# MARKED REDUCTION OF BREAST, ENDOMETRIAL AND OVARIAN CANCER IN USERS OF BIO-IDENTICAL ESTRADIOL AND TESTOSTERONE SUBCUTANEOUS PELLETS

by:

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## ABSTRACT

The Women's Health Initiative (1) in the year 2002 shocked the world with its findings. The study demonstrated a combination of conjugated estrogen and a synthetic progestin increased the incidence of breast cancer after three years of usage. The study did not qualify this to this regimen, but concluded that all estrogen and progesterone would do likewise.

A total of 976 women were treated from 1992 to 2002 with subcutaneous bio-identical estradiol and testosterone pellets, and there were zero cases of breast, endometrial, or ovarian cancer even in the individuals utilizing the therapy for over twenty years. The women in the study with an intact uterus were given micronized progesterone, not a synthetic progestin.

CONCLUSION:

Subcutaneous bio-identical estradiol and testosterone, even with progesterone usage, imparts a protective physiologic environment that markedly reduces the chances of developing breast, endometrial, and ovarian cancer.

pellet therapy (SPT), with appropriate lab work, a complete gynecological examination, and a mammogram. No family history of breast cancer whether in first or second degree relatives excluded any patient from the study, therefore, eliminating any chance of placing any bias in the study. In fact, breast cancer survivors were a part of the study as well. The patients were followed with repeat lab work at one, six and twelve months after insertion, and received annual gynecologic examinations and mammograms and annual lab studies thereafter. All patients were instructed to notify me if any evidence of an abnormality in the breasts, abdomen, or uterus were perceived by the patient or found by any other physician.

The patients received varying dosages of biologically identical 17-beta-estradiol pellets coupled with biologically identical testosterone pellets compounded in pharmacies in the United States. Patients with an intact uterus were given natural micronized progesterone, in compounded oral capsules, sublingual tablets, cream, or in the proprietary form (Prometrium). The dosage of S.P.T. varied according to the patient's symptoms, and levels of serum follicle stimulating hormone (FSH). The pellets were inserted every four to six months according to the emergence of menopausal symptoms or evidence of a rising FSH level.

The hormone pellets were inserted primarily in the gluteal area in the upper outer quadrant of the buttocks. A few patients requested implantation in the abdominal wall, which was done in an area lateral to the superficial epigastric vessels.

The procedure process is as follows: the area for insertion was anesthetized with either one or two percent Xylocaine with epinephrine and sodium bicarbonate; a four to five millimeter stab wound was made with a number eleven (#11) blade; the hormone pellets were then placed in the subcutaneous fat using a pellet trochar; finally, the stab wound was simply bandaged.

The furor that arose after the results of the Women's Health Initiative (WHI) were published in July of 2002 led to the belief that all estrogen and progesterone combinations were likely to increase the development of breast cancer. My current study, completed in January of 2002, proves that the conclusion derived from the WHI was erroneous in the following assumptions: 1) All estrogen and progestins are the same, therefore, carry the same risks for the development of breast cancer; 2) Oral estrogen and progesterone compounds are the same as subcutaneous or transmucosal preparations of estrogen and testosterone; 3) The oral form of conjugated estrogen coupled with a synthetic progestin (medroxyprogesterone) is a good model upon which to base their study and subsequent research. 4. Their outcomes could be considered universal for every form of estrogen and progesterone product given to post-menopausal women.

The purpose of my study was to demonstrate that biologically identical 17-beta-estradiol, when coupled with biologically identical testosterone, and given in the form of subcutaneous pellets with micronized absorbable progesterone did not increase the incidence of breast, endometrial, or ovarian cancer. In providing my results, I will show that the WHI study results do not apply to subcutaneous pellet therapy with bio-identical 17-beta-estradiol and testosterone, and micronized bio-identical progesterone.

## METHODS AND MATERIALS

Nine hundred and seventy-six (976) women were studied over a ten year period (1992 to 2002). The patients were followed in my office, and are still being seen as part of an ongoing study of the effects of subcutaneous pellet hormones on osteoporosis, cardiac disease, and the development of Alzheimer's disease. The patients were evaluated prior to initiating subcutaneous

In the study group, there were only four breast biopsies done in the ten years that were studied.

Figure 2 demonstrates the years of usage of S.P.T. and the number of cases of breast, ovarian and endometrial cancer that developed during the study period. The incidence of breast cancer was calculated at 0.01% (1 in 976). The incidence of endometrial cancer was 0.04% (1 in 246). In fact, if breast cancer development is estimated to be an average of six years, then the corrected incidence of breast cancer for the study is 0.

## DISCUSSION

The use of hormone replacement therapy (HRT) by the perimenopausal and postmenopausal woman is now more controversial than before the WHI study. The confusion by physicians and patients that followed the publication of the Women's Health Initiative, prompted many women to abruptly stop their forms of H.R.T. The study implied that all estrogen coupled with any progestin or progesterone increased the incidence of breast cancer after only three years of use. The study appears flawed and does not apply to all forms of HRT because:

1) Conjugated estrogen and synthetic progestin do not represent all other forms of estrogen and progesterone in chemical structure or biologic activity.

