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### 1 Overview

#### Summary and Quick Facts for Female Hormone Restoration

- Life Extension has long recognized the value of bioidentical hormone replacement therapy, which uses hormones that are identical to those naturally produced in the body. The appeal of bioidentical hormone therapy has not been lost on the public or the medical community: nearly one-third of women who now use hormone therapy do so with bioidentical hormones.
- In this protocol, you will learn how to approach bioidentical HRT judiciously. You will also learn how using readily available blood tests may help guide your therapy in partnership with a qualified healthcare provider.
- In addition to estrogens, a comprehensive hormone restoration program may include progesterone, DHEA, pregnenolone and possibly testosterone. Dietary and supplemental phytoestrogens present a way for women to obtain limited hormonal support without the use of hormone therapy.

#### Why is it Important to Maintain Balanced Female Hormones?

Balancing hormone levels, including progesterone, estrogens (estrone, estradiol, estriol), DHEA, testosterone, and pregnenolone, are important for women's health. Unfortunately, hormone levels in women decline as they age. Postmenopausal women are at an increased risk of several diseases, including cardiovascular disease, Alzheimer's disease, and osteoporosis. Menopause also often causes sleep trouble.

Conventional hormone replacement therapy (ie, with conjugated equine estrogens and synthetic progestin) has been shown to have serious adverse consequences. Fortunately, **bioidentical hormone replacement therapy**

(HRT), as well as natural alternatives like **phytoestrogens**, may offer women safe and effective options to promote youthful hormone levels.

What are the Risks Associated with Conventional Hormone Replacement Therapy?

- Breast cancer
- Coronary heart disease
- Stroke
- Blood clots

What is Bioidentical Hormone Replacement Therapy?

Bioidentical HRT uses hormones that are identical to the ones produced naturally in the body. Bioidentical hormones are not associated with the risks of conventional hormone therapy. They can be obtained through FDA-approved preparations, available in oral, transdermal, or vaginal routes. Alternatively, a high-quality compounding pharmacy can prepare concentrations that may not be available through a conventional preparation.

What are Ways to Test Hormone Levels?

- Saliva
  - Pros: easy, at-home method
  - Cons: levels are highly variable; cannot test for metabolites
- Urine
  - Pros: provides a 24-hour picture of hormone levels
  - Cons: convenience; cost; levels can be artificially elevated
- Blood
  - Pros: relatively inexpensive; readily accessible; well-established reference ranges
  - Cons: levels are highly variable; cannot test for metabolites

What are Natural Ways to Support Healthy Female Hormonal Signaling?

- **Phytoestrogens.** These estrogen-like compounds are found in many plants, the most well-studied being **isoflavones** (from soy) and **lignans** (from flaxseeds and other plants). Phytoestrogens can exert estrogen-like effects in the body and may offer an alternative to HRT for some women. Phytoestrogens are linked to decreased risk of breast cancer, improved cardiovascular health, and reduced menopause symptoms, among other benefits.
- **Siberian rhubarb.** Siberian rhubarb has been used for many years to relieve problems associated with female hormone imbalance. A controlled clinical trial showed that perimenopausal women given Siberian rhubarb experienced improvements in symptoms with no adverse effects.
- **Black cohosh.** Black cohosh has become a popular herb to relieve symptoms of menopause. It has been shown in many clinical trials to improve symptoms like hot flashes, sleep disturbances, low libido, and others.
- **Dong quai.** This traditional Chinese herb is often called the “female ginseng,” as it may relieve painful menstruation, symptoms of menopause, fatigue, and more.
- **Cruciferous vegetables.** Cruciferous vegetables like **broccoli** and **cabbage** contain beneficial compounds that promote healthy estrogen metabolism and may protect against breast cancer-promoting metabolites.
- Other natural ingredients that may promote healthy female hormones include **licorice root**, **Vitex agnus-castus**, **vitamin D**, **fish oil**, and more.

Until 2002, mainstream physicians routinely prescribed conventional hormone replacement therapy (HRT) pills to alleviate menopausal symptoms. Conventional HRT comprises oral conjugated estrogens, derived from the urine of pregnant mares (horses), and synthetic *progestins* (compounds that activate progesterone receptors) such as medroxyprogesterone acetate (NAMS 2017). In 2002, however, the landmark Women’s Health Initiative study identified substantial risks associated with conventional oral HRT:

- 26% increased risk of breast cancer,
- 29% increased risk of coronary heart disease,
- 41% increased risk of stroke, and
- double the risk of blood clots relative to the untreated group.

With time, much of this risk was attributed to medroxyprogesterone acetate, the synthetic progestin used in the WHI studies (Stanczyk 2015). As awareness about these risks associated with conventional oral HRT spread, many women became concerned about using HRT. In the United States, the use of conventional HRT dropped dramatically (Schonberg 2005). A sharp decline in breast cancer incidence observed in 2003 among women over 50 correlated with this decrease in conventional HRT use (Ravdin 2007).

Life Extension was not surprised by the results of the WHI study. The *equine estrogens* and *synthetic progestins* used in the study differ in chemical structure from the natural hormones produced in a woman’s body (Samaras 2014). Many studies have shown that the synthetic progestin medroxyprogesterone acetate poses several health risks, including increased risks of breast cancer, stroke, and cognitive dysfunction (Stanczyk 2015). Life Extension has long recognized the value of **bioidentical hormone replacement therapy**, which uses hormones that are identical to those naturally produced in the body (Moskowitz 2006; Whelan 2011).

Bioidentical HRT may be associated with fewer side effects than conventional HRT. Bioidentical topically applied estrogens appear to pose less blood clot risk—and possibly overall cardiovascular risk—than oral equine estrogens used in conventional HRT (L’Hermite 2017). This was demonstrated in a large case-control study that showed that use of oral equine estrogens alone (not in combination with synthetic progestins) resulted in about 50% greater risk of venous blood clots compared with controls. When equine estrogens were used in combination with synthetic progestins, the risk increased to about 90% greater than that of control participants (Vinogradova 2019). Also, bioidentical progesterone, unlike the most widely used synthetic progestin, does not increase cardiovascular or breast cancer risk (Holtorf 2009). Indeed, the appeal of bioidentical hormone therapy has not been lost on the public or the medical community: nearly one-third of women who now use hormone therapy do so with bioidentical hormones (Gass 2015).

