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The theory of modulated hormone therapy for the treatment of breast cancer in pre- and post-menopausal women

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We present a theory that questions the standard of care for pre- and post-menopausal women with breast cancer. Through the use of modulated hormones to mimic the natural multiphasic fluctuations of estrogen and progesterone cycles of healthy young women, it can be expected that patients will not only exhibit increased quality of life such as better sleep, well-being, and libido, but also memory improvement and less joint pain. Additionally, this regimen may engage genetic pathways that protect women in youth from breast cancers. We present a mathematical basis for the coupling of the hormone cycles through the use of Gaussian curves that provides the foundation of a new format of hormone replacement in women.

I. INTRODUCTION

Throughout the preceding decades, there has been a steady increase in number of breast and other cancers in women age 40 years and older.\textsuperscript{1,2} This increase has been the subject of many studies which range from possible causes and treatments, to methods of handling the physical changes occurring at midlife that may coincide with the increase in cancer.\textsuperscript{3-6}

While the overall conclusions of the clinical studies are valid within the confines of the studies themselves, the misunderstandings of these studies are revealed when considering the body’s normal cycles as a whole integrative system.\textsuperscript{7} This will be discussed in a later section. Investigation into the body’s ability to control cancerous processes\textsuperscript{8-11} via normal hormonal cycles resulting in G1 arrest of the cell cycle and templates of apoptotic estradiol (E2), progesterone (P4), testosterone (T2), and cortisol (C) activity is needed.\textsuperscript{12}

Over the past few decades, hormone studies using Food and Drug Administration (FDA) approved pharmaceutical same daily (static) doses of synthetic conjugated equine estrogen - CEE (ES) and combined CEE and progestins have been performed.\textsuperscript{13} Studies that have investigated the complete gonadal and adrenal hormone\textsuperscript{14} ablation with the drugs tamoxifen (TMX) and aromatase inhibitors have amassed evidence showing that having little to no estrogen benefits women with estrogen receptor positive tumors.\textsuperscript{15,16} Moreover, investigations have come to the conclusion that the natural postmenopausal state, as well as synthetic hormone replacement therapy (HRT), like combined CEE and progestins, could be considered carcinogenic. This can be seen through the increased incidence of breast cancer in those populations.\textsuperscript{17,18}

Within clinical trials for breast cancer, it is required that women with estrogen sensitive breast cancers remove all traces of estrogen from their bodies and refrain from therapeutic replacement options.\textsuperscript{22} This standard treatment using TMX for endogenous hormone receptor blockage for the patient with an estrogen receptor positive tumor typically comes with well-documented reductions in quality of life such as hot flashes, night sweats, loss of libido, insomnia, weight gain, memory loss, thrombotic events as well as chronic depression.\textsuperscript{23}
FIG. 1. The chemical structures for estradiol (E2), tamoxifen (TMX), and progesterone (P4) consisting of carbon (green), oxygen (red), and hydrogen (white) atoms. While E2 and P4 share the ability to bind to a large family of ligand-activated nuclear transcription regulators, which includes receptors for steroids, retinoids, thyroid hormones, and vitamin D, TMX chemical contains a single nitrogen (blue) atom, which changes the binding mechanism to the receptor sites and effectively turns off estrogen’s normal activity by blocking E2’s ability to bind and maintain activity.

Figure 1 shows the molecular structures for E2, TMX, and progesterone (P4). While E2 and P4 share the ability to bind with a large family of ligand-activated nuclear transcription regulators, which include receptors for steroids, retinoids, thyroid hormones, and vitamin D. Since TMX contains a single nitrogen atom, the binding mechanism is altered and results in the drug’s hormonal action at the steroid receptor site to create a static, indefinite it is more of an active prevention shut off of estrogen’s normal activity.

Since the benefits of estradiol replacement on the body and quality of life are well documented, it is our goal to present an alternate theory to the standard of care for treatment of midlife and onward breast cancers. Through an understanding of the fundamental cellular functions of growth and death in the normal reproductive female hormonal cycle, we present the theory that modulated exogenous E2 and P4 hormone replacement therapy may not only increase the conditions listed for quality of life in women with or without cancers but, may also have the potential to reduce the risk and recurrence of cancer within this age group via genetic mechanisms at the receptor level.

II. MODULATION OF HORMONE THERAPY
A. Background

The normal E2 and P4 levels in a healthy, young woman fluctuate predictably in an established template throughout the normal menstrual cycle (~28 days). This cycle’s hallmark is the gradual increases in E2 culminating in a peak on the 12th day of the cycle. The increase in serum E2 beyond a specific threshold (E2T) signals the body to produce P4R (progesterone receptor) and serum T2 via a luteinizing hormone (LH) spike from the pituitary gland (ovulation), as well as diminishes its own growth enhancing effects through a negative feedback loop, via G1 arrest. All of the negative and positive endocrine feedback loops of these hormones over 28 days provide specific functions
TABLE I. List of hormones and their basic functions.