2) Oral H.R.T. does not and cannot produce the normal, steady physiologic level of estrogen and testosterone that the human body produces normally, nor do oral estrogen products maintain the physiologic ratio of estradiol to Estrone of 2:1. (2) (3)

3) Biologically identical 17-beta-estradiol has never been shown to increase the incidence of breast cancer, in any form.

In our study, excessive bleeding was unusual. When it was encountered, it was easily managed with one suture of 4-0 Ethilon and a pressure dressing. In patients with a history of bleeding or adhesive allergy, a single stitch of ethilon suture was routinely used for closure. The suture was removed by the patient in four to five days.

## RESULTS

A total of 976 women were included in this study. Nearly ninety-six percent (936) were perimenopausal or postmenopausal (see Fig 1). Nearly seventy percent (683) had been on other forms of H.R.T. for an average of four years prior to initiating subcutaneous pellet therapy. The majority had been on conjugated estrogen, with or without progestin (Premarin, Prempro, Premphase, Premarin and Provera). Over twenty-five percent (246) of the patients had an intact uterus and were given natural micronized progesterone, either in a combined continuous regimen, or in a cyclic fashion. The type of micronized progesterone regimen was determined by the age of the patient, presence or absence of a menstrual period, and the patient's desire for amenorrhea. Endometrial biopsy and transvaginal ultrasound were done if abnormal bleeding (<3%) occurred during the study.

In the study group, there was only one case of breast cancer during the study period. The patient developed a stage I noninvasive, node negative cancer in the first year of therapy. Therefore, considering the time from the first cancer cell to diagnosis to be seven years, it can be assumed she had the disease prior to starting on S.P.T. (Fig. 2). In this study group, there were no cases of ovarian cancer, and only one case of endometrial cancer. The endometrial cancer was found after the patient's first six months in therapy. The patient had a Stage 3 Grade I, well differentiated tumor who has remained disease free three years after therapy.

hormone steadily throughout a twenty-four hour period, and maintains the physiologic ratio of estradiol to Estrone at 2:1. When minute amounts of testosterone are released in conjunction with minute amounts of 17-beta-estradiol the endometrium realizes an additional benefit. This positive effect of testosterone augments the effect of micronized progesterone in stabilizing the endometrium (5). It certainly would be correct to assume that the use of combined S.P.T. does not increase the incidence of endometrial cancer, and may in fact protect against the development of abnormal endometrial tissue. Within the study group the presence of dysfunctional uterine bleeding was less than 3%. In nearly ninety-nine percent of those patients fibroids were found. Only three hysterectomies were done solely because of fibroids. Hysteroscopy with thermogenic balloon ablation eliminated the other cases of dysfunctional bleeding not corrected by hormonal suppression with progesterone or estradiol dosage adjustment or both. All endometrial specimens were sent to pathology and found to be benign at the time of ablation.

## OVARIAN CANCER

Ovarian cancer has long been a frustrating disease to diagnose in enough time to successfully treat the patient. Yet, in the National Nurses (6) study, women on oral contraceptives were found to show a marked reduction in the incidence of ovarian cancer after five years of usage. The explanation offered is that oral contraceptives rendered the ovary dormant. This is effected by a marked suppression of the serum FSH, thereby halting follicular development. In fact, because of the National Nurses Study, oral contraceptives have been used in high risk individuals to protect against ovarian cyst formation, and reduce the possibility of the development of ovarian cancer. What then explains the absence of ovarian cancer in the present study? The answer lies in the marked suppression of the FSH levels induced in SPT patients. Pellet therapy, like oral

Our findings suggest that Estrogen in subcutaneous pellet form is not just another form of HRT, but a superior therapy, in that the incidences of all three estrogen dependent, female cancers are decreased through this treatment. Why has this therapy been over-looked in the United States? Pellet therapy has been utilized in the United States since 1939 (4), but only a limited number of physicians know of or utilize this form of therapy. The primary reason is lack of education about this form of therapy in the United States, although S.P.T. is utilized routinely throughout the rest of the world. Most of our education about pharmaceuticals is transferred through drug companies to physicians. Drug companies have not embraced this therapy because bio-identical compounded substances cannot be patented and therefore are not a good monetary investment. In addition, physicians are not familiar with compounding and unsure of this method of drug dispensing. The interested physician must make an effort to develop a relationship with a compounding pharmacy, and most do not feel comfortable with this process. Lastly, subcutaneous pellets can only be compounded in F.D.A. approved compounding pharmacies, and therefore doctors have an access problem in obtaining the pellets.

Discussion of our study must also include the unusual lack of female estrogen dependent cancers in the study subjects. What explains the significant absence of three of the more common forms of cancer in women in the study?

## ENDOMETRIAL CANCER

The incidence of endometrial cancer is well known to be diminished if a patient receives progesterone to alter the effects of unopposed estrogen. The study adequately demonstrates that the incidence of endometrial cancer can be even further reduced if an absorbable form of 17-beta-estradiol is utilized. More importantly, subcutaneous pellet therapy releases minute amounts of

represented all forms of estrogen and progesterone. The proper conclusion in this study, and all prior studies using conjugated estrogen, is the usage of conjugated estrogen (Premarin, etc.) increases the incidence of breast cancer development. The implication of all other estrogens in either oral or absorptive forms should not have occurred. There have been no large studies of other forms of estrogen specifically looking at the incidence of breast cancer development over a prolonged period of time until now.

