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## Bioidentical Hormones: Why Are They Still Controversial?

As women enter the menopausal years, they face a difficult decision. Their bodies' production of **estrogen**, **progesterone**, and other hormones needed to maintain youthful vitality rapidly declines.

While individual effects of menopause vary widely, many women suffer because their bodies no longer produce **sex hormones** at sufficient levels required to optimally sustain 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 may adversely affect a woman for the rest of her lifetime in the absence of appropriate hormone replacement. Yet maturing women today are often told by their doctors to *limit* prolonged use of hormone drugs, only long enough to obtain relief from menopausal symptoms and then no more. Unfortunately, this advice fails to recognize the critical differences between hormone drugs *foreign* to women's bodies and hormones *identical* to those naturally produced by women's bodies.

The understandable, factual concern espoused by many mainstream doctors is that FDA-approved estrogen-progestin hormone drugs have been shown to *increase* the risk of cancer and cardiovascular disease. The dilemma facing aging women is that their bodies may still benefit from youthful

hormone levels, but many of their doctors say "no."

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

Mainstream medical practitioners (many of whom prescribed unnatural hormone drugs for decades) and the **FDA** (which still allows these dangerous unnatural hormones to be sold) are now at the forefront urging aging women to avoid their *prolonged* use.

Overlooked by mainstream medicine is a plethora of research findings indicating that women may more 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 status and cruciferous vegetable intake) that may **prevent** and even **reverse** the kind of damage to cell regulatory genes inflicted by some estrogenic compounds.

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



## 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 patented **non-bioidentical** estrogen and progestin drugs 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 mainstream medicine that by replacing the effect of estrogens lost at menopause with non-bioidentical hormones, women would retain some of their protection against heart disease.

Unfortunately, the logic of 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**.<sup>1</sup> 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 coronary heart disease.**"<sup>2</sup>

In 2004, the **non-bioidentical** estrogen-only arm of the study was terminated as well because hormone replacement therapy (HRT) with conjugated equine (horse-derived) estrogen was found to **increase** the risk of stroke.<sup>2</sup> These findings had an immediate impact on the millions of women taking non-bioidentical HRT, of whom up to 50% discontinued their use of non-bioidentical HRT.<sup>3</sup>

## The Bioidentical Hormone Option

**Bioidentical hormones** have the same exact molecular structure as the hormones produced naturally within the body. The body does not distinguish between supplemental bioidentical hormones and the hormones produced within the body.<sup>4</sup> 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 several years as women have sought out a more *natural* approach to restoring hormonal balance.

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Hormone replacement therapy (HRT) pills in their dispensers and patch.



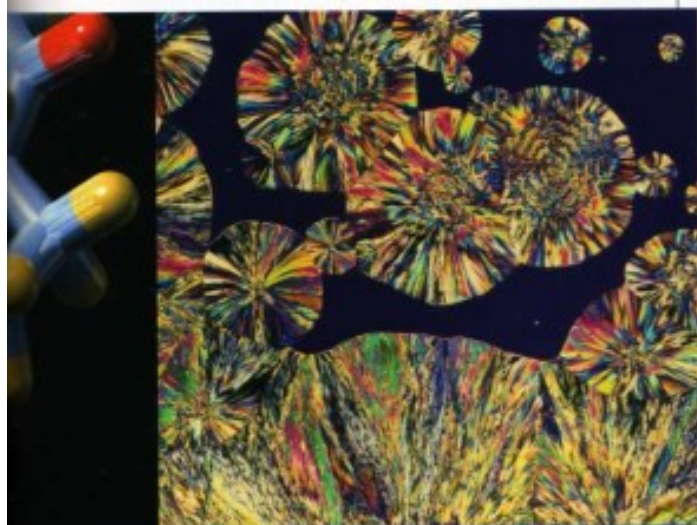
Molecular model of the hormone progesterone: carbon (blue), hydrogen (gold), and oxygen (red).



### Scientific Evidence Suggests 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 bio-identical 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.<sup>5-17</sup> In stark contrast; seven studies have shown that bioidentical *progesterone* **does not induce** estrogen-stimulated breast cell proliferation.<sup>18-24</sup>

Numerous studies have demonstrated an **increased** risk of breast cancer with the use of non-bioidentical *progestins*.<sup>1, 5, 25-48</sup> 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 *progestins* had a **69% increased** risk of breast cancer, compared to women who had never used HRT. 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.<sup>49</sup>



Polarised light micrograph of progesterone crystals. Progesterone is derived from pregnenolone.

### What You Need to Know

#### Bioidentical Hormones

- Non-bioidentical hormones are not identical to the hormones naturally produced within the body. The use of non-bioidentical estrogen and progesterone is associated with the risk of breast cancer, heart attack, and stroke.
- Bioidentical hormones have the same molecular structure as the hormones produced naturally within the body. The body does not distinguish between supplemental bioidentical hormones and the hormones produced within the body. As a result, bioidentical hormones are properly utilized, and are able to be naturally metabolized and excreted from the body.
- Studies suggest that bioidentical progesterone is not associated with an increased risk of breast cancer. Current literature indicates the use of bioidentical progesterone is associated with a decreased risk of breast cancer.
- Three types of estrogen are produced in the body: estriol, estrone, and estradiol. The scientific literature suggests 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, topical estriol is not.
- Research on bioidentical progesterone has shown beneficial effects on cardiovascular health, including decreasing the risk of blood clots, protecting against atherosclerosis (hardening of the arteries), and maintaining healthy HDL levels.
- A review of the scientific literature suggests that bioidentical progesterone may be superior to non-bioidentical progesterone in treating 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 with scientific evidence to potentially protect against the development of breast cancer include green tea, soy isoflavones, fish oil, vitamin D, plant lignans, indole-3-carbinol (I3C; found in cruciferous vegetables), and D-glucarate. Visit [www.lef.org](http://www.lef.org)



In another investigation, these same researchers found a **40% increased** risk of breast cancer for women who used estrogen with non-bioidentical progestin. Interestingly, in women who used estrogen combined with bioidentical progesterone, there was a promising trend toward a **reduced** risk of breast cancer, compared to women who had never used HRT.<sup>25</sup> In essence, bioidentical progesterone appeared to **protect** women against the development of breast cancer. These findings confirm work done six years earlier that found a trend toward a reduced risk of breast cancer in 1,150 women using bioidentical **progesterone**, compared to non-users of progesterone.<sup>50</sup>

