

Dietary Fiber, Perimenopause and Estrogen by Jeffrey S. Bland, Ph.D.

There is a complex interaction among diet, liver detoxification function, ovarian and adrenal gland production of estrogen, as well as the body's management of sex hormone levels.

Dietary fiber, which is more abundant in a vegetable-based diet, is capable of altering the way various estrogen hormones are metabolized. David P. Rose, M.D., from the division of nutrition and endocrinology at the American Health foundation in New York, found women showed significant reductions in a form of estrogen (estrone) that is associated with increased risk of hormone problems after two months on a high fiber diet. **But, there was no change in either progesterone or the estrogen hormone estriol, which helps to stabilize women's estrogen needs.** (*American Journal of Clinical Nutrition*, 1991; 54: 520)

Large numbers of medical studies have demonstrated that when women shift from a diet that is high in meat and dairy products to a more vegetable-based diet, their estrogen hormones tend to normalize. This hormone-normalizing effect is a consequence of both the increased intake of dietary fiber and the effects of various substances found in plant foods upon a woman's metabolism and use of estrogen. Herman Adlecreutz, M.D., Ph.D., a professor at the University of Helsinki, Meilahti Hospital in Finland, has been one of the most productive researchers in the field of plant chemicals and hormones for the past 20 years. His research has conclusively demonstrated many plants contain "weak estrogens" that can help normalize a woman's estrogen balance. **These substances, called phytoestrogens, include isoflavones genistein and daidzein.** (*Journal of Steroid Biochemistry*, 1987; 27: 1135) **[Shaklee Soy Protein]**

Intestinal bacteria have a relationship to the hormones in the body. Individuals who have overgrowth of toxic bacteria in their intestine tract experience a significant alteration in the metabolism and effects of hormones.a diet high in vegetable products and soluble and insoluble fibers, along with accessory nutrients – added as supplements to her diet – that would help stabilize the presence of friendly bacteria (e.g., lactobacillus acidophilus and bifidobacteria bifidus) in the intestinal tract. There is a significant difference in a way different types of dietary fiber affect estrogen metabolism. Estrogen is metabolized principally in the liver, through a series of detoxification enzymes. Studies show soluble and insoluble fibers (e.g., those derived from rice, carrots and apples) have a positive effect on the way the liver metabolizes estrogen (*American Journal of Clinical Nutrition*, 1991; 54: 520-25) **[Shaklee Fiber, Optiflora, Liver DTX]**

Estrogen is not manufactured and secreted by the ovaries alone; it's also secreted by the adrenal glands. Improving adrenal gland function by making sure the diet contains sufficient zinc, vitamin C, vitamin B5 (pantothenic acid) and plant sterols from beans and other plant foods would help support estrogen needs as the ovaries gradually lose their ability to manufacture estrogen. **[B-Complex, Zinc, Vita-C sus, Fiber]**

This information is not intended to replace medical care. This information is not intended to diagnose, treat or cure.

GLA for breakthrough bleeding 1-01

Back last November, I started having break through bleeding during my monthly cycles. The bleeding started to become daily. Along with this I had terrible hot flashes that woke me at night. I thought for sure I was going through early menopause. I went to the doctor and had all kinds of blood work and was told everything was fine. The bleeding continued and I was scheduled to see a specialist around February. I called my sister-in-law and told her my problem. She told me she spoke with you and that you suggested trying GLA. I placed an order and began taking it within two days. Believe it or not, within 1 week the bleeding started to slow down and by the end of the first month had almost stopped. I went to my doctor's appointment and had a cervical biopsy and more blood work. The doctor suggested hormone patches and maybe a stripping of the lining of the uterus if the bleeding didn't stop. I told her I am not allowed to take any hormones because my family has a history of strokes and heart attacks. She told me it was still safe(2 of my cousins had strokes in their early 20's due to birth control pills.) I absolutely refused this form of treatment. She told me she would give it 3 more weeks and then if the bleeding didn't stop, she was going to schedule me for surgery. Well, by the third week, I had been one whole week without bleeding. Thank you GLA!!! So the only way the doctor could explain this was to say my body straightened itself out. They don't seem to believe that herbs would have anything to do with it. So from now on, when I heal myself, I don't let the doctor in on my secrets. Other things that Shaklee has help me with is Joint Health Complex and Osteomatrix for by back and hips. I have had previous back surgery and back therapy didn't work, but this sure did! I take the Soy Protein drink everyday for energy. I work 12 hour days and need all the energy I can get. I just starting taking Alfalfa for asthma & allergies and B-complex for stress. I will let you know how it works.....*Barb M*

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HRT Alternatives

Just wanted to let you know that I was on HRT (following a complete hysterectomy due to a diagnosis of cancerous tumors and cysts) for 2 years, did NOT feel good, gained weight, etc. so when we came into your down-line via John and Genevieve in '94, I studied up on all the Shaklee supplements that I needed and QUIT the HRT. Many people thought I was crazy, but I am here to tell you today.....there is NO OTHER WAY to go as far as I'm concerned. I have had NO symptoms, i.e. hot flashes, etc. and lost 50 pounds on the Shaklee weight loss program (which I have now kept off for almost 2 years). When we heard the news today about that study, I just said "HOORAY" - I did the right thing. I knew **Shaklee's Osteomatrix** would do more for my bone density than anything the doctors could offer me. And, now I have my almost 90-yr-old mother as a good example of what Shaklee can do for us. With her doctor's permission, I took her off of the 7 prescription drugs she was on about 7 years ago. The doctor was wanting to put her on Fosomex(?) and I told him NO - I have a young friend that was almost killed by that drug. She called me when she was desperate.....that she was NOT refilling her prescription and could I please bring her whatever she needed to take. She called me 3 days later to tell me she had slept through the night without having to change her nightclothes or bed linens (due to sweating) for the first time in....she couldn't remember when. When she went back to her doctor 2 months later, he could not believe her excellent health status. ALL her blood work was great - everything - and today she looks 10 years younger than she did 5 years ago.

Back to mother....she has only seen the doctor for physicals for the last 6 years, except for last month when she "found" herself on the kitchen floor and couldn't get up. After someone came to help her up, she went to the doctor the next day and he could find NOTHING wrong. Every year

at her physical her doctor tells her she's in better health than he is and to just keep on doing what she's been doing. All she's on is Shaklee. Ella H

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**Ovarian Cysts Testimony**

As my daughter had ovarian cysts and I wanted her to get rid of them with Shaklee products, I asked one of the nutritionists what to do. Her reply was to simply pick up her Shaklee B-Complex. She explained that B vitamins regulate the estrogen in the body. Too little B--too much estrogen, thus ovarian cysts. She used 10-12 B a day and in four months the cysts were gone, much to the doctor's amazement. Barb explained to me that most female problems stem from too much estrogen. Estrogen accelerates the growth of cells. Endometriosis is uterine cells growing outside the uterus so, if it were my daughter, I would encourage her to get off white sugar, flour, pasta, potatoes, rice , etc., and take lots of B Complex...Barb explained to me that most female problems stem from too much estrogen. Estrogen accelerates the growth of cells. Endometriosis is uterine cells growing outside the uterus so, if it were my daughter, I would encourage her to get off white sugar, flour, pasta, potatoes, rice , etc., and take lots of B Complex...*Rosalie B.*

**Endometriosis - Success with Supplementation**

I started having severe cramps from the time of my first period, which just continue to get worse as the years went by. I took many over-the-counter painkillers that didn't work. When I was 16 I went to a GYN. He put me on different prescription painkillers, which included Annaprox, Vicodin, Darvocet, and Tylenol with codeine, which I took twice as often as prescribed, at double the dosage. This did nothing for my pain. I had pain for 3 to 4 days during ovulation, and 2 days before, during, and 2 days after my menstrual cycle. My cycles were only 21 to 25 days apart. My personality had also started to change. I seemed to be emotional, angry, and frustrated because I never felt well. I also started having other health problems like strep throat, and sinus infections. By high school graduation I was taking pain medication more often than not. As well as many antibiotics. I had a laparoscopy at age 20, at which time they discovered I had stage 3 to 4 Endometriosis of my lower abdomen and on my cervix. Things started getting worse again after about 9 months and I started using painkillers again. I was still having problems emotionally. My husband (boyfriend at the time) said I would be a basket case most of the time. By this time I was having problems with my stomach. I was throwing up about two to three times a week. I have tried many different things to help with the pain and to slow the progression of the Endometriosis. I have taken birth control pills, prescription painkillers, and the depo provera shot. These things helped for short periods of time but always came with many side affects such as weight gain, depression, dizziness, blackouts, and, as I discovered years later, the eating away of my digestive system that lead to the breakdown of my immune system. I never wanted to try any other of the traditional treatments of the Endometriosis because the side affects didn't seem worth it. Also during this time I began having frequent migraines. After looking at my prior health, I feel fortunate to have a son who is now 4 years old. In October 1999 I went to a Shaklee meeting with a friend who was having Good results with the products. I was skeptical but willing to try anything. My biggest goal was to have energy to play with my son and still be able to clean my house. I had tried over the counter medications, vitamins and herbs, but nothing seemed to make a difference. I expected this to be the same way. To say the least I was skeptical. At the meeting I was so impressed by the Science behind Shaklee. I filled out the health questionnaire. When Sherry Atilla called and said that there were big problems, I wasn't surprised. She told me that it seemed like I didn't absorb anything I ate because I was showing signs of not having any vitamins or minerals in my system. She also mentioned that I might have a yeast problem. She had me contact Carol Dalton, a nurse practitioner. It never crossed my mind that I could help my Endometriosis with nutrition. With the help from nurse practitioner, Carol Dalton, and Missy Peden, I have been able to stop taking

