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Bioidentical Hormones

Why are they Still Controversial?

As women enter the menopausal years, they face a difficult decision. Their body's natural production of **estrogen**, **progesterone**, and other hormones needed to maintain health and vigor rapidly decline.

While individual effects of menopause vary widely, most women suffer because their glands no longer produce the ***hormones*** required to regulate critical physiological processes. Depression, irritability and short-term memory lapses are common menopausal complaints, along with hot flashes, night sweats, insomnia and weight gain.

Health problems encountered during menopause can adversely affect a woman for the rest of her lifetime in the absence of *proper* hormone replacement. Yet maturing women today are being told by their doctors to *limit* prolonged use of both pseudo-hormone drugs as well as hormones natural to humans (i.e. bioidentical hormones).

These doctors tell their female patients to take any kind of estrogen-progesterone drug only long enough to adjust to menopausal symptoms and then no more. Unfortunately, these doctors fail or refuse to recognize the critical differences between unnatural-to-human hormone drugs and real hormones entirely natural to humans.

The very real fear espoused by conventional doctors is that *unnatural* estrogen-progestin drugs increase the risk of cancer and other diseases. The dilemma maturing women face is that their healthy cells still benefit from youthful levels of natural hormones, but many of their doctors say "no"..

Scientific studies document that unnatural estrogen/progestin drugs *increase* risk of common age-related diseases including heart attack, stroke and certain cancers. Natural (for humans) hormones (referred to as **bioidentical hormones**) have not been shown to cause these diseases.

There is in fact a body of scientific evidence indicating that ***natural progesterone*** (as opposed to synthetic progestin drugs) and the ***estriol*** form of estrogen may help protect against the very diseases caused by unnatural estrogen-progestin drugs.

Conventional doctors (many who prescribed unnatural hormone drugs for decades) and the **FDA** (who still allows these dangerous unnatural hormones to be sold) are now at the forefront urging aging women to avoid their *prolonged* use. ,

Overlooked (or derided) by mainstream medicine is a plethora of research findings indicating that women may safely benefit from *individualized* doses of natural **estrogens** and **progesterone** over their lifetime. Almost completely ignored are lifestyle changes (such as assuring optimal vitamin D serum status and cruciferous vegetable intake) that might ***reverse*** the kind of damage to cell regulatory genes inflicted by estrogenic compounds.

In this report, we present data showing how women may safely benefit from comprehensive approaches that naturally restore youthful hormone balance, while protecting aging cells against carcinogenic and atherogenic insults.

WHAT YOU NEED TO KNOW: BIOIDENTICAL HORMONES

- Non-bioidentical hormones are not identical in structure, proportion or activity to the hormones naturally produced within the body. The use of non-bioidentical estrogen and progesterone is associated with an increased risk of breast cancer, heart attack, and stroke.
- Bioidentical hormones have the same exact molecular structure as the hormones produced naturally within the body. The body does not distinguish between supplemental bio-identical hormones and the hormones produced within the body. As a result, bioidentical hormones are properly utilized, and are then able to be naturally metabolized and excreted from the body.
- The use of bioidentical progesterone is not associated with an increased risk of breast cancer. In fact, the use of bioidentical progesterone is associated with a decreased risk of breast cancer.
- There are three types of estrogen produced in the body: estriol, estrone, and estradiol. The use of estriol is not associated with an increased risk of breast cancer. While non-bioidentical estrogen replacement therapy is known to increase the risk of uterine cancer, The use of topical estriol is not associated with an increased risk of uterine cancer.
- Bioidentical progesterone has beneficial effects on cardiovascular health, including decreasing the risk of blood clots, protecting against the development of atherosclerosis (hardening of the arteries), as well as maintaining healthy HDL-cholesterol levels.
- Bioidentical progesterone is superior to non-bioidentical progesterone in the treatment of menopausal symptoms. Estriol is also highly effective in the treatment of menopausal symptoms.
- Estriol has been shown to improve bone density, promote youthful skin, and enhance sexual and urinary health.
- Foods and nutrients that can protect against the development of breast cancer include green tea, soy isoflavones, fish oil, vitamin D, plant lignans, indole-3-carbinol (found in cruciferous vegetables), and D-glucarate.

The Rise and Fall of Non-bioidentical Hormone Replacement Therapy

Few topics have attracted as much attention in recent years as ***hormone replacement therapy*** (HRT) among postmenopausal women. For decades, physicians were prescribing non-bioidentical estrogen and progestin—such as Premarin®, Provera®, and Prempro®--to combat the symptoms of menopause. Non-bioidentical hormones are *not identical in structure or activity* to the hormones naturally produced within the body.

Doctors also prescribed non-bioidentical hormones to protect postmenopausal women against osteoporosis and heart disease. The rationale behind heart disease prevention was simple: during their reproductive years, women enjoy lower rates of heart disease than men, supposedly because of the protective effect of estrogen. It seemed only logical to conventional physicians who have not yet recognized or refuse to recognize the critical difference between natural, bio-identical estrogens and unnatural, non-bio-identical estrogens--that by replacing the estrogens lost at menopause with non-bioidentical hormones, women would retain some of their protection against heart disease.

Unfortunately, the logic of conventional non-bioidentical hormone replacement therapy (HRT) turned out to be fatally flawed. In 2002, the results of the Women's Health Initiative were released early. This landmark study followed more than 16,000 women and assessed the effects of non-bioidentical hormone replacement therapy (HRT), including estrogen-only therapy and therapy that combined non-bioidentical estrogen and progestin. The findings were shocking: the estrogen/progestin arm of the study was terminated early because the non-bioidentical hormone therapy not only failed to protect against heart disease, but was shown to **increase the risk of heart attack and breast cancer**.1

In 2004, the non-bioidentical estrogen-only arm of the study was terminated as well because estrogen-only hormone replacement therapy (HRT) was found to ***increase*** the risk of stroke.2 These alarming findings led a team of researchers to boldly state in the prestigious *Journal of the American Medical Association* that "*…**the results indicate that this regimen [non-bioidentical estrogen/progestin] should not be initiated or continued for primary prevention of CHD [coronary heart disease]**."* 3

These findings had an immediate impact on the millions of women taking non-bioidentical HRT, where up to 50 percent discontinued their use of non-bioidentical HRT.

The Proven Safety of Bioidentical Hormones

Bioidentical hormones have the same exact molecular structure as the hormones produced naturally within the body. The body does not distinguish between supplemental bio-identical hormones and the hormones produced within the body. As a result, bioidentical hormones are properly utilized, and are then able to be naturally metabolized and excreted from the body. The use of bioidentical HRT has increased during the last 20 years as women have sought out a more *natural* approach to restoring hormonal balance.

Bioidentical Progesterone Does Not Increase The Risk of Breast Cancer

The well-established body of literature demonstrating the harmful effects of non-bioidentical hormones might lead some women to fear taking bioidentical hormones as well. A review of the published scientific literature indicates those fears are misunderstood and unfounded. For

example, thirteen studies document that non-bioidentical *progestin* significantly **increases** estrogen-stimulated breast cell replication and growth.4-16 In stark contrast, seven studies have shown that bioidentical *progesterone* **inhibits** estrogen-stimulated breast cells.17-23

Numerous studies have demonstrated an ***increased*** risk of breast cancer with the use of non-bioidentical progestin.24-51 However, the use of bioidentical progesterone has not been associated with an increased risk of breast cancer. Quite the contrary, research has revealed that **bioidentical** progesterone **decreases** *the risk of* ***breast cancer.*** In a study published in the journal *Breast Cancer Research and Treatment*, 80,000 postmenopausal women using various forms of HRT were followed for more than 8 years. Women who used estrogen in combination with non-bioidentical progestin had a ***69%*** **increased** risk *of* breast cancer, compared to the control group. However, for women who used bioidentical progesterone in combination with estrogen, the increased risk of breast cancer was **completely eliminated** with a significant ***reduction*** in breast cancer risk compared with non-bioidentical progestin use.52

In another investigation, these same researchers found a **40% increased** risk of breast cancer for women who used estrogen with non-bioidentical progestin. Interestingly, women who used estrogen combined with bioidentical progesterone had a **10% reduced** risk of breast cancer, compared to women who had never used HRT.53 In essence, bioidentical progesterone ***protected*** women against the development of breast cancer. Confirmation of these findings was provided by a study of 1150 women that documented a **20%** reduced risk of breast cancer in women taking bioidentical **progesterone**, compared to non-users of progesterone.149