Compelling research offers further insight into natural 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 to remove a breast lump. 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 compared to placebo. Conversely, the addition of bioidentical progesterone to estrogen resulted in a **significant decrease** in 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.<sup>18</sup>

A growing body of literature has documented a strong connection between a woman's progesterone levels and her subsequent risk for breast cancer. A trial reported in the *International Journal of Cancer* in 2004 measured blood levels of progesterone in 5,963 premenopausal women. Incredibly, the analysis of the data revealed that those women with the **highest** blood levels of **progesterone** levels who had regular

menses experienced an **88% decreased** risk of breast cancer.<sup>51</sup> These findings corroborate 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 **540% increased** risk of *premenopausal* breast cancer, and were **10 times** as likely to die from any cancer.<sup>52</sup>

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 promising trend toward a lower 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.<sup>53</sup>

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.<sup>54,55</sup> One study noted that **65%** of women with a progesterone level of 4.0 ng/mL or more on the day of their surgical treatment of node-positive cancer 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.**"<sup>55</sup>



## Natural Progesterone (Bioidentical) Versus Synthetic Progestins (Non-Bioidentical)

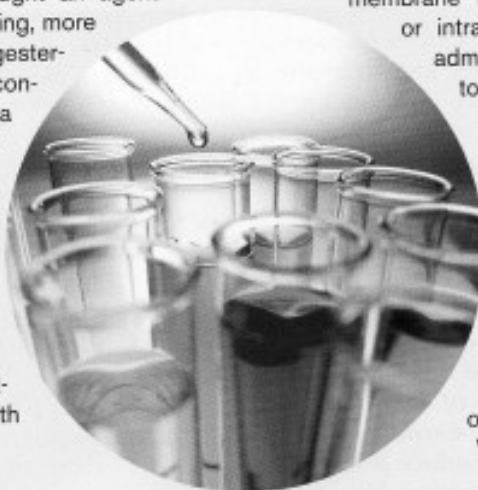
In this article, we define **natural progesterone** as **bioidentical** progesterone and **synthetic progestins** as **non-bioidentical** progestins. It is important that the reader know that **non-bioidentical** progestins are **not** the same as **bioidentical progesterone**.

### 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.<sup>56</sup> 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. The process of micronization allows for steady and even absorption of the medication.<sup>57</sup> Accordingly, 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 highly profitable birth control products.



One of the most common progestins, *medroxy-progesterone acetate* (Provera®), has been linked to blood clots, fluid retention, acne, rashes, weight gain, depression, certain cancers, and other disorders.<sup>58, 59</sup> Non-bioidentical progestins are also able to bind to glucocorticoid, androgen, and mineralocorticoid receptors, which may explain the wide range of adverse side effects many women experience while taking synthetic progestins.<sup>60, 61</sup> The vast majority of research studies have been conducted using progestins rather than natural progesterone, which helps explain the disparity and negativity of the results.

The FDA has also approved a drug called Pro-metrium®, an oral pill containing 200 mg of natural micronized progesterone taken daily. Because orally administered progesterone is metabolized by the liver, it may be contraindicated in patients with certain liver conditions. Initial liver metabolism of progesterone (called "first-pass" metabolism) also creates higher levels of certain metabolites of progesterone than transdermal or transmucosally administered progesterone.<sup>62</sup>

### How To Best Administer Natural Progesterone

Natural progesterone cream may be more efficiently used, since lipophilic (fat-soluble) molecules allow it to be better 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.<sup>63-65</sup>

As one can readily discern from the peer-reviewed published literature, adverse side effects are clearly associated with non-bioidentical progestins, whereas several health benefits have been observed with the use of bioidentical progesterone. Visit [www.lef.org](http://www.lef.org)

### Estriol 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. In the past, **estriol** was believed to have little physiological significance due to its weak estrogenic activity when compared with **estrone** and **estradiol**. Nonetheless, research suggests that estriol's weakness may confer certain beneficial effects in contrast with more potent estrogens.

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 produced by estriol on estrogen receptors. When estriol is given together with estradiol, the estradiol-specific stimulation to cells is decreased.<sup>66</sup> 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.<sup>67</sup>

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 on breast cells: estrogen receptor **alpha** and estrogen receptor **beta**.<sup>68-73</sup> 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.<sup>74-79</sup>

Estrone and estradiol bind to and activate estrogen receptor **alpha**, thereby explaining the known breast cancer-promoting effects of these two hormones.<sup>80,81</sup> **Estriol**, on the other hand, binds to and activates estrogen receptor **beta**.<sup>80,81</sup> 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."<sup>82</sup>



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 31,451 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.<sup>83</sup> Additional evidence 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 low-dose oral or topical **estriol** did not have an increased risk of breast cancer, compared to women who never used HRT.<sup>83</sup>

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.<sup>84</sup> 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.<sup>85-87</sup> In contrast, the use of topical lower-potency estriol is not associated with an increased risk of uterine cancer.<sup>88</sup> Other studies have demonstrated that the use of intravaginal estriol has low risk. 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."*<sup>89</sup>

Although several studies suggest that the oral route of administration of estriol appears relatively safe over the short term (e.g., less than five years), 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 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.<sup>88</sup> Women using topical estriol for at least five years did not have any increased risk.<sup>88</sup> 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.<sup>90-92</sup>

### Safety Concerns

Most of the research cited in this article used oral estrogen as the route of administration. For enhanced safety, topical estriol would be a better choice. Several studies have shown that transdermal and transmucosal estrogen confers fewer health risks than oral estrogen.<sup>88,93-96</sup> Clinical experience of many doctors over the past 20-30 years suggests that transdermal and transmucosal estrogen is also more effective for some women's symptoms.<sup>97</sup> One reason for this difference is 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 metabolized and then excreted.<sup>64,98</sup>

In addition, several studies suggest that bioidentical estrogen has fewer health risks when given with low doses of bioidentical progesterone.<sup>99,100</sup>

### Bioidentical Progesterone and Cardiovascular Health

The *Women's Health Initiative*, a large randomized clinical trial, demonstrated that the addition of non-bioidentical progestins to non-bioidentical estrogen therapy resulted in a substantial increase in the risk of heart attack and stroke.<sup>126</sup> Numerous studies, on the other hand, document that bioidentical progesterone has *beneficial* effects on cardiovascular health.