painkillers for cramps completely! Missy told me from the very beginning to try the GLA when I started to supplement with Shaklee. I didn't need to take any pain medication for cramps during that first period! I am also using natural progesterone cream that Carol Dalton prescribed to slow down the growth of the Endometriosis. Since that time I have only had one period in 9 months where I have had cramps, however, I didn't need to take any pain medication. I have learned with that experience that there are other things that contribute to cramping. For example, excess sugar (white flour) in your diet as well as the caffeine makes the cramping worse. During the month where the cramps were worse I had eaten a lot of sugary foods and drank a lot of caffeinated drinks. I also have found that the relaxation techniques that I have learned in biofeedback for headaches also help with menstrual cramps. I take many different supplements but a few help specifically with Endometriosis pain. Always start any supplement plan with Vita-Lea. Then I have found these to be essential for menstrual pain:

- 6 to 8 B-Complex - to help with PMS and sugar cravings
- 4 - 6 tbs. Soy protein - to help with sugar cravings; also assists with hormone function
- 6 Osteomatrix - natural muscle relaxer for cramps
- 4 GLA - natural anti-inflammatory; also assists with hormone function
- 3 EPA - natural anti-inflammatory

I have now been on a nutritional program with Shaklee supplements for over a year. I have had great results! I am healthier now than I had been in 15 years. I am also 7 months pregnant with my second child. I would encourage anyone who has any serious health issues to do a health evaluation and take a good, hard look at what nutritional needs aren't being met. Shaklee has made an incredible difference in my life and I'm very thankful someone took the time to share it with me.....*Shari*

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Cervical Cancer Testimony...

Our daughter Terri was diagnosed with Stage 5 Cervical Cancer. After receiving the results of her annual Pap test in September, there were some abnormal cells and they requested a biopsy. Three weeks later she had the biopsy which showed two areas with pre-cancerous cells and one area with cancer. The doctor recommended surgery immediately. Most of you know that we worked with Terri counseling her with a diet and Shaklee supplement program. When the Physician reviewed the Biopsy test she stated that she noticed that it did not look as bad as the original results of the first test only 3 weeks earlier. However she did request again that Terri go through surgery as soon as possible.

After receiving the results of the biopsy test with the diagnosis of Stage 5 Cervical Cancer, we established for Terri an aggressive cancer nutrition and I Love Dieting food regime with Shaklee food supplements and enlisted encouragement from many of you who so graciously showed such wonderful support with your prayers and concerned inquiries. We thank each and every one of you so much.

At this time we felt we had made progress with the health program we were using and wanted to know to what extent if any change had actually occurred. So, we sought a second opinion, thinking that it would involve another pap test, but the 2nd Doctor only read the results of the 1st Doctor and concluded the same --that surgery should be done immediately. Both doctors felt that the nutrition regime would not have any positive bearing on the problem. Not satisfied with the 2nd doctor's intent to do surgery so quickly, we continued the aggressive nutrition regime and sought a 3rd opinion where another pap test would be given. Well, it has been 5 months since this all started and today Terri received notice that her latest pap test came back completely NORMAL! Yes!!!.....*Marty & Lynn F*

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Age Is Important In Hormone Therapy Use, Study Suggests

ScienceDaily (Aug. 4, 2007) — Five years ago this summer the National Institutes of Health's stopped early a major portion of the Women's Health Initiative (WHI), a large and ambitious study to address the most common causes of death, disability and impaired quality of life in postmenopausal women.

One part of the WHI sought to determine whether hormone therapy has a positive or negative impact on cardiovascular disease, cancer, and osteoporosis. The estrogen-plus-progestin hormone therapy trial for women with their uteruses intact was stopped in July 2002 after investigators found that the associated health risks of the combination hormone therapy outweighed the benefits.

Less than two years later, in March 2004, NIH announced that it had stopped another portion of the WHI, the estrogen-alone hormone therapy study for women who have had a hysterectomy, in the interest of safety after careful consideration of preliminary data and an average follow-up of nearly seven years.

The abrupt end of the studies and the news stories that followed left many patients confused or scared. Questions still remained about the safety and efficacy of hormone therapy, about who could take it, and for what purpose and what duration.

More information was needed about the risks and benefits of estrogen-alone hormone therapy, long-term risks for short-term use of hormone therapy, the appropriate timing of hormone therapy use in relation to a woman's onset of menopause, and the effects for women who take hormone therapy well after menopause has ended.

The medical community has learned more about hormone therapy since the WHI trials were stopped. A study published in the July 11 issue of the British Medical Journal confirmed that hormone replacement therapy should not be prescribed for the purpose of preventing chronic conditions such as heart disease in older women who are well past menopause. That same study, however, concluded that hormone therapy may be a safe, short-term option for younger women in early menopause to relieve symptoms and improve quality of life.

"If the woman is healthy and has no risk factors, low dose hormone replacement therapy use for a short period of time should confer a small risk to her health," says Helen Roberts, M.D., M.P.H., a senior lecturer of women's health issues at the University of Auckland in New Zealand. Roberts, who wrote an accompanying editorial to the British Medical Journal study, also said women with risk factors such as a previous heart attack, stroke, blood clots, breast cancer or high risk of cardiovascular disease should not use hormone therapy.

Although confusion about hormone therapy persists, this study solidifies some thinking on the issue. Short-term use of hormones in healthy women going through early menopause may not pose serious health risks. Long-term use of hormone therapy to prevent chronic diseases in older women, who begin the therapy many years after menopause, may actually increase their risk of blood clots and heart disease, and should be discouraged.

A limitation of the WHI is that it primarily studied women who began taking hormone therapy long after they had passed menopause. Researchers are still trying to determine the effects of taking hormone therapy for long periods of time if the treatment begins in the early stages of menopause. Some data suggests the health risks are lower for these women, but more studies are needed.

"There has been mounting evidence that a woman's age and amount of time since onset of menopause influence her health outcomes on estrogen, particularly her risk of heart disease," said JoAnn Manson, M.D., Dr.P.H., chief of preventative medicine at Brigham and Women's Hospital in Boston, professor of medicine at Harvard Medical School, and one of the principle investigators of the WHI. "We've recently reported in April of 2007 that when you combine the findings from the estrogen plus progesterone trial and the estrogen alone trial, there is a

suggestion of a lower risk of heart disease in the women who were less than ten years since onset of menopause.”

By contrast, Manson’s analysis shows an increased risk of heart disease for women who were more than 20 years past menopause.

Manson’s research team reported in the June 21 issue of the New England Journal of Medicine that women who were in their 50s in the estrogen alone trial tended to have less coronary artery calcium, if they received estrogen compared to placebo.

“Coronary artery calcium is a marker for plaque build-up in the arteries, hardening of the arteries and it’s a strong predictor of future risk of cardiovascular, of coronary heart disease,” Manson said. “So these results lend support to the theory that estrogen may slow early stages of atherosclerosis.”

As research continues, taking hormone replacement therapy is an individual decision for women that depends on many factors. Women should speak with their health care providers about the potential benefits and risks that may be relevant to them as individuals.

Adapted from materials provided by [Society for Women's Health Research](#).

