Special Report

How To Find Your Way Out of the Hormone Trap

What are women to do now that hormone replacement therapy has no proven health benefits and slightly increases risks for disease?

By Bill Sardi

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"The entire picture of routine postmenopausal estrogen therapy is in a state of complete confusion. We must proceed with circumspection and caution. We need less passion, fewer hypotheses, and more facts." -- GS Berger and WC Fowler Jr, Journal of Reproductive Medicine, April, 1977

Introduction

- Hormone replacement therapy, widely prescribed for decades, is now falling into disfavor. 5000 women each day join the ranks of the 40 million American women already in menopause. Only a small percentage of women continue to take HRT, mostly for symptoms of hot flashes and night sweats and *"retaining beauty"* rather than any health benefits. What now for these women? How will they avoid bone loss, breast cancer, uterine cancer?

- With millions of dollars spent on research, there is still no preventive measure for breast cancer, only treatment after it has been diagnosed, which consists of estrogen-blocking tamoxifen after conventional surgical, chemo or radiation therapy. But tamoxifen itself promotes endometrial cancer and turns on every woman and promotes breast cancer so it cannot be taken for more than five years. Has the wonder drug tamoxifen had its day?

- New aromatase inhibitor drugs, which stop the production of estrogen in fatty tissues, rather than block its entry into cells like tamoxifen, are being widely studied because they prolong tumor remissions more so than tamoxifen. But in the long run aromatase inhibitors only delay the inevitable for women with breast cancer. They don't reduce mortality rates and they may accelerate bone loss and mental depression.

- This pushes American women into the unguided use of phytoestrogens, plant, seeds, beans and herbs that have estrogen-like molecules. But are they any safer or effective?

- Why does crushed whole flaxseed exhibit unusual health benefits for the heart, kidneys, bones, prostate and breast tissues? What is it that whole flaxseeds provide that other herbal phytoestrogens do not, which produces such incredible health benefits? Read the following three-part report.

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PART I: Hormone Replacement Therapy

So much has been said about hormone replacement therapy and the state of breast cancer treatment, yet so many questions still remain to be answered. This limited report will never be able to answer all the remaining questions American women have about supplemental hormones. But it may provide a clearer picture of what is really going on. And it may, for the first time, give interested readers a valid scenario for the prevention of breast cancer altogether.

For almost three decades American women have had estrogen and progesterone, pharmaceutically extracted from horse mare urine, prescribed for the change of life, first to calm the hot flashes and mood issues associated with the change of life, and second to allegedly improve bone health, reduce cardiovascular risk and inhibit the onset of breast cancer.

In 1976 Consumer Reports indicated the use of hormone replacement had almost tripled from 1965 to 1976 and the incidence of cancer rose in women over 50 were in high-socioeconomic groups, the groups most likely to use estrogen therapy. Estrogen therapy was supposed to be restricted solely to women with vaginal shrinkage or a few other narrow indications. Consumer Reports said: *"Earlier reports suggested estrogen might protect against breast cancer; most recent studies suggest the opposite."* [Consumer Reports 41: 642-45, 1976] Doctors weren't there to step into the breech and protect American women. They acquiesced to the pharmaceutical companies because hormone replacement therapy filled their appointment books and the greatest yet-to-be-proven medical experiment was underway.

Phytoestrogens Dismissed

In the meantime, non-prescription, plant-based estrogens (called phytoestrogens) were cast aside and mis-characterized. A 1978 report said phytoestrogens *"can markedly enhance tumor cell proliferation."* [Endocrinology 103: 1860-67, 1978] Of course, this conclusion was drawn from test-tube studies where cells were flooded with plant estrogens rather than being given in doses commonly found in raw plant-food diets. One of the biases revealed in animal and test-tube studies is that they may utilize very high, if not unobtainable, levels of plant estrogens which would then induce the same side effects as estrogen. In one such study, 300 milligrams of black cohosh per kilogram (2.2 pounds) of body weight was given to rodents. That is equivalent to nearly 22,000 milligrams of black cohosh in an adult human, or 1100 black cohosh pills. [J Medicinal Food 4: 171-78, 2001]

So doctors proceeded to prescribe millions of American women pharmaceutical-grade estrogen, and while they conceded estrogen replacement increased the risk of endometrial cancer, this risk was dismissed by prescribing progesterone and advising women on hormone replacement to come in for frequent checkups. [Postgraduate Medicine 62: 73-79, 1977] All the while, doctors were saying food supplements like flaxseed, black cohosh and red clover were unproven, even *"snake oil."*

The Bomb Drops on Hormone Replacement Therapy

For decades doctors continued to prescribe hormones to postmenopausal women under the assumption they improved health for postmenopausal women. But after years of customary use it was time for a scientific review. Did hormone replacement therapy really improve health?

The bomb dropped in July of 2002 with reports that hormone replacement slightly increased the risk of breast cancer and cardiovascular events like strokes. At the time the news report hit the American public, 6 million women were taking these prescribed hormones.

With the news that hormone replacement therapy posed health risks, doctors were so overwhelmed by phone calls from millions of women that they simply shut off their office phones.

Then just 11 months later American women were hearing news stories about hormone replacement therapy increasing their risk for being mentally demented in their later years of life. Among 2229 postmenopausal women who took estrogen plus progesterone replacement pills beginning in 1996

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thru 2002, 40 were diagnosed with probable dementia compared with just 21 in a group of 2303 women who did not use hormone pills. The relative risk doubled among the hormone users. The absolute risk was low, 1.8 percent among hormone users, just 0.9 percent among non-users. Among the 6 million American women now taking hormone replacement therapy this could increase the number of cases of Alzheimer's disease by about 13,800 annually. [J Am Med Assoc 289: 2651-62, 2003] The increased risk was still small but the point had been made. A small increased risk weighed against no potential benefits meant the widespread use of hormone pills had to be re-evaluated. In March of 2003 the FDA approved a lower dose of Prempro, the most popular hormone replacement pill, due to concerns over side effects. Imagine trying to be a sales representative for Wyeth Labs, the producer of Prempro. By May of 2003 postmenopausal women were being told still more bad news.

Here is what Judy Siegel-Itzkovich of the Jerusalem Post had to say about hormone replacement therapy. It can't be said any better than this: *"Middle-aged women should think twice before taking combined progestin-estrogen pills to alleviate their hot flashes, night sweats, and other disturbing menopausal symptoms, according to an analysis of data from last year's US Woman's Health Institute study on the effects of hormone replacement therapy. What pharmaceutical companies have pushed for decades as a 'preventive fountain of youth' for menopausal women, now seems to increase the risk of breast cancer even when taken for only one year."* [Jerusalem Post June 25, 2003; J Am Med Assoc 289: 3243-53, 3254-63, 2003]

With the negative scientific studies, the use of estrogen therapy in Canada has dropped an astonishing 32 percent from 2001 to 2002. [J Am Med Assoc 289: 3241-42, 2003] But statistically the increased risk for breast cancer was small, and some women simply didn't want to face a return to all those hot flashes and mood problems. So a few million women keep taking the pills. And for good reason, at least in the minds of those who take hormone replacement. As a report in New York Times so aptly said, *"Some women said they could never give up the pills, not because they needed them for severe menopause symptoms but because they were convinced that estrogen prevented wrinkles or because it staved off mental fogginess."* [New York Times July 5, 2003]

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Women have been conditioned to accept menopause as a period of life where life-long medication with hormones is normal. Although there have been many warnings against the use of hormone replacement, *"they have either been ignored or trivialized."* [Int J Health Services 31: 769-92, 2001] Not counting the cost of doctor's office visits, hormone replacement pills cost nearly $2 billion in the USA annually.

Even more bombs dropped on hormone replacement therapy (HRT) in August of 2003. First the New England Journal of Medicine reported after five years that HRT (estrogin + progestin) ncreased the risk of a heart attack by a relative 81 percent. [New Eng J Med 239: 523-34, 2003] In the same week the British medical journal The Lancet reported that HRT increased the risk for breast cancer by 5 per 1000 users which resulted in about 20,000 extra cases of breast cancer in Britain over the past decade. [The Lancet 362: August 9, 2003] Incredibly, a spokesperson for one of the hormone drug companies responded to this study by saying: *"The representation of these findings may cause unnecessary alarm and distress to some women taking HRT. These findings do not necessitate any urgent changes to a woman's treatment."* [The Guardian, Aug. 8, 2003]

What will American women do now as menopause approaches and they experience all those symptoms of night sweats, hot flashes and mood changes? It's quite a dilemma since there are about 5000 more American women who reach menopause, the permanent end of menstruation, each day, added to the 40 million who are already in their menopausal years.

