

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, 13].

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 [14-16]. Adrenal androgens have been shown to counteract the growth stimulatory effects of estrogen on breast cancer cells [17]. 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. [18-21]. Testosterone, delivered by pellet implant has also been shown to lower the risk of breast cancer when given with estrogen and estrogen/progestin therapy [11,12, 22]. Long-term follow up data supports the safety of testosterone, delivered by pellet implant.

Although high doses of estradiol delivered by pellet implant have been shown to increase the risk of breast cancer equivalent to oral and topical estrogens [9], a 20 mg. dose of estradiol delivered by pellet implant does not increase the risk of breast cancer [10]. However, even higher doses of estradiol, when used in combination with testosterone implants, do not increase the risk of breast cancer in up to 22-year follow-up [11]. Physiologic doses of estradiol, delivered by implant, in combination with testosterone delivered by implant, reduced the risk of breast cancer [12]. Even in patients with a history of breast cancer, estrogen did not increase the risk of recurrence when used with testosterone implants [13].

Testosterone has been used successfully to treat breast cancer patients [2, 23]. It is highly unlikely that non-oral testosterone would have any long-term negative effect on breast tissue unlike oral synthetic methyl-testosterone [24, 100].

Testosterone, delivered by pellet implant does not convert to estradiol [25, 26] when given with estrogen. However, a 200 mg. testosterone pellet implant alone, demonstrated a non statistically significant rise in estradiol [25]. Oral, synthetic methyl-testosterone is converted to 17- α methyl-estradiol by aromatase [27]. 17- α methyl-estradiol is stimulatory to the breast tissue, binding strongly to ER alpha [27, 28]. This, along with the combined use of ethinyl-

estradiol (Estratest®), may explain the increased incidence of breast cancer with the synthetic, oral methyl-testosterone [24]. 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 [29, 31]. It has been clearly established that testosterone, measured by RIA is inaccurate in women and should not be relied on [29-33]. 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 [98,99]. In addition, women with polycystic ovarian syndrome and elevated testosterone levels do not have an increased risk of breast cancer (RR 0.52) [34, 35].

Androgens (testosterone and DHT) have been reported to 'stimulate breast cells'. However, it was pharmacologic doses of testosterone (>100 times physiologic levels) that stimulated breast cancer cells via the estrogen receptor [36, 103, 104]. Physiologic doses of testosterone and DHT inhibit growth of breast cancer cells via the androgen receptor [14-17].

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 [37-48]. It has also been shown that hormones applied to the mucous membranes are more readily absorbed than hormones applied to the skin [49-52]. Testosterone, applied to the mucous membranes of the labia, has been shown to be absorbed and have systemic effects [51, 53]. 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 [52].

Symptomatic relief of genital urinary symptoms as well as systemic climacteric symptoms with vaginally administered hormones has been described and is dose dependent [47, 54-56].

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, 69-75]. 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 [70,71]. Estriol has a low binding affinity for ER α and does not stimulate breast tissue or increase breast density [63, 79-82]. Vaginal estriol, used in the correct doses, does not increase the risk of endometrial hyperplasia or uterine cancer [57-59, 68]. Unlike oral estriol, vaginal estriol *has* been shown to increase bone density [57, 60]. There is no accumulation of hormones or metabolites with vaginal estrogen or progesterone therapy [46, 52, 58, 61-63].

Vaginal progesterone has preferential distribution to the uterus and protects the uterine lining [76-78]. 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 [48].

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) [72,73].

Progesterone, the bio-identical molecule, has been shown to decrease or have no effect breast proliferation [19, 96, 97]. 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 [62-65, 77, 78]. Vaginal administration of progesterone is preferred in patients with cardiovascular disease, liver disease or hepatic overload [66].

Cancer cells are known to over-express insulin receptors [101]. 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 [102].

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) [70, 71, 83-95].

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 [92]. 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) [93]. 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, insomnia**). 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.