Many FDA-approved commercial preparations now utilize bioidentical hormones, which is helping spread acceptance of bioidentical HRT among conventionally minded physicians. See Table 1 for a list of FDA-approved bioidentical hormone preparations.

Moreover, supplementation with scientifically studied herbs such as Dong quai (*Angelica sinensis*) and licorice (*Glycyrrhiza glabra*) root can further promote healthy metabolism of female hormones and complement the actions of bioidentical HRT.

In this protocol, you will learn how to approach bioidentical HRT judiciously. You will also learn how using readily available blood tests may help guide your therapy in partnership with a qualified healthcare provider.

### 3 Age-Related Hormone Decline and Associated Health Concerns

During the postmenopausal period, when female sex hormone levels have decreased significantly, aging women are at **increased risk of several diseases** including heart disease, osteoporosis, Alzheimer disease, and dementia compared with premenopausal women.

**Heart disease** is the leading cause of death in American women (CDC 2017), and women’s incidence of coronary heart disease increases sharply after menopause (Tandon 2010; Clearfield 2004). Compared with premenopausal women, postmenopausal women have higher blood pressure and higher levels of low-density lipoprotein (LDL)

cholesterol, total cholesterol, triglycerides, and homocysteine levels, as well as markers of chronic inflammation and metabolic disturbance (Saha 2013; Fonseca 2017; Lee 2009). In addition, high-density lipoprotein (HDL) cholesterol levels drop significantly after menopause (Saha 2013; Fonseca 2017). Estrogenic activities are vital for maintaining the integrity of the vascular endothelium, where atherosclerotic changes begin (Arnal 2009). HRT may combat some of these changes. In a clinical trial, 75 peri- and postmenopausal women given compounded transdermal (topical) bioidentical estrogen therapy, with or without progesterone, experienced improvements in cardiovascular risk and inflammatory markers over 36 months (Stephenson 2013).

Menopause and perimenopause are associated with bone loss, which can lead to **osteoporosis** and increased fracture risk. Inadequate estrogen signaling contributes to increased production of pro-inflammatory cytokines, which disturb the balance between bone formation and bone breakdown and cause bone loss (Pietschmann 2016; Weitzmann 2006).

Hormone loss is also associated with **neuronal degeneration** and increased risk of dementia, Alzheimer disease, and Parkinson disease (Depypere 2016; Blair 2015; Rocca 2008). Estrogen stimulates degradation of the toxic protein beta-amyloid, which contributes to Alzheimer disease (Liang 2010). Deficiencies in pregnenolone and dehydroepiandrosterone (DHEA), which are both neuroprotective hormones, are also linked to memory problems and brain cell death associated with Alzheimer disease (Vallee 2016; Yao 2002). These two hormones appear to play an important role in regulating neurotransmitter systems involved in learning and memory, stress, mood, and motivation (Maayan 2008; Zaluska 2009; Vallée 2001; Zheng 2009).

Menopause often causes **disrupted sleep patterns** and associated symptoms such as night sweats (Jehan 2015). Importantly, disordered sleep is linked to increased cardiovascular risk in menopausal women. One study showed that sleep disorders in menopausal women were associated with arterial stiffness—stiff, inflexible arteries are less healthy (Zhou 2017). Evidence from an observational cohort study suggests bioidentical HRT may reduce sleep disturbances in postmenopausal women, but more study is needed (Ruiz 2014).

#### What is Estrogen Dominance?

“Estrogen dominance” is a term used by integrative health practitioners to describe high estrogen levels relative to progesterone levels (Kolan 2022). However, the prevalent use of this term in integrative health circles should not be interpreted to mean that estrogen is inherently bad. Rather, the emphasis should be on maintaining a proper balance of sex hormones (eg, estrogen relative to progesterone). Imbalanced levels, including high estrogen levels, may lead to unpleasant symptoms such as mood swings, altered sex drive, bloating, anxiety, and more. Estrogen dominance may also connote the hormonal milieu that arises in women being treated with unopposed estrogen, such as estrogen-only HRT without progestins or progesterone (Cleveland Clinic 2022). For example, post-menopausal women treated with unopposed estrogen may experience signs and symptoms of estrogen dominance (Valdes 2022).

There are no widely accepted diagnostic criteria or specific estrogen and progesterone levels that categorize women as estrogen dominant. In fact, both high and low levels of estrogen can contribute to acute and chronic diseases (Patel 2018). Establishing whether an imbalance of sex or another type of steroid hormones may be contributing to symptoms requires an individualized approach that can include lab tests to assess hormone levels along with clinical evaluations to determine whether any imbalances correlate with specific symptoms. The end-goal is to carefully adjust the hormonal milieu, generally using bioidentical HRT, to achieve an optimal balance for a given woman. “Optimal” hormone ranges are always relative to the balance of other hormones, must take into account how a given woman feels, and will vary on an individual basis.

*Balancing* steroid hormone levels—including progesterone, estrogens (estrone, estradiol, estriol), DHEA, testosterone, pregnenolone, and sometimes cortisol—is important for maintaining aspects of health under hormonal influence. Hormone levels and their balance influence not only reproductive health and risk of certain cancers, but also mood and psychological health (Borrow 2014), musculoskeletal health (Gao 2015), autoimmunity (Chen 2017; Avila 2018), gastrointestinal health (Chen 2019), and more.

If you are concerned about your estrogen levels, evaluate your hormone levels via lab testing and consult with a doctor experienced in hormonal balancing. A practitioner with experience balancing women’s hormones may be able to recommend interventions to help optimize your hormone levels—whether with medications, HRT,

#### 4 Hormone Replacement Therapy – Background

The rationale for HRT is that replacing hormones lost with age may help prevent manifestations of declining hormone levels. Although this basic premise that historically spurred the advent of conventional HRT was theoretically correct, we now know that optimal hormone restoration is much more nuanced and complex.

All steroid hormones are derived from cholesterol in a **metabolic cascade**. The first hormone in the cascade is pregnenolone, which can subsequently be converted into all other steroid hormones including DHEA, progesterone, testosterone, and various forms of estrogen (Hu 2010). These hormones are interrelated, yet each performs unique physiological functions. Biologically sound hormone therapy should aim to harmonize the physiological response to the milieu of hormonal signaling that is constantly taking place throughout the body.