Reactions to menopause appear to be culturally conditioned in females. Mayan women from Guatemala

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Annual Increased Risk from Use of Estrogen/Progesterone

Risk/benefit	Change per year Source: National Institute on Aging	Annual increase/decrease among estimated 4 million users of hormone replacement
Heart attacks	7 more cases in 10,000 women	+2800 new cases
Breast cancer	8 more cases in 10,000 women	+3200 new cases
Strokes	8 more cases in 10,000 women	+3200 new cases
Blood clots	18 more cases in 10,000 women	+7200 new cases
Dementia	23 more cases in 10,000 women*	+9200 new cases
Hip fractures	5 fewer cases in 10,000 women	-2000 fewer cases
Colon cancer	6 fewer cases in 10,000 women	-2400 fewer cases
	* Over age 65	

Increased Risk for Uterine Cancer with Use of Estrogen

Using no hormones after 10-19 years	+4.4 cases in 10,000 women
Using estrogen alone for 20 years or more	+14 cases in 10,000 women

look forward to menopause and their newfound freedom and consider the symptoms of menopause as evidence of their improved status. [Maturitas 44: 293-97, 2003] Whereas many women in America have been conditioned to run to the doctor for a pill for their hot flashes and night sweats.

Breast Cancer

The rate of breast cancer varies widely worldwide. Japanese and other Asian women only experience a risk of breast cancer about a third to half that of American Caucasian women. [European J Cancer Prevention 11: 519-22, 2002] The reduced risk for breast cancer is often attributed to the consumption of phytoestrogens, primarily soy in Asian diets. However, the effect is not consistent. In a telephone survey of women who were diagnosed with breast cancer, the consumption of plant estrogens had little or no effect upon cancer risk with the average intake of less than one serving of tofu per week. [Am J Epidemiology 154: 434-41, 2001] Possibly much higher consumption is required to exhibit a protective effect.

The assumption has been, since vegetarian women have lower circulating estrogen levels, that this is the primary reason why they exhibit lower rates of breast cancer and that the inclusion of phytoestrogens in plant-food diets is the primary dietary factor involved. This is only partly correct. Estrogen is dumped into the digestive tract at the end of the monthly cycle and women who consume more meat will reabsorb more of their dumped estrogen and thus exhibit higher circulating levels of estrogen and longer periods. To the contrary, women who consume fiber-rich plant foods excrete 2 to 3 times more estrogen in their feces and thus have lower circulating estrogen levels and shorter monthly cycles. [Cancer Research 41: 3771-73, 1981] But while estrogen is a major player in the onset of breast cancer, it's not the only factor. There are other overlooked factors, to be explained in Part III of this report.

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A review of scientific data reveals that advancing age, not necessarily a change in sex hormone levels, is the major factor involved in the onset of breast

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cancer. More than 80 percent of cases of breast cancer occur after age 50 and only 1.5 percent under age 35. [Clinical Obstetrics Gynecology 25: 387-92, 1982]
What many American women have been taught is that breast cancer may be inevitable, that is, it's genetically programmed. The fact that women who moved to the US from countries such as Japan with low breast cancer rates approach the higher risk levels of US women within one generation as a result of their adoption of western lifestyle foods and health practices, is unequivocal proof that breast cancer, for the most part, is not genetic. [Network 10: 1-3, 1989] Very little breast cancer is linked to genetic factors. The Council for Responsible Genetics says only 5 to 10 percent of breast cancer cases involved inherited mutations. [Breast Cancer Genes, Myths & Facts] All women have BRCA1 and BRCA2 genes. Mutations in these genes increase the risk for breast cancer. It is misleading to say that there is about an 80 percent lifetime risk for breast cancer if there are mutations in the BRCA genes. This misstatement is used to sell women on the idea of mastectomy (breast removal). [Journal of the National Cancer Institute, November 7, 93:1585, 2001] Mutations in the BRCA gene do not necessarily result in breast cancer. Colin B. Begg of Memorial Sloan-Kettering Cancer Center in New York said this high risk rate cannot be applied to every woman with mutations of the BRCA genes. The risk is likely much lower than that. [Associated Press, August 20, 2002] But the 80 percent lifetime risk figure is frequently quoted, particularly by surgeons groups.

Here is what one internet resource for women had to advise women about genetic testing and breast cancer:

> Regardless of the test results, *all women* should still take preventive measures to help reduce their risk of breast cancer. These preventive measures include: practicing monthly breast self-examination, having regular clinical breast exams, and having yearly mammograms (at 40 years of age and older). Though testing from BRCA mutations may help identify women who are at a higher risk for breast cancer, 80 percent of women who develop breast cancer have no known risk factors.

But these measures only detect breast cancer at an earlier stage, they have nothing to do with prevention. Breast care centers are just scouting for more treatment to deliver, not to prevent disease from occurring in the first place. Here are the known factors which increase the risk for breast cancer which can be modified by women.

- Alcohol consumption (even moderate consumption is troublesome)
- Red meat consumption
- Lack of whole grains in the diet
- Diets containing corn oil (omega-6 oils) rather than fish oil or flax oil (omega-3 oils)
- Over consumption of fatty foods; the consumption of animal fat is another risk factor, but true to course, this was not shown in a US study of 90,000 nurses. The Japanese increased their intake of animal fat from 10 to 25 percent from 1955 to 1975 without a corresponding increase in the rate of breast cancer. [Tidsskr Nor Laegeforen 30: 1745-48, 1991]
- Being overweight (postmenopausal women)
- Smoking tobacco
- Lack of sunshine (vitamin D)

[J Womens Health 12: 183-92, 2003; Nutrition & Cancer 44: 23-34, 2002; Cancer Causes Control 13: 883-93, 2002]

There is something odd about the statistics provided about breast cancer. It is widely claimed that the lifetime risk to develop breast cancer is 1 in 8 in the USA. That would amount to 16 percent of women. Most cases of breast cancer occur among women after menopause. There are 40 million women in the US in the postmenopausal age group, but only 2 million are known to be living with breast cancer and another 225,000 or so fresh cases are diagnosed annually. About 40,000 of these women die each year. So about 5.5 percent of postmenopausal American women suffer with breast cancer at any given time. The lifetime figure of 1 in 8 is a cumulative figure. This figure has been criticized and health authorities claim it helps to get women to come in for exams on a more regular basis and aids in capturing more funds for research. Over $400 million is spent on breast cancer research annually, about $200 per active breast cancer patient. How much of those research funds actually go towards true prevention is unknown.

Inventing a pill that would truly prevent breast cancer would stop a whole industry. Too many jobs rely upon

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WARNING - For Women with Ductal Carcinoma in Situ (DCIS) and Women at High Risk for Breast Cancer: Serious and life-threatening events associated with **NOLVADEX (tamoxifen citrate)** in the risk reduction setting (women at high risk for cancer and women with DCIS) include uterine malignancies, stroke, and pulmonary embolism.

Incidence rates for these events were estimated from the NSABP P-1 trial. Uterine malignancies consist of both endometrial adenocarcinoma (incidence rate per 1,000 women-years of 2.20 for NOLVADEX vs. 0.71 for placebo) and uterine sarcoma (incidence rate per 1,000 women-years of 0.17 for NOLVADEX vs. 0.0 for placebo). For stroke, the incidence rate per 1,000 women-years was 1.43 for NOLVADEX vs. 1.00 for placebo. For pulmonary embolism, the incidence rate per 1,000 women-years was 0.75 for NOLVADEX vs. 0.25 for placebo. Some of the strokes, pulmonary emboli, and uterine malignancies were fatal.

Health care providers should discuss the potential benefits versus the potential risks of these serious events with women at high risk of breast cancer and women with DCIS considering NOLVADEX to reduce their risk of developing breast cancer.The benefits of NOLVADEX outweigh its risks in women already diagnosed with breast cancer.

The Warning Box For Tamoxifen (Astra-zeneca Pharmaceuticals)

the detection of fresh cases of breast cancer to prevent the disease. There are over 14.5 million health care workers in the US representing 10.5 percent of the workforce. This writer has too often been censored by nurses who guard internet chat rooms for breast cancer patients to *"maintain the status quo"* for the doctors they work for.

PART II: Tamoxifen and Aromatase Inhibitors

Tamoxifen

The one heralded drug that did become widely used for breast cancer is tamoxifen. Its use is limited to treatment among advanced cases of breast cancer.
In 1896 Dr. George Beatson discovered that surgical removal of a woman's ovaries shrinks breast tumors. [Lancet 2: 104-07, 1896] Thereafter efforts have continued to control estrogen to limit the growth of breast cancer. Tamoxifen doesn't inhibit the production of estrogen, it only blocks its entry into cells.

In this modern era, tamoxifen is the *"gold standard"* of breast cancer treatment, heralded as the *"most important drug in the history of the management of breast cancer."*

It is attributed to a decrease of 20 to 30 percent mortality age-adjusted cause-specific breast cancer. It is said that tamoxifen has spared more than 400,000 women who are alive today due to tamoxifen therapy.

The data used to back the claims that tamoxifen is a wonder drug is specious. Based upon a study that was stopped short (less than four years) before adequate long-term data could be analyzed, the US Food & Drug Administration recently widened the use of tamoxifen to high-risk but otherwise healthy American women. But longer-term studies in Italy and Britain (four and eight years) did not confirm the earlier study which was abruptly halted. [Orv Hetil 144: 597-603, 2003] Was the American study intentionally halted to produce a positive result? If tamoxifen is such a godsend, why has only the US approved tamoxifen for use among healthy women? [Gynecology Obstet Fertil 31: 327-36, 2003]

If tamoxifen is such a godsend, why has only the US approved tamoxifen for use among healthy women?