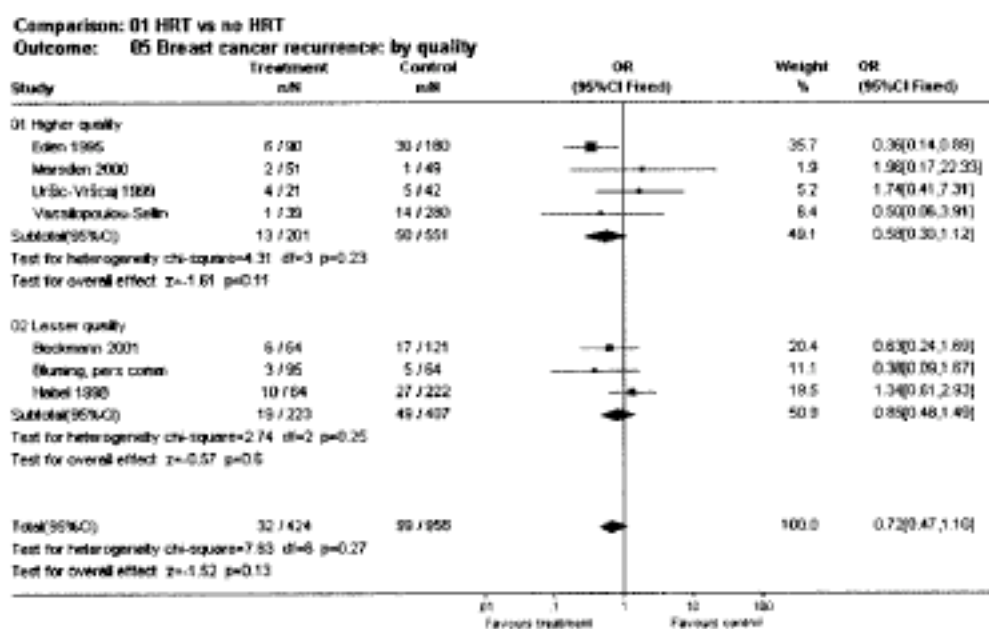
Although historical studies (Thom, Davis) have shown that testosterone implants do not elevate serum estradiol levels, these studies were done in conjunction with estradiol implants. Testosterone can convert to estradiol via aromatase. Breast cancer survivors, not on an aromatase inhibitor as part of their therapy, **may** be placed on anastrozole 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**
 - 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 vaginal dryness and urinary urgency.
3. **Vaginal Estriol 0.5 mg, Progesterone 25 mg and Testosterone 0.5 mg**
 - 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*.

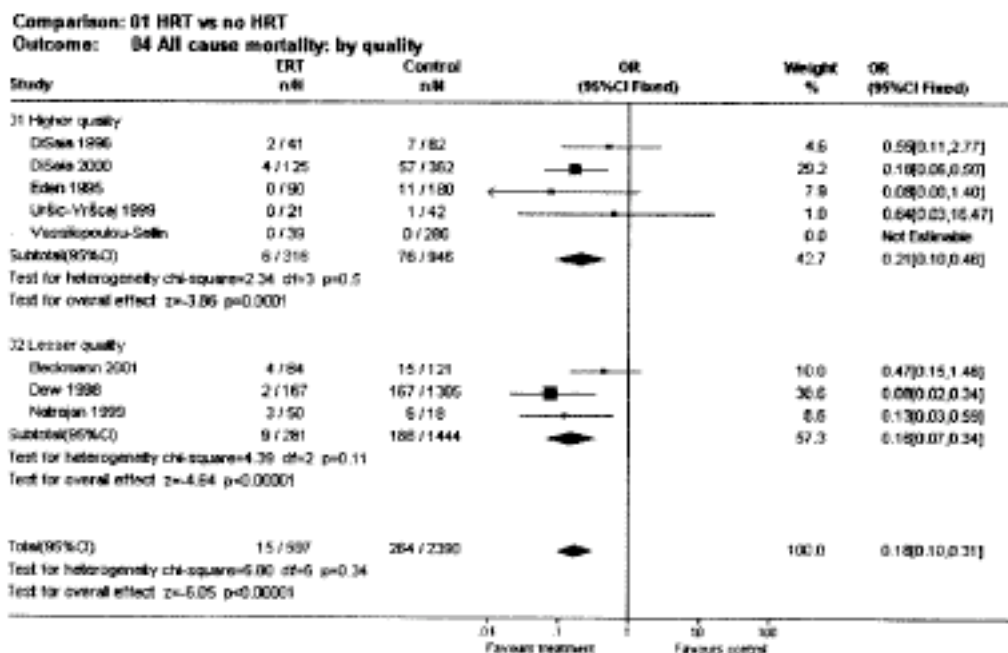
Anastrozole (Arimidex®) 0.5 mg twice weekly *may* be prescribed depending on a physician's decision of 'risk vs. benefit'. A thin patient with low body fat and low risk of recurrent disease may benefit from additional estrogen. Estrogen receptor status may play a role in this decision.