This present study was over a ten year period (1992 - 2002). Nine hundred and seventy six patients were followed for varying lengths of time (see Fig.2). Only one case of breast cancer developed. This individual developed the disease in her first year of usage of subcutaneous estradiol pellets which certainly began prior to starting pellet therapy. With this case excluded, the incidence of breast cancer in the users of S.P.T. was zero (0). What accounts for this marked reduction, since the expected incidence of breast cancer is 1:9 for all females? The risk is thought to only increase with HRT use, while our study showed a decreased incidence well below menopausal non-users of HRT. One of the reasons is that subcutaneous 17-beta-estradiol pellets are composed only of biologically identical estradiol, not synthetic or equine estrogen. Furthermore in the study, the participants with an intact uterus were given micronized progesterone, not a synthetic progestin. The majority of the patients employed a continuous combined therapy regimen. More importantly, S.P.T. releases hormone in a slow-steady manner with little chance of variation for four to six months.(6) This more closely resembles the physiologic release of endogenous hormones. S.P.T. also releases only minute amounts of hormone into the blood stream in a continuous manner unlike oral agents or patches. (2) This dosage of estradiol and how it is delivered closely resembles that of the pre-menopausal female.

contraceptives, suppress FSH levels below 20, in the pre-menopausal range. In addition, the continuous release of hormone from pellets produces a steady suppression of FSH over a four to six month period. This marked suppression of FSH induces a dormant state in the ovary as seen with oral contraceptives. Oral therapy was not found to cause such suppression in the FSH levels, except in higher than recommended doses. Most patients on oral therapy had FSH levels of 40 or higher. It logically follows that lower levels of FSH indicate less ovarian stimulation from the pituitary to the ovary, and therefore a lower risk of ovarian cancer through the use of pellet therapy. This study demonstrates this protective effect elegantly. During the study period and even up to the present there have been no cases of ovarian cancer in our study subjects. The sustained suppression of FSH by the steady continuous release of estradiol induces a state of nonstimulation for the ovary thereby reducing the chance of ovarian cyst formation which predisposes the postmenopausal ovary to malignant degeneration.

## BREAST CANCER

The study called the Women's Health Initiative was stopped prematurely after three years because the participants using the conjugated estrogen and synthetic progestin hormone (Prempro) were developing breast cancer at an increased rate above what had been postulated. In good faith the study was stopped. The results of the study were released and chaos and pandemonium ensued. Patients and physicians were led to believe that all types of estrogen when coupled with a progestin (medroxyprogesterone) did increase the rate of breast cancer development after only three years of usage. The subsequent fallout produced widespread of stoppage of all forms and types of H.R.T. Most physicians recommended that their patients stop H.R.T. This study had one very obvious flaw; the assumption that conjugated estrogen and medroxyprogesterone adequately

through the usage of subcutaneous estradiol and testosterone pellets and imparts a protective effect against the development of breast, endometrial and ovarian cancer.

Furthermore, the usage of subcutaneous estradiol and testosterone pellets should be encouraged because of the positive effects seen on bone density (8); the lack of adverse impact on serum lipids; the lack of adverse effect on cardiovascular health, and superior control of the symptoms associated with the menopause. (6) (12) (14)

Breast cancer incidence is also known to rise as a woman ages. What accounts for this increase? It can certainly be assumed that a woman's own estrogen is breast-protective until the levels of estrogen hormone begin to vacillate (perimenopause) or disappear (post menopause). Younger women (i.e. 40 years old or younger) have a much lower incidence of breast cancer. Does it not seem reasonable to then strive to recreate the physiologic environment seen in that stage of a woman's life; 1) FSH levels kept in premenopausal range; 2) Biologically identical 17-beta-estradiol and testosterone released into the blood stream through direct absorption in a steady physiologic manner; 3) Estradiol to estrogen ratio kept at 2:1.

The only form of therapy that recreates this model is subcutaneous pellets. This study demonstrates that if a woman is given biologically identical 17-beta-estradiol in a low dose, at a steady state, the incidence of breast cancer is markedly reduced. Furthermore, it demonstrates that 17-Beta-Estradiol with testosterone given in pellet form is probably breast protective.

## CONCLUSION

The Women's Health Initiative wrongly implied that all estrogen increases the development of breast cancer after three years. This inaccurate assumption prompted women to discontinue all forms of H.R.T. and suffer the ravages of menopause, and possibly increase their risk of Breast cancer, osteoporosis, dementia and many other diseases. Physicians throughout the world reacted similarly in asking women to stop all forms of H.R.T.

The present retrospective study was done to prove that the usage of bio-identical estradiol, testosterone, and progesterone did not increase the incidence of breast, endometrial and ovarian cancer. The study affirmed that the recreation of the normal physiologic hormonal environment

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