One problem with classical HRT is that conjugated equine estrogens (CEE) stimulate a more pronounced estrogenic signal in some parts of the body compared with the endogenous estrogens produced by a woman's body, potentially leading to adverse consequences (L'Hermitte 2017). CEE, which is obtained from the urine of pregnant mares (horses) (Bhavnani 2003), is usually given in combination with a synthetic progestin, a chemical that stimulates progestogen signaling. However, CEE and chemical progestins cannot replicate the complex network of signaling stimulated by the diverse array of hormones and their metabolites under natural conditions in a woman's body.

Another problem with conventional HRT is that CEE preparations contain other hormones, such as androgens and progestins, that differ from those naturally produced by humans (Notelovitz 2006). Also, because CEE has different forms and proportions of estrogens than those that occur in the body, its use may lead to different and disproportionate amounts of hormone metabolites than would be produced through metabolism of endogenous hormones (Bhavnani 1998). One manifestation of this divergent hormonal metabolism arising from oral equine estrogens is increased blood clotting risk, a well-known side effect of CEE (L'Hermitte 2017).

#### Progesterone

In healthy reproductive-aged women, progesterone and estrogen are in a state of dynamic balance during the menstrual cycle. Progesterone has unique and essential functions in ovulation, implantation, pregnancy, and breast development and function (Ismail 2003; Al-Asmakh 2007), as well as in the brain (Mani 2012).

Progesterone can play a major role in relieving menopausal symptoms. Several studies have reported that women experienced similar or greater reductions in menopausal symptoms and improvements in quality of life, as well as fewer estrogen therapy-related side effects, with progesterone compared with medroxyprogesterone acetate, a synthetic progestin (Hargrove 1989; Montplaisir 2001; Ryan 2001; Lindenfeld 2002). In one study, symptom scores were 30% lower for sleep problems, more than 50% lower for anxiety, 60% lower for depression, 40% lower for cognitive difficulties, and 30% better for sexual function in progesterone users compared with users of a synthetic progestin. In addition, 80% of women using bioidentical progesterone reported overall satisfaction with their hormone therapy (Fitzpatrick 2000).

Progesterone has been shown to be safer than synthetic progestins for cardiovascular health. Certain synthetic progestins, but not progesterone, have been found to worsen the negative effect of oral estrogen therapy on risk of blood clots (Binkowska 2014; Scarabin 2014). The combination of conjugated equine estrogen and the synthetic progestin medroxyprogesterone acetate was found in a large case-control study to more than double the risk of venous thrombosis (Vinogradova 2019). Progesterone has demonstrated cardiovascular safety in postmenopausal women when used alone (Prior 2015). In one study, progesterone enhanced estrogen's positive effect on blood flow to the heart muscle: when added to estrogen therapy, progesterone substantially improved coronary blood flow during treadmill exercise in women with a history of heart attack or coronary artery disease, but a synthetic progestin had no effect (Rosano 2000).

Progesterone plays a role in regulating cognitive function, social behavior, and mood, and has demonstrated neuroprotective and anti-inflammatory properties in the nervous system (Giatti 2016; Arbo 2016). Since some progesterone metabolites have anti-anxiety effects, it is thought that progesterone depletion may contribute to the

increased incidence of anxiety and mood disorders seen in early menopause (Toriizuka 2000).

## Estrogen

There are a number of naturally occurring forms of estrogen. The main estrogens in humans are estrone, estradiol, and estriol (Taioli 2010; Samavat 2015). Estrogens are produced by the ovaries during the reproductive years and in smaller amounts by the adrenal glands and other tissues throughout life. Non-ovarian sources of estrogens become more important after menopause (Rettberg 2014; Simpson 2003).

Estradiol is the most potent form in non-pregnant, reproductive-aged females and primarily aids in the cyclic release of eggs from the ovaries (ovulation) (Barbieri 2014; Chai 2014). Estradiol has beneficial effects on the heart, bone, brain, and colon (Cui 2013). Fluctuations and overall decline in estradiol levels contribute to common peri- and postmenopausal symptoms, such as hot flashes, mood swings, and vaginal atrophy (Freedman 2014; Finch 2014), and estradiol depletion after menopause impacts tissues throughout the body, contributing to a range of disease risks and frailty (Dalal 2015; Nedergaard 2013). Estrone is the dominant estrogen in postmenopausal women; it is produced by fat tissue (Wharton 2012). Estriol is a comparatively weak estrogen; because it is secreted by the placenta, estriol is the main estrogen during pregnancy (Liang 2013; Ali 2017).

The three main types of estrogen can be converted into many metabolites. Estrone, for example, may convert into the following metabolites among others (Ziegler 2015):

- 2-hydroxyestrone
- 4-hydroxyestrone
- 16-alpha-hydroxyestrone

Some evidence suggests metabolism of estrogen into 2-hydroxylated forms may protect against breast cancer in postmenopausal women (Ziegler 2015; Moore 2016). However, more research is needed before firm conclusions can be drawn about the role of ratios among the various estrogen metabolites in breast cancer risk.

**Estriol.** Estriol has weaker estrogenic effects than other forms of estrogen. Studies have shown that estriol effectively treats menopausal hot flashes, night sweats, and insomnia. In addition, some studies have shown that estriol combats menopausal bone loss (Ali 2017). When taken together with estradiol, estriol opposes some of estradiol's stronger estrogenic effects (Holtorf 2009). Applied vaginally, estriol is an excellent treatment for urinary and vaginal symptoms of menopause (L'Hermite 2017).

Estriol has been studied in the context of a range of chronic diseases. Researchers in Japan have conducted numerous trials showing that estriol may improve blood pressure, vascular function, and blood lipids (Takahashi 2000; Hayashi 2000; Kano 2002; Itoi 2000; Yamanaka 2005).

Emerging research suggests estriol has a potential role in the treatment of the autoimmune disease multiple sclerosis as well as other neurodegenerative conditions, in part through modulating immune function. This theory stems from the observation that remission and relapse of multiple sclerosis during and shortly after pregnancy is correlated with the secretion of estriol by the placenta (Ali 2017).

Estriol is not yet available in FDA-approved commercial formulations, but can be obtained through compounding pharmacies.

### What are Xenoestrogens?

Xenoestrogens are exogenous compounds that interact with estrogen-signaling pathways in the body and may contribute to some manifestations of hormonal imbalance. Xenoestrogens mimic the action of estrogen at estrogen receptors. They are part of a broad class of compounds known as **endocrine disruptors**, which can interfere with normal hormonal signaling (Singleton 2003). Xenoestrogens are found in plastics, pesticides, herbicides, and many other sources (Brotons 1995; Sultan 2001).