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 al⁹ represent a matched subset of those in Dew et al.¹⁰ CI, confidence interval; HRT, hormone replacement therapy; OR, odds ratio.

References

1. Loeser A. Mammary Carcinoma, Response to implantation of male hormone and progesterone. *Lancet* 1941; Dec 6: pp 698-700
2. Greenblatt R, Suran R. Indications for Hormonal Pellets in the Therapy of Endocrine and Gynecic Disorders. *Am. J. Obst. & Gynaec* 1949; Feb 37 (2): 249-301.
3. Greenblatt R, Bryner J, Estradiol Pellet Implantation in the Management of Menopause. *The Journal of Reproductive Medicine* 1977; 18 (6): 307-316.
4. Ando S, DeAmicis F, Rago V, Carpino A, Maggiolini M, Panno M, Lanzino M. Breast cancer: from estrogen to androgen receptor. *Mol Cellular Endocrin* 2002; 193: 121-28.
5. Ortmann J, Prifti S, Bohlmann M, Rehberger-Schneider S, Strowitzki T, Rabe T. Testosterone and 5 alpha-dihydrotestosterone inhibit in vitro growth of human breast cancer cell lines. *Gynecol Endocrinol* 2002; 16: 113-20.
6. Lapointe J, Fournier A, Richard V, Labrie C. Androgens down-regulate bcl-2 protooncogene expression in ZR-75-1 human breast cancer cells. *Endocrin* 1999; 140 (1): 1416-21.
7. Kandouz M, Lombet A, Perrot J, Jacob D, Carvajal S, Kazem A, et al. Proapoptotic effects of antiestrogens, progestins and androgen in breast cancer cells. *J Steroid Biochem Mol Biol* 1999; 69: 463-71.
8. Birrell s, Butler L, Harris J, Buchanan G, Tilley W. Disruption of androgen receptor signaling by synthetic progestins may increase the risk of developing breast cancer. *The FASEB Journal* 2007; 2 (21) 1-9.
9. Million Women Study Collaborators. Breast cancer and hormone-replacement therapy in the Million Women Study. *Lancet* 2003; 362: 419-27.
10. Davelaar E, Gerretesen G, Relyveld J. Geen toename van het aantal mammacarcinomen bij subcutaan estradiolgeb. *Ned Tijdschr Geneesk* 1991; 135, 613-15
11. Gambrell D, Natrajan P. Moderate dosage estrogen-androgen therapy improves continuation rates in postmenopausal women; impact of the WHI reports. *Climacteric* 2006; 9; 224-33.
12. Tuter G. Marked reduction of breast, endometrial and ovarian cancer in users of bio-identical estradiol and testosterone subcutaneous pellets. Unpublished data (available upon request).
13. Natrajan P, Gambrell D. Estrogen replacement therapy in patients with early breast cancer. *Am J Obstet Gynecol* 2002; 187 (2): 289-94.
14. Ortmann J, Prifti S, Bohlmann M, Rehberger-Schneider S, Strowitzki T, Rabe T. Testosterone and 5 alpha-dihydrotestosterone inhibit in vitro growth of human breast cancer cell lines. *Gynecol Endocrinol* 2002; 16: 113-20.
15. Szelei J, Jimenez J, Soto A, Luizzi F, Sonnenschein C. Androgen-induced inhibition of proliferation in Human Breast Cancer MCF7 cells transfected with androgen receptor. *Endocrinology* 1997; 138 (4): 1406-12.
16. Hackenberg R, Schulz K-D. Androgen Receptor Mediated Growth Control of Breast Cancer and Endometrial cancer modulated by anti-androgens- and androgen-like steroids. *J. Steroid Biochem Molec Biol*; 56 (1-6):113-17.