## Is Cancer Risk a Reason to Deprive Aging Women of Natural Hormones?

Concern about cancer is an important reason why more aging women do not restore their hormones to more youthful levels. Hormones like estrogen and testosterone affect cell growth and proliferation. Does that mean aging women should simply accept the sex hormone deficiencies they face as a part of "normal" aging?

Based on the data suggesting beneficial effects upon cell growth and maturation, as well as favorable ways to affect estrogen metabolism that point to cancer prevention (by consuming generous amounts of cruciferous vegetables like kale and broccoli, for example), restoring hormones to more youthful levels appears to be an important strategy that should not be ignored.

As we describe later in this article, large human population studies show major reductions in cancer risk and often specific protective mechanisms against hormone-responsive cancers like breast and prostate cancer when vitamin D,<sup>101-103</sup> cruciferous vegetables,<sup>104-112</sup> (a source of indole-3-carbinol, or I3C), soy,<sup>113-117</sup> D-glucarate,<sup>118-121</sup> and lignans<sup>122,123</sup> 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.<sup>124,125</sup>

Misconceptions generated by misinterpreted studies and associated media hype have created an environment in which aging people suffer the agonies caused by sex hormone imbalances, yet do nothing to correct this because of 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—including properly restoring natural hormone balance to reflect a more youthful range—would result in significant reductions in malignant disease.

### 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.<sup>126</sup> A quick look at this chart clearly documents that aging is a primary cause of breast cancer, not hormones like estrogen. If estrogen caused breast cancer, then we would expect to see very high rates of breast cancer in young women of childbearing age, with a dramatic decrease in breast cancer after menopause. This is not observed. The good news is that many of the gene expression changes involved

in the development of breast and other cancers can be favorably altered by taking low-cost nutrients like vitamin D<sup>103,127,128</sup> in the dose of 1,000 IU to 10,000 IU/day, based on individual response.

### Risk of Developing Breast Cancer by Age<sup>126</sup>

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

### Why Young Women with High Estrogen Seldom Develop Breast Cancer

During women's younger years, when breast cancer risk is relatively low compared with advancing age, they enjoy high levels of sex hormones (estrogen, progesterone, dehydroepiandrosterone, and testosterone). As they age and hormone levels decline, breast cancer risk increases. The reason cancer risk increases with "aging" is that the genes in cells that help regulate healthy cell growth can mutate and directly cause cancer. In fact, mutations in cells' regulatory genes are an underlying cause of cancer.<sup>129</sup> 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.<sup>130</sup> Vitamin D also exerts its cancer-preventive influence by helping to control cell differentiation and inducing normal programmed cell disposal (apoptosis).<sup>130</sup>

Strategies to protect against breast and other cancers can easily be incorporated into a woman's lifestyle. We provide a more complete description of what all women (whether or not they choose to take estrogen) should do to reduce their risk of developing breast and other cancers later in this article. Visit [www.lef.org](http://www.lef.org)

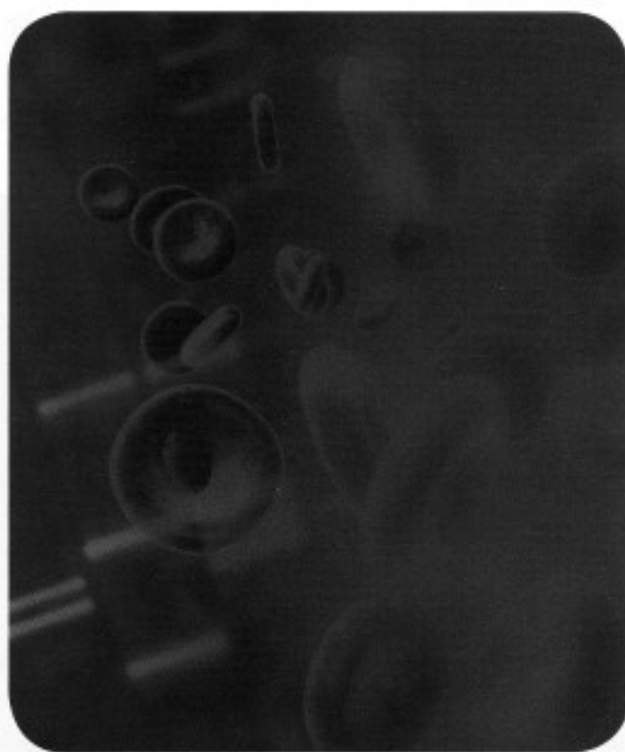
In one trial published in the *Journal of the American College of Cardiology*, researchers studied postmenopausal women with a history of heart attack or coronary artery disease. The women were given estrogen in combination with either bioidentical progesterone or non-bioidentical progestin. After 10 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.<sup>131</sup>

The risk of a blood clot is a serious concern with the use of unnatural estrogen replacement therapy, especially by the oral route. This risk doesn't occur when bioidentical progesterone is added to the mix. 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.<sup>132</sup>

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.<sup>133-135</sup> The story is quite different for bioidentical progesterone, where multiple animal studies have shown that bioidentical progesterone inhibits the process of atherosclerosis.<sup>135-137</sup> 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.<sup>135</sup> In contrast, when the same investigators administered bioidentical progesterone along with estrogen, no such inhibition of estrogen's cardiovascular benefit was seen.<sup>138</sup>

## Bioidentical Progesterone and HDL

**High-density lipoprotein (HDL)** functions to remove cholesterol from the arterial wall and thus helps protect against the development of atherosclerosis.<sup>139</sup> Low HDL is a proven risk factor that contributes to heart disease. Non-bioidentical progestin is known to cause reductions in HDL levels.<sup>140-145</sup> 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.<sup>141,142,146-148</sup> 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.<sup>141</sup> These results confirm earlier preliminary data 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.<sup>142</sup>





### Estriol and Cardiovascular Health

Growing evidence suggests that *estriol* may offer benefits to the cardiovascular system. For instance, Japanese scientists found that a group of menopausal women given 2 mg/day oral estriol for 12 months had a significant **decrease** in both systolic and diastolic **blood pressure**.<sup>149</sup> 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.<sup>150</sup>