Tissues and organ systems throughout the body are sensitive to estrogen signaling and may be influenced by xenoestrogens. Indeed, studies have shown that, in addition to breast cancer, xenoestrogen exposure may contribute to lung, kidney, and reproductive system cancers (Fucic 2012; Wang 2021). As of early 2022, a large research study was ongoing with the goal of understanding the contribution of these and other pollutants to the

risk of developing breast cancer (Amadou 2020). Xenoestrogen exposure has also been shown to alter immune cell function (Nowak 2021), contribute to decreased kidney function (Chen 2021), increase the risk of uterine fibroids (Katz 2016), negatively affect birth outcomes (Bjerragaard-Olesen 2019), possibly increase the risk of obesity and diabetes (Pérez-Bermejo 2021), and may affect benign breast disease and breast tissue changes (Abeer 2018; Trentham-Dietz 2012).

Since xenoestrogens are not actually estrogen, they will not be found by a test that measures estrogen levels. To limit your exposure and potential adverse effects of xenoestrogens, try to **use less plastic, wash your produce thoroughly, and avoid products that include parabens and phthalates**. You can also consider **adding more phytoestrogens** (found abundantly in soy and flaxseeds) and **cruciferous vegetables** to your diet as there is some preliminary data suggesting they block the effects of xenoestrogens (Maharjan 2021; Chavarro 2016; Lee 2018; Williams 2021).

## Beyond Estrogen and Progesterone: The Complete Hormonal Picture

In addition to estrogen and progesterone, it is important to consider the roles of the hormones pregnenolone, DHEA, and testosterone. Ideal bioidentical HRT involves comprehensive evaluation of all declining hormone levels.

**DHEA.** DHEA is a steroidal hormone secreted by the adrenal gland, gonads, and brain (Maninger 2009). Both men and women experience an age-related decline in DHEA (Labrie 2010). Peak levels are typically reached when women are in their 30s, after which they begin to lose approximately 2% per year (Fouany 2013). Decreased levels of DHEA and DHEA-sulfate (DHEA-s, a circulating form of DHEA) after menopause can impact cognition, mood, and sexuality (Pluchino 2015), and are thought to contribute to cancer, insulin resistance, decreased immune defenses, and psychiatric illness (Genazzani 2010).

DHEA has been shown to influence mood and neurological function (Dong 2012), immune function (Bauer 2013), energy and feelings of well-being (Rutkowski 2014), vascular health (Weiss 2012), insulin resistance and inflammatory marker levels (Weiss 2011), and the maintenance of muscle and bone mass (Kenny 2010; Weiss 2009). Furthermore, DHEA has been found to enhance sexual function and the use of intravaginal DHEA in particular has demonstrated efficacy as a treatment for postmenopausal vulvovaginal atrophy (Pluchino 2015; Archer 2015).

**Testosterone.** Like DHEA, testosterone levels in women gradually decrease with age (Schneider 2003). Loss of testosterone affects libido, bone and muscle mass, vasomotor symptoms, cardiovascular health, mood, and well-being (Bain 2007; Simon 2001; Watt 2003; Cameron 2004).

Testosterone therapy in women has been shown to improve quality of life, mood, concentration, bone health, markers of cardiovascular risk, cognitive function, and vulvovaginal atrophy (Braunstein 2002; Davis 2015). In addition, testosterone, both alone and in conjunction with estrogen therapy, has been shown to be effective in treating low libido and increasing sexual satisfaction in women (Bolour 2005; Achilli 2017; Cappelletti 2016; Al-Azzawi 2010). Because DHEA can be converted into testosterone, it may be possible to obtain some of the benefits of testosterone using DHEA (Cameron 2004; Labrie 2017).

**Pregnenolone.** As is the case with some other hormones, a significant reduction of pregnenolone begins when women reach their early 30s (Havlikova 2002). As the initial hormone in the overall steroid hormone cascade, pregnenolone is derived from cholesterol mainly in the adrenals, gonads, brain, and other tissues. In addition to acting as a precursor for other hormones, pregnenolone appears to have direct effects on regulation of neurological function (Vallee 2016; Zheng 2009). Pregnenolone may be especially important for age-related sleep and cognitive changes (Mayo 2003), and deficiencies have been associated with diminished brain function and dementia (Mellon 2007).

## Hormones and Cancer Risk

Although many factors affect breast cancer risk, it is well established that high estrogen levels and increased estrogen exposure over a lifetime, especially due to an early onset of puberty, are associated with an increased risk of breast cancer (Dall 2017). Establishing a proper balance of hormones and incorporating foods and

supplements that support healthy hormone metabolism may help mitigate estrogen's breast cancer-promoting properties.

Current evidence suggests that, while CEE appear not to increase breast cancer risk, the synthetic progestin used in conventional HRT (primarily medroxyprogesterone acetate) is associated with increased risk (L'Hermite 2017). In the **Women's Health Initiative**, CEE alone did not increase breast cancer risk, while CEE plus medroxyprogesterone acetate was associated with increased risk (Chlebowski 2010; Zhao 2014; Shah 2006).

The use of bioidentical progesterone in combination with estrogen has not been found to increase breast cancer risk (Fournier 2008). In fact, *in vitro* research suggests progesterone may actually reduce estrogen-triggered cell proliferation (Mohammed 2015). Although more research is needed to clearly establish the risks and safety of progesterone therapy with regard to breast cancer, evidence to date suggests it is safer than synthetic progestins, particularly medroxyprogesterone acetate (Asi 2016; Prior 2015).

In addition, studies suggest testosterone has anti-proliferative effects on breast tissue, countering the cancer-promoting effect of estrogen (Glaser 2015). In one study, women with breast cancer were found to have lower salivary testosterone levels than cancer-free women (Dimitrakakis 2010). In another study, postmenopausal HRT that included estrogen, progestin, and testosterone was associated with a substantially lower occurrence of breast cancer than that predicted using historical data on HRT without testosterone (Dimitrakakis 2004).

## 5 Moving Forward with Bioidentical HRT

Given the evidence demonstrating the superiority of bioidentical HRT, one prominent HRT researcher proclaimed, *"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"* (Holtorf 2009).

Women should always consult a physician before beginning any HRT, especially if they have had or are at high risk of developing hormone-responsive breast or endometrial cancer. In some cases, prescribing practitioners may want to monitor hormone levels periodically to ensure the attainment of safe and adequate levels (Sood 2011).