Here is how the National Cancer Institute (NCI) helps to promote drugs like tamoxifen to the public, essentially acting as public relations shills for the drug companies.

The NCI reports that 10 million American women are at high risk for breast cancer and maybe ought to see their doctors about taking tamoxifen. The NCI concedes only 2.4 million of these women are likely to benefit from taking the drug, and out of this group of 2.4 million the number of cases of breast cancer

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is likely to be reduced from 58,148 to 28,492. The number of cases of breast cancer appears to be cut in half (49 percent) when viewed as a relative percentage. But in reality, only 2.4 percent of the 2.4 million women would be expected to develop breast cancer if they didn't take tamoxifen and 1.2 percent if they did. So the difference in hard numbers is only 1.2 percent, hardly a way to sell tamoxifen to American women. [J Natl Cancer Institute 95: 526-32, 2003; University of Iowa Press Release, April 4, 2003] So the relative numbers are used instead.

It's very misleading. Yes, admittedly when looking at hard numbers about 20,000 additional women would be spared from breast cancer. The problem is you have to get over 2 million women to take the drug to realize this benefit.

Another one of the hidden facts about tamoxifen is that half of the women with advanced estrogen-positive tumors immediately fail to respond to this drug and are removed from drug therapy. So the studies don't always include these failures. [Drugs 61: 1721-33, 2001]

Even generic tamoxifen at $25.00 per month for a 20 mg pill for 2 million American women would cost $600 million a year to save 20,000 lives over an unspecified period of time, probably a five-year span. So $3 billion is spent and the cost of saving one woman from breast cancer is $150,000! This is not counting the cost of exams, tests, etc. Kinda pricy and the government ought to be looking for less costly alternatives, but not when pharmaceutical companies have politicians in their control.

Current efforts to expand tamoxifen therapy as a preventive agent for breast cancer have begun. High-risk but otherwise healthy women derive some risk reduction if given tamoxifen. Of the 6600 women who took tamoxifen, there were 69 fewer tumors compared to 6000 other women who took a dummy pill. In other words, tamoxifen benefited only about 1 in 100 high-risk women as a preventive measure. Yet it was widely hailed as a breakthrough! [Associated Press Oct. 30, 1998] There has been resistance to the idea of giving healthy women a drug that runs the risk of serious side effects. The National Women's Health Network asked: *"Does this trial represent disease prevention, or disease substitution?"* [Breast Cancer Action, Feb. 26, 1996]

Concerning potential side effects caused by tamoxifen, the National Women's Health Network asked: "Does this represent disease prevention, or disease substitution?"

Side Effects of Tamoxifen

How did tamoxifen ever get approved as a cancer treatment drug? For one thing, it was initially confined to use among advanced cases of cancer as therapy following surgery, chemotherapy and radiation (if that isn't an admission those other conventional treatments don't work, I don't know what is?) The Food & Drug Administration could be coaxed into approving the drug for this group of patients because of the risks of mortality facing post-treatment breast cancer patients. In other words, the side effects could be overlooked given potential mortal consequences from an otherwise unimpeded tumor.

Because tamoxifen permits estrogen to continue being produced from androgens (adrenal hormones, mostly testosterone), women may experience some relief from symptoms of menopause. Women's estrogen production is not blocked, only its entry into cells. The existing estrogen helps to minimize age-related bone loss. Since about two thirds of breast tumors are estrogen-sensitive, tamoxifen may be helpful in prolonging regression and delaying a relapse, as well as preventing or delaying onset in the opposing breast.

But the list of potential benefits of tamoxifen stops there and the realization this drug can turn into a carcinogen on any woman who takes it ought to cause one to get shivers. Here are the major drawbacks of tamoxifen.

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Tamoxifen is listed as a carcinogen (cancer-causing substance) in the 9th edition of the RoC list (reasonably anticipated to cause cancer) prepared by the National Toxicology Program of the Department of Health and Human Services.

1. Tamoxifen is listed as a carcinogen (cancer-causing substance) in the 9th edition of the RoC list (reasonably anticipated to cause cancer) prepared by the National Toxicology Program of the Department of Health and Human Services. [National Toxicology Program, Factsheet, May 2000] Canadian health authorities issued a health warning in 2002 regarding tamoxifen and its side effects. [Health Canada, Nov. 26, 2002] That is because tamoxifen is only an organ-specific anti-cancer agent. It blocks breast tumors but encourages endometrial cancer. It has been known since 1975 that the use of hormone replacement therapy increases the risk of endometrial cancer by 450 percent. [New England Journal Med 293: 1164-67, 1975; Int J Gynecology 12: 496-500, 2002] Some physicians suggest women undergo a complete hysterectomy before they start on the drug to eliminate the risk of endometrial cancer.

2. Estrogen blockers like tamoxifen eventually lead to a dead-end street. Due to what is called *"tamoxifen resistance,"* the drug inevitably turns on every woman within five years. Tamoxifen must be stopped after five years when cellular resistance materializes and turns this drug into a cancer-promoter. [J Steroid Biochem Mol Biol 79: 143-49, 2001; Drugs 61: 1721-33, 2001]

3. While the risk of second breast cancer is reduced with tamoxifen, there is a five-times increased risk of estrogen-negative breast tumors in the breast opposite the first diagnosed tumor. [Fred Hutchinson Cancer Research Center, July 3, 2001]

4. Despite its acclaim, tamoxifen has not been found to increase life expectancy after five years of use. [British Journal Cancer 85: 1280-88, 2001]

Other Side Effects of Tamoxifen

- Tamoxifen may induce irreversible blindness. It is possible for Tamoxifen to cause retinal blindness. [Am J Ophthalmology 131: 386-87, 2001; Cancer Treatment Reports 62: 315-20, 1978; Bulletin Society Belge Ophtalmol 238: 161-68, 1990] Tamoxifen also increases the risk of blinding cataracts, as much as 400 percent. [Breast Cancer Research Treatment 60: 167-72, 2000]

- Tamoxifen may cause premature menopauase, weight gain and mental depression. It may also induce hot flashes, night sweats and vaginal discharge in addition to blood clots, and stroke. [J Natl Cancer Institute Monograph 30: 130-34, 2001]

- Scientists are currently mulling over data to determine if tamoxifen is actually toxic to DNA. [Mutagenesis 18: 395-99, 2003]

Because of the long list of potential side effects, *"Women should be given all of the information about the benefits and risks of tamoxifen use so that they can make an informed decision based on the best data available."* [Annals Pharmacotherapy 37: 268-73, 2003] But are they?

After all the side effects generated by more than 20 years of prescribing tamoxifen, threatened with a new competitor (the aromatase inhibitors), researchers finally decided that just 5 milligrams of tamoxifen may be good enough to prevent relapse of breast cancer after conventional treatment (surgery, chemotherapy, radiation), not 20 milligrams. [American Assoc Cancer Research, April 8, 2003; J Natl Cancer Institute 95: 779-90, 2003]

Despite its acclaimed achievements, health authorities are now asking: *"Has tamoxifen had its day?"* [Breast Cancer Research 4: 213-17, 2002; Nat Review Drug Discovery 2: 205-13, 2003] That's because of a new class of drugs called aromatase inhibitors.

Aromatase Inhibitors

Breast and prostate cells can produce enough sex hormones via activation by the aromatase enzyme to

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stimulate growth of tumors. [Clin Cancer Research 9: 455-59S, 2003]

Oral aromatase inhibitors are now being employed with superior results to tamoxifen. [Breast Cancer Research 4: 213-17, 2002; Nat Review Drug Discovery 2: 205-13, 2003] The superiority of aromatase inhibitors over tamoxifen is demonstration in a recent study. After 4 months of treatment, about 6 out of 10 women taking Femara (letrozole) showed tumor shrinkage versus only 4 in 10 for tamoxifen. [24th Annual San Antonio Breast Cancer Symposium]
Whereas tamoxifen permits production of estrogen and then blocks its entry into cells, the aromatase inhibitors dampen the production of an enzyme responsible for production of estrogen itself.

Now that aromatase inhibitors are under widespread study and about to be prescribed to millions more American women, The New England Journal of Medicine has just published an extensive report on aromatase inhibitors. [New Eng J Med 348: 2431-42, 2003] The report says *"these drugs are effectively challenging tamoxifen for use in postmenopausal patients with estrogen-receptor-positive cancer,"* the majority of breast cancer cases. Aromatase inhibitors don't induce tumor resistance as does tamoxifen. [Endrocrin Relat Cancer 6: 75-92, 1999]

Aromatase inhibitors are also being considered as primary prevention. What this means is that the pharmaceutical companies want to put every woman on these drugs throughout life. Whereas tamoxifen increases the risk of endometrial cancer and blood clots and becomes a cancer promoter over time, the aromatase inhibitors have no such side effects. But they have their own set of problems.

