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Hormones & Breast Cancer Risk

The statistics about breast cancer are sobering. Understanding your risk and ways you can minimize it are best based on fact rather than fear. This handout will summarize the research regarding hormones and breast cancer, and will provide recommendations you can implement to lower your risk.

Currently, breast cancer is the most frequently diagnosed cancer in women, and the second leading cause of cancer deaths—lung cancer is the first. A woman's risk for breast cancer increases with age. Women have approximately a 12% chance of developing breast cancer if they live to be 90 years old; this also means the risk of not getting breast cancer is approximately 88%. Incidence of breast cancer has decreased since 2000, and death rates have decreased since 1989. A woman's chance of dying from breast cancer is approximately 3% (1 in 36). There are expected to be 232,000 cases of invasive breast cancer diagnosed in the US in 2013 with 39,600 deaths.[1] It's worth noting that women are 6 times more likely to die of cardiovascular disease and twice as likely to die of stroke as breast cancer (more on this in the "Putting It All Together" section).

Cancer occurs when cells divide and grow without restraint. The growth and death of cells is usually regulated; however, when normal cell regulators malfunction and cells don't die at the proper rate, they continue to divide, and cancer can develop. Breast cancer usually grows slowly. By the time a tumor is large enough to be felt as a lump, it may have been growing for 10 years and the spread of tumor cells (metastasis) may have already occurred. Therefore, screening methods such as mammography, ultrasound, MRI, or thermography, are important tools in providing early detection. In addition, preventive measures such as a healthy diet and lifestyle, nutritional supplementation, and exercise are crucial.

Knowing the risk factors for breast cancer can help you identify your specific risk. Breast cancer risk factors can be categorized as "modifiable" and "non-modifiable." Although non-modifiable risk factors cannot be altered, modifiable risk factors can be changed based on daily choices regarding diet, exercise, lifestyle habits, and stress management. **Reducing modifiable risk factors may help you prevent breast cancer.**

Non-modifiable risk factors for breast cancer include (check those that apply):

- ☐ Being female
- ☐ Advancing age
- ☐ Family history (mother, sister, or positive BRCA1 or BRCA2 gene mutation)
- ☐ Early menarche (first menstrual period)
- ☐ Late menopause
- ☐ Diethylstilbestrol (DES) use by mother

Modifiable risk factors for breast cancer include:

- ☐ Obesity (BMI > 30)[2]

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- Lack of exercise
- Hormones: conventional HRT—synthetic progestins and, possibly, synthetic estrogens, depending on duration of use; birth control pills (some studies show this, some don't); possibly bioidentical estrogen (depending on mode of delivery, duration of use, and whether hormones are balanced)
- Poor diet: high animal and trans fats, low fiber intake, deficient intake of fruits and vegetables
- Breast trauma
- Late age pregnancy, never having been pregnant, lack of breast feeding
- High alcohol intake (>1 drink per day)
- Cigarette smoking
- Working the "graveyard" shift
- Environmental toxin exposure (radiation, xenoestrogens, second hand smoke)
- Radiation to chest or face before age 30[3]
- Benign breast disease (fibrocystic breast changes, may or may not increase risk)

Breast Cancer & Hormones

Currently every 50-year-old woman has about a 2.8% chance of developing breast cancer by age 60. This translates to an absolute risk of 2.8 breast cancer cases out of 100 women.

Most studies show the overall risk of developing breast cancer is higher with the use of synthetic estrogens and synthetic progestins. That means out of 100 women age 50 using synthetic hormone replacement (according to the Women's Health Initiative data), the number who will develop breast cancer by age 60 is 3.5. What this means is that per 100 women who use synthetic estrogen and synthetic progestin (Prempro®) slightly less than one extra woman will develop breast cancer. That increase, from 2.8 to 3.5 per 100 women, represents a 25% increase in risk.