### Dosing and Delivery Methods

Bioidentical hormone formulations can be obtained as FDA-approved preparations (Table 1) or from a compounding pharmacy with a physician's prescription.

Various preparations and modes of delivery are available for bioidentical hormones. For example, estradiol is available in FDA-approved oral tablets; topical gels, patches, and creams; and vaginal rings and suppositories. Bioidentical micronized progesterone is available as FDA-approved oral pills or vaginal gel (Files 2011; Santoro 2016). Some authors suggest the current evidence indicates that oral micronized progesterone plus topical/transdermal estradiol is the optimal approach to bioidentical HRT (L'Hermite 2017).

Importantly, the non-oral route is preferred for bioidentical estradiol. This is because the liver metabolizes orally ingested estradiol before it is available to the rest of the body. This is called the "first-pass effect." Also, oral estrogens, but not topical or vaginal estrogens, are associated with increased blood clot risk (Simon 2012; Binkowska 2014). Transdermal estradiol, on the other hand, is not associated with increased risk of deep venous thrombosis (Vinogradova 2019). Oral progesterone does not increase the risk of blood clots and is an acceptable method of bioidentical progesterone delivery (Binkowska 2014).

The most commonly prescribed compounded bioidentical estrogen formulas are called *bi-est* and *tri-est*. Bi-est consists of 20% estradiol and 80% estriol, and tri-est contains 10% estradiol, 10% estrone, and 80% estriol (Taylor 2001). Bi-est and tri-est are available in various oral, transdermal, and vaginal preparations (Files 2011). Although some physicians prefer bi-est or tri-est formulations based on their clinical experience, studies have yet to establish that estriol-containing bi-est or tri-est formulations provide clear advantages over FDA-approved bioidentical products that contain estradiol (FDA 2017). In certain situations, an experienced physician tailors an individualized prescription based upon an assessment of symptoms, and sometimes lab values, to the needs of a

specific woman. In addition to estrogens, a comprehensive hormone restoration program may include progesterone, DHEA, pregnenolone, and possibly testosterone (Files 2011).

To obtain contact information for physicians in your area who are knowledgeable about bioidentical HRT, call 1-800-226-2370.

Women taking any kind of estrogen replacement therapy (including bioidentical) should refer to the [Breast Cancer](#) protocol in order to understand the importance of making healthy lifestyle choices that could reduce the risk of breast cancer.

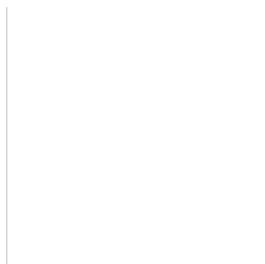
<b>Table 1. FDA-Approved Bioidentical Hormone Preparations</b>			
<b>Hormone</b>	<b>Delivery Preparation</b>	<b>Brand Name</b>	<b>Available Dosages/Strengths</b>
Estradiol	Oral – Pill/Tablet/Capsule (NOTE: even though these preparations are bioidentical, the non-oral route of administration is preferred to avoid the hepatic first-pass effect)	Estrace	0.5 mg; 1 mg; 2 mg
		generic	0.5 mg; 1 mg; 2 mg
	Vaginal Cream	Estrace Vaginal	0.1 mg/g
	Transdermal Patch (typically applied once or twice weekly)	Alora	0.025 mg/day; 0.05 mg/day; 0.075 mg/day; 0.1 mg/day
		Climara	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.06 mg/day; 0.075 mg/day; 0.1 mg/day
		Menostar	0.014 mg/day
		Vivelle-Dot	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.075 mg/day; 0.1 mg/day
		Minivelle	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.1 mg/day
		generic	0.025 mg/day; 0.0375 mg/day; 0.05 mg/day; 0.06 mg/day; 0.075 mg/day; 0.01 mg/day
	Topical Gel or Lotion	Estrasorb	4.35 mg per packet
	EstroGel	0.06% concentration: 0.75 mg per pump	
	Elestrin	0.06% concentration: 0.52 mg per pump	

		Divigel	0.01% concentration: 0.25 mg per packet; 0.5 mg per packet; 1 mg per packet
	Topical Spray	Evamist	1.53 mg per spray
	Vaginal Ring	Estring	Applied once every three months: 0.075 mg/day
	Vaginal Tablet	Vagifem (estradiol hemihydrate)	Typically applied twice weekly: 0.01 mg per tablet
Progesterone (micronized)	Oral – Pill/Tablet/Capsule	Prometrium	100 mg per capsule; 200 mg per capsule
		generic	100 mg per capsule; 200 mg per capsule
	Vaginal Gel	Crinone	4% concentration: 45 mg per applicatorful; 8% concentration: 90 mg per applicatorful

### How Compounded Bioidentical Hormones are Prescribed

Compounded bioidentical hormone prescriptions are primarily based on symptoms and, to some degree, blood test results. A physician experienced in writing compounded bioidentical hormone prescriptions will work closely with a woman to determine a starting dosage.

The strength of a compounded hormone preparation is generally indicated in milligrams (mg) per milliliter (mL) or per cubic centimeter (cc). A milliliter and a cubic centimeter have the same volume. A typical starting dose for bioidentical estrogen cream might read as follows:



Please note this is one example of an initial prescription. It represents the most commonly used bioidentical HRT script for a postmenopausal woman with typical symptoms. A physician experienced in bioidentical hormone replacement would tailor a prescription to the individual's needs.

Women on an estrogen replacement regimen should also be prescribed *progesterone* (in contrast to synthetic progestin drugs like Provera which do not have the same molecular structure as natural progesterone). Progesterone has a number of benefits when properly balanced with estrogen (Prior 2015; Spark 2012), and is particularly helpful for menopause-related sleep disturbances (Leeangkoonsathian 2017; Caufriez 2011). For oral progesterone, a typical dose is between 100–200 mg per day for 10–12 days per month; for transdermal progesterone, a typical dose is 50–100 mg per day (Randel 2012; Cobin 2017). These dosages can vary depending upon a woman's individual biochemical needs. It is usually recommended that progesterone cream be applied twice daily to different parts of the body.

