Estrogen Metabolism and Cancer Risk

The human embryo develops into a woman as a result of estrogen. It helps maintain our breasts, genitalia, vagina, cervix, and parts of our urinary tract. These tissues are estrogen sensitive. Estrogen, though beneficial in many ways to women, has also been linked to cancer of the breast, uterine lining, and cervix. Excessive amounts of estrogen and prolonged exposure to it, can increase our risk for cancer. The same is true for endogenous (produced by ovaries, fat, skin, etc.) and exogenous (estrogen containing contraceptives, hormone replacement, herbicides, pesticides, etc.) estrogens. We may be particularly sensitive to, or may not metabolize estrogen in a healthy manner due to our genetic makeup.

Estrogen Metabolism

Estradiol is the major estrogen in premenopausal women. Estrone and estriol are estrogens produced in smaller amounts. Some of the estrogen is metabolized, then stored or excreted, in the bile or urine. Estradiol may be metabolized to estrone (a weaker estrogen), or the catechol estrogens: 2-hydroxyestrogen, 4-hydroxyestrogen, and 16-alpha-hydroxyestrogen. The latter estrogen can be further metabolized to estriol.

The 4-hydroxyestrogens are carcinogenic, however, they are produced in smaller concentrations and therefore, have less impact on cancer risk.

The 16-alpha-hydroxyestrogens are very estrogenic. They can bind protein, damage DNA, and increase proliferation in estrogen sensitive tissue. They stimulate persistent proliferation in human estrogen receptor positive cancer cells. They can stimulate human papilloma virus (HPV) infection (the virus that causes condyloma acuminata or genital warts, cervical dysplasia, and cancer). HPV can also promote the formation of 16-alpha-hydroxyestrogen. This metabolite can bind to estrogen receptors more tightly than estradiol, and cause heightened activity for days instead of hours. The liver enzymes that produce 16-alpha-hydroxyestrogen have been shown to be stimulated by xenobiotics (carcinogens, pesticides, etc.) Studies have shown that women with breast cancer have 50% more 16-alpha-hydroxylation of their estrogen than those without it.

The 2-hydroxyestrogens are virtually inactive as estrogens. In fact, they are anti-estrogenic and inhibit the growth of breast cancer cells. They are further metabolized to forms which also inhibit cancer formation. The liver enzymes that promote 2-hydroxyestrogen formation are inducible by diet.

2/16 OH Estrogen Ratio

Scientists have studied the various metabolites of estrogen, their presence in the urine, and have discovered significant patterns. The urinary ratio of 2-hydroxyestrogen to 16-alpha-hydroxyestrogen (2/16 OH ratio) is decreased by 30% in breast cancer patients versus control populations in Caucasian, African-American, and Asian women. The ratio was also decreased in women with cervical dysplasia, a precursor of cervical cancer. A ratio less than 1.8 is associated with increased risk for estrogen sensitive cancers. A ratio of greater than 2 is considered optimal.

Ways to Improve 2/16 OH Estrogen Ratio

Fortunately, regular exercise and several dietary interventions have been demonstrated to increase the 2/16 OH estrogen ratio. Fat cells are capable of producing estrogen from circulating androgens (male hormone). Aerobic exercise burns fat. Thus, exercise can decrease the estrogen load in your body, as well as favorably affect your 2/16 OH ratio.
Flaxseed, soy foods, omega-3 fatty acids, and cruciferous vegetables have all been shown to increase the 2/16 OH estrogen ratio.

Flaxseed, a rich source of lignans (phytoestrogens), inhibits the enzymes that produce estrogen, and alter its metabolism to favor 2-hydroxylation over 16-alpha-hydroxylation. The 2/16 OH ratio was increased by 25% in one study when 10 grams (1 tablespoon) of ground flaxseed was consumed daily.

Soy foods are rich in isoflavones (phytoestrogens). They can act as weak estrogens, or antagonists of the stronger estrogens. They are antioxidants, decrease total circulating estrogen levels, and inhibit cell proliferation and new blood vessel formation (the latter two are crucial to cancers). The 2/16 OH ratio was increased by 40% in one trial after consumption of soy foods, averaging 158 milligrams isoflavones per day.

In vitro studies have shown increased 2-hydroxyestrogens in human breast cancer cells grown with omega-3 fatty acids. Docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) are the omega-3 fatty acids found in cold water fish. Alpha-linoleic acid (ALA) is plant-based. DHA decreased the binding of estradiol to its receptor, and inhibited the growth of cervical cells infected with HPV. In contrast, omega-6 fatty acids (linoleic and arachidonic acid) inhibited 2-hydroxylation of estrogen, and increased 16-alpha-hydroxylation. Omega-6 fatty acids are found in corn oil, safflower oil, and many refined processed fast foods. Fish high in omega-3 fatty acids include mackerel, salmon, herring, sardines, and tuna. Two to three servings of these fish per week, or 3 grams of fish oil a day, are considered safe levels of intake. Plant-based sources of omega-3 fatty acids include canola oil, flaxseed, walnuts, soy and pinto beans.

Cruciferous vegetables have also been shown to increase the 2/16 OH ratio. One of their active constituents, indole-3-carbinol, is a potent inducer of 2-hydroxylation. It is an antioxidant, induces death of abnormal cells, and regulates cell cycle progression. In one study 50% of the women with cervical dysplasia, consuming 400 milligrams per day of indole-3-carbinol, demonstrated regression of their disease as opposed to those receiving a placebo. Cruciferous vegetables include cabbage, broccoli, turnips, mustards, kale, rutabagas, brussels sprouts, cauliflower, and collards. For example, a high fiber diet, with 50 grams of cabbage or 100 grams of broccoli twice a week, can increase the 2/16 OH ratio.

We can modify our risk of cancer in estrogen sensitive tissues with regular exercise and conscious, organic whole food choices when available. Supplements play a role in an overall program of wellness. However, they are no substitute for healthy eating. They were meant to do just that...supplement. No pill can reproduce the synergy, intelligence, wisdom, and safety of nature. We can monitor our progress by having our 2/16 OH ratio checked. Since our total exposure to estrogen from our own tissues and outside sources begins with our first day of life, we should set a good example, and be proactive with our children as well.