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).<sup>151</sup>

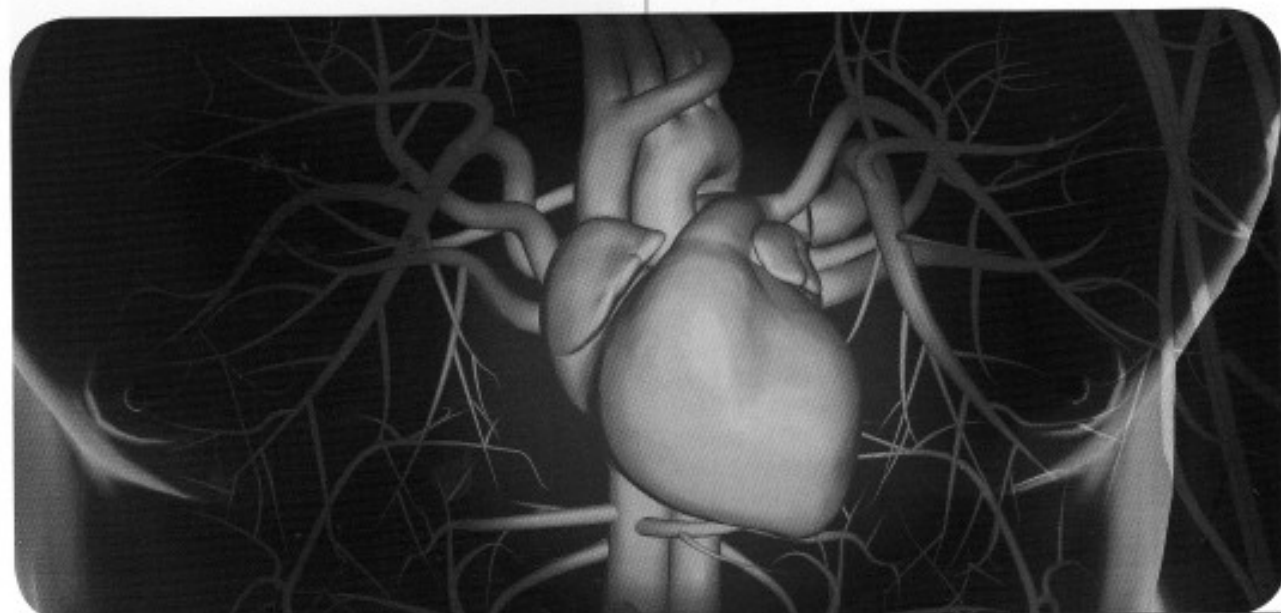
### Bioidentical Progesterone vs. Non-Bioidentical Progestin for the Treatment of Menopausal Symptoms

Four head-to-head studies comparing bioidentical progesterone to non-bioidentical progestin reported that women 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. **Sixty-five percent** 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. **Eighty percent** of women in the study reported overall satisfaction with the bioidentical progesterone formulation.<sup>152</sup> The results of this study provide evidence of the *superiority* of bioidentical progesterone over non-bioidentical progestin in the treatment of menopausal symptoms.

Further research supports the use of bioidentical progesterone in preference 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.<sup>153</sup> 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.<sup>154,155</sup> Bioidentical progesterone also offers improvements in quality of sleep and cognitive function compared with non-bioidentical forms of the hormone.<sup>156,157</sup>





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### 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 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.<sup>158</sup>

In another trial, researchers studied the safety of estriol in the treatment of menopausal symptoms. Fifty-three women with either surgically induced or natural menopause were given 2 mg of oral estriol/day for 12 months. 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."*<sup>149</sup>

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 were also recorded, while the number of women who experienced migraine headaches dropped by two-thirds. Thrombophlebitis

occurred in two patients and there were two cases of mammary cancers, which the investigators did not believe were related to the estriol treatment.<sup>159</sup>

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."*<sup>162</sup>

### 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 ensure 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).<sup>160</sup> 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.<sup>150</sup>

Similar research has confirmed these findings. In this investigation, 25 postmenopausal women were given either 2 mg/day of estriol plus 2 gram/day of calcium lactate, or 2 grams/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 resorption 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.<sup>161</sup>

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 5% increase in bone density, while the group that did not receive estriol experienced a 3% decrease in bone density.<sup>162</sup>



## Estriol Enhances Sexual and Urinary Health

Postmenopausal women often suffer from urinary incontinence or recurrent urinary tract infections caused in part by hormone deficiencies.

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, while only 16% improved in the placebo group.<sup>163</sup>

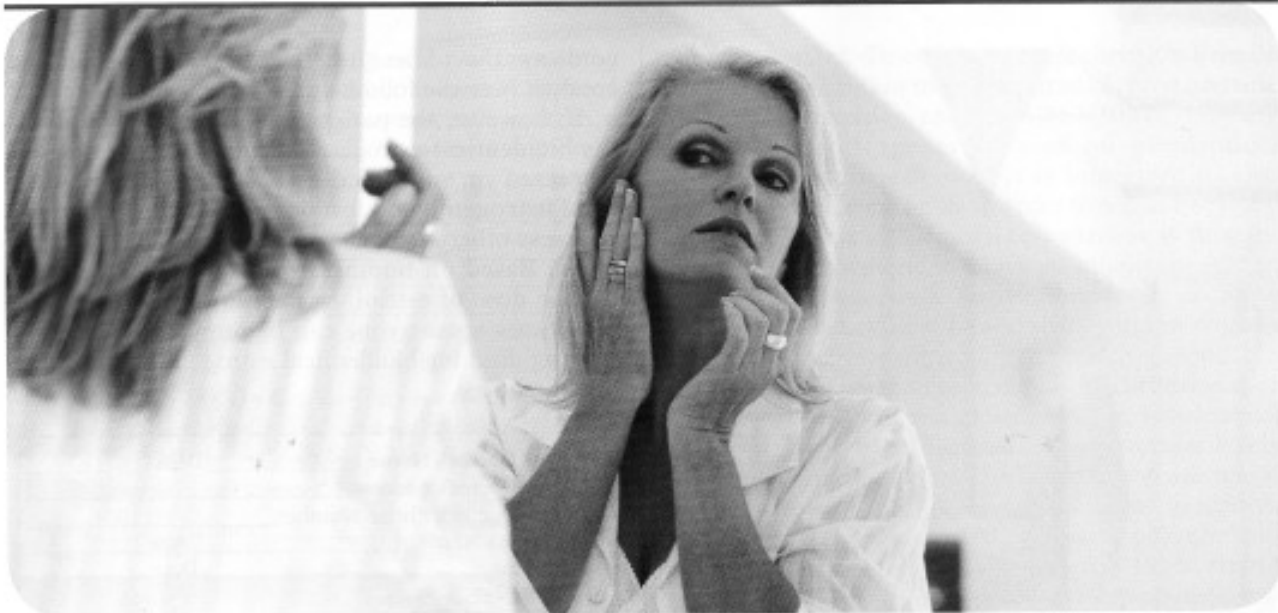
In another randomized, double-blind, placebo-controlled trial, women with recurrent urinary tract infections were given either intravaginal estriol cream (containing 0.5 mg estriol, once daily for two weeks, then twice weekly for eight months) or placebo. Incredibly, the incidence of urinary tract infection was reduced by 91% in the estriol group compared with placebo.<sup>164</sup>