As with estrogen therapy, the dose of progesterone can be adjusted depending on the individual's symptoms and response to treatment. For a postmenopausal woman, a prescription for topical progesterone cream from a compounding pharmacy might be written as follows:

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A prescription for a peri-menopausal woman might read as follows:

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Compounded hormone formulas are applied via a syringe (with no needle) onto the skin or intravaginally, allowing for precise dosage adjustment. In some situations, a baseline blood test may be useful for determining doses of bioidentical hormones. A physician experienced in bioidentical hormone therapy may want to measure testosterone levels and prescribe bioidentical testosterone if needed (Davis 2008).

Since DHEA can be converted to testosterone in a woman's body, a woman with low testosterone might be able to increase her level by taking up to 50 mg DHEA daily, which is available as a dietary supplement (Weiss 2009; Caufriez 2013).

#### Identifying High-Quality Compounding Pharmacies

Given the potential for error inherent in preparing individualized compounded products, it is important that the pharmacy with which you are working adheres to high quality and safety standards.

One way you can ensure your compounding facility adheres to high quality and safety standards is to inquire whether the facility is accredited by the Pharmacy Compounding Accreditation Board (PCAB) (ACHC 2017). More information and relevant directories of accredited facilities can be found at the following link:

<https://www.achc.org/find-a-provider/>

You can also ask your pharmacy directly whether the facility adheres to guidelines laid out by the United States Pharmacopeial Convention (USP). Specifically, USP General Chapter 795 identifies important standards relevant to bioidentical hormone compounding to which a compounding pharmacy should adhere to ensure safety and quality (USP 2014). Reputable pharmacies should be able to provide clear information regarding their adherence to USP guidance. One aspect of the PCAB accreditation mentioned previously is attestation to the accredited facility's adherence to relevant USP guidelines.

## 6 Pros and Cons of Different Hormone Testing Methods

There is continuing debate regarding the best testing methods for hormone status. Hormones can be analyzed in the blood, urine, or saliva. There are benefits and drawbacks to each of these methods.

### Saliva Testing

*Pros* - This easy, at home collection process is a measurement of bioavailable hormone levels.

*Cons* - Accuracy and testing variability are issues to consider. Hormone levels in saliva can vary with saliva flow rate, time of day, timing of hormone therapy, eating, and tooth brushing, as well as gum disease (even if

subclinical), and there are no salivary tests for hormone metabolites (Sood 2011; Larsen 2014).

### Urine Testing

*Pros* - This method provides a 24-hour picture of hormone levels. Because it captures both the peaks and troughs that occur during the day, it is not susceptible to moment-to-moment fluctuations. A 24-hour urine test can be used to assess the three main estrogens— estrone, estradiol, and estriol—as well as progesterone, pregnenolone, testosterone, and DHEA. Urine testing can also be used to assess metabolites like 2- and 16-hydroxyestrone (Larsen 2014). Urine testing is excellent at providing an overview of an individual's hormone metabolism that cannot be seen in blood or saliva.

*Cons* – Urine testing is considered less convenient by some patients, and comprehensive 24-hour urine panels may be more expensive than other types of testing (Larsen 2014). It can show high levels of hormones despite low blood levels for hormones like testosterone which are carried by sex hormone binding globulin (SHBG). If SHBG levels are low in the blood, testosterone is not preserved adequately and the free form is excreted from the kidney in excess and thus can show high levels despite low levels in the blood.

### Blood Testing

*Pros* - This method has been used consistently for decades and has well-established reference ranges. Serum testing is relatively inexpensive, routine, and readily available through blood draw centers (Larsen 2014).

*Cons* - Blood draws involve needle sticks. Blood testing provides only single-point evaluation, and because hormone levels can fluctuate widely during the day, reference ranges are typically broad. Although estradiol, estrone, testosterone, and DHEA can be evaluated, blood testing has limited ability to assess non-pregnancy levels of estriol in women using transdermal preparations so it is not suggested to test blood levels of estriol. Furthermore, with the exception of testosterone, these tests generally measure total amounts (bound and unbound) of hormones being tested, which are not as clinically meaningful as free hormone levels. Finally, there is no blood hormone metabolite testing available (Larsen 2014).

## 7 Nutrients

Phytoestrogens are dietary bioactives and natural compounds found in some plants that are similar in structure to estrogens. Although several types of plant compounds are classified as phytoestrogens (Landete 2016), the most studied of these are isoflavones and lignans (Chen 2015). Phytoestrogens in plants are largely inactive but are metabolized into active compounds by intestinal bacteria (Vitale 2013; Gencel 2012). Once absorbed, activated phytoestrogens exert estrogen-like effects in the body and may be an alternative to bioidentical HRT for some women (Sirotkin 2014; Landete 2016).

Some of the best evidence to support the use of phytoestrogens comes from Asia, where menopausal symptoms are milder and less common, and breast cancer incidence is lower than in Europe and North America. One explanation may be the phytoestrogens found in soy and other plant products commonly consumed in Asian diets (Aso 2010; Cho 2010; Sarkar 2003).

Phytoestrogens bind to estrogen receptors and help modulate estrogen activity (Zittermann 2003; Hajirahimkhan, Dietz 2013; Vitale 2013). The estrogenic effects of phytoestrogens vary but are generally weak relative to estradiol; in the presence of estradiol, they appear to have anti-estrogenic effects as they compete with estradiol for estrogen receptor binding sites (Hajirahimkhan, Dietz 2013; Ko 2014). Phytoestrogens have been shown to reduce menopausal symptoms and may decrease the risk of some chronic diseases including cardiovascular disease, osteoporosis, and breast cancer (Bawa 2010; Cho 2010; Miyake 2009; Vitale 2013; Messina 2014; Mainini 2013).

Intriguingly, phytoestrogens seem to preferentially bind estrogen receptor (ER)-*beta*, as opposed to ER-*alpha*, which is more strongly activated by estradiol and some other mammalian estrogens (Sirotkin 2014; Messina 2014). ER-*beta* activation has been proposed as a mechanism for preventing emotional and neurological aspects of aging and menopause (Vargas 2016), and appears to protect against cancerous changes in breast, ovarian, and possibly other tissues (Gallo 2012; Bardin 2004; Bossard 2012; Omoto 2015).

Dietary and supplemental phytoestrogens present a way for women to obtain limited hormonal support without

the use of hormone therapy.

**Cardiovascular benefits.** Unlike conventional HRT, which has been shown to raise the risk of heart attack among postmenopausal women, phytoestrogens appear to have a positive effect on the heart (Gencel 2012; Sirotkin 2014). In 1999, the FDA authorized the use of health claims on food labels that link increased soy consumption with a reduced risk of coronary artery disease (Vincent 2000).