17. Boccuzzi G, Brignardello E, DiMonaco M, Gatto V, Leonardi L, Pissini A, Gallo M. 5-En-androstene-3 β , 17 β -diol inhibits the growth of MCF-7 breast cancer cells when oestrogen receptors are blocked by oestradiol. *Br. J. Cancer* 1994; 70: 1035-39.
18. Zhou J, Ng S, Adesanya-Famuiya O, Anderson K, Bondy C. Testosterone inhibits estrogen-induced mammary epithelial proliferation and suppresses estrogen receptor expression. *FASEB J* 2000; 14: 1725-30.
19. Dimitrakakis C, Zhou J, Wang J, Belanger A, LaBrie F, Cheng C, Powell D, Bondy C. A physiologic role for testosterone in limiting estrogenic stimulation of the breast. *Menopause* 2003; 10 (4) 292-92.
20. Hofling M, Hirschberg Q, Skoog L, Tani E, Hagerstrom T, vonSchoultz B. Testosterone inhibits estrogen/progestogen-induced breast cell proliferation in postmenopausal women. *Menopause* 2007; 14 (2): 1-8.
21. Slagter M, Gooren L, Scorilas A, Petraki C, Diamandis E. Effects of long-term androgen administration on breast tissue of female-to-male transsexuals. *Journal of Histochemistry & Cytochemistry* 2006; 54 (8): 905-10.
22. Dimitrakakis C., Jones R, Liu A, Bondy C. Breast cancer incidence in postmenopausal women using testosterone in addition to usual hormone therapy. *Menopause* 2004; 11 (5): 531-35.
23. Testosterone Monograph. *Clinical Pharmacology* 2000.
24. Tamimi R, Hankinson S, Chen W, Rosner B, Colditz G. Combined estrogen and testosterone use and risk of breast cancer in postmenopausal women. *Arch Intern Med* 2006; 166: 1483-88.
25. Thom M, Collins W, Studd J. Hormonal profiles in postmenopausal women after therapy with subcutaneous implants. *British Journal of Obstetrics and Gynaecology* 1981; 88: 426-33.
26. Davis S, Walker K, Strauss B. Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause* 2000; 7 (6): 395-401.
27. deGoyer M, Oppers-Tiemissen H, Leysen D, Verheul H, Kloosterboer J. Tibolone is not converted by human aromatase to 7 α -methyl-17 α -ethynlestradiol (7 α -MEE): Analysis with sensitive bioassays for estrogens and androgens and with LC-MS/MS. *Steroids* 2003; 68: 235-43.
28. Kuhl H. Personal communication.
29. LaBrie F, Luu-The V, Labrie C, Belanger A, Simard J, Lin S-X, Pelletier G. Endocrine and intracrine sources of androgens in Women: Inhibition of breast cancer and other roles of androgens and their precursor dehydroepiandrosterone. *Endocrine Reviews* 2003; 24 (2): 152-82.
30. Bachmann G, Bancroft J, Braunstein G, Burger H, Davis S, et al. Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility and Sterility*; 77 (4): 660-65.
31. Somboonporn W, Davis S. Testosterone effects on the breast: Implications for testosterone therapy for women. *Endocrine Reviews* 2004; 25 (3): 374-88.