Compelling research offers further insight into progesterone's ability to defend against breast cancer. In a fascinating study, scientists administered estrogen alone, bioidentical progesterone alone, estrogen plus bioidentical progesterone, or placebo to 40 women prior to surgery for breast cancer. The hormones were applied topically to the breast for about 12 days before surgery. As expected, when given alone estrogen caused a **62% increase** in breast cell proliferation rates (a measure of cancer cell growth) compared to placebo. Conversely, the addition of bioidentical progesterone to estrogen resulted in a **complete reversal** of the estrogen-induced increase in breast cell proliferation rates. Even more impressive was the finding that the group receiving bioidentical progesterone alone had a **66% lower** breast cell proliferation rate compared to the placebo group.54

A growing body of literature has documented a definite connection between a woman's progesterone levels and her subsequent risk for breast cancer. A trial reported in the *International Journal of Caner* in 2004 measured blood levels of progesterone in 5,963 premenopausal women. The analysis of the data revealed that women with the highest blood levels of progesterone had a **60% decreased** risk of breast cancer, compared to women with the lowest progesterone levels. Incredibly, those women with the *highest* **progesterone** levels who had regular menses experienced an **88% decreased** risk of breast cancer.55 These findings were corroborated by another study in which 1,083 women treated for infertility were followed for upwards of **33 years** to determine their subsequent breast cancer risk. Compared to women with normal progesterone levels, those *deficient* in progesterone *had a* ***440%*** **increased** *risk of premenopausal breast* cancer, and were **10 times** as likely to die from any cancer.56

Similarly, researchers at the *University of North Carolina School of Public Health* measured progesterone levels in pregnant women, who were then followed for upwards of **32 years**. The researchers discovered that those women with the highest blood levels of progesterone during pregnancy had a **51% decreased** risk of breast cancer, compared to women with the lowest levels of progesterone during pregnancy. When the researchers analyzed the risk of breast cancer in women under age 51, those with the *highest* **progesterone** levels had a staggering **70% decreased** risk compared to the group with the lowest progesterone levels.59

Findings from two other investigations revealed that survival rates for breast cancer are strongly correlated with the patient's progesterone levels at the time of surgery. One study noted that **65%** of women with a progesterone level of 4.0 ng/ml or more on the day of their surgery were alive **18 years** later, while only **35%** of women with low progesterone levels on the day of surgery were still living after 18 years. The scientists noted that progesterone lowers the expression of *vascular endothelial growth factor*, which promotes the increase in new blood vessels (angiogenesis) that is essential for tumor growth. These scientists concluded: "***This study has confirmed that a raised level of progesterone at the time of tumor excision is associated with an improvement in prognosis for women with operable breast cancer***."57-58

Natural Progesterone (bioidentical) *versus* Synthetic Progestins (non-bioidentical)

In this article, we define **natural progesterone** as bioidentical progesterone and **synthetic progestin** as non-bioidentical **progestin**. It is important that the reader know that non-bioidentical progestin is not the same as bioidentical ***progesterone***.

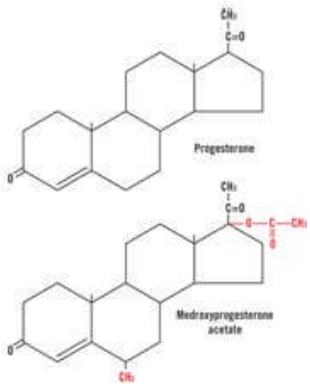
What is Natural Progesterone?

Bioidentical **natural progesterone** is made in the body or made (not extracted) in the laboratory from either soybeans or the Mexican wild yam (Dioscorea villosa). The process was discovered in the 1930s by Pennsylvania State University professor Russell Marker, who transformed *diosgenin* from wild yams into natural progesterone. Natural progesterone refers to bioidentical hormone products that have a molecular structure identical to the hormones our bodies manufacture naturally. One of the most effective forms of bioidentical progesterone is called *micronized progesterone USP*. The process of micronization allows for steady and even absorption of the medication. Micronized progesterone is available through a doctor's prescription or as an OTC topical cream. Both the micronized progesterone and other commercially available progesterone creams contain bioidentical progesterone.

What are Synthetic Progestins?

Unlike natural *progesterone*, non-bioidentical synthetic *progestins* are not molecularly identical to the hormones found naturally in the body. Synthetic progestins were first developed for use as contraceptive agents. Because the half-life of natural progesterone is very short, researchers

sought an agent that would produce longer-lasting, more potent effects than natural progesterone. Birth control pills usually contain a synthetic progestin and a synthetic estrogen. Synthetic progestins are very potent, with just a small dose preventing ovulation and thus functioning as birth control. A slight change in the chemical structure of progesterone has allowed pharmaceutical companies to create patentable and profitable birth control products.



Natural progesterone (above). One example of synthetic progesterone (below)—note the difference in chemical composition as indicated in red.

One of the most common progestins, *medroxyprogesterone acetate* (Provera®), has been linked to blood clots, fluid retention, acne, rashes, weight gain, depression, certain cancers and other disorders. Non-bioidentical progestins are also able to bind to glucocorticoid, androgen, and mineralocorticoid receptors, which explains the wide range of side effects many women experience while taking progestins.[221,222] The vast majority of research studies have been conducted using progestins rather than natural progesterone, which explains the disparity and negativity of the results.

The FDA has also approved a drug called Prometrium®, an oral pill containing 200 mg of natural progesterone taken daily. Because orally administered progesterone is metabolized by the liver, it may be contraindicated in patients with certain liver conditions. Initial liver metabolization of progesterone (called "first-pass" metabolism) also creates much greater quantities of certain metabolites of progesterone than transdermal or transmucosally administered progesterone.

Natural progesterone cream may be more efficiently used, since its highly lipophilic (fat-soluble) molecules allow it be well absorbed through the skin. This is called "transdermal" administration. Even better absorption is obtained if the progesterone is rubbed into a mucous membrane surface (inner aspects of labia or intravaginally), called "trans-mucosal" administration. Another advantage of topical natural progesterone cream is that individualized dosing can be easily facilitated by varying the amount of cream applied.

As one can readily discern from the peer-reviewed published literature, non-bioidentical progestin has demonstrated severe side effects, whereas bioidentical progesterone has a multitude of proven health benefits.

Estriol Does Not Increase the Risk of Breast Cancer

Now that we have set the record straight on bioidentical progesterone and breast cancer risk, let's examine the research concerning **estrogen** and the risk of breast cancer. When discussing estrogen it is important to note that "estrogen" is an umbrella term for many different estrogens including **estriol**, **estrone**, and **estradiol**. All three of these estrogens are produced in the body and have physiological effects. ***Estriol*** was originally thought to have little physiological

significance due to its weak estrogenic activity when compared with ***estrone*** and ***estradiol*.** Nonetheless, research has shown that estriol's weakness may very well be its strength.

The benefits of ***estriol*** may, in part, be explained by its mixed pro-estrogenic and anti-estrogenic effects. Scientists investigated the mixture of stimulating and non-stimulating effects posed by estriol upon estrogen receptors. When estriol is given together with estradiol, the estradiol-specific stimulation to cells is decreased.60 This little-appreciated scientific fact helps to explain how *estriol* can reduce pro-carcinogenic effects of more powerful estrogens like estradiol. Experimental studies suggest that ***estriol*** has a protective effect against radiation-induced cancer of the breast.61

A greater understanding of estriol's anti-estrogenic activity becomes apparent when examining the differing effects of the three primary estrogens upon estrogen receptor *binding* activity. There are two distinct estrogen receptors that estrogen hormones bind to on breast cells: estrogen receptor ***alpha*** and estrogen receptor ***beta***.62-67 The binding of estrogen hormones to estrogen receptor *alpha* **promotes** *breast cell proliferation*, which can lead to breast cancer development. Conversely, the binding of estrogen hormones to estrogen receptor beta **inhibits** breast cell proliferation and prevents breast cancer development.68-73

Estrone and estradiol bind to and activate estrogen receptor ***alpha***, thereby explaining the known breast cancer promoting effects of these two hormones. 74-75 **Estriol**, on the other hand, binds to and activates estrogen receptor ***beta*.**74-75 This critical fact helps to explain estriol's anti-estrogen activity, which led a noted researcher in hormone replacement therapy to state: *"**This unique property of estriol, in contrast to the selective ER [estrogen receptor] alpha binding by other estrogens imparts to estriol a potential for breast cancer prevention, while other estrogens [estrone and estradiol], would be expected to promote breast cancer… Because of its differing effects on ER alpha and ER beta, we would expect that estriol would be less likely to induce proliferative [potential cancerous growth] changes in breast tissue and to be associated with a reduced risk of breast cancer**."106*