The Shaklee Difference - *The principle of “Products in Harmony with Nature and Good Health” guides Shaklee science. Experts in nutrition, public health, food science, analytical chemistry, biochemistry, herbology, microbiology and engineering staff the 52,000 square feet Forrest C. Shaklee Research Center in Hayward, California. They continue the important research and development that makes each product the world stand for quality.*

WOMEN’S HEALTH BULLETIN – JULY 2002 FROM SHAKLEE

A spate of media publicity this July has accompanied news reports that one part of a major study by the National Institute of Health and the Women’s Health Initiative on the use of hormone replacement therapy for postmenopausal women was suddenly halted. This was the part of the trial that examined the longer term effects of taking a combined regimen of estrogen and progestin. The Women’s Health Initiative (WHI) is the first large, long-term trial to compare HRT to placebo in over 16,000 healthy women. Dr. Marcia Stefanick, Stanford Professor and member of Shaklee’s Scientific Advisory Board, is one of the principal investigators of this NIH-sponsored trial. The study was just stopped Monday three years early because the long term risks of HRT had exceeded or offset the benefits.

What they found were small increases in the risk of breast cancer, stroke, heart disease and blood clots. In contrast they found small decreases in the risk of hip fracture and colon cancer. This is big news, because it was thought that HRT was protective of the heart for most healthy women. (An earlier study, called HERS, had already shown that HRT increased the risk of heart attack in women who already had heart disease, at least in the first few years after they started taking HRT).

Federal authorities are urging all women on HRT to contact their doctors about whether they should stop taking it. Here are the risk/benefits in perspective. For every 10,000 women who take HRT for a year, 8 more will develop invasive breast cancer, 8 more will have strokes, and 7 more will have heart attacks compared to 10,000 similar women not taking the drug. On the benefit side, there will be 6 fewer instances of colon cancer

and 5 fewer of hip fracture. Thus the bad news is that the health risks accruing over the long term would unquestionably outweigh the short term benefits of relieving such symptoms as hot flashes and night sweats that have long been effective during and post-menopause. The long term risks began to appear in the trial and included the possibility of contracting the following ailments and diseases: breast cancer, strokes, blood clotting, bone loss, gall bladder disease and other problems.

Dr. Marcia Stefanick, Stanford Professor and Chairwoman of the Women's Health Initiative steering committee remarked: We needed to stop the trial to ensure the patients safety. We got the answer to benefits vs. risks much sooner than we expected, and the risk clearly outweighed the benefits. She added: Women should take this new information very seriously. If it's about quality of life, is it worth the risk?

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Dietary supplementation alternatives

There are a number of avenues opening up for women who are uncomfortable in continuing to follow the newly discouraged estrogen/progestin route:

Black cohosh - This is an herb that has been used in China for centuries for a variety of conditions. Intramedicine, the medical research firm based in Westlake Village, California, reports that scientists have been studying black cohosh's ability to mimic the effects of the hormone estrogen on the body. Clinical studies have reported positive effects on menopausal and post-menopausal complaints when using standardized extracts of the substance. One study has suggested that black cohosh may have a component that produces a hormonal balancing effect in the female reproductive system.

Soy Isoflavones - Soy Isoflavones are said to exert effects similar to that of estrogen which alleviates some symptoms associated with menopause. They also contain phytoestrogens and, although unproven in clinical testing, remain very promising and are already widely used as hormone replacement therapies.

The Broader Picture

A woman's passage through life can be exciting, inspirational and at times challenging. She may be faced with health-related conditions such as breast cancer, osteoporosis, heart disease, PMS, symptoms of menopause and complications of pregnancy. Today, women are often led to believe that these health challenges necessarily require routine pharmacological interventions (i.e. prescription medications). This belief has been popularized at the expense of using diet, nutritional and herbal supplementation and lifestyle as a woman's primary means of achieving optimal health and vitality.

Recent clinical research studies demonstrate that there are specific nutrients which, when combined properly, can have a dramatic effect on the health of a woman, no matter what stage of life she is in or health challenge she is experiencing.

Breast Cancer

Breast cancer is second only to lung cancer as the most common cause of cancer mortality in the United States.¹ 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 United States as a result.

Hormone Replacement Therapy and Breast Cancer

A woman's chance of developing breast cancer significantly increases with age.² As a woman ages, she will naturally reach menopause and a decline in the production of important hormones, such as estrogen which can increase her risk of heart disease and osteoporosis. To help prevent such conditions, estrogen has commonly been prescribed and has been shown to exhibit a number of beneficial effects³ on the body including:

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- Enhanced skin smoothness, firmness and elasticity
- Enhanced moistness of skin and mucous membranes
- Enhanced sex drive in women
- Improved memory
- Reduced risk of osteoporosis
- Reduced risk of heart disease

However, estrogen replacement therapy increases a woman's risk of developing deadly ovarian cancer. One research study looked at 240,073 pre- and post-menopausal women for a period of 7 years and found that women who used estrogen for at least 6 years increased their risk of ovarian cancer by 40%. Even more frightening is the fact that women who used estrogen for 11 or more years increased their risk by 70%!⁴ Many physicians now prescribe a combined drug, which includes estrogen *and* progestin (a synthetic form of the natural hormone, progesterone). The addition of progestin to estrogen significantly reduces a woman's risk of endometrial cancer, but at the same time, it dramatically increases her risk of developing breast cancer and stroke. A recent study published in the *Journal of the American Medical Association* in 2002⁵ found that there is a 60-85% increase in the risk of breast cancer for women who use estrogen, or combined estrogen and progestin therapy. This risk remained irrespective of a woman's family history of breast cancer. Another study published in the *Journal of the American Medical Association*⁶ found that for current and previous users of estrogen-progestin therapy, the risk for breast cancer was 40% higher than for non-users. Further, for each year of use, the risk of developing breast cancer increased 1% for women who used estrogen alone (without progestin) and 8% for women who used estrogen-progestin therapy. Thus, the risk of breast cancer would be predicted to increase by approximately 80% after 10 years of use and 160% after 20 years! This has major implications for assessing the risks and benefits of taking hormone replacement therapy considering the fact that hip fractures and coronary artery disease (major reasons why doctors prescribe these medications in the first place) do not become significant until a decade or more after menopause.

Xenoestrogens and Breast Cancer

Xenoestrogens are environmental compounds with estrogen-like activity that may cause breast cancer in some individuals.⁷ Chlorinated pesticides, such as DDT (used to kill mosquitoes) and its metabolite DDE, are examples of such compounds which have been linked to breast cancer.⁸⁻¹⁰

While not all research has supported the connection,¹¹⁻¹⁶ one group¹⁷ found that high levels of DDE and other toxic xenoestrogens in the body can cause a four-fold increase in one's risk of breast cancer.

To combat the effects of DDE, scientists looked at the ability of isoflavones to inhibit the growth of breast cancer cells that were induced by pesticides. Accordingly, it was found

that isoflavones, such as those found in **soy**, did inhibit the abnormal breast cell growth that was caused by xenoestrogens.¹⁸

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A Closer Look at Tamoxifen

While researchers have not found a definitive cause for breast cancer, it is evident that hormones play a role in the onset and treatment of the disease. For example, researchers have discovered that women who began menstruating earlier in life, and thus have been exposed to more estrogen throughout life, have an increased risk of breast cancer. Further, we have seen that, as described above, taking synthetic hormones can increase a woman's risk of breast cancer, and the longer she takes them, the greater her risk. The drug Tamoxifen reduces estrogen's ability to cause some breast cancer cells to grow by blocking estrogen receptors. However, research has suggested that using Tamoxifen for more than a two year period can actually increase the amount of estrogen circulating in the blood, thereby increasing risk. Further, it has been found that estrogen-receptor positive tumors have the ability to mutate into a cancer cell type that no longer depends on estrogen in order to grow.¹⁹ Tamoxifen also works to help combat cancer in ways that are independent of its ability to block estrogen. For example, Tamoxifen can stop an abnormal cell cycle. A cell has a preprogrammed cycle that it goes through in order to divide. Along the way, there are checkpoints to make sure that abnormal cells do not replicate. However, cancer cells differ from healthy cells in that they have lost these checkpoints and hence they grow and divide very rapidly. Tamoxifen works by restoring a checkpoint and stopping the abnormal cell cycle. It also blocks a cell signal known as protein kinase C that in turn stops cancer genes (oncogenes) from activating. While Tamoxifen does demonstrate benefit in controlling cancer growth, there is evidence that cells can become resistant to the drug, particularly with long-term use. *While hormone replacement therapy, xenoestrogens and even Tamoxifen can increase breast cancer risk, there is evidence suggesting that select foods, nutrients and phytochemicals may play a role in diminishing breast cancer risk. Interestingly, **Vitamin D**, and in particular **Cholecalciferol**, has been shown to act synergistically with Tamoxifen to reduce breast cancer cell growth.*²⁰

