Balanced Hormone Therapy and Breast Cancer
Can hormone therapy be safely used in breast cancer survivors?

Introduction

High levels of estrogen and long periods of unopposed estrogen are thought to be a risk factor for breast cancer. Testosterone balances the action of estrogen, prevents proliferation of breast tissue and has been shown to lower the risk of breast cancer. Vaginal estrogen therapy, in particular vaginal estriol, does *not* increase the risk of breast cancer. Progesterone has *not* been associated with an increase in breast cancer, unlike the synthetic progestins.

Breast Tissue, Testosterone and Pellet Implants

Testosterone has been used to treat patients with advanced breast cancer and has been used (as a hormone implant) as part of endocrine therapy in breast cancer survivors [1, 2, 12].

Clinical evidence supports that testosterone is breast protective [4-8]. Androgens are known to inhibit breast cancer in almost every breast cell line via the androgen receptor [13-15]. Adrenal androgens have been shown to counteract the growth stimulatory affects of estrogen on breast cancer cells [16]. Non-oral testosterone, including testosterone delivered by pellet implant, has been shown to prevent breast proliferation, decrease estrogen receptor alpha and prevent the stimulation of breast tissue from estrogen/progestin therapy. [17-20]. Breast density is inversely associated with testosterone levels. Testosterone, delivered by pellet implant has also been shown to lower the risk of breast cancer when given with estrogen and estrogen/progestin therapy [11, 21]. Long-term follow up data supports the safety of testosterone, delivered by pellet implant.

Estradiol delivered by pellet implant has been shown to increase the risk of breast cancer equivalent to oral and topical estrogens [9]. However, when used in combination with testosterone implants, even high doses of estradiol did not increase the risk of breast cancer in up to 22-year follow-up [11]. Even in patients with a history of breast cancer, estrogen did not increase the risk of recurrence when used with testosterone implants [12].

Testosterone has been used successfully to treat breast cancer patients [2, 22]. It is highly unlikely that non-oral testosterone would have any long-term negative effect on breast tissue unlike oral synthetic methyl-testosterone [23, 99].

Testosterone, delivered by pellet implant does not raise serum levels estradiol [24, 25] when given with estrogen. However, a 200 mg. testosterone pellet implant alone, demonstrated a non statistically significant rise in estradiol [24]. Oral, synthetic methyl-testosterone is converted to 17-α methyl-estradiol by aromatase [26], which is found in large quantities in the fatty tissue of the GI tract. 17-α methyl-estradiol is stimulatory to the breast tissue, binding strongly to ER alpha [26, 27]. This, along with the combined use of ethinyl-estradiol (Estratest®), may explain the increased incidence of breast cancer with the synthetic, oral

methyl-testosterone [23]. Methyl testosterone may also act as an endocrine disrupter by preventing testosterone from binding to the androgen receptor.

Although some retrospective, epidemiologic/statistical studies using inaccurate methodologies to measure testosterone (RIA), have shown an increased incidence of breast cancer 'associated' with elevated testosterone levels, other studies have show a decreased risk or no difference [28, 30]. It has been clearly established that testosterone, measured by RIA is inaccurate in women and should not be relied on [28-32]. Higher levels of testosterone are associated with higher levels of estrogen. After adjusting for estrogen levels, androgens had a negligible impact on breast cancer risk [97,98]. In addition, women with polycystic ovarian syndrome and elevated testosterone levels do not have an increased risk of breast cancer (RR 0.52) [33, 34].

Recent data (under publication*) has shown that newly diagnosed breast cancer patients have lower salivary testosterone levels compared to controls. Also, women with higher testosterone levels have higher estradiol levels.

Androgens (testosterone and DHT) have been reported to 'stimulate breast cells'. However, in these studies it was pharmacologic doses of testosterone (up to >100 times physiologic levels) that stimulated breast cancer cells via the estrogen receptor [35, 102, 103]. Physiologic doses of testosterone and DHT inhibit growth of breast cancer cells via the androgen receptor [13-16].

