Breast Cancer, Toxic Exposure and Detoxification

Breast cancer is second only to lung cancer as the most common cause of cancer mortality in the US. Further, in the year 2000 alone, 182,000 new cases of breast cancer were diagnosed and there were 40,800 associated female deaths in the US as a result. In fact, breast cancer is the leading cause of death in women between the ages of 35 and 54. A key contributing factor, that is supported by clinical research, to the onset of breast is toxic exposure, in the form of synthetic hormone replacement therapy and chemicals in the food, air and water supply.

The Toxic Effects of Synthetic Hormone Replacement Therapy

A woman's chance of developing breast cancer significantly increases with age (Table 1).  

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<thead>
<tr>
<th>Age</th>
<th>Breast Cancer Risk</th>
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<th>Breast Cancer Risk</th>
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<tbody>
<tr>
<td>By 30</td>
<td>1 out of 2,212</td>
<td>By 70</td>
<td>1 out of 14</td>
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<td>By 40</td>
<td>1 out of 235</td>
<td>By 80</td>
<td>1 out of 10</td>
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<td>By 50</td>
<td>1 out of 54</td>
<td>By 90</td>
<td>1 out of 8</td>
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<td>By 60</td>
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As a woman ages, she will naturally approach menopause and the cessation of ovarian function, increasing her chances of taking hormone replacement therapy (HRT) to reduce symptoms commonly associated with menopause and to prevent the onset of heart disease and osteoporosis. In fact, surveys by the North American Menopause Society show that about a third of US women ages 45 to 65 – some 16 million women – use hormone supplements, either estrogen alone or combined with progesterin. Disturbingly, HRT increases a woman’s risk of breast cancer, sometimes by more than 50% and, we now know, it fails to prevent heart disease and in fact increases a woman’s chance of developing a life-threatening blood clot or a stroke. The now famous study published in 2002 in the Journal of the American Medical Association provided definitive evidence that the use of combined HRT (meaning conjugated equine estrogens and medroxyprogesterone acetate (Prempro) significantly increases a woman’s chance of developing breast cancer. This was a randomized, placebo-controlled trial, which was a component of the Women’s Health Initiative, a multi-part study begun by the National Institutes of Health that enrolled more than 160,000 postmenopausal women at 40 US medical centers between 1993 and 1998.

The purpose of the study was to investigate the efficacy and safety of long-term hormone replacement therapy in preventing diseases in postmenopausal women such as heart disease, breast and colorectal cancers, and osteoporosis. Over 16,000 postmenopausal women with an intact uterus participated in this trial, receiving conjugated estrogens (at .625 mg/day) plus medroxyprogesterone acetate (at 2.5 mg per day) combined in one tablet or placebo. Considered one of the largest studies of women’s health ever taken, it made headlines when the review committee for the study halted the study three years early (final results were due out in 2005). They determined that the number of cases of invasive breast cancer in the combined HRT group crossed the boundary established for the study as a signal of increased risk.

For example, the estrogen/progesterin therapy used in this trial resulted in a 26% increase in breast cancer. The combined HRT also resulted in:

- 41% increase in strokes
- 29% increase in heart attacks
- Doubled rates of blood clots in legs and lungs
- 37% fewer incidences of colorectal cancer
- 33% fewer hip fractures
- 24% fewer total fractures

It is interesting to note that other parts of the WHI trial, including a study evaluating the effects of estrogen alone (Premarin), in postmenopausal women without a uterus, continued. This study continued irrespective of the fact that a cohort observational study involving over 44,000 postmenopausal women without a uterus, published in same issue of JAMA (334-341) by Lacey et al. found that estrogen-only HRT resulted in a 300% increase in ovarian cancer. Finally, in March of this year, the NIH discontinued this phase of the trial because estrogen had no effect on preventing heart disease after 7 years of continuous use, and it was shown to increase the risk of stroke. A separate report points to “probable” dementia and/or mild cognitive impairment associated with estrogen-alone therapy.

Toxic Exposure from the Air, Water, and Food Supply

Beyond the toxic effects of synthetic HRT, which women have been exposed to for decades, environmental chemicals in the air, water and food supply have a well-documented effect on breast cancer risk. For the last 40 years, substantial evidence has surfaced on the hormone-like effects of environmental chemicals such as pesticides and industrial chemicals in humans.