The Benefits of Soy

Recent epidemiological studies suggest that the rate of breast cancer is lower in cultures that consume a diet traditionally high in soy products,²² and the benefits of Soy have been documented in medical literature since 2838 BC.²¹

Results of human clinical trials, animal studies, and in-vitro experiments show results consistent with the epidemiological evidence, confirming the benefits of soy in maintaining breast health.²³⁻²⁸

Several constituents have been isolated from **soy** including isoflavones, phytosterols, protease inhibitors, inositol hexaphosphate, and saponins.²⁹ From this group, isoflavones are one of the most promising agents found in soy for the treatment and prevention of breast cancer.³⁰⁻³²

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Isoflavones possess antioxidant and phytoestrogenic properties. They have been shown to influence intracellular enzymes, protein synthesis, growth factor action, malignant cell proliferation, differentiation, and angiogenesis.³³

Three isoflavones in particular appear to be particularly promising. They are Genistein, Daidzein, and to a lesser extent, Glycitein. As we are discovering, *soy not only plays a powerful role in supplying health giving properties to humans, it also plays a vital role in the symbiotic relationship between plants, bacteria, and our surrounding atmosphere.*³⁴

When Genistein is secreted from the roots of soybeans, it interacts with the microorganism, *Bradyrhizobium japonicum*.³⁵ This interaction results in the formation of root nodules that contain the bacteria. These root nodules then convert atmospheric nitrogen to ammonia that can be used directly by the plant.³⁶⁻³⁸

Research studies suggest that soy consumption reduces serum estradiol in premenopausal women.

Women with higher serum estradiol levels are at an increased risk of developing breast cancer.³⁹

Additionally, soy favorably alters the ratio of certain estrogen metabolites that are associated with breast cancer risk.⁴⁰ Genistein is a component of soy that suppresses breast cancer cell growth by stimulating apoptosis (cancer cell death),⁴¹ and influencing enzymes that regulate cancer cell growth and replication.⁴² Soy also inhibits angiogenesis, which is a process that supplies cancerous tumors with blood.⁴³

In addition to soy, **alfalfa** may show promise in reducing cancer risk primarily due to its chlorophyll content. Studies indicate that chlorophyll and its derivatives have potential anticarcinogenic (cancer fighting) effects in animals and humans. Although researchers are still trying to understand exactly how these phytonutrients work to fight cancer, we know that it is demonstrating a beneficial effect.⁴⁴⁻⁴⁷

Alfalfa does contain some phytoestrogens (plant substances that act like estrogen in the body), and so in theory, it may interact with estrogen sensitive diseases such as some forms of breast cancer, although there is no evidence to substantiate this theory.

In the March 17, 1999 issue of the *Journal of the National Cancer Institute*, associations between intakes of specific nutrients and breast cancer risk were investigated in 83,234 women who were participating in the famous Nurses Health Study. Breast cancer risks were significantly lower in women who consumed **vitamins A and C**. Further, epidemiological evidence indicates that premenopausal women with a positive family history of breast cancer who consume higher amounts of **vitamin A** have a reduced risk of breast cancer.⁴⁸ In another study published in *Cancer Research* in 1997, researchers found that **vitamin E succinate** inhibits the growth of, and induces the destruction of, estrogen receptor negative human breast cancer cells.⁴⁹ These findings suggest a clinical role for vitamin E succinate in the treatment, and possible prevention, of human breast cancers. While research studies on alpha-tocopherol alone have not shown benefit in reducing breast cancer, the *combined* effects of a **mixture of tocopherols** have demonstrated characteristics that correlate with a reduction in risk of breast cancer.⁵⁰ Additionally, the antioxidant **selenium** has demonstrated clinical benefit in reducing the incidence of cancer and of cancer mortality by inhibiting tumor growth and stimulating apoptosis.⁵¹⁻⁵⁴

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Menopause

Menopause is characterized by the cessation of menstruation, which results from a natural decline in ovarian function. This decline generally takes place between the ages of 45 and 55. A woman will also experience an artificial menopause if she has had her ovaries removed, has had radiation exposure to her ovaries, or has been exposed to select chemotherapeutic agents. In any case, symptoms commonly associated with menopause include:

Hot flashes Vertigo
Headaches Joint pain
Depression Hair loss, and
Lack of concentration Sleep disturbances
Anxiety

These symptoms are most often related to a natural decline in the production of estrogen, which can also increase her risk for developing heart disease and osteoporosis. Typically, a woman's primary care physician will recommend hormone replacement therapy (HRT) as a means of reducing her symptoms and in an attempt to reduce her risk of heart disease and osteoporosis. However, as discussed above, HRT comes with a number of risks, including the risk of developing breast cancer or stroke.

Soy has been shown, through clinical research studies, to improve menopause-related symptoms, prevent estrogen-deficiency diseases such as heart disease, stroke, and osteoporosis, and in recent years, has demonstrated great promise in preventing breast cancer in women.

Menopause and Heart Disease

In developed nations, the leading overall cause of mortality in women is heart disease⁵⁵ and the risk of the disease increases dramatically after menopause. The loss of estrogen during menopause is thought to be the reason for the increased risk.

Phytoestrogens such as **soy** reduce a woman's risk of heart disease, particularly after menopause, without the added concern of increasing her risk of breast and ovarian cancers (as is the case with synthetic hormone replacement therapy). Specifically, phytoestrogens such as **soy** significantly reduce cholesterol levels (and particularly LDL cholesterol) and prevent atherosclerosis.

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The Benefits of Soy

Soy not only protects a woman's heart. The table below lists the wide range of clinical benefits that phytoestrogens like soy have on menopausal women.

Table 1: Effects of phytoestrogens, like soy, on menopausal women.⁵⁵

Evidence is accumulating that plant phytoestrogens, like soy isoflavones, offer some of the same benefits as synthetic hormone replacement therapy without the harmful side effects.^{55, 56} In February of 2002 researchers conducted an expansive review⁵⁷ of all of the main studies published to date on the efficacy of **soy** in reducing the symptoms of menopause. Based on this exhaustive review, the researchers concluded that **extracts of soy alleviate both the short-term symptoms of menopause (such as hot flashes, vaginal dryness, mood swings, and anxiety) AND the long-term effects**

menopause (such as osteoporosis and heart disease). Further, these researchers concluded that **soy supplementation might likely reduce the risk of breast cancer.** As you can see, soy is an important food with powerful medicinal properties specific for helping menopausal women.

- Bone Loss**
- Bone mineral density**
- Cholesterol**
- LDL oxidation**
- Perimenopausal hot flashes**
- Cancer incidence**
- Atherosclerotic lesions**
- Platelet aggregation**
- Angiogenesis (blood supply to cancer cells)**
- Neoplastic proliferation**
- Antioxidant enzymes**
- Vascular reactivity**

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Premenstrual Syndrome (PMS)

Premenstrual syndrome (PMS) affects approximately 95% of all women of reproductive age. The psychological and physical symptoms of PMS can be so severe that they disrupt everyday life. Physical symptoms include bloating, weight gain, breast pain and/or tenderness, abdominal discomfort, lack of energy, and headaches. Common psychological symptoms include irritability, anxiety, tension, aggression, feelings of being unable to cope, and a sense of loss of control.

Although the original description of the syndrome was first described in 1931, the exact cause of PMS is still unclear. What we do know for sure is that synthetic hormone replacement therapy can cause premenstrual syndrome (PMS) with symptoms ranging from bloating to irritability and depression. There are currently at least 327 different treatments available for premenstrual syndrome, reflecting the confusion surrounding its cause. Fortunately, there are safe, non-toxic nutritive options that address the symptoms associated with PMS, without side effects. During the premenstrual period, **calcium** levels drop, causing mood changes and other symptoms associated with PMS that improve with calcium supplementation.^{59, 60} **Vitamin B6** has also demonstrated excellent benefit in improving PMS symptoms like breast tenderness and depression. A comprehensive review, published in the *British Medical Journal*,⁶¹ based on the results of 940 patients with PMS, found that vitamin B6 relieved physical and mental premenstrual symptoms, including depression associated with PMS. **Vitamin E** also successfully treats depression, in addition to anxiety and cravings associated with PMS.^{62, 63} **Grape seed extract** (*Vitis vinifera*) can help too, as it contains natural antioxidant compounds called oligoproanthocyanidins that relieve cramps and depression associated with this syndrome.⁵⁸

Osteoporosis

Osteoporosis is a debilitating condition that occurs primarily in postmenopausal females and often results in serious bone fractures. Approximately 10 million individuals in the

United States already have osteoporosis and another 18 million are estimated to have a low bone density, placing them at increased risk for osteoporosis later in life. While 50% of all women over the age of 50 will have an osteoporosis-related fracture in their lifetime, this condition is by no means an old person's disease. In fact, younger individuals with hormonal challenges, and particularly women in their 20s who suffer from anorexia or menstrual abnormalities, are at risk of developing this difficult-to-treat condition. While many new treatments are available for osteoporosis, most of them fall short in their ability to significantly improve bone density. *The very best treatment for the condition is prevention.* Lifestyle changes such as quitting smoking, reducing alcohol and caffeine intake, and incorporating weight bearing and aerobic exercise into your daily fitness regimen are essential.