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 aging 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."**<sup>165</sup> 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."**<sup>166</sup>

In a study conducted in Japan, oral estriol (2 mg/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."**<sup>167</sup>

## 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 microcircula-



tion to our skin is reduced as we grow older, thereby depriving our skin of the small amount of natural hormones our body still makes.<sup>168</sup> A large number of published scientific studies reveal that estrogen exerts potent anti-aging effects on the skin.<sup>169-173</sup> 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 environmentally-induced skin aging. According to the findings of a scientific study published in 2007, ***“Estrogens prevent skin aging. They increase skin thickness and improve skin moisture.”***<sup>178</sup> Another recent study came to the same conclusion, i.e. ***“skin aging can be significantly delayed by the administration of estrogen.”***<sup>170</sup>

A critical mechanism by which estrogen maintains a youthful plump appearance is by increasing 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.<sup>169</sup>

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.<sup>169,172</sup>

Estrogens exert significant effects on skin physiology by modulating the effects of key epidermal and dermal cells.<sup>170</sup> In fact, the skin is an important estrogen-responsive tissue, and without the growth

promoting effects of estrogen, it literally withers away.<sup>171</sup> The very thin skin observed in the elderly can be directly correlated to a lack of estrogens needed to generate collagen and maintain skin thickness.<sup>171</sup>

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 were 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.<sup>172</sup> 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 perimenopausal 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 in decreased wrinkle depth, with no systemic hormonal side effects noted.<sup>173</sup>

In another study, 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 on the treated side 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.<sup>179</sup>

### 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 **1-866-864-3027**.

Most practitioners use the level of **estradiol** in women's blood, along with an assessment of the patient's clinical 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. A health care practitioner may also measure levels of estrone and estriol to obtain a more comprehensive assessment of a woman's estrogen status.

In menopause, a woman typically has an estradiol blood level of **0-19 pg/mL**. With the use of bioidentical estrogen topical cream (e.g., compounded estriol and estradiol), the blood estradiol level may go to **100 pg/mL** or higher, which indicates to the prescribing doctor that the compounded estrogen formula is being *absorbed* and has increased the patient's estradiol level to a more youthful range.

If the patient reports that her menopausal symptoms have resolved, most practitioners would

continue the patient on the current program and conduct periodic follow-up.

If, however, the patient is still having symptoms, the bioidentical estrogen topical cream dose can be increased or additional tests ordered such as the **total estrogen** blood test or a **urinary estrogen** test to assess other estrogens and their associated 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 bioidentical estrogen topical cream might read as:

Your Doctor's Name _____	DEA# _____
Your Doctor's Address _____	
Your Doctor's Phone Number _____	
Patient's Name _____	Age _____
Address _____	Date _____
<i>BI-EST cream:</i>	
<i>0.5 mg estradiol/2.0 mg estriol per mL</i>	
<i>Apply 1 mL topically every day. #60 mL</i>	
Refill _____ times	(Signature) _____

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 bioidentical estrogen topical cream dose can be increased when severe symptoms of estrogen deficiency are present.

Women given estrogen replacement should also be prescribed *natural progesterone* (in contrast to synthetic progestin drugs like Provera®) in a dose that achieves a youthful balance. Natural progesterone produces many benefits when properly balanced with estrogen. The typical dose for topical progesterone cream may vary between 50-200 mg, depending upon a woman's unique, individual biochemical needs.

A typical starting dose for over-the-counter (OTC) progesterone cream is one-quarter teaspoon of a 2.5% strength progesterone cream applied to a different part of the body twice each day:

- Premenstrual and perimenopausal women: 1/4 tsp. of a 2.5% progesterone topical cream (approximately 30 mg. natural progesterone) 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 can be adjusted up or down depending on a woman's symptoms and her response to treatment. If using *natural progesterone* cream from a pharmacy, a prescription could be written as follows for a postmenopausal woman:

Your Doctor's Name	DEA#
Your Doctor's Address	
Your Doctor's Phone Number	
Patient's Name	Age
Address	Date
<i>PROGESTERONE cream 50 mg/mL</i> <i>Directions: Apply 1 mL (pump) topically</i> <i>twice daily or at bedtime days 1-25</i> <i>Dispense: 1 or 2 month supply</i>	
Refill	times
(Signature)	

A prescription for a premenopausal woman could also read:

Your Doctor's Name	DEA#
Your Doctor's Address	
Your Doctor's Phone Number	
Patient's Name	Age
Address	Date
<i>PROGESTERONE cream 25 mg/0.1 cc</i> <i>Directions: Apply 0.1 cc to the labia or</i> <i>intravaginally daily on days 10-25 of a 28</i> <i>day "cycle". Dispense: 1 or 2 month supply</i>	
Refill	times
(Signature)	

Some 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 onto 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:

<b>Estradiol</b>	<b>90-250 pg/mL</b>
<b>Progesterone</b>	<b>2.0-6.0 ng/mL</b>
<b>Free testosterone</b>	<b>1.0-2.2 pg/mL</b>