32. Rivera-Woll L, Papalia M, Davis S, Burger H. Androgen insufficiency in women: diagnostic and therapeutic implications. *Human Reproduction Update* 2004; 10 (5): 421-32.
33. Stanczyk F, Lee J, Santen R. Standardization of steroid hormone assays: Why, How, and When? *Cancer Epidemiol Biomarkers Prev* 2007; 16 (9): 1713-1719.
34. Anderson K, Sellers T, Chen P-L, Rich S, Hong C-P, Folsom A. Association of Stein-Leventhal Syndrome with the incidence of postmenopausal breast carcinoma in a large prospective study of women in Iowa. *Cancer* 1997; 79 (3); 494-99.
35. Gammon M, Thompson D. Polycystic ovaries and the risk of breast cancer. *American Journal of Epidemiology* 1991; 134 (8): 818-24.
36. Zava D, McGuire W. Androgen action through estrogen receptor in a human breast cancer cell line. *Endocrinology* 1978; 103: 624-31.
37. Schiff I, Tulchinsky D, Ryan K. Vaginal absorption of estrone and 17 β -estradiol. *Fertility and Sterility* 1977; 28;10, pp 1063-66
38. Schiff I, Wentworth B, Koos B, Ryan K, Tulchinsky D. Effect of estriol administration on the hypogonadal woman. *Fertility and Sterility* 1978; 30:3, pp 278-82
39. Punnonen R, Vilks S, Grönroos M, Rauramo L. The vaginal absorption of oestrogens in post-menopausal women. *Maturitas* 1980; 2:4, pp 321-26
40. Heimer G, Englund D. Estriol: absorption after long-term vaginal treatment and gastrointestinal absorption as influenced by a meal. *Acta Obstet Gynecol Scand* 1984; 63:6, pp 563-67
41. Heimer G, Englund D. Plasma oestriol following vaginal administration: morning versus evening insertion and influence of food. *Maturitas* 1986; 8, pp 239-43
42. Mattson L, Cullberg G. Vaginal absorption of two estriol preparations. A comparative study in postmenopausal women. *Acta Obstet Gynecol Scand*. 1983; 62: 5, pp 393-96
43. Cedars M, Judd H. Nonoral routes of estrogen administration. *The Menopause* 1987; 14:1 pp 269-98
44. Carlström K, Pschera H, Lunnell N. Serum levels of oestrogens, progesterone, follicle-stimulating hormone and sex-hormone-binding globulin during simultaneous vaginal administration of 17 beta-oestradiol and progesterone in the pre- and post-menopause. *Maturitas* 1988; 10, pp 307-16
45. Suh-Burgmann E, Sivret J, Duska L, Carmen M, Seiden M. Long-term administration of intravaginal dehydroepiandrosterone on regression of low-grade cervical dysplasia-a pilot study. *Gynecol Obstet Invest* 2003; 55, pp 25-31
46. Keller PJ, Riedmann R, Fischer M, Gerber C. Oestrogens, gonadotropins and prolactin after intra-vaginal administration of oestriol in post-menopausal women. *Maturitas* 1981; 3, pp 47-53
47. Rigg LA, Hermann H, Yen SS. Absorption of estrogens from vaginal creams. *N Engl J Med* 1978; 298, pp 195-97
48. Rosano G, Webb C, Chierchia S, Morgani G, Gabraele M, Sarrel P, Ziegler D, Collins P. Natural progesterone, but not medroxyprogesterone acetate, enhances the beneficial effect of estrogen on exercise-induced myocardial ischemia in postmenopausal women. *J Am Col Card* 2000; 36:7, pp 2154-59