A study published in the *International Journal of Cancer* in 2004 reported on the use of hormone replacement therapy (HRT) and breast cancer incidence in 31,450 postmenopausal women. The analysis of the data determined that women who used **estriol** did not have an increased risk of breast cancer, compared to women who never used HRT.76 Further confirmation of estriol's safety was provided by a study that compared use of HRT in 3,345 women over age 50 with breast cancer to 3,454 women without breast cancer. Those women who used non-bioidentical estrogen had a risk of breast cancer that was ***double*** that of women who never used HRT. However, women who used **estriol** did not have an increased risk of breast cancer, compared to women who never used HRT.77

Intriguing research has uncovered that ***estriol*** might confer a protective effect against the development of breast cancer. This was demonstrated in an unpublished 35- to 40-year prospective study of 15,000 women who had pregnancies between 1959 and 1967. The women had samples of their blood frozen for 30 years or more. In 1997, the researchers thawed the blood and measured hormone levels to determine the relationship between estriol levels during pregnancy and subsequent incidence of breast cancer. The researchers found that breast cancer

risk was **reduced** by **58%** among women with the highest **estriol** levels compared to those with the lowest estriol levels.78 This study has important implications, as the findings suggest that having *optimal* estriol levels can play a pivotal role in the prevention of breast cancer.

Estriol and Uterine Cancer

The increased risk of uterine cancer in users of non-bioidentical estrogen is well-established in the scientific literature.79-80 In contrast, the use of topical lower-potency estriol is not associated with an increased risk of uterine cancer.81-83 The use of intravaginal estriol has also been shown to be quite safe. A review of 12 studies determined that the use of intravaginal estriol did not result in endometrial proliferation (abnormal overgrowth of the cells lining the uterus with the potential to become cancerous). The authors of the study concluded that "***single daily treatment with intravaginal estriol in the recommended doses in postmenopausal women is safe and without an increased risk of endometrial proliferation or hyperplasia***."84

Although the oral route of administration of estriol appears relatively safe over the short-term, the topical application is preferred for long-term use. For example, one study found an increased risk of endometrial atypical hyperplasia and endometrial cancer with oral use of estriol, but not with ***topically-applied*** estriol over at least a five-year period. Compared with individuals who did not take estriol, those who took oral estriol for at least five years had a significantly greater risk of uterine cancer. Women using topical estriol for at least five years did not have any increased risk.83 As you will read in the "Safety" box, several studies suggest that the use of topical bioidentical **progesterone** cream may further reduce the risk to the endometrium.133-135 In fact, even mainstream medicine long ago learned that when estrogen is given to women with an intact uterus, progesterone is required to oppose the cell proliferating effects that most estrogens exert in uterine tissues.

SAFETY CONCERNS

Most of the research cited in this article used oral estrogen as the route of administration. However, for enhanced safety, topical estriol would be a better choice. Several studies have shown that transdermal and transmucosal estrogen confers less health risk as a route of administration than oral estrogen.[83,140-143] Clinical experience of many doctors over the past 20-30 years suggests that transdermal and transmucosal estrogen is also more effective for some women. This is largely thought to be due to the 'first-pass effect'—meaning that orally ingested drugs are often first metabolized in the liver, before having any activity in the body. Orally ingested estrogen hormones are among these drugs that are first metabolized in the liver before exerting their effects in the body. Physicians experienced in hormone replacement often observe that women treated with oral estrogens show high levels of estrogen metabolites in 24-hour urine specimens, suggesting that most of the orally ingested hormones are being excreted.

In addition, several studies suggest that bioidentical estrogen has less health risk when given with low doses of bioidentical progesterone.[144,145]

IS CANCER RISK A REASON TO DEPRIVE AGING WOMEN OF NATURAL HORMONES?

Concern about cancer is the primary reason why more women do not restore their hormones to more youthful levels. Like much of what we eat, estrogen and testosterone affect cell proliferation. Does that mean women should shrivel up, degenerate, and die from the sex hormone deficiencies they face as a part of "normal" aging?

Based on the data showing how people may reduce their rate of cancer and favorably affect estrogen metabolism in ways that point to cancer prevention (by consuming lots of cruciferous vegetables, for example), it is difficult to buy into the argument that natural sex hormones should only be enjoyed by the young.

As we describe later in this article, large human population studies show huge reductions in cancer risk and often a specific protective mechanisms against estrogen's negative pathways when vitamin D [229-234], cruciferous vegetables[235-245] (a source of indole-3-carbinol, or I3C), soy [246-250], D-glucarate[251-255], and lignans[256-257] are consumed. Dramatic cancer rate reductions also occur when red meat, high-fat dairy, and other deleterious foods are reduced or eliminated from the diet. [258-259]

Misconceptions generated by conflicting studies and media hype have created an environment in which aging people suffer the agonies and shortened life spans caused by sex hormone imbalances, yet do nothing to correct this due to fear of cancer. When one looks at what the real cancer risk factors are, it would appear that altering one's lifestyle at any age would result in significant reductions in malignant disease, including those who properly restore their natural hormone balance to reflect a more youthful range.

The Real Cause of Breast Cancer

To fully understand the carcinogenic effects of aging, we have reprinted a chart showing women's breast cancer risk by age [260]. A quick look at this chart clearly documents that aging is the primary cause of breast cancer. The good news is that many of the gene expression changes involved in the development of breast cancer can be favorably altered by taking low-cost nutrients like vitamin D [261-263] in the dose of 1,000 IU to 10,000 IU/day, based on individual need.

Risk of Developing Breast Cancer by Age[260]

By age 25: 1 in 19,608
By age 30: 1 in 2,525
By age 40: 1 in 217
By age 45: 1 in 93
By age 50: 1 in 50
By age 55: 1 in 33
By age 60: 1 in 24
By age 65: 1 in 17
By age 70: 1 in 14
By age 75: 1 in 11
By age 80: 1 in 10
By age 85: 1 in 9

Why Young Women with High Estrogen Seldom Contract Breast Cancer

During women's younger years, when breast cancer is virtually non-existent, they enjoy high levels of our sex hormones (estrogen, progesterone, dehydroepiandrosterone, and testosterone). As they age and hormone levels decline, breast cancer risks increase. The reason "aging" causes cancer is that the genes in cells that *regulate* cell proliferation become increasingly mutated. The accumulation of mutations to the cells' regulatory genes is the underlying cause of cancer[264]. It is encouraging to know that there are low-cost nutrients that favorably restore healthy gene function and reduce cancer risk in the process.

One study cites evidence that **vitamin D** can exert its cancer-preventing effect by counteracting the growth-promoting effect of estrogens [265] Vitamin D also exerts its cancer-preventive influence by helping to control cell differentiation and inducing normal programmed cell disposal (apoptosis) [265]

Based on the enormity of these data, it would appear that maturing women can safely restore many of the hormones they need to sustain life—without encountering adverse effects. Based on the totality of evidence that exists to date, ***estriol*** and ***natural progesterone*** demonstrate many benefits, including a potential reduction in risk of breast cancer.

Definitive measures to protect against breast and other cancers can easily be incorporated into a woman's lifestyle. We describe a more complete description of what all women (whether or not they choose to take estrogen) should do to reduce their risk of contracting breast and other cancers later in this article.