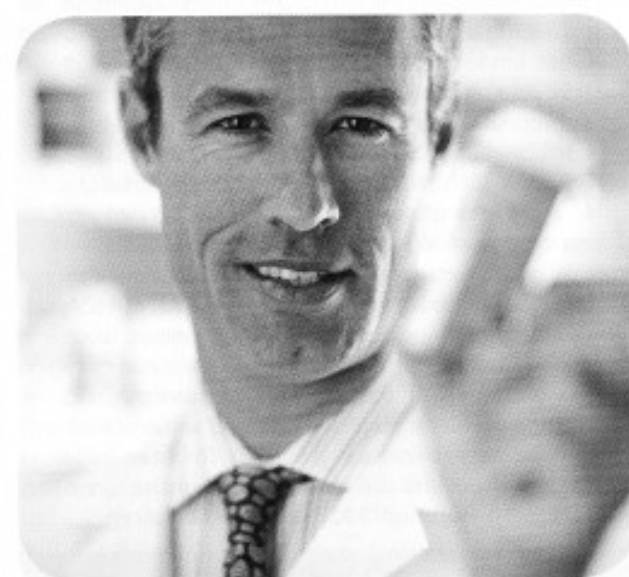
Before a prescription for bioidentical hormones can be written, it is important to have a baseline blood test so the doctor knows what dose of bioidentical estrogens, progesterone, and possibly testosterone

may be needed. To order a comprehensive Female Blood Test Panel that includes estradiol, progesterone, and free testosterone, call **1-866-864-3027**.

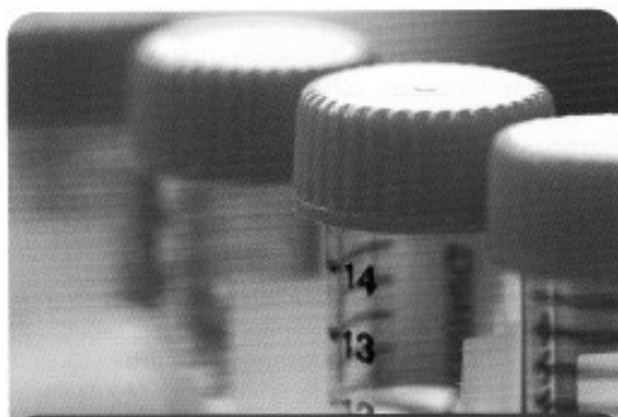
Although this paper focuses on bioidentical estrogen and progesterone, it is important to also address testosterone levels in order to achieve optimal hormonal balance. Although testosterone is thought of as a male hormone, it plays an important role in women's health as well. Testosterone levels decrease 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.<sup>180-183</sup> 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.<sup>184</sup> 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.<sup>185</sup>

Too much free testosterone in an aging woman induces abdominal weight gain,<sup>186,187</sup> as does a deficiency of estradiol.<sup>188-191</sup> Progesterone may be weight-neutral,<sup>192</sup> though some complementary practitioners claim it helps facilitate weight loss. Some doctors seek to increase progesterone levels up to 15 ng/mL.

The overall objective is to achieve a more youthful 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 the patient metabolizes the hormones 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,"<sup>110,193,194</sup> and the estrogen quotient, or "EQ," which is a mathematical calculation of estradiol/estrogen+estradiol. The follow-up also includes levels of 2-methoxyestradiol, an estrogen with potent anti-carcinogenic 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 profile if necessary to optimize the safety of hormone therapy. (A more in-depth explanation of the 2/16 hydroxyestrogen test 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-hour comprehensive urine test, call 1-866-864-3027 or visit [www.lef.org](http://www.lef.org).

### Why Skeptics Are Still Concerned About Estriol

Based on what you have read so far, topical **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 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 all estrogens is that they undergo alterations in the body that can result in these estrogens cascading into either pro-carcinogenic or anti-carcinogenic compounds. The good news is that one can affect 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 do 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 all women should do to *reduce* 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 and 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.

### Anticancer Nutrients That Complement Bioidentical HRT

#### CRITICAL IMPORTANCE OF VITAMIN D

Young women (under age 30) almost never develop breast cancer. As women age, their cell growth-regulatory genes accumulate mutations. As our bodies age, we become less proficient at rapidly repairing (or removing) damage to the cells and tissues of our bodies. When genes that regulate cell division undergo mutation, the 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 changes to genes involved in the growth and proliferation of breast tissue cells, estrogen can promote cancer cell propagation. The good news is that the ingestion of vitamin D, cruciferous vegetables, and other compounds can *prevent* and *help repair* 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.<sup>195-198</sup> 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 nearly **70% reduction** in their risk of breast cancer, compared to women with the lowest vitamin D levels.<sup>199</sup>

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.<sup>101</sup>

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.<sup>127</sup> After only four years, the risk of developing any cancer was **60% lower** in the vitamin D (and calcium) group, compared with those who received calcium only. 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 pre-existing 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. These doses have been shown to be both effective and safe in human trials.<sup>200,201</sup> The heavier one is, the more supplemental vitamin D they often require. (Note that vitamin D status in the body is measured as serum 25-hydroxyvitamin D.)

#### CRUCIFEROUS VEGETABLES PROTECT AGAINST TUMOR-PROLIFERATING 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.<sup>104,202</sup> Cruciferous vegetable compounds also help neutralize the many carcinogens we are inevitably exposed to each day.<sup>106-109,203</sup> One of the 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-hydroxyestrone*) that promotes breast and other cancers.<sup>193,194</sup>

To emphasize the critical importance of *indole-3-carbinol* (I3C), please understand that aging women still produce estrogen. All the estrogen in women's bodies (both endogenously produced and supplemental) can follow two primary metabolic pathways in the body. If estrogen is converted to *16-alpha-hydroxyestrone*, then the risk of breast and other cancers is increased. If on the other hand, the estrogen is converted to *2-hydroxyestrone*, then the risk for breast and other cancers is decreased.<sup>204,205</sup>

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 among premenopausal women, higher levels of *2-hydroxyestrone* were associated with protection against breast cancer.<sup>204</sup> This same finding has been shown in additional studies of different populations.<sup>206,207</sup>

The toxic estrogen metabolite *16-alpha-hydroxyestrone* acts as a breast tumor promoter.<sup>110</sup> By contrast, estrogen metabolized via the *2-hydroxyestrone* pathway does not exhibit adverse estrogenic activity in breast tissue.<sup>110</sup> 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.<sup>208</sup>

Cruciferous vegetable compounds (such as I3C) are effective in shifting estrogen metabolism to the more beneficial pathway, thus reducing levels of toxic *16-alpha-hydroxyestrone* and increasing levels of protective *2-hydroxyestrone*.<sup>110-112,205</sup>

This beneficial modulation of estrogen is associated with reduced risk of breast and other cancers, including cervical and head and neck cancers.<sup>106,204,205</sup> 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 in combination with the anti-estrogenic chemotherapeutic agent tamoxifen inhibited the growth of human breast cancer cells by an astounding **90%**.<sup>209</sup>

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.<sup>210</sup>

#### 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.<sup>125,211,212</sup>

One recent study showed that women who a Western-style style, high in meats and sweets, had nearly **twice the risk** of developing estrogen receptor-



positive breast cancer, compared with women who ate a traditional Asian diet high in soy and vegetables.<sup>125</sup> This and other studies provide evidence that compounds found in soy have a breast cancer-preventive effect.