The aromatase enzyme is found in high concentrations in the ovaries, and in low levels in fat, liver, muscle, brain, normal and abnormal breast tissue. The production of residual estrogen production after menopause is solely from these non-glandular sources, particularly from subcutaneous fat. (This is the probable reason why obesity increases the risk for breast cancer in postmenopausal women.) Whereas menopause causes a 16-fold drop in the blood plasma levels of estrogen, menopausal breast tissue will exhibit concentrations of estrogen 10 times that found in blood plasma. This makes the breast the most likely tissue for estrogen-related tumors to emanate.

These aromatase inhibitors need to be mild since the first generation drug, aminoglutethimide, previously used as an anticonvulsant, induced adrenal insufficiency, drowsiness and skin rashes. But the third-generation aromatase inhibitors are three times more potent than aminoglutethimide! [Clin Breast Cancer 1: 9-14S, 2000] Pharmaceutical aromatase inhibitors are *"remarkably potent"* at inhibiting aromatase activity. [Expert Opin Investig Drugs 12: 337-51, 2003] Letrozole is such a strong estrogen inhibitor only 1 milligram is needed to produce an effect. [Annals Oncology 14: 62-70, 2003]

Strong inhibition of estrogen is likely to result in depressed mood. [Cell Mol Neurobiol. 16:325-44, 1996; J Clin Psychopharmacology 11: 121-26, 1991] The long-term effect of aromatase inhibitors on mood is unknown. Doctors are likely to dismiss this biological origin of depression and attribute it to psychogenic factors surrounding diagnosis and treatment. Therefore, many women undergoing cancer treatment with these drugs may be inappropriately placed on antidepressant drugs.

There is no question that aromatase inhibitors are going to replace tamoxifen since they result in prolonged tumor regression. But the use of aromatase inhibiting drugs is not indicated for premenopausal women with breast cancer who have normal ovarian function. Ditto for women with estrogen or progesterone-receptor-negative tumors. [J Clin Oncol 19: 2596-2606, 2001]

Many studies are now underway with aromatase inhibitor drugs. One study has been ongoing for the past seven years. Even though tumor regression is prolonged, absolute freedom from relapse *"appears to be very small so far, and no survival benefit has emerged."* [New Eng J Med 348: 2431-42, 2003]

Side effects, reported as mild in most studies, include headache, vaginal dryness, hot flashes and musculoskeletal pain, similar to those experienced with tamoxifen. [New Eng J Med 348: 2431-42, 2003] There is a clear reduced risk of blood clots and uterine cancer with the aromatase inhibitors. However, one aromatase inhibitor, anastrozole (Arimidex), produces a higher incidence of musculoskeletal symptoms and

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fractures than reported with tamoxifen. [Lancet 359: 2131-39, 2002]

Obviously, tamoxifen preserves the production of estrogen but just blocks its entry into cells, so estrogen still exhibits beneficial effects upon bone mineralization. But the aromatase inhibitors block the production of estrogen altogether, and bone health is compromised. It's a major drawback of these drugs. The importance of maintaining some estrogen production in the body is underscored by the report of a man who could not produce aromatase, had no detectable levels of estrogen and experienced rapid bone loss. Succinctly, widespread use of aromatase inhibitors could make osteoporosis a bigger epidemic among postmenopausal women than it is today. [Calcified Tissue International 59: 179-83, 1996]

Aromatase inhibitors in postmenopausal women increase total serum cholesterol. [Eur J Cancer 37: 1510-13, 2001] Since sex hormones are made from cholesterol, the reduced estrogen synthesis facilitated by the aromatase inhibitors probably sends a signal to the liver to produce more cholesterol in an attempt to maintain youthful levels of hormones. [Med Hypotheses 59:751-6, 2002]

Aromatase inhibitors are being promoted not only as breast cancer treatment, but may also be useful for uterine fibroids and endometriosis as well as male prostate cancer. [Cancer Investigations 19: 649-59, 2001]

Sex hormones are implicated in colon cancer as well as breast cancer. Cells in the colon can produce aromatase, the enzyme that stimulates estrogen which in turn excites growth of tumor cells. Drugs like raloxifene, used for treatment of age-related bone loss, and tamoxifen, an anti-cancer drug, inhibit production of aromatase in colon cancer cells and thus inhibit their growth. [J Steroidal Biochem Mol Biol 71: 223-30, 1999]

Combinations of tamoxifen and aromatase inhibitors have not been shown to be advantageous. [Forum 12: 45-59, 2002]

Since aromatase inhibitors strongly reduce production of estrogen, they may induce calcifications throughout the body. Low levels of estrogen apparently induce loss of calcium from bones which results in calcifications throughout the body, including the arteries and breast. [J Med Screen 9: 38-39, 2002; Acta Pathol Mcirobiol Immunol Scandinavia 93: 13-16, 1985; Arteriosclerosis Thromb Vasc Biol 20: 1926-31, 2000; Atherosclerosis 34: 469-74, 1979] Of interest is a study where researchers noted that the rapid disappearance of calcifications in breast mammograms was indicative of the onset of breast malignancies. [British J Radiology 72: 3-8, 1999] This spontaneous resolution of calcifications in breast tissue could indicate a rise or resumption in estrogen production and thus a signal for tumors to grow. Hormone replacement therapy is associated with a lower incidence of calcifications in postmenopausal women. [British J Radiology 60: 457-58, 1987]

Of interest to many, grapes and mushrooms contain chemicals that mildly inhibit aromatase, the enzyme that generates estrogen. [Ann NY Academy Sci 963: 229-38, 2002]

Health Effects of Low Estrogen	Health Effects of High Estrogen
Bone thinning (osteoporosis)	Maintains bone mineralization
Depressed mood	Maintains elevated mood
Loss of moisture-holding hyaluronic acid (skin, eyes, joints)	Sends "grow" signal to cells
Calcifications (breast, arteries, heart valves, kidney stones, bone spurs)	Releases iron from carrier molecule; increases ability for iron to enter cells
	Increases need for magnesium and vitamin C

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Comparison: Tamoxifen vs. Aromatase Inhibitors

Tamoxifen (Nolvadex)	**Aromatase Inhibitors**
Currently about 1 million American women receiving tamoxifen	Under clinical investigation Femara (letrozole, Novartis) Aromasin (exemestane, Pharmacia) Arimidex (anastrozole, AstraZeneca)
Primary use: "gold standard" for treatment and recurrence of advanced breast cancer following surgery, chemo or radiation therapy.	**Primary use:** after 5-year tamoxifen therapy or in place of tamoxifen; combined or alternate use with tamoxifen of no extra benefit; potential use as 1st preventive breast cancer drug; possible use for uterine fibroids, endometriosis, prostate cancer; not indicated for premenopausal women with breast cancer who have normal ovarian function. Ditto for women with estrogen or progesterone-receptor-negative tumors.
Action: blocks entry of estrogen into cells; does not impair estrogen production Increases fertility; evidence this drug acts as a pro-estrogen over time.	**Action:** inhibits aromatase enzyme required to produce estrogen; 3rd generation drugs more potent
Proposed benefits: heralded 49% reduction in invasive breast cancer is a relative number; in hard numbers, improvement in survival compared to no treatment, in hard numbers: 3.5% (The Lancet 339: 71-85, 1992) About 1 in 10 women will benefit from taking tamoxifen; only 1% benefit among high-risk women when taken for prevention	**Proposed benefits:** prevents estrogen from being formed in the first place; prolongs remission after conventional breast cancer treatment, but no significant decrease in mortality rates
Active against estrogen-positive and negative breast tumors (different mechanisms)	Active against estrogen-positive tumors
Bone: Retains bone integrity because it does not impair estrogen synthesis	**Bone:** weakens bone due to loss of estrogen production
Side effects: • Claim is that "benefits far outweigh the risks" • Can only be taken for 5 years; then tamoxifen resistance begins • Selective anti-cancer agent: reduces risk of recurrence after treatment for breast cancer, but increases risk of uterine cancer; 400% increased-risk women over 50; increase of 2 cases of uterine cancer per 1000 women; uterine sarcoma increases 2 per 10,000 users; doctors often recommend surgical removal of uterus to eliminate this risk • Cataracts, retinal blindness • Migraines • Blood clotting, strokes • Hot flushes	**Side effects:** • Decreased mood • Headache, nausea, peripheral edema, fatigue, vomiting, indigestion, hot flushes and vaginal dryness [Endocrin Relat Cancer 6: 325-32, 1999] • Possible calcifications throughout the body including breast tissue

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PART III: The Phytoestrogens

Hormone replacement therapy during menopause is only utilized by 8 to 10 percent of eligible women, mostly due to concern over health risks. Furthermore, there is no proven drug that women in their fertile years can take to ward off future breast cancer. So the door is wide open for plant estrogens, called phytoestrogens, to be self employed by American women. No question, many American women are increasing their consumption of soy, flax and other plant foods, primarily for health reasons. In addition to the widely advertised herbal phytoestrogens, the diet has some natural ones. Green beans, alfalfa sprout, mung bean sprout and kudzu root also exhibit estrogenic properties. [J Agric Food Chem 51: 2193-99, 2003]

Women are trying extracts of black cohosh, red clover, vitex, dong quai or a host of other plant estrogens in an attempt to beat the sometimes difficult symptoms of menopause.

