Breast Cancer, Hormones, and Aromatase Inhibitor Therapy

Misunderstandings About the Hormone-Fed Cancer

It is well known there is an association of Estrogen with breast cancer, and we often hear of breast cancer as a "hormone-fed tumor." However, to label the cancer as *hormone-fed* often leads to erroneous assumptions. It's reported that in up to 85% of breast cancers, the malignant cells contain Estrogen receptors (ER+), which can facilitate tumor growth with Estrogen exposure. But, the misunderstanding lies in the belief that the tumor first developed because of Estrogen, or that Estrogen promotes *initiation* of breast cancer. This has not been demonstrated, and we must remember *association does not imply causation*. The misguided belief that Estrogen is dangerous has caused enormous harm for women. In fact, after decades of scientific study, it has not been demonstrated that hormone therapy increases incidence of breast cancer. Rather, considering the totality of data, we can conclude it's more likely that hormone replacement therapy, *when administered knowledgeably,* protects against the formation of breast cancer. Moreover, depletion of the sex hormones (Estrogen, Testosterone, Progesterone) constitutes a detrimental condition deserving of treatment – by replenishment of these hormones.

Is Depletion of Sex Hormones (Menopause) a Disease?

When insulin or thyroid hormones are depleted, no doctor would argue for withholding treatment with the appropriate hormone, but the sex hormones don't seem to earn the same respect. Yet, it's well known that when sex hormones are depleted in midlife, healthy body systems begin to fail:

- Coronary artery plaques are more likely to develop, potentially leading to deadly heart attack/stroke.
- Neurodegenerative changes develop in the brain, leading to memory loss, often dementia (100% fatal).
- Bone mineral density begins a steep decline, potentially leading to osteoporosis and fracture mortality.
- Metabolic changes promote chronic inflammation, potentially leading to colon cancer and other cancers.
- Sexual health and mental health are often severely disrupted, harming relationships and quality of life.

When these things happen it's largely *because* of sex hormone depletion. This absolutely describes a disease process – and we have known the cure for decades!

Side note: It's unfortunate that the sex hormones were named *sex hormones*, as the term often leads to the mistaken conclusion that these precious molecules are expendable after the reproductive phase of life. They should be renamed *vitality hormones*, as they are certainly indispensable, and crucial for optimal whole body health, and longevity well beyond reproductive years. *Yes, hormone replacement therapy has been shown to increase longevity.*

What Is the Cause of Breast Cancer?

Despite the oft-repeated myth that Estrogen is responsible for breast cancer, medical science has yet to elucidate the underlying processes driving the transformation of a normal breast cell to a malignant breast cell. However, we have some clues about how some breast tumors grow, once they have been established. First, let us digress for a brief discussion of Estrogen biosynthesis.

Estrogen is made from Testosterone or other androgens through a process called *aromatization*. A protein called ***aromatase*** is required for that process. Most of us are familiar with the concept of Estrogen produced by the ovaries being secreted into the bloodstream. But, through aromatase activity, Estrogen is also produced in various other tissues, thus providing Estrogen right where it's needed, for a multitude of functions throughout the body. The tissue-produced Estrogen acts on the spot, and is not measurable with a blood test, because it's located inside cells, not floating around in the bloodstream.

Molecular study has demonstrated that one step in breast cancer growth involves genetic machinery within cells in the immediate vicinity of malignant breast cells. Within these neighboring cells, genes coding for the aromatase protein receive strong signals to ramp up production of aromatase to extraordinary levels. This, of course, leads to production of abnormally high concentrations of Estrogen, thus forming an Estrogen factory within the tumor. Essentially, the tumor is producing it's own fuel. It has been proposed that this localized tissue over-production of Estrogen contributes more to the growth of a breast tumor than Estrogen derived from blood circulation (ie. the fraction of Estrogen produced by ovaries). This proposal makes sense, since the vast majority (90%) of breast cancers occur in postmenopausal women with no ovarian Estrogen production, thus no circulating Estrogen.

The abundance of localized tumor Estrogen is thought to promote growth of ER+ tumors. However, it is important to keep in mind, that the tumor tissue is present through a pathologic process yet to be elucidated. It is erroneous thinking to believe that having physiologic (normal) levels of Estrogen in your body, whether produced by the body or administered as Estrogen hormone therapy, is a *cause* of deadly disease. The fact is, *not* having Estrogen in your body contributes to deadly disease – for example: heart attack, dementia, osteoporotic fracture, and colon cancer.