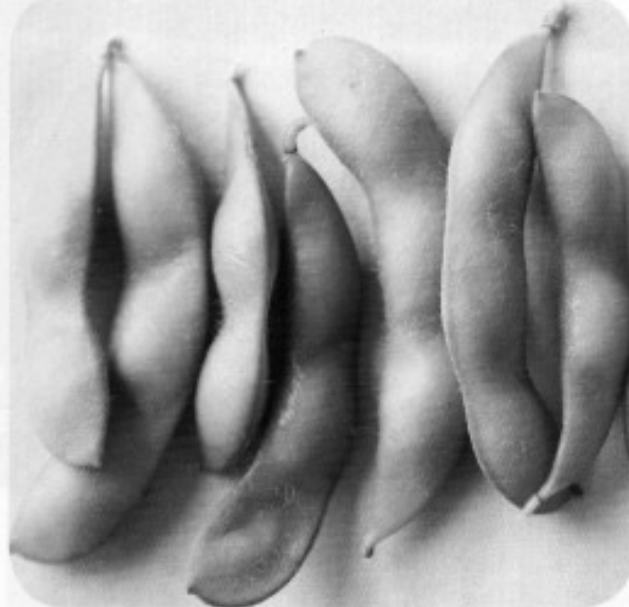
Isoflavones derived from soy have shown great promise in providing natural protection against multiple types of cancer.<sup>114-116</sup> Two of the best known soy isoflavones are genistein and daidzein.

Isoflavones 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.<sup>113-116,211-217</sup>

Studies conducted in Asia found that breast cancer risk was significantly lower among Asian women who consumed large quantities of isoflavones and other soy products, compared with those who consumed less of these healthful nutrients.<sup>115</sup> Because animal studies have shown that a diet high in soy and genistein can protect against breast, colon, and skin tumors, it seemed reasonable to think that soy could also help prevent human cancers and, in particular, breast cancer.<sup>218</sup> Yet many mainstream medical practitioners remain skeptical that something as simple as soy could have such a profound effect on human health.

Soy isoflavones are correctly classified as *selective estrogen receptor modulators*.<sup>219</sup> Due to their unique molecular structure, soy isoflavones can act as both estrogen receptor agonists and receptor blockers. In fact, elegant biochemical studies have shown that some isoflavones bind to the cancer-protective estrogen beta receptor six to eight-fold more readily than native estrogen.<sup>219</sup> 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.<sup>219</sup>

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.<sup>117</sup> 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.<sup>115</sup>



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.<sup>220</sup> 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 (in fact, they were the amounts that could be obtained from a healthy American-style diet).

#### 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 more 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 **30% more** 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 developed *estrogen receptor-positive* breast tumors, those who ate the Western-style diet experienced a **90% increased**





risk!<sup>125</sup> This is in stark contrast to a study that demonstrated a **52% decreased** risk of breast cancer in women with the highest intake of vegetables and fruits, compared to the lowest intake.<sup>221</sup>

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) fatty acids, this ratio is reversed in meat from free-range animals, with significantly more omega-3 than omega-6 fatty acids.<sup>222</sup> 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. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (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 of breast cancer, compared to those with the lowest levels.<sup>223</sup>

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% decreased** risk of breast cancer, compared to women with the lowest levels of DHA in their breast tissue.<sup>224</sup>

#### WHY PLANT FOODS ARE SO IMPORTANT

The body is bombarded with carcinogens on a daily basis. These cancer-causing agents include pesticides, overcooked 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.<sup>225,226</sup> 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.<sup>227</sup>

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.<sup>227</sup>

**D-Glucarate** functions by inhibiting the 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-hydroxyestrone* and beta-glucuronidase enzyme activity are associated with an increased incidence of breast cancer.<sup>228</sup> D-Glucarate is thought to *decrease* estrogen's effects by favorably affecting estrogen's metabolism and elimination.

Research studies have shown that D-glucarate inhibits breast tumor incidence.<sup>118,119</sup> 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.<sup>229</sup> Another report showed a more than **70% decrease** in mammary tumor development in rats exposed to carcinogens that were also administered D-glucarate.<sup>120</sup> 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.<sup>121</sup> Inhibition at the initiation stage is a very important part of D-glucarate's actions, as it reduces the risk that cancer will even start.

Eating lots of the right fruits (grapefruit, apples, cherries) and vegetables (broccoli, Brussels sprouts) supplies the body with D-glucarate, though 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.<sup>122,123</sup> 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. The scientists determined that premenopausal women with the highest lignan intake had a **44% reduced** risk of developing breast cancer.<sup>122</sup>

Scientists in Italy suggest a mechanism for the protective effect. Their research indicates that higher blood levels of a phytoestrogen called *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."<sup>123</sup>

Scientists at the University of Toronto reported that **flax lignans** can slow down the growth of breast cancer in women. Thirty-two 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



#### Methods to Reduce Breast Cancer Risk

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 (I3C) 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 and vegetables 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 the risk of up to 90% of all cancers.
8. Consumption of green tea is associated with a decreased risk of breast cancer.