Generally speaking, phytoestrogen extracts in pill form all deliver about 50-100 milligrams of active ingredient. Doses below 2 milligrams per kilogram of body weight are considered safe. Thus, a 100-pound female could safely consume up to 90 mg, a 160-pound female up to 145 mg and a 200-pound female up to 180 mg of plant estrogen extract. [British Journal Nutrition 89: 898-906, 2003]

Plant estrogens reduce the number and intensity of hot flashes by a modest 10 to 20 percent. [J Nutrition 133: 1983-86S, 2003] That's not enough to be considered reliable. However, one recent study found that flaxseed (40 grams a day) reduced symptoms of menopause equivalent to hormone replacement therapy. [Obstet Gynecol 100:495-504, 2002] Though one study with flaxseeds reduced menopausal symptoms by 60 to 70 percent.

Researchers say there aren't enough published studies which identify the active ingredients in phytoestrogen products or that indicate the proper dosage to be used. [International Journal Fertility Womens Medicine 48: 64-68, 2003]

In a landmark study published in 1997, researchers obtained urine and blood samples from women who were newly diagnosed with breast cancer and compared them with healthy women. Among the soy plant estrogens (genistein, daidzen and equol) and the lignans from fiber-rich foods like rye and flax (enterodiol, enterolactone and matairesinol), only equol from soy and enterolactone from flax were associated with substantial risk reduction for breast cancer. [Lancet 350: 990-94, 1997]

Black Cohosh

Black Cohosh Flower

Black cohosh is an herb widely used in Europe and marketed in the USA under the brand name Remifemin.

Standardized extracts of black cohosh (Remifemin) have demonstrated an ability to reduce postmenopausal complaints and are also useful for women who have undergone hysterectomy. [Alternative Therapy Health Med 7: 93-100, 2001] Black cohosh appears to improve complaints surrounding the monthly cycle. [J Steroid Biochem Mol Biol 83: 133-47, 2002]

However, a study published in 2001 did not find that women who had completed breast cancer treatment experienced a reduction of hot flashes when taking black cohosh. [J Clin Oncol 19: 2739-45, 2001]

Approximately 30 percent of women experience menstrually-related migraine attacks. The provision of soy, black cohosh or dong quai extracts has been shown to relieve symptoms and reduce frequency of these attacks. [Biomed Pharmacotherapy 56: 283-88, 2002]

The current recommended dose of black cohosh is 40-80 mg per day. A popular commercial extract of

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black cohosh, Remifemin, provides 20 milligrams per pill. Weight gain, nausea, vomiting, headaches and dizziness have been reported as side effects. [Nutrition Clinical Care 5: 283-89, 2002] Gastrointestinal upset and rashes are the most common among the few reported side effects from black cohosh. [Menopause 10: 58-64, 2003]

Surprisingly, even though this herb is classified among the phytoestrogens, recent studies have not confirmed it has estrogen-like properties. Since 1985 it has been believed that an isoflavonone called formononetin in black cohosh is responsible for its mechanism of action. But a recent laboratory analysis has been unable to detect formononetin in samples of this herb. [Phytomedicine 9: 461-67, 2002] A study conducted in Austria confirmed the estrogen-like activity of soy and red clover, but not black cohosh. [J Steroid Biochemistry Mol Biol 84: 259-68, 2003] One report says that while biological action of black cohosh may involve estrogen effects, *"new data dispute the estrogen theory and indicate that extracts of black cohosh do not bind to the estrogen receptor, up-regulate estrogen-dependent genes, or stimulate the growth of estrogen-dependent tumors in animal models."* [Nutrition Reviews 61: 183,86, 2003] Non-estrogenic components of black cohosh are believed to relieve symptoms of menopause and lower doses (~40 mg) appear to work as well as higher doses (~125 mg). [J Womens Health Gender Based Medicine 11: 163-74, 2002]

When black cohosh is combined with tamoxifen, it appears to enhance the anti-estrogen effects of the drug. [Breast Cancer Research Treatment 76: 1-10, 2002]

A recent review declared black cohosh to be relatively safe. [Menopause 10: 58-64, 2003] Black cohosh also appears to be safe for women to use during menopause. [Breast Cancer Research Treatment 76: 1-10, 2002]

Despite its widespread use in Europe, a review of four studies involving black cohosh extract did not yield *"compelling evidence"* for this herb as a hormone-replacement agent in menopause. [Euro J Clin Pharmacology 58: 235-41, 2002]

While available evidence on the effects of plant estrogens in regards to breast cancer is contradictory, extracts from black cohosh have been shown to inhibit the growth of breast cancer cells. [J Steroid Biochem Mol Biol 80: 125-30, 2002] Components of black cohosh also serve as antioxidants and may help protect DNA from damage. [J Agriculture Food Chem 50: 7022-28, 2002] However, one researcher recently gave mice bred to develop breast cancer the human equivalent dose of black cohosh. These mice were more than twice as likely to develop breast tumors and for the tumors to spread to the lung. [American Association Cancer Research, Vicki Davis, Mylan School of Pharmacy, Duquesne University, Reuters July 12, 2003] But this is an unpublished study and various methods (MTT tetrazolium assay) of testing for growth in breast cancer cells may produce false positive results and thus, until the method of testing can be scrutinized, this recent report must be withheld from evidence used to judge black cohosh. [Planta Medica 68: 445-48, 2002]

Bottom line: black cohosh is probably safe to use for symptoms of PMS and menopause. The reported skin rashes appear to be similar to side effects reported with the first-generation aromatase inhibitors. The contrary results surrounding black cohosh in regards to growth of breast cancer cells raises questions on the validity of the testing.

Chasteberry (Vitex)

This fruit extract from a shrub native to west Asia and southwestern Europe has been traditionally used for thousands of years to quell symptoms involving menstrual difficulties. In a study of 1634 patients, a remarkable 93 percent reported a decrease in the number of premenstrual symptoms, with no serious side effects. [J Womens Health Gender Based Med 9: 315-20, 2000]

Dong Quai

Dong quai is an herbal phytoestrogen from China. It is not as popularly used as red clover, soy or black cohosh.

Dong quai may thin the blood, may induce skin light sensitivity, and may induce abnormal heart rhythm. It should not be used with blood thinners. [Pharmacotherapy 19: 870-76, 1999] Like red clover,

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because of its potential to over-thin the blood or interfere with drugs, its widespread use may be unwise.

In one study, dong quai and ginseng induced the growth of human breast cancer cells in the laboratory dish, while black cohosh and and licorice root did not. [Menopause 9: 145-50, 2002]

Red Clover

Red clover sprouts
(International Sprout Growers Assn)

Red clover extract, widely marketed in the USA as Promensil or Rimostil, has been shown to reduce hot flushes among menopausal women. [Maturitas 42: 187-93, 2002] Though a recent study of Rimostil (57 mg plant estrogens) and Promensil (82 mg plant estrogens) did not provide evidence for relief from hot flushes among postmenopausal women experiencing 35 or more hot flushes per week. [J Am Med Assn 290: 207-14, 2003]

Red clover does not seem to have a protective effect upon uterine tissue. [Menopause 8: 338-46, 2001]

Red clover has a higher affinity to block androgens and progesterone receptors than soy products. For comparison, black cohosh exhibits very little if any ability to block androgens and progesterone. [J Steroid Biochem Mol Biol 84: 259-68, 2003; Reproductive Fertility Dev 13: 325-29, 2001]

Red clover isoflavones are capable of reducing an enlarged prostate gland. [Prostate 56: 54-64, 2003] In one study, men with prostate cancer who were given 160 mg per day of red clover extract did not exhibit improved PSA, Gleason scores or serum testosterone levels, but the supplement did halt the progression of the tumors by increasing cell death. [Cancer Epidemiology Biomarkers Prevention 11: 1689-96, 2002]

A test conducted in Australia shows that red clover extract taken in doses ranging from 28 to 85 mg per day significantly raised HDL cholesterol and improved bone mineral density by 4.1 percent. [Menopause 8: 259-65, 2001]

However, in another study, an 86-mg extract of red clover was not found to exhibit cholesterol-lowering properties. [British Journal Nutrition 89: 467-74, 2003] But while red clover may or may not alter cholesterol profiles, it appears to improve the elasticity of large arteries and prevent high blood pressure. [J Clinical Endocrinol Metab 84: 895-98, 1999]

Molecules called coumarins in red clover raise concerns over blood clotting effects. [Atherosclerosis 152: 143-37, 2000; Menopause 8: 333-37, 2001] For this reason, widespread use of red clover extract may not be wise. When millions of women are likely to be involved, the potential for side effects, particularly serious ones like blood clotting problems, must be almost nonexistent.