Bioidentical Progesterone and Cardiovascular Health

The *Women's Health Initiative*, a large randomized clinical trial, demonstrated that the addition of non-bioidentical progestin to non-bioidentical estrogen therapy resulted in a substantial increase in the risk of heart attack and stroke 85-87. Numerous studies, on the other hand, document that *bioidentical* progesterone has *beneficial* effects on cardiovascular health. In one trial published in the *Journal of the American College of Cardiology*, researchers studied postmenopausal women with a history of heart attack or coronary artery disease. The women were given estrogen in combination with either bioidentical progesterone or non-bioidentical progestin. After 10 days of treatment the women underwent exercise treadmill tests. Compared to the non-bioidentical progestin group, the amount of time it took to produce myocardial ischemia (reduced blood flow to the heart) on the exercise treadmill was substantially *improved* in the bioidentical progesterone group.88

The risk of a blood clot is a serious concern with the use of unnatural estrogen replacement therapy. Some doctors are concerned about blood clots when bio-identical estrogen is taken by mouth and not transdermally.This risk doesn't occur with bio-identical progesterone. One investigation compared the risk of blood clots in postmenopausal women taking bioidentical progesterone to the risk in women taking non-bioidentical progestin. The group of women who used non-bioidentical progestin in combination with estrogen had a startling **290% greater** risk of **blood clots**, compared to the group who never used HRT. In a reversal of fortunes, the group receiving bioidentical progesterone in combination with estrogen had a **30% decreased** risk of **blood clots**, compared to women who never used HRT.89

Atherosclerosis (hardening of the arteries) is the leading cause of heart disease. Several studies have determined that non-bioidentical progestin promotes the formation of atherosclerosis.90-92 The story is quite different for bioidentical progesterone, where multiple studies have shown that bioidentical progesterone *inhibits* the process of atherosclerosis.93-97 To illustrate, scientists fed postmenopausal monkeys a diet which is known to cause atherosclerosis for 30 months. The scientists then divided the monkeys into groups that received estrogen alone, estrogen plus non-bioidentical progestin, or a control group that did not receive hormones. The control group developed substantial atherosclerotic plaque. The administration of estrogen resulted in a **72%** decrease in atherosclerotic plaque, compared to the control group. Treatment with non-bioidentical progestin yielded disturbing results. The group that received estrogen combined with non-bioidentical progestin had a similar amount of atherosclerotic plaque as the control group, meaning that non-bioidentical progestin completely ***reversed*** estrogen's inhibitory effects on the formation of atherosclerosis.96 In a very similar experiment, the same scientists found that the administration of estrogen combined with *bioidentical* progesterone led to a **50% decrease** in atherosclerotic plaque formation.97

Bioidentical Progesterone and HDL

HDL (*high-density lipoprotein*) functions to *remove* cholesterol from the arterial wall and thus helps protect against the development of atherosclerosis. Low HDL is a proven risk factor that contributes to heart disease. Non-bioidentical progestin is known to cause reductions in HDL levels.98,99,125-129 One mechanism by which bioidentical progesterone enhances cardiovascular health is its ability to maintain or even increase **HDL** levels in women receiving estrogen replacement therapy.99,125, 130-132 In one study published in the *Journal of the American Medical Association*, 875 postmenopausal women were randomized to receive estrogen alone, estrogen combined with non-bioidentical progestin, estrogen combined with bioidentical progesterone, or placebo. The results demonstrated that the group receiving bioidentical progesterone experienced significantly higher **HDL** levels than the group receiving non-bioidentical progestin.99 Corroboration of these results were provided by researchers who administered estrogen combined with either non-bioidentical progestin or bioidentical progesterone to postmenopausal women. The use of non-bioidentical progestin resulted in an undesirable **15% decrease** in **HDL** levels, whereas there was no decrease in HDL levels in those patients prescribed bioidentical progesterone.125

Estriol and Cardiovascular Health

Growing evidence suggests that *estriol* may offer benefits to the cardiovascular system. For instance, Japanese scientists found that some women with natural menopause given 2 mg/day oral estriol for 12 months had a significant decrease in both systolic and diastolic **blood pressure**.81 Another study compared the use of oral estriol at a dose of 2 mg/day for 10 months in 20 postmenopausal and 29 elderly women. Some of the elderly women had decreases in total cholesterol and triglycerides and an increase in beneficial HDL.108

To examine the effects of estriol on atherosclerosis, researchers conducted an experiment in which female rabbits were fed a high cholesterol diet with or without supplemental estriol. The rabbits had their ovaries removed surgically to mimic menopause. Remarkably, the group receiving **estriol** had **75% less** atherosclerosis than the group fed the high cholesterol diet alone (without estriol).148

Bioidentical Progesterone vs. Non-Bioidentical Progestin for the Treatment of Menopausal Symptoms

Now that we have dispelled the myth the bioidentical hormones cause the same diseases as non-bioidentical hormones, let's examine the research comparing the effectiveness of bioidentical to non-bioidentical progestin for the treatment of menopausal symptoms. You may not be not be surprised to learn that bioidentical progesterone has outperformed non-bioidentical progestin in the treatment of menopausal symptoms. In fact, **four** head-to-head studies comparing bioidentical progesterone to non-bioidentical progestin reported that women in all **four studies** experienced greater satisfaction, improved quality of life, and fewer side effects when they were switched from non-bioidentical progestin to bioidentical progesterone.

In a *landmark study*, researchers at the *Mayo Clinic* studied 176 menopausal women receiving hormone replacement therapy. All of these women had previously taken hormone replacement therapy with non-bioidentical progestin, but were switched at a later date to bioidentical progesterone. The findings across the board showed that women had substantially **greater improvement** in their symptoms when using bioidentical progesterone, compared to non-bioidentical progestin. ***65%*** *of the women believed that HRT combined with* bioidentical progesterone was **better** *than HRT combined with non-bioidentical progestin*. The beneficial effects of bioidentical progesterone compared to non-bioidentical progestin included a **30%** reduction in sleep problems, a **50%** reduction in anxiety, a **60%** reduction in depression, a **25%** reduction in menstrual bleeding, a **40%** reduction in cognitive difficulties, and a **30%** improvement in sexual function.100 The results of this study provide resounding evidence of the *superiority* of bioidentical progesterone over non-bioidentical progestin in the treatment of menopausal symptoms.

Further research has confirmed that bioidentical progesterone is preferable to non-bioidentical progestin. One study of menopausal women receiving HRT found that those receiving non-bioidentical progestin experienced greater vaginal bleeding and breast tenderness than those receiving bioidentical progesterone.101 Additionally, two other studies with menopausal women also determined that HRT with non-bioidentical progestin was associated with greater vaginal bleeding compared to those receiving bioidentical progesterone. 102-103 Investigations comparing bioidentical progesterone to non-bioidentical progestin revealed *greater improvements* in quality of sleep, cognitive function, and menstrual problems in the groups receiving bioidentical progesterone. 104-105

Estriol and Menopausal Symptoms

Studies have shown estriol to be effective in the treatment of menopausal symptoms. In one investigation, 52 postmenopausal women were given either 2 mg, 4 mg, 6 mg, or 8 mg/day of oral estriol for six months. In all patients, vasomotor symptoms of menopause (such as hot flashes) were decreased. The most improvement was experienced by women taking the highest dose of 8 mg. There were no signs of endometrial hyperplasia confirmed by endometrial biopsy over the six-month treatment period. Mammograms were obtained on six of the patients who had breast hyperplasia at the study's outset, and no further changes were seen.136

In another trial, researchers studied the safety of estriol in the treatment of menopausal symptoms. 53 women with either surgically induced or natural menopause were given 2 mg of oral estriol/day for 12 months. Endometrial and breast assessments done with endometrial biopsy and breast ultrasound found normal results in all women. The authors concluded that over a 12-month period, "***estriol appeared to be safe and effective in relieving symptoms of menopausal women***."81

A 5-year study demonstrated the successful use of estriol in the treatment of menopausal symptoms. In **71%** of the participants, hot flashes and sweating were eliminated completely, while in **21%** they were weaker and occurred less frequently. Depressive moods were abolished in **24%** of the women and were reduced in severity in another **33%**. Reductions in

forgetfulness, loss of concentration, irritability, and heart palpitations also were recorded. The number of women who experienced migraine headaches dropped by two thirds. All of this occurred without notable side effects.146

Given the wealth of data demonstrating the superiority of bioidentical HRT over non-bioidentical HRT, a noted researcher in hormone replacement therapy proclaimed that "***physiological data and clinical outcomes demonstrate that bioidentical hormones are associated with lower risks, including the risk of breast cancer and cardiovascular disease, and are more efficacious than their…animal derived [non-bioidentical] counterparts. Until evidence is found to the contrary, bioidentical hormones remain the preferred method of HRT****."* 106

Beyond Menopause: Enhancing Health with Bioidentical Hormones

The benefits of bioidentical hormones are by no means limited to the relief of menopausal symptoms. Maturing women can reap long-term health benefits by restoring youthful hormonal balance with the use of bioidentical hormones. The **Life Extension Foundation** has written extensively regarding the importance of maintaining optimal hormone balance as we age in order to insure optimal health.