Since the creation of organic and inorganic chemicals in the late 19th century, the global community has faced an exponential rise in the production and subsequent exposure to such...
The purpose of the program/study is to determine levels of various pesticide residues, contaminants, and nutrients in foods, in order to estimate the amount of these chemicals that are being ingested by specific age sex groups in the United States population. To do this, the FDA has personnel purchase foods from grocery stores four times per year, one from each of four geographic regions of the country. Each “Market Basket” is a composite of like foods purchased in three cities in a given region. They then go on to prepare the foods as they would normally be prepared in the average household, and they analyze it.

Amazingly, DDE was found in 100% of the samples of raisins, spinach (fresh and frozen), chili con carne (beef and bean), and beef that they analyzed. It was found in 93% of the samples of American processed cheese, hamburger, hot-dogs, bologna, collards, chicken, turkey and ice cream sandwiches. It was found in 87% of the samples of lamb chops, salami, canned spinach, meatloaf and butter. It was found in 81% of the samples of cheddar cheese, pork sausage, quarter-pounders, white sauce, and creamed spinach (Figure 2).

Since 1976, the Environmental Protection Agency (EPA) has been running the National Human Adipose Tissue Survey that provides further evidence of the presence of xenoestrogens in the environment and their direct effect on our bodies. This is an annual program whereby the EPA collects and chemically analyzes a nationwide sample of adipose tissue specimens for the presence of xenoestrogens. The tissue is analyzed for organochlorine pesticides, PCBs, dioxins and furans, volatile organics, semivolatile organics, and trace elements. Not surprisingly, DDE was found in 91-98% of the samples tested. OCDD was found in 100% of the adipose tissues sampled – and OCDD is a dioxin.

**Dioxins and Breast Cancer**

The main dietary source of dioxin is meat and dairy products. We know that dioxin latches onto the aryl hydrocarbon receptor, through which it gains access to cells and has as great an effect on breast cancer cell growth as 17 betaestradiol, a recognized and known cause of breast cancer cell growth.

Providentially, there are foods that help to brighten this grim reality of living in a world where xenoestrogens are ubiquitous and breast cancer continues to take the lives of far too many women each year. Broccoli, and in particular, the indole 3 carbinol (I3C) found in broccoli, interferes with xenoestrogens,
including DDT and dioxin by blocking access to cells via the aryl hydrocarbon receptor. Consequently, I3C cuts the rate of DNA damage in breast tissue exposed to chemicals by nearly 92%.10

There are other components, such as d-glucarate in broccoli, that support the detoxification of xenoestrogens and that are of equal if not more importance to breast cancer prevention as I3C. However, if you do choose to recommend or carry I3C as a dietary supplement in your practice, rather than recommending an increase in the consumption of broccoli, I suggest using a product that is housed in a glass versus plastic bottle. There is research that now suggests a direct effect of Bisphenol A (BPA) on estrogen receptors. BPA is widely used in the production of transparent PET bottles and in the lining of tin cans and it represents another xenoestrogen showing estrogen-like activity,11 with researchers cautioning that it may contribute to breast cancer risk.

**Heterocyclic Amines and Breast Cancer**

Heterocyclic amines (HA) are another class of xenoestrogens associated with breast cancer risk. Results from the famous Iowa Women's Health Study12 found that women who consistently eat well-done steak, hamburgers and bacon have a 4.62 fold increased risk of breast cancer. Cooking foods at high temperatures causes the formation of HA's which are linked to breast cancer. And interestingly enough, even grilled salmon contains sufficient levels of HAs to cause gene mutation.

Women who have a polymorphism, or genetic variation, of N-acetyltransferases (NAT) alleles are at a higher risk of damage from HAs.13,14 NAT are major enzymes of breast tissue that activate aromatic and heterocyclic amines, such as those found in cigarette smoke and well-cooked red meat. Researchers found that certain polymorphisms, or genetic variations, of NAT alleles found in humans are significantly more highly correlated with breast cancer risk due to smoking and red meat consumption than others. These alleles code for the "rapid/intermediate acetylator phenotype" in which heterocyclic amines are more quickly activated, increasing the risk of toxic DNA damage leading to cancer. Women with the rapid/intermediate acetylator phenotype may be at significantly higher risk for breast cancer if they smoke and consume meat cooked at high temperatures.