Additional factors include consuming a diet that is high in calcium and low in phosphorous, and incorporating select phytonutrients, vitamins and minerals into your health regimen.

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Alfalfa, for example, contains key phytonutrients that maintain proper bone mineral density.⁶⁴

Vitamin K also plays a significant role in preventing and treating osteoporosis. It works together with **calcium**, **vitamin D**, **boron** and **magnesium**, to increase bone mineral density and to maintain calcium balance.

Using data on 72,000 women who participated in the Nurses Health Study, researchers found that those women who consumed the most **vitamin K** over a ten year period were approximately one third less likely to get a hip fracture.⁶⁵ Interestingly, the significance of taking vitamin K was greater than taking synthetic estrogen, which didn't demonstrate a protective effect. In another study, postmenopausal women who consumed 1 mg of vitamin K daily for 2 weeks showed increased levels of a critical bone-building protein.⁶⁶ Interestingly, supplementation with vitamin K has also been shown to cut the risk of bone fracture by a third in women who have a naturally tendency to be deficient in calcium.⁶⁷

Calcium is probably the most widely recognized nutrient used for the prevention of osteoporosis in postmenopausal women. Interestingly, it has little effect on bone loss in the 5 years immediately after menopause.⁶⁸⁻⁷¹ After this period however; calcium supplementation has a significant benefit on bone loss. In fact, researchers estimate that **30 years of continuous calcium supplementation after menopause will result in a 10% improvement in bone mineral density, and a 50% overall reduction in fracture rates**, compared with women who do not take calcium supplements.⁶⁹

High phosphorous beverages, and specifically soft drinks, can cause a severe calcium imbalance, making supplementation with this mineral very important, particularly in children. Soda consumption among children and adolescents rose 41percent in the time period of 1989-1991 compared to 1994- 1995.⁷² Accordingly, in a study of 127 children aged 8-16, 39 percent of the female children had a history of bone fracture and consumed larger amounts of cola than those without a history of bone fracture.⁷³

When supplementing with calcium, it is important to also maintain healthy levels of **magnesium** in the diet, as an increase in calcium intake can lead to unfavorable calcium to magnesium ratios. Magnesium also plays an essential role in preventing

osteoporosis in both men and women.⁷⁴ In menopausal women, for example, a deficiency in this mineral is linked to osteoporosis, while supplementation with magnesium reduces bone loss in men.⁷⁵ **Vitamin D** is another essential nutrient that functions to keep bones strong and healthy, particularly in post menopausal women.^{76, 77,79} In a group of women with osteoporosis hospitalized for hip fractures, 50 percent were found to have signs of vitamin D deficiency, while treatment with vitamin D supplementation was shown to significantly prevent the disease.⁷⁸

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The benefits of vitamin D on bone health are dependent on the presence of proper amounts of **boron**, which helps to convert the vitamin to a more useable form.⁸⁰⁻⁸³ Human studies show that boron actually reduces calcium loss in bones, and activates and increases estrogen levels, which are associated with bone loss. In a clinical study done at the USDA,⁸⁴ boron was administered to postmenopausal women at high risk for osteoporosis. The results showed that boron promoted an estrogenic effect and improved calcium and magnesium metabolism. Another study confirmed these results, finding that boron reduced calcium and magnesium loss from the body.⁸⁵

Pregnancy and Pregnancy-related Complications

Phytonutrients, vitamins and minerals play a significant role in addressing common symptoms associated with pregnancy, in addition to preventing serious pregnancy-related complications.

Hemorrhaging

Pregnant women at-risk for hemorrhaging, for example, may find benefit from chlorophyll-rich green vegetables such as **spinach** and **alfalfa**. Chlorophyll contains the vegetable-derived bloodclotting factor, phylloquinone (a form of **vitamin K**),⁸⁶ that protects the mother from hemorrhaging during labor and also protects newborn infants from intracranial hemorrhage.⁸⁸⁻⁹⁰

The risk of intracranial hemorrhage due to a **vitamin K** deficiency is particularly high for premature neonates, affecting 35% to 45% of all neonates weighing under 1500 grams.⁸⁷ Vitamin K deficiency is a concern for healthy neonates as well, because they naturally have lower levels of blood clotting factors, making them prone to excessive bleeding, especially in the brain. In a study of 383 pregnant women in Japan, researchers demonstrated that vitamin K crosses the placental barrier and significantly protects infants from hemorrhage. Pregnant women who supplement their diet with vitamin K also improve prothrombin levels and prothrombin times (important for preventing too much blood loss) in their babies.^{89, 90} Accordingly, maternal **vitamin K** supplementation and consumption of a diet or supplements rich in natural sources of vitamin K (such as chlorophyll-rich **spinach and alfalfa**) are beneficial for pregnant women. In addition to being a source of vitamin K, chlorophyll is an antagonist of guanidine, a toxin released into the blood because of burns, trauma (including pregnancy-associated trauma), or muscle fatigue. Its purpose is to help eliminate dead or defective cells. This is a beneficial and natural phenomenon to the extent that it eliminates bad cells. However, a pregnant woman with a history of miscarriage and/or threatened abortion may be predisposed to producing an excess of guanidine that can ultimately cause more damage than repair.⁹¹⁻⁹⁴

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Preeclampsia

Preeclampsia, which occurs in 4-6% of all deliveries, is an important cause of morbidity and mortality in expecting mothers.⁹⁵ Women with preeclampsia typically miscarry or deliver prematurely and have lower birth weight babies than women without the disorder.⁹⁵ The disease is associated with an increase in harmful free radical production, and a decrease in body stores of protective antioxidants such as vitamin E. **Vitamin E** improves oxygen transport to maternal tissues, replaces antioxidant-loss, and prevents preeclampsia in at risk women.⁹⁶ Appropriately, the chemical name for vitamin E, tocopherol comes from the Greek words *tokos* meaning offspring and *phero* meaning to bring forth.

The addition of vitamin C to vitamin E further protects a pregnant woman from experiencing preeclampsia. In a large, double-blind, placebo-controlled trial, 283 pregnant women at risk for preeclampsia were randomly assigned to receive either vitamin C and vitamin E, or placebo from 16-22 weeks of gestation.⁹⁷ At the time of delivery, those women that took the vitamin supplements significantly reduced their risk of preeclampsia as compared to those women who did not. More recently, researchers⁹⁸ examined 30 healthy pregnant women and 30 preeclamptic pregnant women for plasma levels of **vitamins C and E** and found that preeclamptic women had significantly lower plasma levels of vitamin C and vitamin E. This study concluded that consuming **vitamins C and E** would help to prevent pregnancy-related preeclampsia.

Calcium supplementation has also been shown to reduce a woman's risk of preeclampsia, particularly if she is known to be deficient in this nutrient.⁹⁹⁻¹⁰¹ Calcium can also reduce leg cramps in women during the second half of pregnancy.¹⁰²

Other Pregnancy-Related Complications

Vitamin A reduces pregnancy related complications as well. In one trial, vitamin A acetate supplements taken weekly before, during and after pregnancy by malnourished women reduced pregnancy-related death by 40%.¹⁰³ This vitamin also reduces the occurrence of pregnancy-related night blindness, post-partum diarrhea and fever in malnourished women.^{104, 105}

The B vitamins also play a role in maintaining a healthy pregnancy. **Vitamin B6** reduces pregnancy-induced nausea and vomiting^{106,107} and **folic acid** reduces the risk of neural tube birth defects.¹⁰⁸⁻¹¹⁰ Interestingly, research identified a solid relationship between folic acid deficiencies and birth defects as early as 1965.^{111,112} The United States Public Health Service failed to share this critical knowledge with the country until 1992, finally recommending that all women of childbearing age, capable of becoming pregnant, consume 400 g of folic acid per day.¹¹¹ *It took the scientific community almost 30 years to accept that a nutrient deficiency might cause a gross distortion in human neuronal development and come forward with the information. In light of this fact, one wonders if we should wait for the scientific community to analyze and agree upon all nutrient-related research before we act to insure that our family and loved ones are getting the essential nutrients they need for optimal health.*

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Oral Contraceptives and Nutrient Depletion

Oral contraceptives (OCs) can deplete the body of essential vitamins and minerals.