49. Oriba H, Bucks D, Maibach H. Percutaneous absorption of hydrocortisone and testosterone on the vulva and forearm: effect of the menopause and site. *Br J Derm* 1996; 134, pp 229-233
50. Corbo D, Liu JC, Chien Y. Drug absorption through mucosal membranes: effect of mucosal route and penetrant hydrophilicity. *Pharmaceutical Research* 1989; 6:10, pp 848-52
51. Friedrich E, Kalra P. Serum Levels of Sex Hormone in Vulvar Lichen Sclerosus, and the Effect of Topical Testosterone. *The N Engl J Med* 1981; 310, pp 488-91
52. Nahoul K, Dehennin L, Jondet M, Roger M. Profiles of plasma estrogens, progesterone and their metabolites after oral or vaginal administration of estradiol or progesterone. *Maturitas* 1993;16, pp 185-202
53. Zeisler E, Bancher-Todesca D, Sator M, Schneider B, Gitsch G. Short-term effects of topical testosterone in vulvar lichen sclerosus. *Obstet.Gynecol* 1997; 89(2): 297-99
54. Mandel F, Geola F, Meldrum D, Lu J, Eggena P, Sambhi M, Hershmann J, Judd H. Biological effects of various doses of vaginally administered conjugated equine estrogens in postmenopausal women. *J Clin Endo Met* 1983; 57:1, pp 133-39
55. Bottiglione F, Volpe A, Esposito G, Aloysio D. Transvaginal estriol administration in postmenopausal women: a double blind comparative study of two different doses. *Maturitas* 1995; 22, pp 227-32
56. Schiff I, Tulchinsky D, Ryan K, Kadner S, Levitz M. Plasma estriol and its conjugates following oral and vaginal administration of estriol to postmenopausal women: Correlations with gonadotropin levels. *Am. J. Obstet. Gynecol.* 1980; 138:8, pp.1137-41
57. Blum M. Benefits of vaginal estriol cream combined with clonidine HCl for menopausal syndrome treatment. *Clin Exp Obst Gyn* 1985; 12 (1-2): 1-2.
58. Fink RS, Collins W, Papadaki L, O'Reilly B, Ginsburg J. Vaginal oestriol: Effective menopausal therapy not associated with endometrial hyperplasia. *J Gynaec Endocrinol* 1985; 1: 1-11.
59. Weiderpass E, Baron J, Adami H, Magnusson C, Lindgren A, Bergstrom R, Correia N, Persson I. Low-potency oestrogen and risk of endometrial cancer: a case-control study. *Lancet* 1999; 353: 1824-28.
60. Michaelsson K, Baron J, Farahmand B, Ljunghall S. Use of low potency estrogens does not reduce the risk of hip fractures. *Bone* 2002; 30 (4): 613-18.
61. Trevoux R, Van der Velden W, Popovic D. Ovestin vaginal cream and suppositories for the treatment of menopausal vaginal atrophy. *Reproduction* 1982; 6: 101-6.
62. Levy T, Yairi Y, Bar-Hava I, Shalev J, Orvieto R, Ben-Rafael Z. Pharmacokinetics of the progesterone-containing vaginal table and its use in assisted reproduction. *Steroids* 2000; 65: 645-49.
63. Kuhl H. Pharmacology of estrogens and progestogens: influence of different routes of administration. *Climacteric* 2005; 8: 3-63.
64. Ficicioglu C, Gurbuz B, Tasdemir S, Yalti S, Canova H. High local endometrial effect of vaginal progesterone gel. *Gynecol Endocrinol* 2004; 18: 240-243.
65. deLignieres B, Dennerstein L, Backstrom T. Influence of route of administration on progesterone metabolism. *Maturitas* 1995; 21: 251-57.

66. Jaaskelainen a, Shaerer E, deZiegler D. Vaginal progesterone in menopause: long term acceptability of a new therapeutic option for physiological progesterone replacement. *Maturitas* 1997; OFC: 57.
67. Ando S, DeAmicis F, Rago V, Carpino A, Maggiolini M, Panno M, Lanzino M. Breast cancer: from estrogen to androgen receptor. *Mol Cellular Endocrin* 2002; 193: 121-28.
68. Vooijs, GP, Geurts TBP. Review of the endometrial safety during intravaginal treatment with estriol. *Obstet Gynecol* 1995; 62: 101-06
69. Bergkivist L, Adami H, Persson I, Hoover R, Schairer C. The risk of breast cancer after estrogen and estrogen-progestin replacement. *NEJM* 1985; 321 (5): 293-97
70. Dew J, Eden J, Beller E, Magarey C, Schwartz P, Crea P, Wren B. A cohort study of hormone replacement therapy given to women previously treated for breast cancer. *Climacteric* 1998; 1: 137-42.
71. Dew J, Wren B, Eden J. A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer. *Climacteric* 2003; 6: 45-52
72. Fournier A, Berrino F, Riboli E, Avenel V, Clavel-Chapelon F. Breast cancer risk in relation to different types of hormone replacement therapy in the E3N-EPIC cohort. *Int. J. Cancer* 2004; 114: 448-54.
73. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies; results from the E3N cohort study. *Breast Cancer Res Treat* 2007; DOI 10.1007/s10549-007-9523-x
74. Lyytinen H, Pukkala E, Ylikorkala O. Breast cancer risk in postmenopausal women using estrogen-only therapy. *Obstet Gynecol* 2006; 108 (6): 1354-60.
75. Rosenberg L, Magnusson C, Lindstrom E, Wedren S, Hall P, Dickman P. Menopausal hormone therapy and other breast cancer risk factors in relation to the risk of different histological subtypes of breast cancer: a case-control study. *Breast Cancer Research* 2006; 8 (1).
76. Ross D, Cooper A, Pryse-Davies J, Bergeron C, Collins W, Whitehead M. Randomized, double-blind, dose-ranging study of the endometrial effects of a vaginal progesterone gel in estrogen-treated postmenopausal women. *Am J Obstet. Gynecol.* 1997; 177:4, pp 937-41
77. Cicinelli E, Cignarelli M, Sabatelli S, Romano F, Schonauer L, Padovano R, Einer-Jensen N. Plasma concentrations of progesterone are higher in the uterine artery than in the radial artery after vaginal administration of micronized progesterone in an oil-based solution to postmenopausal women. *Fertility and Sterility* 1998; 69:3, 471-73
78. Levine H, Watson N, Comparison of the pharmacokinetics of Crinone 8% administered vaginally versus Prometrium administered orally in postmenopausal women. *Fertility and Sterility* 2000; 73:3 pp 516-21
79. Bergink E, Kloosterboer J, van der Vies J. Oestrogen Binding Proteins in the Female Genital Tract. *J Steroid Biochem* 1984; 20; 48 pp 1057-60.
80. Valdiva 00
81. Takahashi 00
82. Minaguchi 96
83. Guidoizzi 99
84. Disaia 00
85. O'Meara 01