There is an endless supply of xenoestrogens in the environment. Even at small doses, where there is no documented effect on human health, these chemicals do in fact cause great damage to the body, when they are combined.

**Combined No-Observed-Effect-Concentrations of Environmental Chemicals (NOECs)**

A study completed by Dr. Silva and colleagues15 demonstrated that estrogenic chemicals below their NOECs act together to produce significant effects. These researchers tested multi-component mixtures of eight weak environmental chemicals known to bind to estrogen receptors, including hydroxylated polychlorinated biphenyls, benzophenones, parabens, bisphenol A and genistein. The mixtures were prepared so that no one chemical would contribute disproportionately to the overall effect based on their known individual potencies. Concentrations of the individual components ranged from 0.004 μM to 1.04 μM. The researchers measured the estrogenic effects of the low dose chemical mixture utilizing the Yeast Estrogen Screen. Using this reporter gene assay, they first demonstrated that each chemical tested activated the genetically

modified yeast cells' estrogen receptor protein.

The additive combined effects of the weak estrogenic compounds were then calculated using four separate models: concentration addition, toxicity equivalency factors, effect summation, and independent action. From these estimations, the researchers determined that the concentration addition and toxicity equivalency factor approach were valid methods for the calculation of additive mixture effects, as there was excellent agreement between prediction and observation. Remarkably, there were substantial mixture effects even though each chemical was present at levels well below its NOEC. The researchers concluded that estrogenic agents are able to act together to produce significant effects when combined at concentrations below their NOECs. The results of this study highlight the limitations of assessing chemical toxicity on a chemical-by-chemical basis. Conventional risk assessments of toxic environmental chemicals ignore the likelihood of combined actions, which will almost certainly lead to significant underestimations of risk.

In reality, humans and wildlife are exposed to compounds, typically nonspecific, mixtures of chemicals. Fortunately, there are whole foods that, when consumed as a regular part of the diet, reduce the adverse combined effects of NOECs of environmental toxic chemicals, as described in the Silva study.

**Whole Foods that Support Detoxification**

A review of the epidemiological studies to date that demonstrate an inverse correlation between high vegetable consumption and cancer risk revealed that 57% of all such studies show a protection against breast cancer with high vegetable intake. The relative median risk (low vs. high consumption of vegetables) was 1.3.16

Likewise, a high intake of fruits and vegetables correlates with decreased breast cancer risk in premenopausal women. However, supplements of vitamins A, C, and E, and multivitamins, were not associated with overall risk, supporting a whole food philosophy.17 Fruits and vegetables contain numerous tertiary, non-nutritive compounds including isoflavones, dithiolthiones, indoles, flavonoids, and phenols, all of which have proposed mechanisms of action and relative sites along the normal to abnormal cell transformation pathways that inhibit carcinogenesis and provide chemoprotection, sometimes by supporting the actions of the Human Detoxification System (Figure 3).

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Figure 3 - The potential mechanisms and sites for the inhibition of carcinogenesis by protective tertiary compounds found within a whole food matrix.

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**Key**

1. Act as substrates/inhibitors of activating enzymes blocking the activation of the pro-carcinogen.
2. Inactivate the ultimate carcinogenic species directly or by inducing deactive enzymes, e.g., quinone reductase, catalase, superoxide dismutase, glutathione peroxide, UDP glucosonytranferases (UDPGT), glutathione-S-transferase, etc.
3. Induce specific DNA repair enzymes.
4. Stimulate the process of apoptosis in initiated cells.
5. Inhibit cell division of regulate the induction and activity of specific hormones or membrane receptors for growth factors and nuclear gene expression systems.
Therapeutic Nutrition

With regard to the detoxifying effects of whole foods, Steack et al. examined the effects of a mixture of glucosinolate breakdown products from Brussels sprouts (a member of the Cruciferous family of vegetables), on the induction of liver detoxification enzymes in rats. The mixture (full strength, 60%, and 20%) elevated levels of cytochrome P450 1A (CYP1A), glutathione-S-transferase (GST), quinone reductase (QR), glutathione reductase (GR), and glutathione (GSH) in a dose dependent manner, supporting the hypothesis that glucosinolates found in green vegetables are important in the regulation of hepatic detoxification.