Estriol Increases Bone Mineral Density

One of the unfortunate consequences of decreased estrogen production in maturing women is the loss of bone density, with the potential to develop osteoporosis. A Japanese study involving 75 postmenopausal women found that after 50 weeks of treatment with 2 mg/day of oral estriol cyclically and 800 mg/day of calcium lactate, women had an increase in bone mineral density with no increased risk of endometrial hyperplasia (uterine tissue overgrowth that may precede cancer).107 In a second study emanating from Japan, researchers treated postmenopausal and elderly women with 2 mg/day of oral estriol and 1,000 mg/day of calcium lactate versus 1,000 mg/day calcium lactate alone. Bone mineral density significantly increased in women who received *estriol*, while the women who *did not* take estriol experienced a decrease in bone mineral density.108

Similar research has confirmed these findings. In this investigation, 25 postmenopausal women were given either 2mg/day of estriol plus 2 gram/day of calcium lactate, or 2 gram/day of calcium lactate alone for one year. Bone mineral density was significantly reduced in the group that received calcium alone (without estriol). In contrast, the group that received estriol plus calcium experienced a ***1.66% increase*** in bone mineral density after one year. Furthermore, biochemical markers of bone metabolism were significantly decreased in the estriol group. *"**These data indicate that the acceleration of bone turnover usually observed after menopause was prevented by treatment with E3 [estriol]**"*, the authors of this study noted. 109

The most dramatic improvements in bone density were reported by scientists in the *Journal of Bone and Mineral Metabolism*. In this study, 41 women over age 49 with decreased bone density received either 2 mg/day estriol orally with calcium, or calcium alone for 10 months.

The group receiving **estriol** experienced a striking **4.53% increase** in bone density, while the group that did not receive estriol experienced a **3.62% decrease** in bone density.147

Estriol Enhances Sexual and Urinary Health

Postmenopausal women who suffer from urinary incontinence or recurrent urinary tract infections will be pleased to know that estriol offers relief from these troublesome symptoms. In a prospective, randomized, placebo-controlled study, 88 women were given 2 mg intravaginal estriol suppositories (once daily for two weeks, then twice weekly for six months) or placebo. Of the women in the estriol group, **68%** reported improvement in symptoms of incontinence. 110

In another randomized, double-blind, placebo-controlled trial, women with recurrent urinary tract infections were given either intravaginal estriol cream (containing 0.5 mg estriol, once daily for two weeks, then twice weekly for eight months) or placebo. Incredibly, the incidence of urinary tract infection was **reduced by 91%** in the estriol group compared with placebo. 111

The substantial decrease in estrogen that occurs after menopause can lead to a condition called *atrophic vaginitis*. The symptoms, which include vaginal dryness, vaginal burning, and painful sex can be quite bothersome for maturing women. Fortunately, the use of **estriol** can offer relief for women suffering from these symptoms. One group of researchers, who prescribed oral estriol to 62 postmenopausal women with vaginal symptoms in a double-blind and placebo-controlled fashion, concluded that "***estriol has a remarkably beneficial effect on the vaginal epithelium***."137 Another group of researchers prescribed an estriol cream for women with atrophic vaginitis. After 4 weeks of treatment, the researchers noted that "***atrophy of vaginal epithelium and chronic vaginitis stopped or significantly decreased…The subjective complaints relating to the estrogen deficiency (vaginal burning and dryness, itching, dyspareunia [painful sex] and urinary dysfunctions) ceased. Side-effects and complications during the treatment were not found***."138

In a study conducted in Japan, oral estriol (2mg/day) was administered to 59 postmenopausal women complaining of vaginal itching or discharge. After 14 days of treatment, substantial improvements were noted in the women's vaginal flora. The authors of the study concluded: "***Estriol…has the potential to be highly useful for the treatment of atrophic vaginitis***."139

Estriol Promotes Youthful Skin

One reason that facial skin "shrivels" as we age is that our natural hormone production markedly declines. To make matters worse, blood microcirculation to our skin is reduced as we grow older, thereby depriving our skin of the small amount of natural hormones our body still makes. A large number of published scientific studies reveal that estrogen exerts potent anti-aging effects on the skin.112-123 The topical application of natural estrogen can produce dramatic improvements to the skin without systemic absorption concerns.

The deficiency of estrogen that characterizes menopause exacerbates the
effects of both normal and environmental skin aging. According to the findings of a scientific study published last year, "***estrogens prevent skin aging. They increase skin thickness and improve skin moisture."123 Another recent study came to the same conclusion, i.e. "skin aging can be significantly delayed by the administration of estrogen***."113

A critical mechanism by which estrogen maintains a youthful plump appearance is to increase the synthesis of **collagen**, which is the skin's underlying support structure. Collagen atrophy is a major factor in skin aging. There is a strong correlation between skin collagen loss and estrogen deficiency at menopause.112

Skin aging, especially in the face, is associated with a progressive increase in sagging tissues and a reduction in elasticity. In menopausal and postmenopausal women, estrogen administration increases collagen content, dermal thickness and elasticity, while decreasing aging dry skin.112,115

Estrogens exert significant effects on skin physiology by modulating the effects of key epidermal and dermal cells.113 In fact, the skin is an important estrogen-responsive endocrine tissue.114 Without the growth promoting effects of estrogen, the skin literally withers away. The very thin skin observed in the elderly can be directly correlated to lack of estrogens needed to generate collagen and maintain skin thickness.114

Topical estrogen application has been shown to be safe and effective in preventing skin aging. In a study published in February 2007, a group of women who were already taking oral estrogen drugs were given a topical 0.01% estrogen cream. After only four months, both dermal and epidermal thickness was enhanced, as well as dermal collagen levels. This study showed that topical estrogen application provided rapid and definitive anti-aging effects even in women who had high systemic estrogen blood levels.115 The significance of this study is that it shows how quickly a small amount of estrogen delivered directly into the skin induces profound anti-aging effects.

A six-month study of peri- and postmenopausal women was conducted at the *University of Vienna in Austria* comparing the topical application of estriol and estradiol creams. The doctors found that skin symptoms of aging improved, and that those treated with *estriol* obtained superior results, with no systemic hormonal side effects noted.116

Twenty women with mild crow's feet, rough-textured skin, and moderate skin tone with some blotching and imperfections applied a topical solution containing estriol with 15 other ingredients on only one side of their faces over a six-week period. All of the subjects reported that their skin texture was smoother and that the quality of their skin had improved, while **90%** and **80%** said that the moisture content and elasticity of their skin had increased, respectively, giving them a healthier and younger-looking appearance. Clinical assessments showed a baseline improvement of **19%** increase in elasticity and **9%** increase in moisture in the skin after just one week.124

How Bioidentical Estrogen-Progesterone Is Prescribed

Currently, widespread commercial availability of individually tailored bioidentical hormone prescriptions is lacking. As a result, many physicians utilize **compounding pharmacies** to dispense **bioidentical hormone** prescriptions for their patients. To obtain the phone number of a compounding pharmacist, call 1-800-226-2370.

Most practitioners use the level of **estradiol** in women's blood, along with an assessment of the patient's symptoms to prescribe the initial dose of bioidentical estrogen. The estradiol blood level must be considered in context to the other hormones such as progesterone. Looking at the estradiol blood level alone as a target is somewhat effective but not entirely comprehensive. A practitioner may also measure levels of estrone and estriol to obtain a more comprehensive assessment of a woman's estrogen status.

Here is an example of how estradiol reading is commonly used as an approximation. In menopause, a woman typically has an estradiol blood level of **0-19** pg/mL. If with **bi-est** topical cream (compounded estriol and estradiol), the blood estradiol level goes up to **100** pg/mL, for example, then the doctor knows that the bi-est is being *absorbed* and has increased the patient's estradiol level to a more youthful range.

A doctor may then assume that the other estrogens also went up, and if the patient reports her menopausal symptoms have resolved and is happy, most practitioners would stop there and continue the patient on the dosage she has been using and do periodic follow-up.

If, however, the patient is still having symptoms, the **bi-est** topical cream dose can be increased or additional tests ordered such as the **total estrogen** blood test or a **urinary estrogen** test to get a better handle on the other estrogens and their metabolites. Based on findings from these tests, a more precise dose of estriol, estradiol, progesterone and sometimes testosterone can be prescribed A typical starting dose for **bi-est** topical cream prescription might read as:

Bi-est: 0.5 mg estradiol/2.0 mg estriol per mL
Apply 1 mL topically every day
#60 mL

Please note that this is a general suggestion for an initial prescription. A physician experienced in bioidentical hormone replacement will tailor the prescription to the person's individual needs.

The **bi-est** dose can be increased when severe symptoms of estrogen deficiency are present.

.Any women with an intact uterus must also be prescribed *natural progesterone* (not synthetic progestin drugs like Provera®) in a dose that achieves a youthful balance. Natural progesterone produces many benefits when properly balanced
with estrogen. A typical twice-daily dose is one-quarter teaspoon of a 2.5% OTC natural progesterone cream applied to a different part of the body twice each day. Progesterone can help

the skin appear younger, and many women apply it on certain days to their facial skin. It can also be applied to the breasts and inner thighs. Suggested dosing is as follows:

- Premenstrual and perimenopausal women: 1/4 tsp. twice daily starting on day 12 of the menstrual cycle continuing up to day 28.
- Menopausal women: 1/4 tsp. twice daily for 21 days followed by 7 days off.
- The dose for progesterone may vary between 50-200 mg.