Soy Phytoestrogens

Phytoestrogens from soy (genistein, equol, daidzen) are widely promoted as cancer fighters. Much more can be said about soy than in this short report. Suffice to say that there is a royal battle going on in scientific circles over the use of soy to combat symptoms of menopause and prevent breast cancer.

There is also cause for concern. Soy phytoestrogens may stimulate growth of breast cancer cells under certain circumstances. [Journal Nutrition 133: 1983-86S, 2003]

A world authority on soy, Mark Messina, says *"The available data justify the recommendation that patients with frequent hot flushes consider trying soyfoods or isoflavone supplements for the alleviation of their symptoms."* [J Med Food 6: 1-11, 2003] However, another researcher (MS Kurzer) from the University

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of Minnesota writes that *"until safety with respect to breast cancer is established, phytoestrogen supplements (like soy) should not be recommended."* [J Nutr 133: 1983-86S, 2003] Other researchers in Finland say *"no negative effects of soy on breast cancer have been observed"* and that soy may be *"slightly protective"* against breast cancer. [J Steroid Biochem Mol Biol 83: 113-18, 2002]

Soy provides a unique combination of estrogen-like molecules, iron binders (IP6 phytic acid, and a small amount of omega-3 oils, only exceeded in quantity by flaxseed oil in nature, all three which are anti-breast cancer agents. [J Nutr. 130: 820-6, 2000; Am J Clin Nutr 51:809-14, 1990] The importance of this triad in the prevention of breast cancer will be described more fully below.

1 cup miso soup (soybean paste)	109.7 per 100,000 risk for breast cancer
3 cups miso soup (soybean paste)	57.2 per 100,000 risk for breast cancer

A remarkable study has recently been published which sheds light on why there may be variability in the rates of breast and prostate cancer among populations that consume significant amounts of phytoestrogens. Japanese researchers found no protective effects from soyfoods among 21,852 Japanese females age 40-59 years. However, researchers did discover a marked reduction in breast cancer risk with increasing consumption of miso soup, which is made from soybean paste. The incidence of breast cancer dropped from 109.7 to 57.2 per 100,000 Japanese women when they increased their miso soup consumption from one to three cups a day. [Journal Natl Cancer Institute 95: 906-13, 2003] It is obvious that the hot water in soup making produced a hot-water extract of the soy isoflavones which produced the health benefits.

Genistein

Genistein is a principal plant estrogen molecule found in red clover and soy and deserves special attention.

Genistein inhibits breast cancer growth at low concentrations and promotes growth of breast cancer at high concentrations. When soy is consumed as a whole food, it doesn't appear to significantly increase or decrease the risk for breast cancer. [J Nutrition 3095-3108S, 2001; Oncology Reports 6: 1383-87, 1999]

In one study, only genistein from soy, and not lignans, were found to be protective for prostate cancer. [Yonsei Med J 43: 236-41, 2002]

Phytoestrogen source	Botanical or latin (L) and trade names	Potential drawbacks
Red clover (genistein)	Trifolium pratense L; Promensil, Rimostil	Blood thinning; may promote tumor growth
Chasteberry	Vitex agnus castus	May promote tumor growth
Kudzu	Pueraria lobata L	May promote tumor growth
Hops	Humulus lupulus L	May promote tumor growth
Dong quai	Angelica sinensis	Blood thinning; may promote tumor growth
Licorice root	Glycyrrhiza glabra	May promote tumor growth
Black cohosh	Cimicifuga racemosa L; Remifemin	Relatively safe (rashes?); may not be a true phytoestrogen
Soy isoflavones (genistein, daidzen, equol); provides phytoestrogens with small amounts of iron-binding phytic acid and omega-3 oil.	Glycine max; many trade names- Soylife	Soy phytoestrogens alone, under certain circumstances, may promote growth of tumors.
Flaxseed lignans (enterolactone); highest source of omega-3 oil in nature with ample amount of iron-binding IP6 phytic acid and lignans.	Linum usitatissimum (linseed)	Blocks tumor growth because of omega-3 content and iron binders (IP6 phytic acid), countering estrogen-like effects

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Flax Lignans

Lignans started out as unidentified estrogen-like compounds in urine extracts of females which were called Compound X. Their dietary source was only confirmed later. [Nature 287: 738-40, 1980] They are the most promising of all the plant estrogen modifiers and probably the safest.

Lignans are estrogen-like molecules found in whole grains, like rye and flaxseed. Very small amounts of lignans are provided in coffee and tea. [Brit J Nut 79: 37-45, 1998]

Flaxseed is an unusually high source of lignans, providing 80 to 700 times more lignans than found in other grains. It does not seem possible to experience estrogen-related adverse effects consuming a diet rich in lignans because they exhibit only 1/10,000th the effect of estrogen. Flaxseed lignans do more than just block the hormone receptor sites on living cells like tamoxifen does. As early as 1993 it was determined that lignans are weak inhibitors of estrogen production by virtue of their ability to inhibit aromatase, the enzyme responsible for estrogen production. [J Steroid Biochem Mol Biol 44: 147-53, 1993]

Widespread Health Benefits of Flaxseed and Lignans

While the focus of this report centers on breast cancer, the health benefits of lignans are not confined to breast or prostate tissue.

Flax Lignans and Heart Disease

In a recently published study conducted in Finland, high circulating levels of lignans were associated with reduced coronary heart disease and mortality from heart disease in middle aged men. [Archives Internal Medicine 163: 1099-1104, 2003]

Lignans may partly accomplish a reduction in coronary heart disease in males by moderating cholesterol levels. Flaxseed consumption lowers cholesterol. [J Clinical Endodrinol Metabol 87: 1527-32, 2002] While concentrated lignan extracts have not been evaluated for cholesterol profiles, it is known that healthy men with the highest circulating levels of enterolactone, the primary lignan component in flaxseed, exhibit much lower rates of acute heart attacks than with low levels of enterolactone. [Lancet 354: 2112-15, 1999]

Almost two decades ago studies were conducted showing that lignans also had some similar properties to digitalis (Lanoxin, Digoxin), a drug used to strengthen heart pump action. [J Hypertension 4: 161-64S, 1986; Biochem Biophys Res Comm 134: 1064-70, 1986]

Flax Lignans and Kidney Disease

The provision of flaxseed lignans to the diet of animals and humans has been shown to spare the kidneys from assault in autoimmune diseases like lupus. [Lupus. 9:429-36, 2000 Am J Kidney Dis. 22:326-32, 1993; Kidney Int. 48:475-80, 1995]

Prostate Cancer and Lignans

Like other phytoestrogens, enterolactone and enterodiol, two lignans in flaxseed, inhibit the growth of prostate cancer cells. [Anticancer Research 21: 3995-99, 2001] In mice genetically engineered to develop prostate cancer, dietary flaxseed reduced the size and aggressiveness of tumors and 3 percent of these animals never developed prostate cancer. Tumors in the group that didn't get flaxseed in their diet were twice as large as those tumors in animals given flaxseed. [Duke University Med Center, Nov. 11, 2002; Urology 60: 919-24, 2002] Men who added ground flaxseed to their diets for 34 days experienced lower PSA levels and a drop in testosterone levels. [Urology 58: 47-52, 2001]

Breast Cancer and Flaxseed Lignans

In Finland, Sweden and Australia, low dietary intake levels of dietary lignans is associated with an increased risk of breast, prostate and colon cancer. [Baillieres Clin Endocrinol Metab 12: 605-23, 1998] Excretion of lignans is low among women with breast cancer, a fact that has been known for nearly two decades. [Clin Chim Acta 158: 147-54, 1986] This means the consumption of lignan-rich foods is also low in women with breast tumors.

Lignans in the diet have been working in the fat cells of the body to inhibit estrogen production by calming

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down estrogen production. [J Steroid Biochem Mol Biol 50: 205-12, 1994] Essentially, flaxseed lignans are aromatase inhibitors.

The addition of ground flaxseed and flaxseed oil to the daily diet increases the circulating levels of enterolactone, the primary phytoestrogen in flaxseed. [European J Clinical Nutrition 56: 157-65, 2002] Generally, very low circulation levels of enterolactone are associated with breast cancer, though sporadic cases can be found among females who have high enterolactone levels. [European J Nutrition 41: 168-76, 200] Apparently it's important to find the right amount for daily consumption.

Flaxseed, about three tablespoons a day, appears to slow the growth of breast and prostate tumors once diagnosed. [US Berkeley Wellness Letter, May 2002] Chemically-induced breast tumors in rats are 67 percent smaller when fed flaxseed powder. But the effect is not consistent. [Nutrition Cancer 17: 153-59, 1992] This is likely attributed to the variable amount of lignans in the flax or other factors discussed below.