Estriol, Progesterone and Vaginal Delivery of Hormones

Vaginal delivery of hormones, including estriol, estradiol, estrone, progesterone and testosterone, has been well established in the literature. It has been shown in multiple studies that hormones administered vaginally are absorbed systemically, bypass hepatic metabolism and are biologically active [36-47]. It has also been shown that hormones applied to the mucous membranes are more readily absorbed than hormones applied to the skin [48-51]. Testosterone, applied to the mucous membranes of the labia, has been shown to be absorbed and have systemic effects [50, 52]. Hormones applied vaginally achieve higher plasma levels than if taken orally and the vaginal route appears to be more adequate than the oral one for hormone replacement therapy [51].

Symptomatic relief of genital urinary symptoms as well as systemic climacteric symptoms with vaginally administered hormones has been described and is dose dependent [46, 53-55].

The long-term safety of vaginal estrogen therapy has been established in the literature. Multiple large studies, including the Million Women's Study and Fournier's E3N French Cohort study, have repeatedly shown that ***vaginal estriol*** does not increase the risk of breast cancer (RR 0.67-0.70) [9, 68-74]. There is no data to the contrary. Vaginal estriol use in breast cancer patients does not increase the risk of recurrence (RR 0.57) or death [69,70]. Estriol has a low binding affinity for ERα and does not stimulate breast tissue or increase breast density [62, 78-81]. Vaginal estriol, used in the correct doses, does not increase the risk

of endometrial hyperplasia or uterine cancer [56-58, 67]. Unlike oral estriol, vaginal estriol *has* been shown to increase bone density [56, 59]. There is no accumulation of hormones or metabolites with vaginal estrogen or progesterone therapy [45, 51, 57, 60-62].

Vaginal progesterone has preferential distribution to the uterus and protects the uterine lining [75-77]. Unlike the oral synthetic progestins, vaginal progesterone does not negate the beneficial effects of estrogen on the heart and enhances the effect of estrogen on exercise induced myocardial ischemia [47].

In Fournier's E3N French prospective, cohort study, **progesterone** did *not* increase the risk breast cancer (RR 0.9) like the synthetic progestins (RR 1.4) [71,72].

Progesterone, the bio-identical molecule, has been shown to decrease or have no effect breast proliferation [18, 95, 96]. It is highly unlikely that vaginal progesterone would have a negative effect on breast tissue. Progesterone, applied vaginally, has a high local effect on the endometrium without systemic side effects (bloating, sedation, persistent hot flashes) due to high plasma progesterone levels and metabolites [61-64, 76, 77]. Vaginal administration of progesterone is preferred in patients with cardiovascular disease, liver disease or hepatic overload [65].

Cancer cells are known to over-express insulin receptors [100]. A diet of whole foods with limited refined carbohydrates may lower the risk of cancer. Hyperinsulinemia has been associated with a higher incidence of breast cancer, increased recurrence of disease and increased mortality. Synthetic progestins increase insulin receptor content and insulin stimulation of growth in human breast cancer cells [101].

Hormone Replacement Therapy in breast cancer survivors

In the past, a history of breast cancer has been a relative contraindication to 'Hormone Replacement Therapy' in women. This approach has continued, despite a lack of data to support the position. Hormone replacement therapy (HRT) most often refers to estrogen, with or without synthetic progestins to protect the uterine lining. The addition of synthetic progestins traditionally are employed in conjunction with estrogen to modulate the proliferative effect estrogen has on the uterine lining as protection against endometrial cancer.

The majority of studies investigating hormone replacement therapy in breast cancer patients show lower cancer recurrence rates (RR 0.72) as well as, significantly lower mortality rates in treated patients (RR 0.18) [69, 70, 82-94].

The HABITS trial, a large, prospective clinical trial on the safety of HRT after breast cancer, showed an increase in the recurrence of breast cancer in women taking **estrogen**, **estrogen/progestin** therapy [91]. However, the patient selection, as well as, the HRT regimens in the HABITS trial were so variable that one cannot determine whether or not there were subgroups of breast cancer survivors who could take HRT without risk of recurrence of breast cancer. The majority of women in the HABITS trial were treated with **synthetic progestins**, which have consistently been shown to increase the risk of breast cancer. When

the use of synthetic progestins was *limited* in the prospective 'sister' trial completed in Stockholm, the risk of cancer recurrence was *not* increased (RR 0.82) [92]. In addition, the Stockholm trial showed the risk of death from all causes was not increased with HRT (RR 0.5). The Stockholm trial did have a slightly higher per-cent of patients treated with tamoxifen.