The dose can be adjusted up or down depending on the symptoms and response. If using *natural progesterone* cream from a pharmacy, the prescription may be written as follows for a postmenopausal woman:

PROGESTERONE cream 50 mg/mL
Directions: Apply 1 mL (pump) topically
twice daily or at bedtime) days 1-25
Dispense: 1 or 2 month supply

A prescription for a premenopausal woman might read:

PROGESTERONE crème 25 milligrams / 0.1 cc
Directions: Apply 0.2 cc to the labia or intravaginally daily
on days 10-25 of a 28 day "cycle"
Dispense: 1 or 2 month supply

Some women, particularly with weak adrenal function, are advised to also use 25 milligrams (0.1cc) for days 1-10 of a 28 day "cycle"

Most physicians will prescribe topical progesterone in a similar way to estrogens, in milligrams per fraction of a cubic centimeter (cc). These dosages are "pressed out" of a syringe on to the skin, and have the dual advantages of more precise dosage adjustment and smaller volume of "crème", which is less likely to make a mess on clothing.

A blood level target to strive for in aging women might be:

Estradiol	**90-250 pg/mL**
Progesterone	**2.0-6.0 ng/mL**
Free testosterone	**1.0-2.2 pg/mL**

Before a prescription for bioidentical hormones can be written, it is important to have a baseline blood test so the doctor knows what dose of bioidentical estrogens, progesterone and possibly

testosterone may be needed. To order a comprehensive Female Blood Test Panel that includes estradiol, progesterone and free testosterone, call **1-818-990-1166**

Although this paper focuses on bioidentical estrogen and progesterone, it is important to also address testosterone levels in order to achieve optimal hormonal balance. Although testosterone is thought of as a male hormone, it plays an important role in women's health as well. Testosterone levels decrease in women as they age. Low testosterone in women can have a negative impact upon sex drive, mood and well-being, bone and muscle mass, and cardiovascular health. A physician experienced in bioidentical hormone therapy will measure testosterone levels in women, and prescribe bioidentical testosterone if levels are low. Correcting low testosterone in women usually requires a 150 to 300 mcg patch or an individually prescribed testosterone cream. Since DHEA (dehydroepiandrosterone) can convert to testosterone in a woman's body, a woman with low testosterone might be able to increase her testosterone level by taking 15 mg to 25 mg a day of DHEA, which is available as a low cost dietary supplement.

Too much free testosterone in an aging woman induces abdominal weight gain [223, 224], as does a *deficiency* of estradiol [225-228]. Progesterone may be weight neutral, though some complementary practitioners claim it helps facilitate weight loss. Some doctors seek to increase progesterone levels up to 15 ng/mL.

The objective is to achieve a more youthful sex hormone balance to improve the patient's appearance, state of health and well-being. The use of estrogen drugs is contraindicated in women with existing estrogen-receptor positive cancer.

Testing Hormone Metabolites in the Urine

Some physicians prefer to follow their initial bioidentical hormone prescription with a comprehensive hormone analysis performed on a urine specimen collected over 24 hours. This much more complete evaluation allows not only evaluation of the levels of the hormones in the prescription, but also whether they metabolize into other estrogen metabolites as safely as possible.

This follow-up automatically measures two ratios important to assessment of estrogen related cancer risk—the "2/16 hydroxyestrogen ratio", the relationship of estriol to estradiol and estrone (the "EQ", estrogen quotient—and also levels of 2-methoxyestradiol, an estrogen with potent anticarcinogenic potential, and 4-hydroxyestrone, an estrogen metabolite with strong pro-carcinogenic tendencies. With this comprehensive evaluation, your physician can more precisely recommend appropriate vitamins, minerals, and botanicals to correct your estrogen metabolism if necessary to optimize hormone safety. (A more indepth explanation of the 2/16 hydroxyestrogen appears later in this paper.)

The comprehensive hormone evaluation also includes measurement of testosterone, DHEA, progesterone and some of their metabolites, once again checking for both hormone levels and "hormone safety". Cortisol, cortisone, aldosterone, and other

important natural steroids and some of their metabolites are measured as well. To obtain information about this 24 comprehensive urine test, call **1-818-990-1166**

Why Skeptics Are Still Concerned About Estriol

Based on what you have read so far, **estriol** appears to be a safe and optimal antidote to correct *estrogen deficits*. Not everyone agrees, however.

Some doctors are concerned that the long-term use of **estriol** might *increase* cancer risk. These doctors seem unaware of the substantial evidence indicating that estriol may *reduce* breast cancer incidence, or of documented methods to *protect* against estrogen-induced side effects.

Unlike cynics who view *any* form of estrogen as a carcinogen, the **Life Extension Foundation** has examined the published studies to ascertain what real risks may exist when supplementing with estriol (and other estrogens)..

One concern about <u>all</u> estrogens is that they undergo alterations in the body that can result in these estrogens cascading into either pro-carcinogen or anti-carcinogen compounds. The good news is that one can largely <u>control</u> whether estrogens *increase* or *decrease* cancer risk via their diet and/or supplement intake.

Skeptics view ***estriol*** supplementation in a vacuum, as if women will take estriol and nothing else. You have already read extensive documentation about how ***natural progesterone*** significantly protects against estrogen-induced cancers. What you will read next is what <u>all</u> women should do to <u>reduce</u> breast and other cancer risk (whether or not they take supplemental estrogen).

These recommendations are based on large human population studies showing huge reductions in cancer risk <u>and</u> specific protective mechanisms against estrogen's negative pathways when vitamin D, cruciferous vegetables, soy, D-glucarate, and/or plant lignans are consumed. These cancer rate reductions also occur when red meat, high-fat dairy, and other deleterious foods are reduced or eliminated from the diet.

Critical importance of Vitamin D

Young women (under age 30) almost never develop breast cancer. The reason is that their genes that regulate cellular proliferation have not yet mutated in an adverse way. As women age, their cell growth regulatory genes accumulate mutations. When genes that regulate cell division mutate, a result can be uncontrolled cell propagation that results in tumor formation. Aging women experience a dramatic rise in cancer incidence, even as their estrogen levels plummet.

In the presence of mutations to cell regulatory genes, estrogen can promote cancer cell propagation. The good news is that the ingestion of vitamin D, cruciferous vegetables and other compounds can *reverse* gene mutations and thus reduce cancer risk. All women (including those who maintain youthful estrogen levels) should make sure they are ingesting optimal amounts of vitamin D and other compounds that favorably alter gene expression.

Vitamin D confers significant protective effects against breast cancer. Laboratory studies have shown that vitamin D suppresses growth of breast cancer by 1) blocking signals that stimulate cancer cell growth, 2) by enhancing signals that inhibit cancer cell growth, and 3) by favorably altering gene regulators of the cell cycle.151 This three-pronged effect of vitamin D can prevent mutated cells from becoming malignant and even induce cancer cell death (apoptosis).

Studies have found a strong correlation between blood levels of vitamin D and the risk of breast cancer. A case-control study comparing 1,394 postmenopausal breast cancer patients with 1,365 controls showed that low blood levels of vitamin D were significantly related to breast cancer risk. In fact, women with the highest levels of vitamin D had a **70% reduction** in their risk of breast cancer.152

Similar research examining the relationship between blood levels of vitamin D and breast cancer risk revealed that women with blood vitamin D levels of approximately **52** ng/mL had a **50% lower** risk of breast cancer compared with women who had vitamin D levels below **13** ng/mL.153

In a one report, the effects of administering **1,100 IU** a day of vitamin D (with calcium) was evaluated in 1,180 postmenopausal women.150 After only four years, the risk of contracting any cancer was **60% lower** in the vitamin D (and calcium) group, compared with the placebo arm of the study. The scientists then performed a more detailed analysis of the data. When excluding cancers diagnosed in the first year of the study, which would have included preexisting cancers present at the time participants began taking vitamin D, they found an astounding **77% reduction** in cancer incidence in the group receiving vitamin D, compared with placebo.

Ensuring vitamin D blood levels over **50** ng/mL is a critical step in reducing cancer risk. ***Life Extension*** is finding that many people require **5,000 IU** a day of supplemental vitamin D3 and higher to achieve these optimal blood levels. The heavier one is, the more supplemental vitamin D they often require. (Note that vitamin D status in the body is measured as *25-hydroxvitamin D* serum.)