Bone Strength and Flax Lignans

Another compelling potential health benefit from flaxseed is its ability to help maintain bone strength. Women with osteoporosis excrete less enterolactone, the primary estrogen molecule in flaxseed, meaning their dietary consumption of lignans is low. [Clin Endocrinol 56: 321-28, 2002] Flaxseed and flaxseed oil, along with fish oils, inhibit the production of chemicals that lead to loss of bone density. [Alternative Medicine Review 6: 61-77, 2001]

In Korea, higher consumption of lignans as evidenced by concentrated urinary excretion, in particular enterolactone, a primary estrogen-like molecule from flaxseed, was found to be related to strong bone mineral density. [Clin Endocrinology 56: 321-28, 2002]

Whereas pharmaceutical aromatase inhibitors inhibit the production of estrogen to the point where they compromise bone health, flaxseed supplementation appears to mildly reduce estrogen levels, LDL cholesterol and triglycerides, but does not block age-related bone loss. [J Clin Endocrinol Metab 87: 1527-32, 2002]

In rodents, flaxseed lignans appear to enhance bone mineral content, but in later life this protective quality does not persist. [British J Nut 86: 499-505, 2001] But at least flaxseed lignans do not promote degradation of bone as do pharmaceutical aromatase inhibitors.

Antibiotics and Lignans

Another confounding factor that increases the risk of breast cancer in developed countries is the overuse of antibiotics. Lignans in the diet convert into protective enterolactone by intestinal bacteria. One study reveals that recent users of antibiotics exhibit lower concentrations of enterolactone in their blood circulation. [Am J Epidemiology 155: 472-77, 2002]

Other Benefits of Flaxseed Lignans

It has been known for some time that consumption of flaxseed powder, by virtue of its ability to reduce estrogen production, slightly raises relative concentrations of testosterone in women at a certain time during the month. [J Clinical Endocrin Metab 77: 1215-19, 1993] Since testosterone drives sexual interest in females (as it does in males), this means that flaxseed lignans may increase women's desire for midlife sexual activity.

While virtually all the studies concerning flaxseed and health involved the provision of whole flaxseed, the emphasis has been solely upon its phytoestrogen lignan content. Yet it is apparent that flaxseed exhibits unusual health benefits not observed in other herbal phytoestrogens such as red clover or black cohosh. A

Iron Needs Throughout Life

	Growth Years	Years of Fertility	Change of Life
Males	High iron needs	Markedly lower iron needs	Lower iron needs
Females	High iron needs	High iron needs (unless hysterectomy)	Markedly lower iron needs

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possible explanation of the reasons for the widespread health benefits attributed to whole ground flaxseeds is described below.

The world's first lignan extract is now available.
(Brevail, 9921 Carmel Mountain Rd. #339
San Diego, CA 92129. 1.888.503.8300
www.brevail.com Email: info@brevail.com)

The recent introduction of the world's first lignan extract (Brevail, Lignan Research) is noteworthy. Brevail assuredly provides 50 milligrams of lignans extracted from flaxseed whereas the lignan content of flaxseeds themselves can vary considerably. The omega-3 and IP6 phytic acid content of this product is currently unknown and the product may be more appropriate for women dealing with symptoms of PMS or the onset of menopause than for breast cancer itself. Many women already report improved well-being, stronger nails, more interest in mid-life bedroom activity, and fewer menopausal symptoms using Brevail. A recent study shows that about a third of women age 18-25 years of age have polycystic ovaries which causes a relative rise in testosterone and the appearance of facial hair and acne. [Clin Endocrinology 51: 779-86, 1999] Brevail may be beneficial to these women.

Flax Lignans and Iron Control

While the etiology of breast cancer is linked to high life-time exposure to estrogen, there are disparities in studies that attempt to establish this association. [J Steroid Biochem Mol Biol 80: 163-74, 2002] Estrogen alone is not the sole governing factor in breast cancer.

If estrogens alone were the primary factor in breast cancer, then why don't more women get this form of cancer during their fertile years when hormone levels are very high?

One answer to this question is that these high hormone levels occur when iron levels are low and metallic minerals like iron are either being lost in the monthly menstrual flow or being donated to a developing baby.

It should not be a surprise that precisely when women lose their ability to control iron, when monthly blood loss with accompanying iron depletion ceases, is exactly when the risk of breast cancer rises dramatically. For example, the liver stores iron and iron stores in the liver are higher among women in whom menstruation has stopped before the age of 50. [Ann Internal Med 127: 105-10, 1997]

When women are still having monthly cycles in their fertile years the likelihood of developing breast cancer is only 1 in 231 up to age 39. But there is an abrupt elevation in risk from age 40 to 59 years to 1 in 25 women, and from 60-79 years of age to 1 in 15 women, [Breast Cancer Family Foundation] which coincides with the buildup of iron.

It is well established that the iron content of cells increases the risk of cancer. [Environmental Health Perspectives 87: 291-300, 1990; Pathobiology 60: 2-9, 1992] *"Iron has not received much attention in discussions of estrogen-induced carcinogenesis and human hormone-associated cancer."* An elevated dietary intake of iron enhances the incidence of breast tumors in animals. The buildup of iron in the body has been specifically linked to higher mortality rates due to cancer among postmenopausal women. [Int J Epidemiology 24: 665-70, 1995]

Risks for Breast Cancer	Regulation of Iron
Menopause; advanced age	Loss of menstruation and blood loss of iron
Alcohol	Increases dietary absorption of iron
Plant food diets	Iron more difficult to absorb from plants
Red meat consumption	Contains highly absorbable form of iron
Soy and flax consumption	Provides phytic acid to control (chelate) iron

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Estrogen administration increases iron accumulation. [Current Medical Chemistry 8: 839-49, 2001] Metabolites of estrogen (4-hydroxyestrogens) can induce release of iron from its carrier molecule (ferritin) to generate the dreaded hydroxyl radical, the rusting agent that contributes to the initiation of breast tumors via DNA mutation. [Archives Biochemistry Biophysics 346: 180-86, 1997; Mutation Research 475: 153-59, 2001; Zentralbl Gynakol 124: 559-65, 2002]

The accumulation of iron among postmenopausal women is also attributed to other common health problems among postmenopausal women such as high cholesterol and coronary heart disease. [Arteriosclerosis Thrombosis 14: 857-61, 1994]

While iron is necessary for life and the production of hemoglobin in red blood cells, when it is unbound from its carrier proteins (what is called *"free iron"),* then it becomes a rusting agent that can induce the hydroxyl radical which is the primary *"culprit in cancer."* [Stem Cells 12: 289-303, 1994] Metastatic (spreading) breast tumors exhibit a two-fold increase in hydroxyl radical damage compared to non-spreading tumor cells. [Proceedings Natl Acad Sci 93: 2557-63, 1996]

The role of iron in breast cancer is demonstrated by experiments where animals are given estrogen supplements along with an iron-fortified diet. The incidence of kidney tumors is two to four times higher with an estrogen + iron regimen than when estrogen is given with an iron-poor diet. No tumors are observed in animals treated with low or high-iron diets. Circulating levels of iron are much higher in animals given a high-iron diet plus estrogen. [Carcinogenesis 19: 1285-90, 1998] Of particular interest is the fact that breast cancer cells exhibit 5 to 15 times more receptors for iron deposition (transferrin receptors) than normal cells. Iron-carrying proteins like transferrin are growth factors for breast tumors. [Med Oncol Tumor Pharmacotherapy 8: 229-33, 1991]

The removal of iron via chelation is believed to be a viable method of preventing and treating cancer.

The removal of iron via chelation is believed to be a viable method of preventing and treating cancer. [European J Cancer Prevention 5: 19-36, 1996] Bran obtained from whole grains, which contains the iron-binding molecule called IP6, phytic acid, has been shown to inhibit the growth of breast tumors in laboratory experiments and in animals. [Archives Latinoamerica Nutrition 49: 309-17, 1999] IP6 phytic acid, found in relatively high amounts in flaxseed, sesame seed and rice bran, reproducibly inhibits experimental breast tumors in laboratory animals. [Carcinogenesis 16: 1055-58, 1995]

Conventional medicine is not unaware of the important role iron plays in breast cancer. It's just the researchers are attempting to develop patentable molecules for use as drugs to treat existing cases of breast cancer rather than study flaxseed which could potentially be used for prevention on a widespread basis. For example, researchers are studying an iron-binding drug to treat mammary tumors. [Anticancer Research 22: 2685-92, 2002]

It is interesting to note that alcohol consumption is associated with increased risk for breast cancer. Alcohol increases the absorption of iron from the diet and *"accumulation of iron coupled with diminished antioxidant defenses in breast tissue with advancing age"* which explains the associated between breast cancer and alcohol. [Free Radical Biology Medicine 26: 348-54, 1999]

Another widely known risk for breast cancer is the increased consumption of animal meat combined with a decrease in the consumption of plant foods. Animal meat provides iron in a form (heme iron) that is more readily absorbed than in plant foods (non-heme iron). [Oncology Reports 6: 865-70, 1999]

The body attempts to withhold iron when tumors, infection or chronic inflammation arise. This appears to be a survival mechanism. [Blood Rev 9: 33-45, 1995] So the withholding of iron via dietary binding or chelating factors like IP6 phytic acid would also inhibit the growth of tumors.