Balanced Hormone Therapy for Breast Cancer Survivors

Breast cancer survivors treated with hormone therapy should notify their oncologist. The patient's oncologist must be in agreement with therapy.

Patients should acknowledge the possibility of recurrence with or without hormone therapy. The Habits and Stockholm trials along with other data (Meurer 02) should be reviewed with the patient. Opinions by uninformed physicians should be questioned. *Unsubstantiated* 'Clinical Guidelines' should be labeled as such.

Pre and Post Implant Testing and Evaluation

The patient's physician will determine what testing is needed to best treat their patient. **Testosterone pellet therapy** is indicated for symptoms of testosterone deficiency (**fatigue, decreased libido, memory loss, lack of motivation, depression, anxiety, insomnia, aches, pains, hot flashes etc.**). A free testosterone in the lower third of normal, or low total testosterone may be helpful for diagnosing testosterone deficiency.

If a patient is on a testosterone implant, it is recommended that a CBC, estradiol and FSH be obtained annually. Testosterone levels fluctuate and have little or no clinical significance.

Although historical studies (Thom, Davis) have shown that testosterone implants do not elevate serum estradiol levels, these studies were done in conjunction with estradiol implants. Testosterone can convert to estradiol via aromatase. Breast cancer survivors, not on an aromatase inhibitor as part of their therapy, **may** be placed on anastozole 1mg, ½ pill twice weekly to prevent the conversion of testosterone to estradiol. This dose lowers estradiol levels and is not prescribed as therapy for breast cancer.

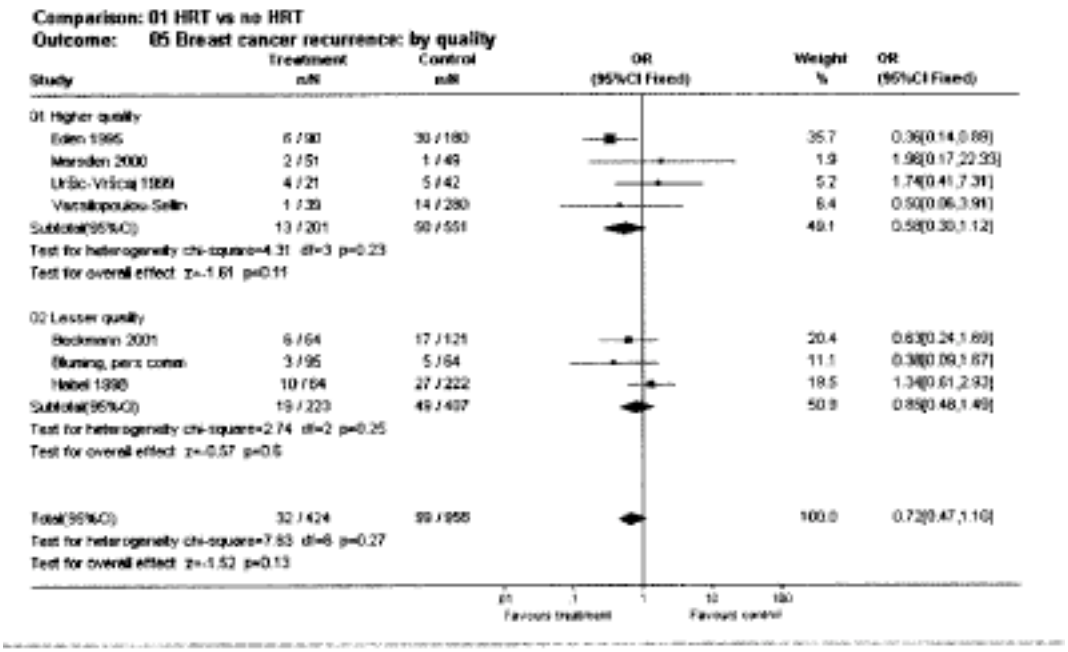
Options for Therapy for Breast Cancer Survivors