Based on the cumulative data, it is absurd for doctors to disparage the use of **bioidentical hormone** replacement therapy (HRT) while *ignoring* the proven role that low vitamin D levels play in the development of a host of age-related diseases (including cancer).

Cruciferous Vegetables Protect Against Estrogen Metabolites

Scientists have identified compounds in cruciferous vegetables (broccoli, cauliflower, Brussels sprouts, cabbage, kale) that specifically *neutralize* dangerous breakdown products of estrogen

that promote cancer growth.154-159 Cruciferous vegetable compounds also help neutralize the many carcinogens we are inevitably exposed to each day.160,161

One of best studied cruciferous vegetable compounds is called *indole-3-carbinol* (I3C). Women seeking to restore youthful hormone balance should make sure to obtain enough I3C from their diet or by taking standardized supplements. The reason for this is that I3C *increases* levels of a cancer-protective estrogen metabolite (*2-hydroxyestrone*), while suppressing a dangerous estrogen metabolite (*16-alpha-hydroxy-estrone*) that promotes breast and other cancers.162,163

To emphasize the critical importance of *indole-3-carbinol* (I3C), please understand that aging women still produce estrogen, and that the estrogen they supplement with can follow two primary metabolic pathways in the body. If estrogen is converted to *16-alpha-hydroxy-estrone*, then the risk of breast and other cancers is increased. If on the other hand, we convert estrogen to *2-hydroxy-estrone*, then the risk for breast and other cancers is decreased.164-166

I3C can readily be obtained by eating lots of cruciferous vegetables and/or taking I3C in dietary supplement form.

To confirm the theory that certain estrogen metabolites can contribute to cancer, researchers analyzed data gathered from over 10,000 Italian women over more than five years. The objective was to determine how dietary and hormonal factors influence breast cancer risk. They found that women were much less likely to develop breast cancer when they had higher levels of *2-hydroxy-estrone*.164 This same finding has been shown in additional studies of different populations.167,168

The toxic estrogen metabolite *16-alpha-hydroxy-estrone* acts as a breast tumor promoter.169 By contrast, estrogen metabolized via the *2-hydroxy-estrone* pathway does not exhibit adverse estrogenic activity in breast tissue.169 Additionally, a form of this less active estrogen metabolite is believed to prevent the formation of blood vessels necessary to feed growing cancers, thus helping to arrest tumor growth.170

Cruciferous vegetable compounds (such as I3C) are effective in shifting estrogen metabolism to the more beneficial pathway, thus reducing levels of toxic *16- alpha-hydroxy-estrone* and increasing levels of protective *2-hydroxyestrone*. 166,169,171,172

This beneficial modulation of estrogen is associated with reduced risk of breast and other cancers, including cervical and head and neck cancers.157,164-166 Cruciferous vegetable compounds thus play an important role in fighting cancer. To illustrate, research conducted at the University of California at Berkeley documented that I3C inhibited the growth of human breast cancer cells by an astounding **90%.** 174

Interestingly, an assay study performed at the *National Cancer Institute* determined that I3C was superior to 80 other natural substances with regard to anti-cancer potential.173

Soy Slashes Breast Cancer Risk

For the past decade, a controversy has raged over whether people can reduce their risk of cancer by increasing their consumption of soy foods or soy supplements. In response to the debate, a number of studies were initiated in the 1990s to ascertain soy's effects on human health.

Over the past few years, the results of these studies began to be released. While ignored by the mainstream media, the startling findings indicate that breast (and prostate) cancer risk can be cut in half if people consume more soy.175-178

One recent study showed a remarkable **90% <u>reduction</u>** in estrogen receptor-positive breast cancers in women who consumed lots of vegetables and soy (in lieu of a Western-style diet).175 This and other studies provide persuasive evidence that compounds found in soy have a breast cancer preventive effect.

Isoflavones derived from soy have shown great promise in providing natural protection against multiple types of cancer.179-181 Isoflavones are phytochemical constituents of soy, with two of the best known being genistein and daidzein.

The isoflavones are believed to exert a number of positive biological effects on the human body, and many practitioners of integrative medicine (and even a small but growing number in mainstream medicine) now believe that consumption of soy and isoflavones can reduce the risk of many chronic diseases, including cancer, heart disease, and osteoporosis.176-186

Studies conducted in Asia found that Asian women, who consume many more isoflavones than American women, have significantly lower risks of developing breast cancer.187 Because animal studies have shown that a diet high in soy and genistein can protect against breast, colon, and skin tumors,188 it seemed reasonable to think that soy could also help prevent human cancers and, in particular, breast cancer. Yet many mainstream medical practitioners remain skeptical that something as simple as soy could have such a profound effect on human health.

Some in the medical establishment believe that soy isoflavones have no role in preventing serious diseases such as cancer. Others believe that soy isoflavones should not be used as nutritional supplements because isoflavones act as natural estrogens and could cause many of the same problems—such as increased risk of stroke—that synthetic estrogens are now known to cause.

In fact, soy isoflavones do not simply act as "natural" estrogens. Soy isoflavones are correctly classified as *selective estrogen receptor modulators*. Due to their unique molecular structure, soy isoflavones can act as either estrogen receptor agonists or receptor blockers. With this ability, soy isoflavones are thought by many to confer the beneficial effects of estrogen without its potentially dangerous side effects, especially in hormonally sensitive tissues found in both the breast and endometrium.189

Numerous studies show the potential benefits to women of incorporating soy in their diets to help prevent breast cancer. A landmark case control study of women in Singapore, involving 200 case subjects and 420 control subjects, found that women with the highest consumption of soy-based products had a markedly decreased risk of developing breast cancer.190 An even larger

Japanese case-control study, involving 1,186 subjects and 23,163 controls, also showed that women with increased tofu (soybean curd) intake had a significantly decreased risk of developing breast cancer compared with women who consumed small amounts of soy-based products such as tofu.178 Finally, a very large population-based, prospective study of 21,852 Japanese women aged 40-59 found that women with the highest intake of soy isoflavones reduced their risk of breast cancer by up to **54%** compared with women with the lowest intake of soy isoflavones.187

Despite the evidence-based research showing soy isoflavones' preventive effects on breast cancer, along with epidemiological studies highlighting the much lower rates of breast cancer among Asian women who consume significant amounts of soy-based products, some doctors still caution women against using soy-based foods and supplements. They contend that because soy isoflavones have been labeled as estrogen "mimics," they could potentially worsen or even cause breast cancer. With the current knowledge that soy isoflavones act as *selective estrogen receptor modulators* and are not simply estrogen "mimics," these arguments do not hold up.

In addition to being a chemopreventive supplement for breast cancer, soy isoflavones are also thought to be effective in warding off other types of cancer that afflict women, including endometrial cancer. A recent case control study reported the effects of soy isoflavones and other phytoestrogens on the risk of developing endometrial cancer.191 The study compared 500 women aged 35-79 who developed endometrial cancer between 1996 and 1999 with 470 age- and ethnicity-matched controls. As in studies examining the effects of isoflavones on breast cancer, this study showed that women with a higher intake of soy isoflavones had a significantly lower risk of developing endometrial cancer. Even more interesting was that the levels of isoflavones needed to provide protection against endometrial cancer were found to be much lower than the amount believed necessary to protect against breast cancer.

Meat Increases Breast Cancer Risk

Studies that look at human populations (epidemiological studies) have consistently shown that what we eat affects our cancer risk. Women who eat red meat suffer higher breast cancer rates. In one of the better documented studies, postmenopausal women in China who ate a Western-style diet (which included beef, pork, and desserts) were **60% <u>more</u>** likely to develop breast cancer than those eating a diet based on vegetables and soy. Even more startling was the finding that in women who contracted *estrogen receptor-positive* breast tumors, those who ate the Western-style diet experienced a **90% <u>increased</u>** risk!192 This is in stark contrast to a study that demonstrated a **52% <u>decreased</u>** risk of breast cancer in women with the highest intake of vegetables and fruits, compared to the lowest intake.193

However, it's not known whether meat from "free range" animals (beef, buffalo, wild game, chicken, pigs) also increases breast cancer risk. While even organically raised grain fed animals (like commercially raised grain-fed animals) have much more omega-6 (pro-inflammatory) fatty acids than omega-3 (anti-inflammatory) amino acids, this ratio is reversed, with significantly more omega-3 than omega-6 in meat from free range animals. Theoretically, this much more natural ratio should be associated with lower breast (and other) cancer risk, but research still needs to be done on this point.