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cancerous tissue after surgery revealed that markers of tumor growth were reduced by **30%-71%** in the 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."***<sup>230</sup>

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 a promising trend toward a lower risk of developing this carcinoma of the uterine lining.<sup>220</sup> 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 flaxseed 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 is the catechins, particularly *epigallocatechin gallate* (EGCG). Copious evidence supports a role for these compounds in preventing breast cancer. In laboratory studies, green tea polyphenols and EGCG have been shown to suppress the growth and reproduction of human breast cancer cells.<sup>231,232</sup> 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.<sup>232,233</sup>

Other exciting benefits of green tea include inhibition of *vascular endothelial growth factor* (VEGF) production,<sup>233,234</sup> which cuts off the blood supply needed for tumor growth; down-regulation of estrogen receptor-alpha function in breast cancer cells;<sup>235</sup> reduction of tumor invasiveness;<sup>233</sup> and increased apoptosis, or programmed cell death, in cancer cells.<sup>236</sup>

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 was reduced by **68%** in mice consuming EGCG daily.<sup>237</sup>

But green tea's benefits aren't restricted to animal or laboratory models. 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.<sup>238</sup>

The medical establishment questions the use of *bioidentical hormones* out of concern about cancer risks. Earlier in this article, we outlined persuasive data showing the anti-cancer properties of **estriol** and **natural progesterone**.

When factoring in the potent anti-cancer effects that occur in response to consuming healthy foods (such as broccoli and soy) and supplements (such as vitamin D and fish oil), while avoiding carcinogenic foods (such as sugar and well-done meat), the argument that maturing women should forever be denied their full complement of *natural* sex hormones does not stand up to scientific scrutiny.



## Conclusion

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

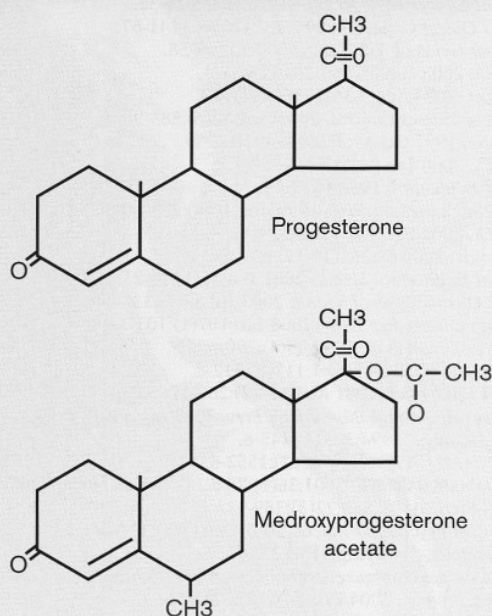
*"A thorough review of the medical literature clearly supports the claim that bioidentical hormones have some distinctly different, often opposite, physiological effects to those of their synthetic [non-bioidentical counterpart] hormones. With respect to the risk for breast cancer, heart disease, heart 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."*<sup>82</sup>

Given the preponderance of evidence, maturing women should feel confident that **bioidentical** hormone replacement, when appropriately prescribed, offers a safer and potentially even more effective alternative to conventional hormone replacement with non-bioidentical hormone drugs to help relieve menopausal symptoms and optimize long-term health. The addition of several proven nutrients to a bioidentical hormone regimen may help optimize estrogen metabolism and reduce cancer risk even further, offering an optimal, balanced approach to health maintenance. ●

If you have any questions on the scientific content of this article, please call a Life Extension® Health Advisor at 1-866-864-3027 or visit [www.lef.org](http://www.lef.org).

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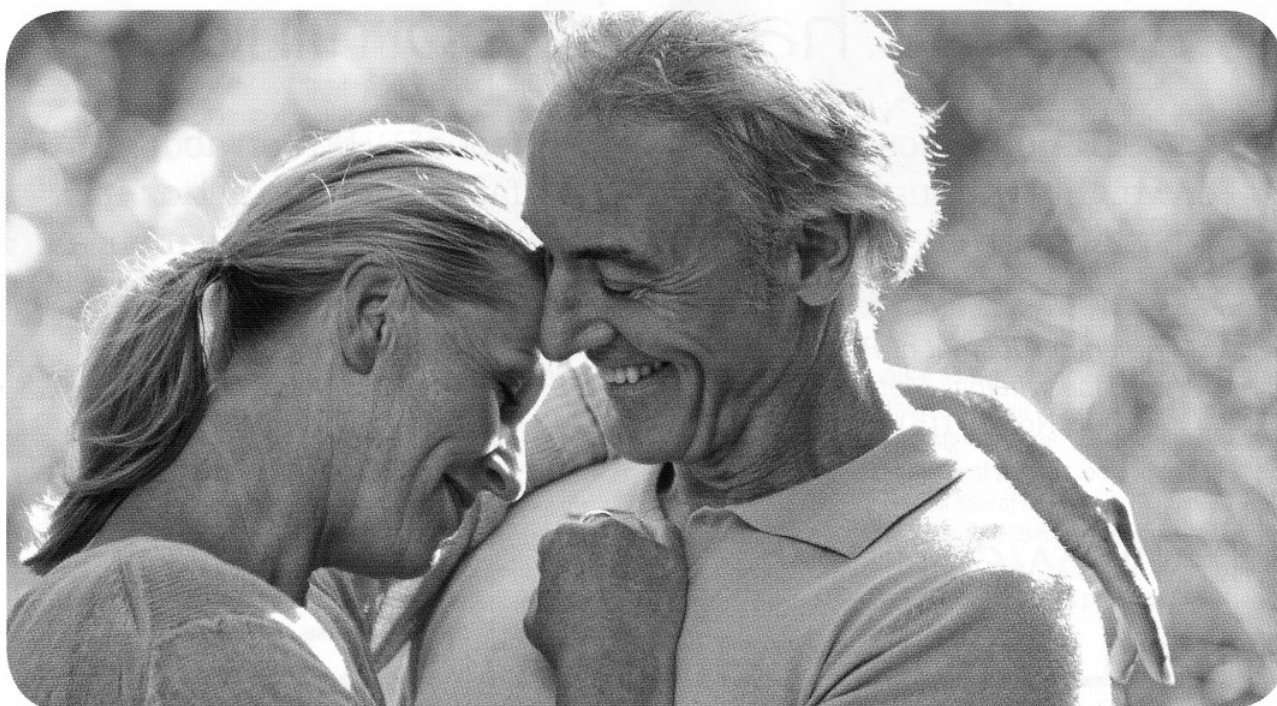
Natural progesterone (above). One example of synthetic progesterone (below)—note the difference in chemical composition as indicated in red.

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