For comparison to other risk factors, some studies show obesity (especially around the waist) and high insulin levels in women who'd never used HRT can cause increase the risk of getting or dying from breast cancer 50 to 150%.[4–7] In addition, some antibiotics used for more than 500 days in a lifetime, or more than 25 prescriptions over 17 years, can increase the risk by 150% to 200%.[8]

When evaluating information regarding hormone use and breast cancer risk, it's necessary to determine

- what hormone is being discussed
  - synthetic estrogen versus bioidentical (human) estradiol or bioidentical (human) estriol
  - synthetic progestins versus bioidentical (human) progesterone
  - synthetic methyltestosterone versus bioidentical (human) testosterone
- mode of delivery

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- oral
- transdermal
- topical
- pellet
- vaginal

as the risk varies widely across these variables. In addition, risk varies based on the number of years of hormone use. Not enough studies have been performed using individualized dosages of compounded hormones (based on lab testing, clinical assessment, and risk factors) since most studies use uniform modes of delivery and dosages of hormones for all women. However, one recently published small study of 189 women reported no increased risk of breast cancer, blood clots, or strokes with bioidentical hormones that were prescribed based on individualized dosages (determined via blood testing and symptom control). Women in this study were monitored for one to three years, and most had significant improvements in menopausal symptoms.[9]

The following summary is meant to give you succinct information based on available research regarding estrogens, progestins and progesterone, and testosterone with regard to breast cancer risk.

Estrogen & Breast Cancer

Estrogens, especially estradiol and estrone, stimulate proliferation of both breast tissue and breast cancer cells. There is much confusion about the use of estrogen replacement therapy (ERT) and breast cancer risk; this is true for the use of bioidentical estrogens as well as synthetic forms, such as Premarin.

It's helpful to review the results from large, well-conducted studies—the Women's Health Initiative, the Million Women Study, and the Nurses' Health Study—as well as trends seen in smaller studies, to clarify the relationship between ERT and breast cancer risk.

The Women's Health Initiative found an increased risk of breast cancer in women using the synthetic estrogen Premarin along with the synthetic progestin Provera (Prempro), but not in women using Premarin alone.[10] The Million Women Study showed an increased risk with ERT (bioidentical and synthetic) and an even higher risk with estrogen plus synthetic progestins.[11] Lastly, the Nurses' Health Study also found an increased risk only in women using long-term (more than 15 years) estrogen replacement.[12]

A few studies (one with 261 women, one with 508 women) have shown no increased risk of breast cancer,[13,14] or risk of recurrence in women who'd been treated for breast cancer (123 women)[15] with estradiol pellets, especially if used in combination with testosterone.[16]

Several studies evaluating hormone replacement in breast cancer survivors have been favorable. One meta-analysis of nine observational studies found no risk of recurrence in breast cancer survivors who used hormone replacement.[17] Another paper that reviewed literature published before 2003 found an increased risk of recurrence in breast cancer survivors who did not use hormone replacement versus those who did.[18] Another study of 277 breast cancer

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survivors who used estrogen replacement did not show increased recurrence rates after more than three years of treatment; in fact, the women who used estrogen replacement had a lower chance of dying from all causes.[19] In a longer, 5-year trial, 77 breast cancer survivors who used estrogen replacement were compared to 222 breast cancer survivors not on ERT. The women who did not use ERT were more likely to experience a recurrence of breast cancer (13.5%) versus women who used ERT (3.6%).[20]

Vaginal estrogens, especially estriol, do not increase the risk for breast cancer;[21–25] vaginal estriol also does not increase the risk for recurrence in breast cancer survivors.[26] There is no accumulation of hormones or metabolites with vaginal estrogen or progesterone therapy.[27–29]

Although the media appears to portray estrogen as the smoking gun regarding hormones and breast cancer, it's important to remember that most breast cancer occurs in women over 50. Younger women have the highest estrogen production, but the lowest risk for breast cancer. This may be related to the fact that younger women are more likely to be ovulating, and have higher levels of progesterone and testosterone (the hormones that balance estrogen in breast tissue) than older women do.

Synthetic Progestins, Bioidentical Progesterone, & Breast Cancer

The data is irrefutable that synthetic progestins (such as Provera®) significantly increase the risk for breast cancer. However, bioidentical progesterone is a different molecule than synthetic progestins and has a different effect on breast cancer risk.

Progesterone deficiency (in women who don't ovulate or who don't make enough progesterone) has been shown to increase the risk for breast cancer. In one study progesterone deficient women had a 5.4 times increased risk of pre-menopausal breast cancer, and a 10 times increased risk of death from all malignant cancers.[30] Another study evaluated hormone levels in women under age 45 who developed pre-menopausal breast cancer. There was no association between serum SHBG (sex hormone binding globulin), estradiol, testosterone or androstenedione and premenopausal breast cancer risk. The only link was an inverse relationship between risk and luteal phase progesterone levels—women with the highest progesterone levels had the lowest risk.[31] The risk of developing breast cancer seems to be decreased in women with high luteal phase progesterone levels.[32,33]