There are many studies examining the cardiovascular effects of phytoestrogens. Overall, research suggests isoflavones may lower high blood pressure (Sureda 2017; Messina 2014), improve lipid disturbances, lower homocysteine levels (Li 2016), improve vascular health, and prevent atherosclerosis (Gencel 2012; Messina 2014). Lignans similarly have been associated with lower blood pressure (Khalesi 2015), improved lipid metabolism (Gencel 2012), and reduced cardiac risk (Chun 2014; Landete 2016).

In addition to their ability to weakly activate estrogen receptors, phytoestrogens have strong anti-inflammatory and oxidative stress-reducing effects, which may contribute to their cardiovascular benefits (Gencel 2012; Landete 2016).

**Brain protection.** Estrogen and estrogen-like compounds protect brain cells from degenerative changes due to aging, oxidative stress, and stroke-induced damage (Nabavi 2015; Evsen 2013; Bhavnani 2003; Linford 2002). Several studies have shown that the phytoestrogen genistein protects experimental animals from the effects of brain ischemia, the kind of injury seen in stroke (Schreihofer 2009; Donzelli 2010; Ma 2010). In addition, genistein has demonstrated anti-apoptotic activity, protecting cultured brain cells from self-destructing over time (Yu 2009).

**Osteoporosis and bone health.** A number of studies have been conducted on phytoestrogens and bone health. Clinical trials have found that phytoestrogens can increase bone mineralization, reduce bone resorption, enhance bone formation, and improve markers of bone metabolism. Taken together, their findings suggest phytoestrogens (mainly soy foods and isoflavones) may help mitigate bone loss after menopause (Messina 2014; Abdi 2016; Chiang 2013).

**Cancer protection.** A number of studies have noted an **association between isoflavone consumption and decreased breast cancer risk** (Wada 2013; Dong 2011; Fritz 2013). Soy isoflavones are safe in women with a high risk of breast cancer, including breast cancer survivors (Fritz 2013; Messina 2016), and do not increase the risk of uterine cancer (Parazzini 2015). In addition, flaxseeds, which are high in phytoestrogenic lignans, have been shown to reduce breast cancer risk and reduce breast cancer tumor growth (Mason 2014; Flower 2014).

Phytoestrogens may protect against breast cancer in part by improving estrogen metabolism. A diet containing 113–202 mg daily (depending on body size) of genistein and daidzein was found in one trial to increase the ratio of protective 2-hydroxylated estrogens to harmful 16-hydroxylated estrogens in the urine of premenopausal women, an effect that may contribute to a lower long-term risk of breast cancer (Lu 2000). Furthermore, emerging evidence suggests phytoestrogens inhibit aromatase, the enzyme that catalyzes the conversion of testosterone to estrogen, and this effect may contribute to their association with lower breast cancer risk (Lephart 2015).

**Lignans** are phytoestrogens found mainly in flaxseeds, with smaller amounts occurring in sesame seeds, some sprouts, and many other plant foods. A comprehensive review of 21 studies found that postmenopausal women with higher lignan intake were significantly less likely to get breast cancer (Buck 2010).

In one clinical trial, 32 women awaiting surgery for breast cancer were randomized to receive a muffin either with or without (control group) 25 grams of flaxseed. Analysis of the cancerous tissue after surgery revealed that markers of tumor growth were reduced by 30–71% in the flaxseed group, but not in the control group (Thompson 2005). A study published in 2010 found that a combination of lignans, indole-3-carbinol (I3C), and calcium-D-glucarate along with other herbs favorably altered the ratio of estrogen metabolites in 47 pre- and 49 postmenopausal women (Laidlaw 2010).

**Menopause symptoms.** Several studies have demonstrated that natural phytoestrogens can improve **menopausal symptoms** (Sirotkin 2014), particularly hot flashes (Chen 2015). A comprehensive meta-analysis that included results from 17 clinical trials found that treatment with an average of 54 mg of genistein per day for between six weeks and 12 months safely decreased hot flash frequency by 20.6% and hot flash severity by 26.2% (Taku 2012).

## Additional Natural Ingredients to Target the Symptoms of Menopause

**Siberian rhubarb.** A special extract from **Siberian rhubarb** (also known as rhapontic rhubarb, *Rheum rhaponticum*) has been used in Germany for decades to treat problems related to female hormone imbalance, including infrequent or absent menstrual periods, and peri- and postmenopausal symptoms (Heger et al., 2006).

In the first randomized controlled clinical trial using this supplement, 109 symptomatic peri-menopausal women were given either an enteric coated tablet providing 4 mg per day of the standardized Siberian rhubarb extract or placebo for 12 weeks. After four weeks, menopause-related symptoms diminished significantly more in the Siberian rhubarb group compared with placebo, and by week 12, the difference was even more pronounced, and was measurable for each of the 11 symptoms considered in the trial. A clinically meaningful decrease in symptoms was reported by 45 of 54 women receiving the extract (83%) and one of 55 women receiving placebo (less than 2%). Furthermore, extensive investigation into possible adverse effects attributable to the Siberian rhubarb extract found none (Heger et al., 2006). A subgroup of participants then went on to use the same extract in an open-label trial for 48 to 96 weeks. In general, the women experienced continued improvement in their menopausal symptoms with no adverse side effects (Hasper et al., 2009).

Another study using the data from the initial trial found the standardized Siberian rhubarb extract to be more effective than placebo specifically for relieving menopause-related anxiety and improving general well-being. In 33 of 39 rhubarb-treated women whose anxiety was "severe" or "moderate" at the beginning of the trial (85%), anxiety was reduced to "slight" after 12 weeks. The study also noted a correlation between decreased anxiety and reduced hot flashes (Kaszkin-Bettag et al., 2007).

Other studies have confirmed the benefits of the Siberian rhubarb extract: treatment with the extract led to decreases in overall menopausal symptom scores, as well as reductions in all individual symptoms tracked, in a six-month open-label study with 363 participants (Kaszkin-Bettag et al., 2008) and a 12-week randomized controlled trial with 112 participants (Kaszkin-Bettag et al., 2009).

