased formation.[64] The authors concluded, "These findings support the hypothesis that I3C-induced estrogen 2-hydroxylation results in decreased concentration of several metabolites known to activate the estrogen receptor. This effect may lower estrogenic stimulation in women."

In a double-blind, placebo-controlled study of 57 women at increased risk for breast cancer, supplementation with I3C (300-400 mg/d for 4 weeks) proved to be a promising chemopreventive agent as measured by the increased 2-OH:16α-OH ratio.[68]

Not only does I3C promote healthier estrogen metabolism, but it may also act as a "weak" or anti-estrogen. Through competitive inhibition, I3C has been shown to prevent the receptor binding of "stronger," more stimulating estrogens.[69] Other mechanisms relating to I3C's influence on tissue health involve modulating ER activity, detoxifying xenoestrogens, modulating cell cycle regulation, and preventing the adhesion, migration, and invasion of cancer cell lines.[67,70,71]

B Vitamins

The B vitamins, such as B_6, B_{12}, and folate, function as important cofactors for enzymes involved in estrogen conjugation and methylation. Therefore, decreased levels of B vitamins can disrupt estrogen detoxification and lead to increased levels of circulating estrogens. For instance, folate (as a precursor to SAM) is an essential cofactor for the methylation of catechol estrogens, 2-OH and 4-OH, which reduces their conversion to the carcinogenic quinones.[11] Supplying an intermediate metablite of folate called 5-formyltetrahydrofolate, which bypasses complicated enzyme pathways resulting in higher levels of folate's end metabolite, is especially beneficial for some individuals.[72]

Another way in which certain B vitamins play a role in estrogen activity is through a potential to modulate the cell's response to activation of the ER. It has been demonstrated that elevated intracellular concentrations of the active form of vitamin B_6 can lead to significantly decreased gene transcription responses when estrogen binds to the ER.[73] By modulating estrogen-induced gene expression in this way, vitamin B_6 can attenuate the biological effects of estrogen. B vitamins also play a role in the prevention of cancer because they are crucial for DNA synthesis and repair as well as the process of DNA methylation, which is essential for DNA stability and integrity and is an important regulator of gene expression.

Calcium D-Glucarate

Calcium D-glucarate is a natural compound found in foods that appears to have some influence on breast cancer by aiding in detoxification and the regulation of estrogen.[74] It not only inhibits β-glucuronidase, but also increases the activity of the glucuronidation Phase II pathway, with the net effect being that more estrogen and other toxins are eliminated from the body.[75] Calcium D-glucarate has been found in animal models to lower estradiol levels and inhibit the initiation, promotion, and progression of cancer.[74] Even after exposure to carcinogens, calcium D-glucarate was found to decrease breast cancer formation.[76]

Other Beneficial Phytonutrients

There are many other naturally occurring compounds derived from a variety of plant sources that promote healthy estrogen metabolism. Curcumin is a polyphenol complex from the curry spice turmeric, a member of the ginger family. A combination of curcumin and the isoflavone genistein has shown synergy in reducing xenoestrogen-induced growth of ER-positive and ER-negative breast cancer cells.[77] Curcumin also increases hepatic levels of glutathione and induces glutathione-S-transferase (GST) and glucuronyl transferase, important in the Phase II detoxification of quinones produced from the oxidation of catechol estrogens.[78,79] Furthermore, many antioxidant nutrients and phytonutrients can reduce the oxidation of catechol estrogen metabolites into quinones. Notable players in this group include vitamins E and C, α-lipoic acid, N-acetylcysteine, the mineral selenium, curcumin, and green tea polyphenols.

D-Limonene, a naturally occurring monoterpene found in the oils of citrus fruits, promotes the detoxification of estrogen by inducing Phase I and Phase II enzymes in the liver, including GST.[80] This compound has also shown great promise in the prevention and treatment of breast and other cancers.[81]

There are also many hormone-modulating herbs that have a long history of traditional use in treating women's health conditions. These include black cohosh *(Cimicifuga racemosa)*, chasteberry *(Vitex agnus castus)*, ginseng *(Panax ginseng)*, dong quai *(Angelica sinensis)*, and licorice *(Glycyrrhiza uralensis)*. While the mechanism of action of these herbs in promoting healthy estrogen balance varies, many have been found to contain phytoestrogens.

For a comprehensive discussion of the use of nutritional supplements and herbs in treating PMS, menopause, and other women's health conditions, please refer to the articles titled, *Premenstrual Syndrome: A Natural Approach to Management; A Healthy Menstrual Cycle; A Natural Approach to Menopause;* and *Black Cohosh and Chasteberry: Herbs Valued by Women for Centuries.*

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