Table 2 outlines

some ways in which OCs may interfere with nutrient metabolism.¹¹³

Table 2. Effects of OCs on metabolism of specific nutrients.¹¹³

Nutrient Effect of OCs

Folate Reduces the body's ability to absorb folate

Vitamin B12 Significantly reduces B12 levels in the serum

Vitamin C Reduces the body's ability to absorb and properly utilize vitamin C

Vitamin K Increases vitamin K levels in the blood

Zinc Decreases absorption, and increases the urinary excretion of zinc

Iron Increases iron levels by reducing the amount of blood loss during menstruation

Copper Decreases copper levels in the blood

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Overview: Nutritive Options for Women

Following is a reference guide that highlights the key nutrients that are associated with the prevention and/or treatment of prevalent health challenges that women face today, as described throughout this section.

General Support *Soy protein, multiple vitamin/mineral supplement*

Breast Cancer ²¹⁻⁵⁴ *Soy protein, alfalfa, vitamin A, vitamin C, vitamin E, selenium and mixed tocopherols*

Heart Disease ⁵⁵ *Soy protein*

Menopause ⁵⁵⁻⁵⁷ *Soy protein*

Oral Contraceptives ¹¹³ *Folate, vitamin B12, vitamin C, zinc and copper*

Osteoporosis ⁶⁴⁻⁸⁵ *Soy protein, alfalfa, boron, calcium, magnesium vitamin D and vitamin K*

PMS ⁵⁸⁻⁶³ *Grape seed extract (in Shaklee Vitamin E), calcium, vitamin B6 (B-Complex), vitamin E*

Pregnancy ⁸⁶⁻¹¹² *Alfalfa, spinach, calcium, folate (B-Complex), vitamin B6, vitamin C, vitamin E and vitamin K (in Alfalfa and the Vita-Lea)*

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References

1. Greenlee RT, Murray T, Bolden S, Wingo PA. Cancer statistics, 2000. *CA Cancer J Clin* 2000 Jan-Feb;50(1):7-33.
2. Nogueira SM, Appling SE. Breast cancer: genetics, risks, and strategies. *Nurs Clin North Am* 2000 Sep;35(3):663-9.
3. Castelo-Branco C, Figueras F, Martinez de Osaba MJ, Vanrell JA. Facial wrinkling in postmenopausal women. Effects of smoking status and hormone replacement therapy. *Maturitas* 1998 May 20;29(1):75-86.
4. Rodriguez C, Calle EE, Coates RJ, Miracle-McMahill HL, Thun MJ, Heath CW Jr. Estrogen replacement therapy and fatal ovarian cancer. *Am J Epidemiol* 1995 May 1;141(9):828-35.
5. Chen CL, Weiss NS, Newcomb P, Barlow W, White E. Hormone replacement therapy in relation to breast cancer. *JAMA* 2002 Feb 13;287(6):734-41.
6. Schairer C, Lubin J, Troisi R, Sturgeon S, Brinton L, Hoover R. Menopausal estrogen and estrogen-progestin replacement therapy and breast cancer risk. *JAMA* 2000 Jan 26;283(4):485-91.
7. Verma SP, Goldin BR, Lin PS. The inhibition of the estrogenic effects of pesticides and environmental chemicals by curcumin and isoflavonoids. *Environ Health Perspect* 1998 Dec;106(12):807-12.
8. Dewailly E, Dodin S, Verreault R, Ayotte P, Sauve L, Morin J, Brisson J. High organochlorine body burden in women with estrogen receptor-positive breast cancer. *J Natl Cancer Inst* 1994 Feb 2;86(3):232-4.
9. Falck F Jr, Ricci A Jr, Wolff MS, Godbold J, Deckers P. Pesticides and polychlorinated biphenyl residues in human breast lipids and their relation to breast cancer. *Arch Environ Health* 1992 Mar-Apr;47(2):143-6.
10. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst* 1993 Apr 21;85(8):648-52.
11. Krieger N, Wolff MS, Hiatt RA, Rivera M, Vogelstein J, Orentreich N. Breast cancer and serum organochlorines: a prospective study among white, black, and Asian women. *J Natl Cancer Inst* 1994 Apr 20;86(8):589-99.
12. Hunter DJ, Kelsey KT. Pesticide residues and breast cancer: the harvest of a silent spring? *J Natl Cancer Inst* 1993 Apr 21;85(8):598-9.
13. Moysich KB, Ambrosone CB, Vena JE, Shields PG, Mendola P, Kostyniak P, Greizerstein H, Graham S, Marshall JR, Schisterman EF, Freudenheim JL. Environmental organochlorine exposure and postmenopausal breast cancer risk. *Cancer Epidemiol Biomarkers Prev* 1998 Mar;7(3):181-8.
14. Lopez-Carrillo L, Blair A, Lopez-Cervantes M, Cebrian M, Rueda C, Reyes R, Mohar A, Bravo J. Dichlorodiphenyltrichloroethane serum levels and breast cancer risk: a case-control study from Mexico. *Cancer Res* 1997 Sep 1;57(17):3728-32.
15. van t Veer P, Lobbezoo IE, Martin-Moreno JM, Guallar E, Gomez-Aracena J, Kardinaal AF, Kohlmeier L, Martin BC, Strain JJ, Thamm M, van Zoonen P, Baumann BA, Huttunen JK, Kok FJ. DDT (dicophane) and postmenopausal breast cancer in Europe: case-control study. *BMJ* 1997 Jul 12;315(7100):81-5.
16. Laden F, Hankinson SE, Wolff MS, Colditz GA, Willett WC, Speizer FE, Hunter DJ. Plasma organochlorine levels and the risk of breast cancer: an extended follow-up in the Nurses Health Study. *Int J Cancer* 2001 Feb 15;91(4):568-74.
17. Wolff MS, Toniolo PG, Lee EW, Rivera M, Dubin N. Blood levels of organochlorine residues and risk of breast cancer. *J Natl Cancer Inst* 1993 Apr 21;85(8):648-52.
18. Verma SP, Goldin BR. Effect of soy-derived isoflavonoids on the induced growth of MCF-7 cells by estrogenic environmental chemicals. *Nutr Cancer* 1998;30(3):232-9.
19. Wolmark N, Dunn BK. The role of Tamoxifen in breast cancer prevention: issues sparked by the NSABP Breast Cancer Prevention Trial (P-1). *Ann N Y Acad Sci* 2001 Dec;949:99-108.
20. Vink-van Wijngaarden T, Pols HA, Buurman CJ, van den Bermd GJ, Dorssers LC, Birkenhager JC, van Leeuwen JP. Inhibition of breast cancer cell growth by combined treatment with vitamin D3 analogues and Tamoxifen. *Cancer Res* 1994 Nov 1;54(21):5711-7.
21. Adolph WH, Kiang PC. The nutritional value of soy bean products. *China Med J* 34:268-275, 1920.
22. Messina M, Persky V, Setchell KDR, Barnes S. Soy intake and cancer risk: A review of the in vitro and in vivo data. *Nutr Cancer* 1994; 21:113- 131.
23. Tham DM, Gardner CD, Haskell WL. Potential health benefits of dietary phytoestrogens: A review of the clinical, epidemiological, and mechanistic evidence. *J Clin End & Metab* 1998;83:2223-2235.
24. Mazur WM, Duke JA, Wahala K, Rasku S, Adlercreutz H. Isoflavonoids and lignans in legumes: Nutritional and health aspects in humans. *J Nutr Biochem* 1998;9:193-200.
25. Peterson G, Barnes S. Genistein inhibition of the growth of human breast cancer cells: Independence from estrogen receptors and multi- drug resistance gene product. *Biochem Biophys Res Commun* 1991;179:661-667.
26. Traganos F, Ardelt B, Halko N, Bruno S, Darzynkiewicz Z. Effects of genistein on the growth and cell cycle progression of normal human lymphocytes and human leukemic MOLT-4 and HL-60 cells. *Cancer Res* 1992;52:6200-6208.
27. Barnes S, Grubbs C, Setchell KDR, Carlson J. Soybeans inhibit breast tumor in models of breast cancer. In: Pariza MW, Aeschbacher H-U, Felton JS, Sato S, Eds. *Mutagens and Carcinogens in the Diet*. New York: Wiley-Liss, pp239-253, 1990.