Aromatase Inhibitors: Therapy to Reduce Tissue Production of Estrogen

Given the effect of aromatase to dramatically increase Estrogen levels produced in tumor tissue, drugs called ***aromatase inhibitors*** **(AI's)** have been developed to block the action of aromatase, with the goal of halting tumor growth. An aromatase inhibitor is not selective; it will block production of Estrogen in *all* the body's tissues, with the exception of some ovarian derived Estrogen. So, a premenopausal woman using AI therapy may still have circulating Estrogen, but a for postmenopausal woman on AI therapy, the body will be virtually devoid of Estrogen. The problem with this, as described above, is that many body systems depend on Estrogen to maintain optimal health.

Besides the significant health risk of Estrogen depletion in all tissues, the majority of those who ingest AI therapy will experience significant musculoskeletal pain, joint pain, nausea, and intense side effects related to loss of Estrogen: hot flashes, night sweats, insomnia, depression, brain fog, vaginal dryness, and sexual dysfunction. Because AI therapy is poorly tolerated, it is often quickly discontinued.

Fortunately, a novel development provides a solution to the side effects of AI therapy, and it has to do with the method of delivery. The traditional delivery of AI therapy consists of ingestion of a daily oral tablet, but now there is the option of a subcutaneous implant. For example, an AI called **Anastrozole** can be compounded into a tiny pellet, designed for injection beneath the skin. The pellet then resides in the fatty tissue, and Anastrozole is absorbed directly into the circulation, a tiny bit at a time. This delivery system avoids *liver first-pass metabolism*, a process wherein the liver removes a large percentage of the drug for excretion from the body, and is also responsible for some of the medication's side effects. Using a subcutaneous pellet allows a much lower dose to be effective. A subcutaneous Anastrozole implant delivering approximately .05 mg/day into the circulation effectively blocks aromatase activity. This dose is *one-twentieth* of the poorly tolerated 1 mg daily oral dose of Anastrozole. Preliminary clinical studies have shown the subcutaneous Anastrozole pellet to be safe, and not associated with body aches and nausea experienced with oral AI therapy. The implant completely dissolves over a few months, and a new one is implanted 3-4 times per year for consistent, effective dosing.

Add-Back Hormone Therapy Provides Relief

Being completely devoid of sex hormones is not a good thing for your body. However, when Estrogen is depleted as a result of AI therapy, the other sex hormones (Testosterone and Progesterone) can be supplemented to compensate for the loss of Estrogen. This is known as "add-back" hormone therapy, and it allows AI treatment to be well tolerated and safe, compared to AI treatment with no add-back hormone therapy. Testosterone, in particular, is an ideal hormone to add-back in this scenario, and it can be combined with Anastrozole in a single pellet containing Testosterone + Anastrozole (T+A).

Many are surprised to learn of the importance of Testosterone's role in female hormone health, and that the amount of Testosterone produced in the female body is 10–20 fold the amount of Estrogen produced. *Yes it's true!* Far from being exclusively a *male hormone*, Testosterone is also an essential *female hormone*, exerting its effects through binding to androgen receptors located throughout the female body. Testosterone provides many similar benefits as Estrogen in the non-reproductive tissues of the female body, plus some extra benefits not provided by Estrogen. Testosterone improves bone mineral density, muscle mass, and reduces musculoskeletal and arthritis pain. Testosterone is protective of the heart and brain for women. Testosterone has been shown to improve mood, anxiety, fatigue, sexual health, libido, and general sense of well being. And, you guessed it – absence of Testosterone adversely affects all of the above. Another hormone beneficial for add-back hormone therapy is Progesterone, which exerts anti-proliferative effects on breast tissue.

Use of AI + Hormone Add-Back Therapy For Breast Health, Overall Health, and Quality of Life

Aromatase inhibitors, such as Anastrozole, have been FDA approved for treatment of ER+ breast cancer. Anastrozole is also sometimes prescribed for risk reduction in women at high risk for breast cancer; those with family history or abnormal breast biopsy; or for extended treatment of breast cancer.

It's important to understand that by the time a breast tumor is detected, it has already been present for several years, even up to 20 years, depending on the growth rate, and ER+ tumors tend to have a slower growth rate (are less aggressive) than ER negative ones. When AI therapy is prescribed, it is under the presumption that an early, yet undetected tumor may be present, and the AI is expected to slow or stop tumor progression.

Testosterone may offer additional benefit in reducing breast cancer risk. It has been reported in numerous scientific reports that Testosterone exerts protective effects on breast tissue through its binding to androgen receptors in the breast, reducing tissue proliferation and even reducing breast cancer growth. With this in mind, subcutaneous pellets of Testosterone + Anastaozole (T+A) have been developed and studied by researchers Rebecca Glaser, MD and Constantine Dimitrakakis, MD. The team has published their findings from study of 1,267 pre and postmenopausal women over a ten-year period, reporting lower breast cancer incidence with the T implant alone, and with T+A implant therapy.