Breast cancer risk does not increase with the use of bioidentical progesterone supplementation (oral micronized progesterone, such as Prometrium,® topical progesterone cream, or intravaginal progesterone).[34–36]

Testosterone and Breast Cancer

The role of testosterone in breast cancer is often confusing, due to the use of synthetic, methyltestosterone versus bioidentical testosterone in many studies. In animal and human studies, testosterone supplementation does not increase breast cancer risk.[37–39]

Testosterone inhibits the growth of breast cancer cells via the androgen receptor.[40–44] Testosterone works by preventing breast cells from dividing and multiplying, and by inducing

apoptosis (programmed cell death).[45–49] Adrenal androgens (DHEA and androstenedione) and testosterone counteract the way estrogen stimulates the growth of breast cancer cells.[50–52]

Some studies have found that if a woman has androgen-receptor positive breast cancer, her prognosis is better than a woman who doesn't.[53,54] In women with breast cancer treated with anti-estrogens (such as Tamoxifen®), those given androgens have better outcomes.[55,56] Interestingly, synthetic progestins may increase the risk of breast cancer by blocking the androgen receptor and negating the protective effects of testosterone on breast tissue.[57]

An excellent paper reviewing data from preclinical, clinical, and epidemiological studies evaluated the body of research regarding testosterone and breast cancer risk.[58] The authors suggest that several lines of evidence argue against increased breast cancer risk with testosterone (T). They include (1) breast tumor cells treated with androgens do not increase growth. On the contrary, androgens appear to be protective as they inhibit tumor cell growth. (2) Many epidemiological studies claiming an association between T and breast cancer did not adjust for estrogen levels. Studies adjusted for estrogen levels report no association between T and breast cancer. (3) Data from clinical studies where women with endocrine and sexual disorders received androgen supplementation do not show any increase in incidence of breast cancer. (4) Women with polycystic ovary disease, who exhibit high levels of androgens, do not show increased risk of breast cancer compared with the general population. (5) Female to male transsexuals, who receive supraphysiological doses of T for long time periods prior to surgical procedures do not report increased risk of breast cancer. (6) Finally, women with hormone responsive primary breast cancer are treated with aromatase inhibitors, which block conversion of androgens to estrogens, thus elevating androgen levels. These women do not experience increased tumor growth. The conclusion of the paper was that the evidence available strongly suggests that T does not increase breast cancer risk in women.

Clinical studies have shown that testosterone given as a patch or pellet can prevent breast proliferation and decrease estrogen receptors.[59,60] In addition, women who receive testosterone pellets have been shown to have no increased risk of breast cancer even though they were taking estrogen and synthetic progestins.[61] In one study, testosterone pellets showed no increased risk of recurrence in breast cancer survivors.[62]

Lowering your risk for breast cancer

Benjamin Franklin's famous words—*an ounce of prevention is worth a pound of cure*—are certainly applicable to all areas of health. The following recommendations have been shown to lower breast cancer risk:

- **Eat a healthy, Mediterranean-type diet.** This type of diet has been shown to significantly lower breast cancer risk.[63] A Mediterranean diet consists mainly of vegetables, fruit, whole grains, seafood, nuts, and olive oil. The standard American diet (appropriately called the "SAD" diet) consists mainly of meat, fried food, potatoes, pizza, and white flour products—avoid or significantly limit eating a SAD diet.

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- **Drink alcohol in moderation or not at all.** One alcoholic drink per day increases breast cancer risk by 10%, and two drinks increase the risk by 20 to 40%.[64]

- **Exercise!** Sustained physical activity for 30-45 minutes, 3 to 7 times per week, has been shown to decrease the risk of breast cancer between 20 and 60%[65,66]

- **If feasible, have children and breast feed at a younger age.** Giving birth before age 25 and having multiple children is known to be breast protective. Most research shows that, regardless of the mother's age, breastfeeding also lowers breast cancer risk.[67,68]

- **Maintain normal weight**—obesity can significantly increase your risk for breast cancer.[69–71]

- **Don't smoke.** Cigarettes are known carcinogens for many different types of cancer, including breast cancer.[72] Smoking also dramatically increases free radicals, shortens telomeres, and accelerates aging.