28. Hawrylewicz EJ, Huang HH, Blair Vrh. Dietary soybean isolate and methionine supplementation affect mammary tumor progression in rats. *J Nutr* 1991;121:1693-1698.
29. Mazur WM, Duke JA, Wahala K, Rasku S, Adlercreutz H. Isoflavonoids and lignans in legumes: Nutritional and health aspects in humans. *J Nutrit Biochem* 1998;9:193-200.
30. Harborne JB. Nature, distribution, and function of plant flavonoids. *Prog Clin Biol Res* 213:15-24, 1986.
31. Parniske M, Ahlbom B, Werner D. Isoflavonoid-inducible resistance to the phytoalexin glyceollin in soybean rhizobia. *J Bact* 1991;173:3432- 3439.
32. Coward L, Barnes NC, Setchell KDR, Barnes S. The antitumor isoflavones, genistein and daidzein, in soybean foods of American and Asian diets. *J Agric Food Chem* 1993;41:1961-1967.
33. Harborne JB, Mabry TJ. *The Flavonoids*. London: Chapman & Hall, 1988.
34. Baker ME. Evolution of regulation of steroid-mediated intercellular communication in vertebrates: Insights from flavonoids, signals that mediate plant-rhizobia symbiosis. *J Steroid Biochem Mol Biol* 1992;41:301-310.
35. Smit G, Puvanesarajah V, Carlson RW, Barbour WM, Stacey G. Bradyrhizobium japonicum nodd DI can be specifically induced by soybean flavonoids that do not induce the nod YABCSUU operon. *J Biol Chem* 1992;267:310.-318.
36. Barbour WM, Hattermann DR, Stacey G. Chemotaxis of Bradyrhizobium japonicum to soybean exudates. *Appl Environ Microbiol* 1991;57:2635-2639.
37. Cunningham S, Kollyneyer WD, Stacey G. Chemical control of inter strain competition for soybean nodulation by Bradyrhizobium japonicum *Appl Environ Microbiol* 1991;57:1886-1892.
38. Lerouge P, Roche P, Faucher C, Maillet F, Truchet G, Prome J-C, Dénarié J. Symbiotic host-specificity of Rhizobium meliloti is determined by a sulphated and acetylated glucosamine oligosaccharide signal. *Nature (London)* 1990; 344:781-788.
39. Lu LJ, Anderson KE, Grady JJ, et al. Decreased ovarian hormones during a soya diet: implications for breast cancer prevention. *Cancer Res* 2000;60:4112-21.
40. Xu X, Duncan AM, Wangen KE, Kurzer MS. Soy consumption alters endogenous estrogen metabolism in postmenopausal women. *Cancer Epidemiol Biomarkers Prev* 2000;9:781-6.
41. Nakagawa H, Yamamoto D, Kiyozuka Y, et al. Effects of genistein and synergistic action in combination with eicosapentaenoic acid on the growth of breast cancer cell lines. *J Cancer Res Clin Oncol* 2000;126:448-54.
42. Messina M, Barnes S, Setchell KD. Phyto-oestrogens and breast cancer. *Lancet* 1997;350:971-2.
43. Harborne JB, Mabry TJ. *The Flavonoids*. London: Chapman & Hall, 1988.
44. Chung WY, Lee JM, Lee WY, Surh YJ, Park KK. Protective effects of hemin and tetrakis(4-benzoic acid)porphyrin on bacterial mutagenesis and mouse skin carcinogenesis induced by 7,12-dimethylbenz[a]anthracene. *Mutat Res* 2000 Dec 20;472(1-2):139-45.
45. Hayatsu H, Negishi T, Arimoto S, Hayatsu T. Porphyrins as potential inhibitors against exposure to carcinogens and mutagens. *Mutat Res* 1993 Nov;290(1):79-85.
46. Sarkar D, Sharma A, Talukder G. Chlorophyll and chlorophyllin as modifiers of genotoxic effects. *Mutat Res* 1994 Dec;318(3):239-47.
47. Yun CH, Jeong HG, Jhoun JW, Guengerich FP. Non-specific inhibition of cytochrome P450 activities by chlorophyllin in human and rat liver microsomes. *Carcinogenesis* 1995 Jun;16(6):1437-40.
48. Zhang S, Hunter DJ, Forman MR, et al. Dietary carotenoids and vitamins A, C, and E and risk of breast cancer. *J Natl Cancer Inst* 1999;91(6):547-56.
49. Turley JM, Ruscetti FW, Kim SJ, Fu T, Gou FV, Birchenall-Roberts MC. Vitamin E succinate inhibits proliferation of BT-20 human breast cancer cells: increased binding of cyclin A negatively regulates E2F transactivation activity. *Cancer Res* 1997 Jul 1;57(13):2668-75.
50. Schwenke DC. Does lack of tocopherols and tocotrienols put women at increased risk of breast cancer? *J Nutr Biochem* 2002 Jan;13(1):2-20.
51. Clark LC, Combs GF Jr, Turnbull BW, et al. Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. *JAMA* 1996;276:1957-63.
52. Clark LC, Dalkin B, Krongrad A, et al. Decreased incidence of prostate cancer with selenium supplementation: results of a double-blind cancer prevention trial. *Br J Urol* 1998;81:730-4.
53. Mark SD, Wang W, Fraumeni JF Jr, et al. Do nutritional supplements lower the risk of stroke or hypertension? *Epidemiology* 1998;9:9-15.
54. Rayman MP. The importance of selenium to human health. *Lancet* 2000;356:233-41.
55. Lissen, L. W. and J. P. Cooke. Phytoestrogens and cardiovascular health. *J Am Coll Cardiol* 2000;35(6): 1403-1410.
56. Nestel PJ, Pomeroy S, Kay S, Komesaroff P, Behrsing J, Cameron JD, West L. Soy isoflavones improve systemic arterial compliance but not plasma lipids in menopausal and perimenopausal women. *Arterioscler Thromb Vasc Biol* 1997;17(12): 3392-3398.
57. Arena S, Rappa C, Del Frate E, Cenci S, Villani C. A natural alternative to menopausal hormone replacement therapy. *Phytoestrogens. Minerva Ginecol* 2002 Feb;54(1):53-7.
58. Schwitters B and Masquelier J. *OPC in practice: The hidden story of proanthocyanidins, nature's most powerful and patented antioxidant*. Rome, Alfa Omega Editrice, 1995.
59. Thys-Jacobs S. Micronutrients and the premenstrual syndrome: The case for calcium. *J Am Coll Nutr* 2000;19(2):220-7.
60. Bendich A. The potential for dietary supplements to reduce premenstrual syndrome (PMS) symptoms. *J Am Coll Nutrition* 2000;19:3-12.
61. Wyatt KM, Dimmock PW, Jones PW, O'Brien PM. Efficacy of vitamin B6 in the treatment of premenstrual syndrome. *BMJ* 1999;318:1375-81.
62. London RS, Murphy L, Kitlowski KE, Reynolds MA. Efficacy of alpha-tocopherol in the treatment of the premenstrual syndrome. *J Reprod Med* 1987;32:400-4.
63. London RS, Sundaram GS, Murphy L, Goldstein PJ. The effect of alpha-tocopherol on premenstrual symptomatology: a double-blind study. *J Am Coll Nutr* 1983;2:115-22.
64. Draper CR, Edel MJ, Dick IM, Randall AG, Martin GB, Prince RL. Phytoestrogens reduce bone loss and bone resorption in oophorectomized rats. *J Nutr* 1997 Sep;127(9):1795-9.