The following Brussels sprout glucosinolate breakdown products and amounts were used in the mixture fed to the rats:
- Indole-3-carbinal (13C; 56 mg/kg)
- Iberin (38 mg/kg)
- Phenylethylisothiocyanate (PEITC; 0.1 mg/kg)
- Cyanohydroxybutene (crambene; 50 mg/kg)

The amounts reflect the proportionate amounts of each glucosinolate compound found in Brussels sprouts standardized to 50 mg crambene/kg (induces glutathione without toxic effects). It is important to note that in this study the individual glucosinolate breakdown products were also tested. While indole-3-carbinal (13C) was the only glucosinolate in the mixture to significantly increase enzyme activity, the glucosinolate mixture containing 13C was considerably more effective, supporting a synergistic mechanism of action between the compounds. This suggests that bioactive molecules ingested as part of a complete nutritional regimen may be considerably more effective than the isolated active principles used alone.

Isothiocyanates have also been shown to act as anticarcinogens by inducing detoxification of environmental mutagens. Sulforaphane blocked 7,12-dimethylbenz(a)-anthracene-induced mammary tumors in rats and broccoli extract was a potent inducer of detoxification enzymes in a mouse hepatoma cell assay, probably due to sulforaphane as well.

Fifty percent of people completely lack the glutathione-S-transferase M1 (GSTM1) enzyme due to a homozygous gene deletion. This enzyme is responsible for the rapid conjugation of isothiocyanates to glutathione for excretion (Phase II). Lin et al. hypothesized that people with this mutation would maintain higher levels of isothiocyanates in the body due to decreased excretion and should show a lower incidence of colorectal adenomas, the precursors of colorectal cancer, if isothiocyanates are indeed anticarcinogenic. The researchers found that broccoli and kale, but not cabbage, cauliflower, or Brussels sprouts, were significantly associated with lower prevalence of colorectal carcinomas in a sample of nearly a thousand people (459 adenoma cases and 507 controls sampled from patients undergoing cancer sigmoidoscopy screening in southern California). The presence of the GSTM1 null genotype alone did not significantly correlate with the occurrence of colorectal carcinoma. However, the GSTM1 null genotype did correlate with a significant reduction in incidence of colorectal carcinoma when it was covaried with broccoli and total cruciferous vegetable consumption (p=0.001 and p=0.02, respectively). The lowest incidence of colorectal carcinoma occurred in GSTM1 null individuals in the highest quartile of broccoli consumption, supporting the hypothesis that isothiocyanates in crucifers may be excreted more slowly in urine in GSTM1 individuals. However, neither urinary nor serum isothiocyanate measurements were taken in the subjects, so other mechanisms cannot be ruled out. It is clear from the body of research available that consumption of higher levels of cruciferous vegetables is indicated for reducing the risk of breast cancer.

Another cruciferous vegetable that has specific effects on breast cancer risk is broccoli. In addition to its glucosinolate content, broccoli contains a particularly high level of D-glucarate (broccoli contains the highest percentage of any plant studied), a compound that confers a protective effect against breast cancer. D-glucarate also supports detoxification and the removal of xenosterogens. It is currently being used in a phase I human trial at Memorial Sloan-Kettering Cancer Center in women at high risk for developing breast cancer. This study is in collaboration with the National Cancer Institute and the National Institutes of Health. Yet another member of this same family of vegetables is cabbage. Supporting the whole food philosophy, we know that in addition to glucosinolates, cabbage contains other compounds that have a recognized effect on breast cancer. Some known medicinal constituents in cabbage include:
- 4-Me-glucobrassicin
- Folate
- 4-OH-glucobrassicin
- Glutamine
- Sinigrin
- Flavonoids
- Glucoiberin
- Isothiocyanates
- Phenolic compounds
- Indole-3-carbinal

Folic acid, present in cabbage, works with vitamin B12 to enhance DNA Methylation in the conversion of estrogen to the more protective 2 hydroxyestrone metabolite. Cabbage also is a rich source of glutamine. When glutamine levels drop, intestinal epithelial cells and lymphocytes begin to lose function, compromising the integrity of the epithelium and leaving the intestine vulnerable to microbial translocation (passage of bacteria or toxins into the bloodstream via the intestinal wall). Gut-associated lymphoid tissue (GALT) also requires glutamine for optimal function. GALT comprises the Peyers patches and lymphoid follicles scattered throughout the intestinal mucosa. Maintenance of immune function and a healthy intestinal tract is vital to supporting one's ability to eliminate environmental toxins from the body.