To date, the T+A pellet is not available as an FDA approved medication, because there has not been a pharmaceutical company willing to take on the development and marketing of the product. One of the barriers is the extreme expense of new drug development, combined with the fact that Testosterone, being a bioidentical hormone, is a naturally occurring compound, thus cannot be patent protected. Accordingly, the T+A pellet has not been studied as rigorously as the oral tablet, but clinical data has been published, suggesting the T+A regimen to be well tolerated and safe. Testosterone + Anastrozole pellets are available through custom compounding. We have been working for many years with a limited number of compounding pharmacies for numerous bioidentical hormone formulations, and have observed excellent consistency and quality.

You Are a Whole Person!

You are not just a pair of breasts. Your whole body needs attention when disease is present in any organ or system. Aromatase Inhibitors *without* add-back hormone therapy may reduce risk of breast tumor growth, but at what cost? When evaluating risk of using hormone replacement therapy, it is just as important to consider the risks of *withholding* hormone therapy. It is critical to keep the entire body functioning well for long-term health and quality of life. This means taking the condition of hormone depletion seriously, and recognizing the tremendous toll it would exert on physical and emotional health for the rest of your life. The choice is yours.

KEY POINTS:

- Estrogen is produced in the body by conversion of Testosterone through aromatization, requiring the protein *aromatase*.
- Breast cancer tissue contains abnormally large amounts of aromatase, thus producing excessive Estrogen within the tumor, which then can promote tumor growth.
- Aromatase inhibitor therapy, such as Anastrozole, can be used to block Estrogen production in breast cancer tissue.
- Anastrozole blocks Estrogen production in all tissues (with the exception of ovaries in the premenopausal woman).
- For a postmenopausal woman, Anastrozole therapy leads to profound Estrogen depletion.
- Testosterone is anti-proliferative (protective) for breast tissue, through binding to androgen receptors.
- Add-back hormone therapy with Testosterone alleviates adverse consequences of Anastrozole-induced Estrogen depletion.
- Delivery of Anastrozole in the form of a very low dose subcutaneous pellet avoids body aches and other side effects arising from oral delivery of the drug.

FAQ's: Aromatase Inhibitor Therapy

Q: ***My cancer doctor said if I take Anastrozole to lower risk of breast cancer, I must stop using my hormone therapy. But, I feel so terrible without my hormone therapy! Is it safe to use hormone replacement therapy to control menopausal symptoms while using Anastrozole therapy?***

A: As discussed previously, no hormone *causes* cancer, including Estrogen. However, if one wishes to avoid Estrogen therapy with the assumption they may have undetected malignant breast tissue in their body, there are other hormonal options to control menopausal symptoms. One may limit hormone replacement therapy to bioidentical Testosterone and/or bioidentical Progesterone therapy, for neither has been demonstrated to promote breast cancer development or growth.

Studies have shown that Testosterone therapy has an anti-proliferative effect on breast tissue. When delivered as a subcutaneous implant (with or without Anastrozole included), Testosterone is safe and effective to relieve symptoms of menopause, via binding to androgen receptors throughout the body. Furthermore, treatment with Testosterone + Anastrozole assures that the supplemental Testosterone will not convert to Estrogen, so if the goal is eliminating Estrogen from the body, it can be accomplished when menopausal hormone therapy is limited to Testosterone.

Bioidentical Progesterone does not have a proliferative effect on breast tissue, and should be considered safe to administer in the setting of Anastrozole therapy. However, Progesterone alone is not likely to relieve the full range of menopausal symptoms. Progesterone-only hormone therapy has potential to at least partly relieve night sweats and insomnia, but the extensive benefits documented for Testosterone and Estradiol have not been observed for Progesterone, when used alone for hormone therapy.

Q: ***If I use Testosterone therapy without aromatase inhibitor therapy, should I worry about aromatase in my body converting a large amount of the Testosterone to Estrogen?***

A: The concern would be if you already have an existing tumor, which presumably would contain abnormally high levels of aromatase. However, just as your normal production of hormones in younger years did not cause excessive aromatase production, using Estrogen, Testosterone, and Progesterone as hormone replacement therapy does not cause excessive aromatase to develop. Regarding safety of Testosterone therapy, it has been demonstrated that Testosterone is protective of breast tissue, having anti-proliferative effects through binding to androgen receptors present within normal breast cells and within the majority of breast cancers. This was the basis for historically treating breast cancer with Testosterone therapy, and the practice was effective, sometimes even leading to regression of metastatic disease.

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Laura Grant, MD, NCMP 3/5/2023