- **Empty your "stress bucket" daily.** Chronic, prolonged stress impairs your cell's ability to repair DNA damage, leading to an increased possibility of defective cell division and cancer formation.[73]

- **Maintain a serum vitamin D level >30 ng/mL, possibly 40-70 ng/mL.** Vitamin D and sunlight exposure are breast cancer protective.[74] If you don't know your vitamin D level, consider supplementing with 1000 IU of vitamin D3 per day; this dosage has been shown to lower overall cancer risk by 60%.[75]

- **Go through a yearly detox program.** Many studies have linked environmental toxins to breast cancer.[76] Yearly detoxification can enable you to minimize exposure and enhance metabolism and excretion of stored toxins.

Some nutritional supplements may help lower your risk for breast cancer. They include:

- **Indol-3-carbinol**—200 to 600 mg per day. Indol-3-carbinol enhances estrogen metabolism and has been shown to lower breast cancer risk.[77]
- **DIM (diindolmethane) found in HormoneSynergy Estro Protect**—DIM is the active metabolite of indol-3-carbinol. DIM supplementation increases 2-hydroxylation of estrogen. Animal and human studies have shown that DIM increases the ratio of the protective "good" 2-hydroxyestrone to 16 alpha hydroxyestrone.[78,79] In a study of postmenopausal women, subjects who took DIM showed a 47% increase in this ratio, compared to women who took the placebo.[80] Other studies suggest that DIM plays a role in supporting normal cell proliferation in estrogen-sensitive tissues.[81,82] Dosage is 150 to 300 mg per day.
- **Green tea** contains EGCG (epigallocatechin gallate), which helps block vascular endothelial growth factor (VEGF), preventing formation of blood vessels that feed tumors. Green tea has also been shown to inhibit the growth of cancerous tumors,

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and increase their death.[83,84] Suggested dosage is 300-1500 mg of green tea capsules per day. For breast cancer prevention, drinking three to five cups of green tea per day is recommended.

- **Melatonin** is a potent antioxidant that inhibits breast cancer cell growth.[85–87] A high percentage of women with breast cancer have low melatonin levels.[88] As previously mentioned, women who work the "graveyard" shift have a higher risk for breast cancer; therefore, avoid working through the night to prevent disruption of this powerful hormone. If you supplement with melatonin, the recommended dosage depends on prevention (3-5 mg before bed) or breast cancer treatment (beneficial dosage may be significantly higher).
- **Fish oil**—Higher omega-3 (fish oil) to omega-6 ratio may reduce the risk of breast cancer.[89,90] Fish oil has been shown to retard the growth of breast cancer in the laboratory, and inhibit breast cancer from developing and spreading in animal studies. Take 1,000 to 6,000 mg EPA and DHA per day.
- **Antioxidants**—especially carotenoids (such as beta-carotene, lycopene, lutein, and zeaxanthin), C, E, selenium, and zinc may lower breast cancer risk (as well as improve telomere length to slow aging).[91,92]

Putting It All Together

Understandably, many women are afraid of breast cancer—it is much too common, and is too often fatal. It may be helpful to keep in mind that the 3 most common chronic diseases in women are cardiovascular disease (heart attack and stroke), Alzheimer's and other forms of dementia, and osteoporosis. These conditions may be prevented or their impact reduced by maintaining optimal hormone levels.

For example, decreased estrogen and testosterone are associated with metabolic changes that increase a woman's risk for cardiovascular disease (higher total and LDL cholesterol, higher triglycerides, and lower HDL cholesterol). Estrogen replacement can improve cholesterol levels and the health of blood vessels. Body composition changes that occur with menopause include increased total body fat, especially with accumulation around the waist, and decreased lean body mass. This increased fat to lean body mass and muscle ratio increases the risk for diabetes, cardiovascular disease, dementia, and some forms of cancer. This change in body composition may improve with bioidentical hormone (especially testosterone) supplementation.[93]

Because bone loss is usually asymptomatic, it's common to underestimate the consequences of osteoporosis. Currently, 20 to 30% of menopausal women have osteopororis. One third of women over 50 will have an osteoporosis-related bone fracture; this risk increases to 50% of women over age 60. The risk for hip fracture is equal to the risk for breast, uterine, and ovarian cancers—combined. Not only is a hip fracture debilitating, but a woman has the same risk of dying from a hip fracture as she does from breast cancer.

Other long-term problems with menopause include cognitive impairment, thinning skin, urinary frequency, vaginal dryness, tooth and gum disease, weight gain, sleep problems, and sexual

dysfunction. Considering the fact that bioidentical hormones can help with all of these symptoms and conditions, it's important to weigh your specific risks and benefits when deciding whether to use bioidentical hormones.

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