Vegetables that are rich in chlorophylls are also beneficial in supporting the detoxification of environmental chemicals that contribute to breast cancer development. Chlorophylls form molecular complexes with toxins, inactivating them by preventing their binding to DNA and cellular receptors. Chlorophylls also specifically inhibit cytochrome P450 detoxification activity. It is important to keep in mind that chlorophyll-rich vegetables, such as broccoli, Brussels sprouts and kale, are also rich in indole-3-carbinol, calcium-glucarate, and other compounds recognized for their actions in preventing breast cancer and supporting the elimination of cancer-causing environmental toxins.

Finally, flaxseed, the richest known source of plant lignans (a sub classification of phytoestrogens), has been shown to have chemoprotective effects in women. Some of its effects may be mediated through its influence on endogenous hormone production and metabolism. Two competing pathways in estrogen metabolism involve production of the 2-hydroxylated and 16 alpha-hydroxylated metabolites. Because of the proposed differences in biological activities of these metabolites, the balance of the two pathways has been used as a biomarker for breast cancer risk. Researchers examined the effects of flaxseed consumption on urinary estrogen metabolite excretion in postmenopausal women. What they found was that
postmenopausal women eating 5 to 10 g of ground flax per day showed an increase in urinary 2-hydroxyestrone excretion, in a linear dose-response fashion suggesting a chemoprotective role for flax seeds (p<0.0005). What is also promising about flax seeds is that they help to improve the cardiovascular risk profile in postmenopausal women. Given the toxic effects of synthetic hormone replacement therapy, which is often recommended to augment cardiovascular risk in these women, it is hopeful to know that there are foods which not only offer breast cancer protection, but also help to prevent the need to take in something as toxic to a woman's body as synthetic hormone replacement therapy.

Researchers studied the association between dietary phytoestrogen intake and metabolic cardiovascular risk factors in postmenopausal women. For this purpose, 939 postmenopausal women were included in the cross-sectional study. Postmenopausal women who consumed a significant amount of lignan-rich foods had less weight concentrated around their waist (lower WHR) than those who ate little or none suggesting an improvement in metabolic cardiovascular risk profile.

Final Thought

Breast cancer has strong environmental factors (such as toxins in the food, air and water supply, and synthetic HRT) and strong genetic factors. We ought to view breast cancer, and its causes, as a matter of nature and nurture, rather than nature versus nurture. We should not view cancer as having a single "cause," but understand that a combination of these factors brings about cancer. There must be a critical number of "hits" to a person's DNA that occur before we see the onset of cancer. By "hits" I mean damage. Whether it be hits that we are born with (genetic predisposition), or hits that occur after we are born (such as environmental toxins damaging our DNA). Knowing this, I will add that it is my belief that preventing or augmenting the effects of "hits" that we receive after we are born is most effectively accomplished through the use of foods, such as broccoli, Brussels sprouts and other chlorophyll-rich foods, such as cabbage and flax seeds.

The Commonwealth Scientific and Industrial Research Organisation (CSIRO) held a conference in Melbourne entitled "Beyond the Human Genome." in February of 2002. And what was reported was that research in the CSIRO and elsewhere has shown that we can reduce our levels of genetic damage by consuming optimum levels of vitamins and minerals from our foods. In fact, according to Dr. Bruce Ames of the University of California at Berkeley, who researches the effects of micronutrient deficiencies on gene health; Deficiency of vitamin B12, folic acid, B6, niacin, vitamin C, vitamin E, iron or zinc, appears to mimic radiation in damaging DNA caused by single- and double-strand breaks, oxidative lesions or both...half of the population may be deficient in at least one of these micronutrients.

Studies done by Dr. Ames and many others, some of which presented their material at the Melbourne conference, have shown that gene damage through inappropriate diet may be as significant as genetic mutation brought about by toxic chemicals and radiation. Imagine the prevalence of damage ("hits") caused by inappropriate diet and a toxic environment.

References