86. Peters 01
87. Durna 02
88. Decker 03
89. Durna 04
90. Vassilopoulou-Sellin 99
91. Martunen 01
92. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer-is it safe?), a randomized comparison: trial stopped. *Lancet* 2004; 363: Feb; 453-55.
93. Von Schultz E, Rutqvist L. Menopausal Hormone Therapy After Breast Cancer: The Stockholm Randomized Trial. *J Natl Cancer Inst* 2005; 97 pp 533-35.
94. Meurer L, Lena S. Cancer recurrence and mortality in women using hormone replacement therapy after breast cancer: Meta-analysis. *The Journal of Family Practice* 2002; 51:2 pp 1056-62.
95. Col N, Kim H, Chlebowski R. Menopausal hormone therapy after breast cancer: a met-analysis and critical appraisal of the evidence. *Breast Cancer Research* 2005; 7:4 pp 535-40.
96. Chang K-J, Fournier S, Lee T, deLignieres B, Linares-Cruz G. Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertility and Sterility* 1995; 83:4 pp 785-91.
97. Plu-Bureau G, Le M, Thalabard J, Sitruk-Ware R, Mauvais-Jarvis P. Percutaneous progesterone use and risk of breast cancer: Results from a French cohort study of premenopausal women with benign breast disease. *Cancer Detection and Prevention* 1999; 24:4 pp 290-96.
98. Key, Endogenous Hormones and Breast Cancer Collaborative Group. Body Mass Index, Serum Sex Hormones, and Breast Cancer Risk in Postmenopausal Women. *Journal of the National Cancer Institute* 2003; 95:16 pp. 1218-26.
99. Thomas H, Key T, Allen D, Moore J, Dowsett M, Fentiman I, Wang D. A prospective study of endogenous serum hormone concentrations and breast cancer risk in premenopausal women on the island of Guernsey. *British Journal of Cancer* 1997; 75:7 pp. 1075-79.
100. Ness R, Albano J, McTiernan A, Cauley J. Influence of Estrogen Plus Testosterone Supplementation on Breast Cancer. *Archives of Internal Medicine* 2009; 169:1 pp. 41-46.
101. Papa V, Belfiore A. Insulin receptors in breast cancer: Biological and clinical role. *J. Endocrinol. Invest.* 1996; 19: pp. 324-33.
102. Papa v, Reese C, Brunetti A, Vigneri R, Siiteri P, Goldfine I. Progestins increase insulin receptor content and insulin stimulation of growth in human breast carcinoma cells. *Cancer Research* 1990; 50: pp. 7858-62.
103. Marugo M, Bernasconi D, Miglietta L, Fazzuli L, Ravera F, Cassulo S, Gordano G. Effects of dihydrotestosterone and hydroxyflutamide on androgen receptors in cultured human breast cancer cells (EVSA-T). *J. Steroid Biochem. Molec. Biol* 1992; 42:5 pp. 547-54.

104. Hackenburg R, Hofmann J, Hölzel F, Schulz K-D. Stimulatory effects of androgen and antiandrogen on the in vitro proliferation of human mammary carcinoma cells. *Cancer Research Clinical Oncology* 1998; 114 pp 593-601.