1. **Testosterone pellet implant alone** 75-150 mg implanted every 3-5 months
2. **Testosterone pellet implant** with **vaginal estriol 0.5 mg and progesterone 25 mg (**added *temporarily* for severe vaginal dryness)
    a. Testosterone pellet implant 75-150 mg implanted every 3-5 months
    b. Vaginal Estriol 2 mg, Progesterone 100mg per cc of cream base dosed 0.25 mg *2-3 times weekly* as needed for severe vaginal dryness and urinary urgency.
3. **Vaginal Estriol 0.5 mg, Progesterone 25 mg and Testosterone 0.5 mg** (minimal systemic symptoms)
    a. Vaginal Estriol 2 mg, Progesterone 100 mg, Testosterone 2 mg per cc of cream dosed 0.25 mg daily for 14 days then *2-3 times weekly*.

A**nastrozole (Arimidex®) 0.5 mg twice weekly** *may* be prescribed depending on a physician's decision of 'risk vs. benefit'. A thin patient with low body fat and low risk of recurrent disease may benefit from additional estrogen. Estrogen receptor status may play a role in this decision.

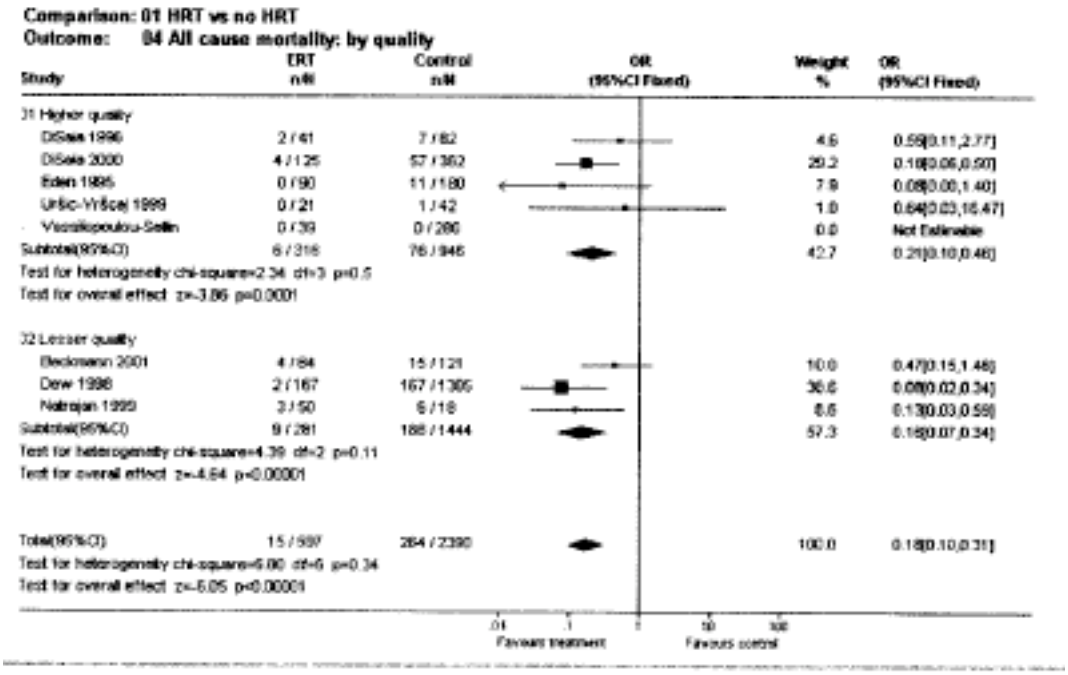
Graphs

Graphic summary of studies on recurrence of breast cancer in ERT users vs nonusers



CI, confidence interval; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; OR, odds ratio.

Graphic summary of studies of total mortality among users vs nonusers of estrogen replacement therapy



Subjects in Eden et al[9] represent a matched subset of those in Daw et al.[10]. CI, confidence interval; HRT, hormone replacement therapy; OR, odds ratio.

Meurer02

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