65. Feskanich D, Weber P, Willett WC, et al. Vitamin K intake and hip fractures in women: a prospective study. *Am J Clin Nutr* 1999;69(1):74-9.
66. Knapen MH, Hamulyak K, Vermeer C. The effect of vitamin K supplementation on circulating osteocalcin (bone Gla protein) and urinary calcium excretion. *Ann Intern Med* 1989;111:1001-5.
67. Knapen MH, Jie KS, Hamulyak K, Vermeer C. Vitamin K-induced changes in markers for osteoblast activity and urinary calcium loss. *Calcif Tissue Int* 1993 Aug;53(2):81-5.
68. Heaney RP. Calcium, dairy products and osteoporosis. *J Am Coll Nutr* 2000;19(2):83S-99S.
69. Chiu KM. Efficacy of calcium supplements on bone mass in postmenopausal women. *J Gerontol Med Sci* 1999;54A(6):M275-80.
70. Deal C. Can calcium and vitamin D supplementation adequately treat most patients with osteoporosis? *Cleve Clin J Med* 2000;67(10):696-8.
71. Kanis JA. The use of calcium in the management of osteoporosis. *Bone* 1999;24(4):279-90.
72. Wyshak G. Teenaged girls, carbonated beverage consumption, and bone fractures. *Arch Pediatr Adolesc Med* 2000 Jun;154(6):610-13.
73. Ballew C, Kuester S, Gillespie C. Beverage choices affect adequacy of children's nutrient intakes. *Arch Pediatr Adolesc Med* 2000 Nov;154(11):1148-52.
74. Dreosti IE. Magnesium status and health. *Nutr Rev* 1995 Sep;53(9 Pt 2):S23-7.
75. Dimai HP, Porta S, Wirnsberger G, Lindschinger M, Pamperl I, Dobnig H, Wilders-Truschign M, Lau KH. Daily oral magnesium supplementation suppresses bone turnover in young adult males. *J Clin Endocrinol Metab* 1998 Aug;83(8):2742-8.
76. LeBoff MS, Kohlmeier L, Hurwitz S, Franklin J, Wright J, Glowacki J. Occult vitamin D deficiency in postmenopausal US women with acute hip fracture. *J Am Med Assoc* 1999;281:1505-1511.
77. Dawson-Hughes B, Harris SS, Krall EA, Dallal GE, Falconer G, Green CL. Rates of bone loss in postmenopausal women randomly assigned to one of two dosages of vitamin D. *Am J Clin Nutr* 1995;61:1140-45.
78. Reid IR. The roles of calcium and vitamin D in the prevention of osteoporosis. *Endocrinol Metab Clin North Am* 1998;27:389-98.
79. Reid IR. Therapy of osteoporosis: Calcium, vitamin D, and exercise. *Am J Med Sci* 1996;312:278-86.
80. Naghii MR, Samman S. Role of boron in nutrition and metabolism. *Prog Food Nutr Sci*. 1993;17:331-49.
81. Hunt CD, Herbel JL. Effects of dietary boron on calcium and mineral metabolism in the Streptozotocin-injected, vitamin D3-deprived rat. *Magn Trace Elem*. 1991-2;10:387-408.
82. Volpe SL, Taper LJ, Meacham S. The relationship between boron and magnesium status and bone mineral density in the human: a review. *Magn Res*. 1003;6:291-296.
83. Naghii MR, Wall L, Samman S. The boron content of selected foods and the estimation of its daily intake among free-living subjects. *J Amer Col Nutrit*. 1996;15(6):614-619.
84. Nielsen FH, Hunt CD, Mullen LM, Hunt JR. Effect of dietary boron on mineral, estrogen and testosterone metabolism in postmenopausal women. *FASEB J*. 1987;1:394-397.
85. Nielsen FH. Biochemical and physiological consequences of boron deprivation in humans. *Environ Health Perspect*. 1994;102(suppl 7):59-63.
86. Igarashi, O. 1993. Vitamin K. *Nippon Rinsho* 51(4): 910-918.
87. Morales WJ, Angel JL, O'Brien WF, Knuppel RA, Marsalisi F. The use of antenatal vitamin K in the prevention of early neonatal intraventricular hemorrhage. *Am J Obstet Gynecol* 1988;159(3): 774-779.
88. Thorp JA, Gaston L, Caspers DR, Pal ML. Current concepts and controversies in the use of vitamin K. *Drugs* 1995;49(3): 376-387.
89. Owen, G. M. Use of vitamin K1 in pregnancy. *Am J Obstet Gynecol* 1967;99: 368-373.
90. Deblay MF, Vert P, Andre M, Marchal F. Transplacental vitamin K prevents hemorrhagic disease of infant of epileptic mother. *Lancet* 1982;1: 1247.
91. Rairigh RL, Parker TA, Ivy DD, Kinsella JP, Fan ID, Abman SH. Role of inducible nitric oxide synthase in the pulmonary vascular response to birth-related stimuli in the ovine fetus. *Circ Res* 2001;13;88(7):721-6.
92. Nakatsuka M, Asagiri K, Noguchi S, Habara T, Kudo T. Nafamostat mesilate, a serine protease inhibitor, suppresses lipopolysaccharide-induced nitric oxide synthesis and apoptosis in cultured human trophoblasts. *Life Sci* 2000;67(10):1243-50.
93. Farina M, Ribeiro ML, Ogando D, Gimeno M, Franchi AM. IL1alpha augments prostaglandin synthesis in pregnant rat uteri by a nitric oxide mediated mechanism. *Prostaglandins Leukot Essent Fatty Acids* 2000;62(4):243-7.
94. Athanassakis I, Aifantis I, Ranella A, Giouremou K, Vassiliadis S. Inhibition of nitric oxide production rescues LPS-induced fetal abortion in mice. *Nitric Oxide* 1999;3(3): 216-224.
95. Poston, L. and L. C. Chappell. Is oxidative stress involved in the aetiology of preeclampsia? *Acta Paediatr Suppl* 2001;90(436): 3-5.
96. Gratacos E, Casals E, Deulofeu R, Gomez O, Cararach V, Alonso PL, Fortuny A. Serum and placental lipid peroxides in chronic hypertension during pregnancy with and without superimposed preeclampsia. *Hypertens Pregnancy* 1999;18(2): 139-146.
97. Chappell LC, Seed PT, Briley AL, Kelly FJ, Lee R, Hunt BJ, Parmar K, Bewley SJ, Shennan AH, Steer PJ, Poston L. Effect of antioxidants on the occurrence of pre-eclampsia in women at increased risk: A randomised trial. *Lancet* 1999;354(9181): 810-816.
98. Kharb, S. Vitamin E and C in preeclampsia. *Eur J Obstet Gynecol Reprod Biol* 2000;93(1): 37-39.
99. Purwar M, Kulkarni H, Motghare V, Dhole S. Calcium supplementation and prevention of pregnancy induced hypertension. *J Obstet Gynaecol Res* 1996;22(5):425-30.
100. Crowther CA, Hiller JE, Pridmore B, et al. Calcium supplementation in nulliparous women for the prevention of pregnancy-induced hypertension, preeclampsia and preterm birth: an Australian randomized trial. *FRACOG and the ACT Study Group. Aust N Z J Obstet Gynaecol*, 1999;39:12-8.
101. Power ML, Heaney RP, Kalkwarf HJ, et al. The role of calcium in health and disease. *Am J Obstet Gynecol* 1999;181:1560-9.
102. Hammar M, Larsson L, Tegler L. Calcium treatment of leg cramps in pregnancy. Effect on clinical symptoms and total serum and ionized serum calcium concentrations. *Acta Obstet Gynecol Scand* 1981;60:345-7.
103. West KP Jr, Katz J, Khattry SK, et al. Double-blind cluster, randomised trial of low dose supplementation with vitamin A or beta carotene on mortality related to pregnancy in Nepal. *The NNIPS-2 Study Group. BMJ* 1999;318(7183):570-5.
104. Christian P, West KP, Khattry SK, et al. Vitamin A or beta-carotene supplementation reduces symptoms of illness in pregnant and lactating Nepali women. *J Nutr* 2000;130:2675-82.

105. Christian P, West KP Jr, Khattry SK, et al. Vitamin A or beta-carotene supplementation reduces but does not eliminate maternal night blindness in Nepal. *J Nutr* 1998;128(9):1458-63.
106. Vutyavanich T, Wongtra-ngan S, Ruangsri R. Pyridoxine for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled trial. *Am J Obstet Gynecol* 1995;173(3 Pt 1):881-4.
107. Sahakian V, Rouse D, Sipes S, et al. Vitamin B6 is effective therapy for nausea and vomiting of pregnancy: a randomized, double-blind, placebo-controlled study. *Obstet Gynecol* 1991;78(1):33-6.
108. Micromedex Healthcare Series. Englewood, CO: MICROMEDEX Inc.
109. McKevey GK, ed. AHFS Drug Information. Bethesda, MD: American Society of Health-System Pharmacists, 1998.
110. US Food and Drug Administration, Center for Food Safety, and Applied Nutrition, Office of Nutritional Products, Labeling, and Dietary Supplements. Letter regarding dietary supplement health claim for folic acid with respect to neural tube defects. 2000. <http://vm.cfsan.fda.gov/~dms/ds-ltr7.html>. (Accessed 16 October 2000).
111. Aubard Y, Piver P, Chinchilla AM, Baudet JH. Folates and the neural tube. Review of the literature. *J Gynecol Obstet Biol Reprod* 1997;26(6):576-84.
112. Grant, H. C.. Folate deficiency and neurological disease. *Lancet* 1965;2(7416): 763-767.
113. Tyrer LB. Nutrition and the pill. *J Reprod Med* 1984 Jul;29(7 Suppl):547-50.