Transferrin is the transport molecule or delivery truck for iron in the blood circulation. Transferrin carries iron back to the liver for storage and transferrin receptors permit transferrin to carry iron into cells. Malignant cells have more transferrin receptors. It would make

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sense that estrogen increases transferrin receptors in female tissues so as to facilitate the delivery of iron as a growth factor for a developing baby. [Proc Annual Meet Am Soc Clin Oncol 11:A75, 1992]

Widely overlooked is that fact that the risk for breast cancer dramatically increases as females cease menstruation and thus lose their ability to control iron via blood loss.

Widely overlooked is that fact that the risk for breast cancer dramatically increases as females cease menstruation and thus lose their ability to control iron via blood loss. About 80 percent of the iron in the body is found in red blood cells. The increased stores of iron in postmenopausal females are linked to an increased mortality from cancer. [Int J Epidemiol. 24:665-70, 1995] The parallel rise in heart disease in postmenopausal females can also be attributed to an increase in iron stores due to cessation of menstrual blood loss. [Arterioscler Thromb. 14:857-61, 1994] Menstruating females exhibit half the stores of iron compared to middle-aged men and have half the rates of heart disease, diabetes and cancer. [Lancet. Jun 13;1: 1293-4; 1981; Iron Time Bomb, B Sardi, 2001]

It has been known for some time that breast tumors thrive in an environment rich in omega-6 fatty acids, as provided in corn, safflower and sunflower oil for example, compared to a diet rich in omega-3 fatty acids provided in flaxseed. The risk to develop breast cancer is significantly diminished by the consumption of omega-3 fatty acids as provided in flaxseed. [J Nutrition 133:1409-14, 2003]

In an animal study, flaxseed inhibited growth in established human breast tumors and inhibited metastasis (spreading), and this effect is partly due to its inhibition of growth factors (insulin-like growth factor I and epidermal growth factor receptor expression). [Nutrition Cancer. 43:187-92, 2002]

The consumption of omega-3 oils in a favorable balance over omega-6 oils is attributed to prevention of a variety of diseases seen commonly in populations consuming western diets. [Biomed Pharmacotherapy 56:365-79]

Miracle Triad of Flaxseed

Ground flaxseed meal provides a unique triad of breast cancer blocking nutrients: omega-3 oils, iron-binding IP6 phytic acid, and lignans.

Too much has been made of the phytoestrogen content of flaxseed, and for that matter all herbal estrogen modifiers. Whole ground flaxseed exhibits unique properties for health promotion over and above those provided by other plant estrogens such as red clover, black cohosh or vitex. Flaxseed has unique components that (1) inhibit the synthesis of estrogen; (2) control iron (phytic acid IP6); and (3) favorably balance omega-3s over omega-6 fatty acids. While soy also provides phytoestrogens with omega-3 oil and phytic acid, the last two are minor components and not provided in ample amounts as in a tablespoon of crushed flaxseeds.

Two tablespoons (15 grams) of ground flax seed (Forti-Flax, Barleans), an organically-grown, herbicide-free source of cold-milled flaxseeds, which is low in calories (70), provides better than 50 milligrams of flax lignans, 320 milligrams of iron-binding IP6 phytic acid and 3000 milligrams of omega-3 fatty acids in a 3-to-1 ratio over omega-6 fatty acids. This is an unusual array of the right nutrients to prevent, treat or block the recurrence of breast and prostate cancers. Crushed flaxseed must be utilized to obtain the lignans and omega-3 oils. The provision of a capsule with standardized amounts of flax lignans, phytic acid and

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omega-3 fatty acids would provide a more assured source of these nutritional factors.

Summary

It is obvious that commercial interests reign supreme over women's health concerns. Profiteering off of women's monthly hormonal swings and the cessation of their menstrual cycle in mid-life is widespread. It is a chilling fact that, after decades of research, there still is no effective preventive measure for breast cancer.

The expansion of tamoxifen for use among healthy women is not justified by the scientific data and pronouncements by health agencies for at-risk women to take this drug are irresponsible. The use of a drug that can turn on its users and become a cancer promoter is certainly playing with fire.

Newer aromatase inhibitors eliminate some of the side effects posed by tamoxifen for breast cancer patients following conventional cancer treatment, but cannot be safely used as a preventive measure among healthy women who are still having a monthly cycle. The widespread use of aromatase inhibitor drugs would likely cause rates of osteoporosis and mental depression to skyrocket upwards.

The use of phytoestrogens is generally unguided but understandably practiced due to modern medicine leaving women in a lurch regarding advice on hormonal regulation. Some phytoestrogens (red clover, dong quai) may over-thin the blood and may not be safe for use by large numbers of women. The use of phytoestrogens may quell some of the symptoms of PMS and menopause, but they too are likely to be found to increase the risk and spread of breast tumors because they mimic the *"grow"* signal in cells. The use of concentrated phytoestrogen extracts as dietary supplements, over and above levels provided by typical plant-food diets, may actually be found to increase the risk of breast cancer over time.

Herbal phytoestrogens (red clover, dong quai, vitex) should be distinguished from phytoestrogens provided in beans and seeds, such as from soybeans and flaxseed. Soy and flaxseed phytoestrogens are provided in a natural matrix of iron controllers (IP6 phytic acid) and omega-3 oils, with flaxseed providing the only significant source of all three of these nutrients.

It is evident, when estrogen levels are the highest, during pregnancy and the fertile years, that breast cancer rates are very low, which discounts the idea that estrogen is the sole governing factor in breast health. It is also obvious that women's risk for breast cancer rises upon the loss of their control of iron, either by surgical or age-induced menopause. Iron plays the preeminent governing role in breast cancer and estrogen plays an important role as a release agent for iron. Iron bound to proteins is harmless, proven by iron bound to the red hemoglobin pigment which does not induce oxidation, tissue damage or DNA mutation. On the other hand, unbound iron is a *"rusting agent"* that can induce the feared hydroxyl radical, believed to be the primary agent that initiates breast cancer. [Arch Biochem Biophys. 346: 180-6, 1997; Proc Natl Acad Sci U S A. 93:2557-63, 1996]

Since the accumulation of iron is the primary controlling factor in breast cancer, efforts to prevent this type of tumor prior to menopause are not likely to be fruitful and may not even be necessary. Fertile women control iron effectively via menstruation. The idea of lifetime exposure to estrogen as a risk factor for breast cancer is a flawed concept. Except for vitamin D, nearly every major risk factor or preventive measure for breast cancer (alcohol consumption, red meat, exercise, age, vegetable consumption), involves the control of iron.

Prevention of breast cancer should ensue immediately following cessation of menstruation and continue throughout the remainder of life and consist of iron chelation, provision of omega-3 oils and the calming of estrogen production via safe and natural plant molecules such as low-dose lignans.

Flaxseed meal provides a unique concentrated source of omega-3 oils, iron binders (IP6 phytic acid) and lignan as an estrogen controlling agent. Flaxseed does not have any of the drawbacks of tamoxifen or pharmaceutical aromatase inhibitors and is inexpensive.

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The cure for breast cancer? Fine quality IP6 phytic acid rice bran extract, Tsuno Food Industrial Co., Wakayama, Japan. Available in the USA under various brand names.

Flaxseed meal provides a unique concentrated source of omega-3 oils, iron binders (IP6 phytic acid) and lignan as an estrogen controlling agent. Flaxseed does not have any of the drawbacks of tamoxifen or pharmaceutical aromatase inhibitors and is inexpensive. The superiority of lignan compounds was recently demonstrated in a laboratory test which revealed its ability to inhibit DNA mutation and to chelate iron. [Free Radical Research 31: 149-60, 1999]

While whole grains and flaxseed are rich in IP6 phytic acid, this natural grain and seed component may only serve to help prevent rather than treat existing tumors. In laboratory experiments where breast tumors were chemically induced, IP6 phytic acid in bran cereal was not nearly as effective at inhibition of tumor growth or the quantity of tumors as was purified IP6 extracted from rice bran. [Nutrition Cancer 28: 7-13, 1997; Anticancer Research 19: 3671-74, 1999] Purified IP6 phytic as a dietary supplement, which about 70 percent is unbound to minerals and ready to attach and remove unbound iron, has both a preventive and therapeutic effect. In two other laboratory experiments where mammary tumors were induced in rats by feeding them corn or sesame oil, the provision of purified IP6 phytic acid extracted from rice bran reduced the number and size of breast tumors. [Carcinogenesis 16: 1055-58, 1995; Cancer Letters 75: 95-102, 1993] In a telling experiment, the provision of supplemental iron or calcium to mice increased markers for breast tumor growth, while the provision of IP6 phytic acid as a mineral-binder, brought about reductions in tumor markers. More remarkable, the provision of IP6 phytic acid simultaneously with supplemental iron and calcium still brought about a reduction in tumor markers! [Carcinogenesis 12: 2041-45, 1991]

The complete blockage of estrogen production or estrogen entry into cells during the post-menopausal years is counterproductive because it trades the risk of breast and uterine cancer for the onset of osteoporosis and mental depression. Hormonal harmony must be pursued by more reliable means than what is currently practiced today.

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