Fish Oil and Breast Cancer Risk

In addition to fish oil's well-known cardiovascular benefits, research has revealed that omega-3 rich fish oil might offer protection against breast cancer as well. *EPA and DHA* are the two most important components of fish oil One investigation documented a **49%** decreased risk of breast cancer in women with the highest dietary intake of omega-3 fatty acids, compared to those with the lowest intake. Furthermore, women with the highest red blood cell levels of EPA had a remarkable ***73%*** decreased risk breast cancer, compared to those with the lowest levels.194

A group of researchers in France compared levels of DHA in breast tissue in 241 patients with breast cancer and 88 patients with non-cancerous benign breast disease. They reported that women with the **highest levels of DHA** in their breast tissue had a **69% <u>decreased</u>** risk of breast cancer, compared to women with the lowest levels of DHA in their breast tissue.195

Why Plant Foods are so important

The body is bombarded with carcinogens on a daily basis. These cancer-causing agents include pesticides, over-cooked food, alcohol, food additives, tobacco, fungal mutagens, and industrial pollutants. While avoiding carcinogens is difficult, it may be possible to mitigate their lethal effects by providing the body with a specific plant extract that facilitates the detoxification and removal of these dangerous substances from the body.

A compound called **D-glucarate** is found in grapefruit, apples, oranges, broccoli, and Brussels sprouts.196,197 D-Glucarate has been shown to protect against cancer-causing agents by supporting detoxification and removal of dangerous chemicals, and also by protecting against the mutating effects that these carcinogens induce on cellular DNA.198

There are several mechanisms by which the body detoxifies itself. One way of guarding against toxic overload involves a pathway of detoxification in the body whereby carcinogens are combined with water-soluble substances, thus making them more easily removed from the body. This process is called *glucuronidation,* and D-glucarate has been shown to support this important detoxification mechanism.198

D-Glucarate functions by inhibiting the dangerous beta-glucuronidase enzyme, thus protecting the critical "glucuronidation" detoxification mechanism. One example of the importance of glucuronidation can be seen in the risk factors for breast cancer. Excess levels of *16-alpha-hydroxy-estrone* and the beta-glucuronidase enzyme are associated with an increased incidence of breast cancer.199 D-Glucarate is thought to *decrease* estrogen levels by affecting estrogen's elimination.

Research studies have shown that D-glucarate inhibits breast tumor incidence.200,201 One study in rats that already had breast cancer showed that oral D-glucarate administration resulted in a

50% inhibition of beta-glucuronidase, which led to a 30% reduction in mammary tumor growth during the promotion stage and a four-fold reduction in the absolute number of tumors.202 Another study showed a more than **70%** decrease in mammary tumor development in rats exposed to carcinogens who were also administered D-glucarate.203 Still another study looked at the effects of D-glucarate on the initiation and promotional stages of mammary cancer. The results showed a reduction of **28%** during the initiation stage, while cell replication was reduced by **42%** during the promotion stage.204 Inhibition at the initiation stage is a very important part of D-glucarate's actions, as it lessens the risk that cancer will even start.

Eating lots of the right fruits (grapefruit, apples, cherries, and vegetables (broccoli, Brussel sprouts) supplies the body with D-glucarate. It is also available in dietary supplements designed to support breast health.

How Lignans Protect the Breast

A number of published studies indicate that dietary lignans may protect against cancer by favorably altering estrogen metabolism, inhibiting angiogenesis, and inducing cancer cells to self destruct.205-207 The greatest support for a role of lignans in cancer prevention has been shown for premenopausal breast cancer.

Researchers in New York assessed breast cancer risk and dietary lignan intake in more than 3,000 women, including about 1,100 patients with confirmed breast cancer and approximately 2,000 cancer-free women who served as controls. Using statistical analysis, the scientists determined that premenopausal women with the highest lignan intake had a **44% <u>reduced</u>** risk of developing breast cancer.206

Scientists in Italy reported similar findings. Their research indicates that higher blood levels of *enterolactone*— the primary lignan derived by the body from flaxseed—are associated with a lower risk of breast cancer. Conversely, the researchers noted, "*values of serum enterolactone were significantly lower in women who subsequently developed breast cancer*," leading them to conclude that the enterolactone "had a strong protective effect on breast cancer risk."207

Scientists at the University of Toronto reported that **flax lignans** can *slow down the growth of breast cancer* in women. 32 women awaiting surgery for breast cancer were randomized to receive a muffin containing 25 grams of flaxseeds or a muffin that did not contain flaxseed (control group). Analysis of the cancerous tissue after surgery revealed that markers of tumor growth were reduced by **30%-71%** in flaxseed group, while the control group did not experience any reduction in markers of tumor growth. The scientists concluded that "***dietary flaxseed has the potential to reduce tumor growth in patients with breast cancer."***208

Lignans may also protect against endometrial cancer, a condition associated with prolonged exposure to unopposed estrogens (this means estrogen administered without progesterone). Researchers in California assessed lignan intake and cancer status among nearly 1,000 women in the San Francisco area and determined that women with the highest dietary lignan intake

experienced the lowest risk of developing this carcinoma of the uterine lining. The relationship between lignans and endometrial cancer risk reduction was slightly stronger among postmenopausal women.

Based on a lot of favorable publicity, health-conscious people are increasingly adding flax seed to their diet for the purpose of obtaining the beneficial lignans. Highly concentrated lignan extracts are also available in dietary supplements.

Green Tea's Anti-Cancer Effects

Green tea is rich in plant compounds known as polyphenols. The most active group of green tea polyphenols are the catechins, particularly *epigallocatechin gallate* (EGCG). Laboratory data from cell culture and animal models provide convincing evidence for the anticancer effects of green tea polyphenols, or of EGCG, on breast cancer.209-212 In laboratory studies, green tea polyphenols and EGCG have been shown to suppress the growth and reproduction of human breast cancer cells.213,214 Of even greater interest, these beneficial compounds in green tea delay the appearance of tumors in mouse models of breast cancer and cut down on the total tumor burden (amount of cancer in the body) when human breast cancer cells are injected into laboratory mice.214,215

Other exciting benefits of green tea include inhibition of *vascular endothelial growth factor* (VEGF) production,215,216 which cuts off the blood supply needed for tumor growth; down-regulation of estrogen receptor-alpha function in breast cancer cells;217 reduction of tumor invasiveness;215 and increased apoptosis, or programmed cell death, in cancer cells.218

One experiment showed that EGCG, 50-100 mg/kg/day, added to the drinking water of female mice inhibited growth of breast cancer. After five weeks of EGCG treatment, the weight of breast tumors were reduced by **68%** in mice consuming EGCG daily.219

An investigation found a **47%** decreased risk of breast cancer in women who drank at least 3 cups per day of green tea, compared to those who did not consume any green tea.220

METHODS TO REDUCE BREAST CANCER RISK: *WHAT YOU NEED TO KNOW*

1. An enlightened cancer-prevention strategy is to utilize nutritional strategies that have been shown to favorably affect gene expression. One of the simplest ways to protect against cancer is to optimize intake of vitamin D.

2. Minimizing red meat, high-fat dairy, and sweets and consuming more vegetables, fish, and soy products can help reduce the risk of breast and other cancers.

3. Cruciferous vegetable compounds such as indole-3-carbinol can help prevent breast, prostate, and other cancers by favorably altering estrogen metabolism. A simple urine test can confirm that you are consuming the correct amount to ensure optimal cancer protection.

4. Consuming soy isoflavones is associated with a decreased risk of breast cancer.

5. A compound derived from fruits called D-glucarate helps promote the healthy detoxification of estrogen and carcinogens, reducing cancer risk.

6. Dietary lignans offer outstanding protection against breast, endometrial, and prostate malignancies.

7. Consuming the right foods and supplements could reduce up to 90% of all cancers.

8. Consumption of green tea is associated with a decreased risk of breast cancer.

Conclusion

Dr. Kent Holtorf, MD, a specialist in bioidentical hormone therapy and anti-aging medicine stated:

> "***A thorough review of the medical literature supports the claim that bioidentical hormones have some distinctly different, often opposite, physiological effects to those of their synthetic [non-bioidentical] counterparts. With respect to the risk for breast cancer, heart disease, heart attack, and stroke, substantial scientific and medical evidence demonstrates that bioidentical hormones are safer and more efficacious forms of HRT than commonly used synthetic versions*.**"**[106]

Given the preponderance of evidence, maturing women should feel confident in safely supplementing with properly prescribed **bioidentical hormone** therapy to relieve menopausal symptoms and optimize long-term health.

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