Laboratory research has revealed that Siberian rhubarb extract and its active components selectively activate ER- $\beta$ , having no effect on ER- $\alpha$  (Wober et al., 2007, Konda et al., 2014). ER- $\beta$  activation has been proposed as a mechanism for preventing emotional and neurological aspects of aging and menopause (Vargas et al., 2016), and appears to protect against cancerous changes in breast, ovarian, and possibly other tissues (Gallo et al., 2012, Bardin et al., 2004, Bossard et al., 2012, Omoto and Iwase, 2015).

**Black cohosh.** Black cohosh (*Actaea racemosa* or *Cimicifuga racemosa*) root has a long history of traditional use in treating gynecologic disorders and has become a popular herbal medicine for relieving menopausal symptoms (NIH 2017). Randomized controlled trials have demonstrated its efficacy in treating menopausal symptoms such as hot flashes, low libido, sleep disturbance, and other physical and emotional symptoms (Jiang 2015; Shahnazi 2013; Mohammad-Alizadeh-Charandabi 2013; Ross 2012). Black cohosh has a track record of safety and the preponderance of evidence supports its use in treating menopausal symptoms (Shams 2010; Beer 2013; Czuczwar 2017; Sarri 2017). Black cohosh and closely related species have conveyed anti-proliferative effects on breast cancer cells in the laboratory (Fang 2010; Al-Akoum 2007; Hostanska 2004), and the use of black cohosh is not associated with increased breast cancer risk or recurrence rates (Fritz 2014). Data from one clinical trial and several animal studies suggest it is comparable to estradiol and another anti-osteoporosis medication for preventing bone loss (Nisslein 2003; Seidlova-Wuttke 2005; Wuttke 2003; Seidlova-Wuttke 2003).

**Dong quai.** Dong quai (*Angelica sinensis*) is used in traditional Chinese medicine for gynecological symptoms such as painful menstruation or pelvic pain, recovery from childbirth or illness, and fatigue/low vitality, and is therefore referred to as "female ginseng" (Al-Bareeq 2010; Goh 2001; Hardy 2000). Randomized controlled trials have shown that dong quai, in combination with other plant extracts, can relieve symptoms of menopause (Trimarco 2016; Kupfersztain 2003), and in one animal study dong quai was as effective as estradiol at preventing bone loss (Lim 2014).

**Licorice root.** Licorice (*Glycyrrhiza glabra*) root exerts estrogen-like effects with selective activation of ER-beta (Hajirahimkhan, Simmler 2013). Laboratory research suggests licorice constituents inhibit serotonin reuptake, an effect that may contribute to its positive impact on menopausal symptoms (Ofir 2003; Hajirahimkhan, Dietz 2013). In a randomized controlled trial, treatment with 330 mg of licorice root three times daily reduced both

frequency and severity of menopausal hot flashes more than placebo during eight weeks of treatment and for two weeks following the end of treatment (Nahidi 2012). Licorice root constituents have also been shown in the laboratory to support arterial and bone health, thus reducing the risk of cardiovascular disease and osteoporosis (Somjen, Knoll 2004; Somjen, Katzburg 2004).

**Vitex agnus-castus.** Herbal formulas containing extracts from *Vitex agnus-castus* (Vitex), also known as chasteberry, have been shown to improve menopausal symptoms such as sleep disturbance, hot flashes, and psychosocial wellness (De Franciscis 2017; van Die 2009; Rotem 2007). Vitex, obtained from the dried fruit of the chaste tree, has been used in the context of women's health for centuries. It has been shown to modulate hormonal and neurotransmitter signaling and to relieve premenstrual symptoms in several small studies. Laboratory studies have shown that compounds in vitex can bind estrogen receptors and modulate hormone-responsive genes (Dietz 2016).

#### Nutrients to Support Healthy Estrogen Metabolism

**Vitamin D.** Vitamin D appears to confer significant protective effects against breast cancer. Women with higher vitamin D levels had a nearly 70% reduction in their risk of breast cancer compared to women with the lowest levels in one study (Abbas 2008), while another study linked low vitamin D levels with reduced survival in breast cancer patients (Vrieling 2011). Laboratory studies have shown that vitamin D suppresses growth and development of breast cancer by:

- blocking signals that stimulate cancer cell growth
- enhancing signals that inhibit cancer cell growth
- modulating mammary gland sensitivity to carcinogenesis (Welsh 2017)
- inducing cancer cell death (apoptosis) (Thyer 2013; Fleet 2012)

**Cruciferous vegetables.** **Cruciferous vegetables** such as, cauliflower, cabbage, kale, and Brussels sprouts contain compounds that may help detoxify estrogen breakdown products that promote cancer growth (Marconett 2012; Lampe 2009; Ambrosone 2004). One such compound is I3C, which prevents the conversion of estrogen to the breast cancer-promoting metabolite *16-alpha-hydroxyestrone*, while increasing conversion to the cancer-fighting metabolite *2-hydroxyestrone* form (Acharya 2010; Weng 2008; Muti 2000).

**Fish oil.** Fish oil, with its high omega-3 fatty acid content, reduces cancer risk by a number of mechanisms. Fish oil reduces oxidative stress and suppresses production of many inflammatory mediators that contribute to cancer development (Saoudi 2017; Kansal 2011). It can sensitize tumor cells to chemotherapy effects even when metastases are present, potentially reducing the doses of chemotherapy required for treatment (Bougnoux 2009). In an animal model of breast cancer, fish oil supplementation was shown to reduce bone metastasis (Mandal 2010).

**Green tea.** Green tea polyphenols, particularly one called epigallocatechin gallate (EGCG), suppressed the growth and reproduction of human breast cancer cells in the laboratory and reduced the number of breast cancer tumors in animal models of the disease (Thangapazham, Passi 2007; Thangapazham, Singh 2007; Leong 2008). Green tea has also inhibited the production of tumor blood vessels while down-regulating cancer-promoting estrogen receptors and increasing apoptosis (Leong 2008; Masuda 2002; Farabegoli 2007; Hsuuw 2007).

**Pomegranate.** Pomegranate has been extensively studied for its antioxidant properties and cancer-fighting potential (Taheri Rouhi 2017; Li 2017; Panth 2017). With respect to breast cancer, pomegranate is an especially promising agent due to its ability to inhibit the cancer-promoting enzyme aromatase and suppress the generation of blood vessels by tumors (Toi 2003; Sturgeon 2010).

Update History

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The protocols raise many issues that are subject to change as new data emerge. None of our suggested protocol regimens can guarantee health benefits. Life Extension has not performed independent verification of the data contained in the referenced materials, and expressly disclaims responsibility for any error in the literature.

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