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Examples Action or Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogen (E2)</td>
<td>Controls over 9000 gene products and 400 metabolic processes such as the induction of LH resulting in ovulation and the provocation of the P4 receptor.</td>
</tr>
<tr>
<td>Progesterone (P4)</td>
<td>Modulates estrogen at the receptor level, re-mylenates nerve and remodels bone due to apoptotic events.</td>
</tr>
<tr>
<td>Testosterone (T2)</td>
<td>Down-regulates E2Rα by 35%, converts through aromatase to E2, builds muscle, is used in a proprietary manner (synaptically) in the brain, and controls immune response.</td>
</tr>
<tr>
<td>Cortisol (C)</td>
<td>Primary immunomodulator in the body and controller of binding globulins for sex steroid availability to the receptors through SHBG, universal zeitgeber and partner to melatonin’s control on estrogen reception. Cortisol is a primary stress response hormone.</td>
</tr>
</tbody>
</table>

in the human body, as well as enact apoptotic and differentiating mechanisms at the receptor level (described in Table I) in soft tissues.

Studies have all shown that low chronic E2 produces consistent growth in all soft tissues in the body including potentially cancerous tumors. These uniform conclusions may be due to the lower static levels and constant distribution of ES< E2T. This leads to an abnormal state of constant ES and is contradictory to the normal reproductive process in healthy women. The absence of undulating and peaking E2 denies the potential of an LH spike and a PR. There is no T2 surge concurrent with ovulation or the following P4 surge from a viable corpus luteum to fill P4 receptors. This leads to induction of progesterone. The peak of E2 on day 12 of the menstrual cycle is what starts this process of G1 arrest and provocation of P4 receptor, both of which have been shown to reduce cancerous cells already present, and the growth potential of new ones as well. The fall off of these rhythms at mid-life restricts what was a normal cycle from keeping the growth and death of all cells in the body in predictable templates.

B. Modulation of Estrogen and Progesterone

Given the normal hormonal cycle of a healthy young woman, we propose the hormones E2 and P4 be provided to menopausal and post-menopausal patients in a modulated manner to attain normal serum levels of a 20 year-old in an attempt to mimic a natural, youthful cycle (shown in Fig. 2(d)). Since menopausal and post-menopausal women experience fluctuating and diminishing levels of E2 naturally, which results in the cession of ovulation and the absence of P4, it is reasonable to associate those events with the rise in the onset of breast cancers at mid-life. As uterine function deteriorates, along with the associated changes to normal menstrual cycle, we estimate that by age 52 the same deteriorating endocrine feedback loops from organ to brain are creating increased cancer potential in the breast as well.

Figure 2(a)–2(d) shows the theoretical progression from static hormonal doses to modulated doses. By increasing E2 beyond the threshold value of G1 arrest, the body will produce P4 and T2 via LH, assuring ovulation and appropriate apoptosis. The production of P4 from the resulting corpus luteum actually reduces the E2 action levels at the E2Rα receptor sites all over the body. With the E2 levels lower than the threshold of the termination of action, P4 will eventually diminish. The incline of the E2 curve is aided by Follicle Stimulating Hormone (FSH) ripening appropriate ovum and the rigidity of the E2 curve is caused by cortisol boluses that occur throughout the day (~4/day). Cortisol via Sex Hormone Binding Globulin (SHBG) releases E2, P4 and T2 during the day (Shown in Fig. 2).

The curves in Fig. 2(a)–2(d) are produced through coupled Gaussian distributions, which represent hormones levels with respect to time (time in this case is a normal cycle of 28 days).
FIG. 2. Transformation of hormone levels in response to hormone coupling $g_1$ with modulated estrogen (E2 – solid black).

(a) Static estrogen (ES) provided constantly throughout the cycle. Since $ES < E2T$, no progesterone (P4 – dashed red) or testosterone (T2 – dotted blue) is produced. (b) Small amounts of P4 and T2 produced in response to small E2 modulation exceeding the threshold value. (c) Moderate E2 modulation. (d) Normal cycle due to maximum E2 modulation. The ridges in the E2 dosage are produced by the cortisol (C) modulation through a normal day.

The distributions for E2, P4, and T2 are given by

$$f_{E2} = f_C + (1 - g_1) \left( \frac{A_{E2,1}}{2\sigma_{E2}} e^{-\frac{(t - \mu_{E2,1})^2}{2\sigma_{E2}^2}} + \frac{g_1 A_{E2,2}}{2\sigma_{E2}} e^{-\frac{(t - \mu_{E2,2})^2}{2\sigma_{E2}^2}} \right) - g_1 g_2 f_{P4},$$

$$f_{P4} = \frac{g_1 A_{P4}}{\sigma_{P4}} e^{-\frac{(t - \mu_{P4})^2}{2\sigma_{P4}^2}},$$

and

$$f_C = A_c \cos(3\pi \mu_c t)^2 \cos(\pi \mu_c t)^2,$$

and

$$f_T = \frac{g_1 A_T}{\sigma_T} e^{-\frac{(t - \mu_T)^2}{2\sigma_T^2}},$$

where $A$ is the amplitude for the hormone levels ($A_{E2,1} = 10$, $A_{E2,2} = 6$, $A_{PR} = 6$, $A_c = 0.2$, and $A_T = 3$), $\mu$ is the mean peak position ($\mu_{E2,1} = 7$ days, $\mu_{E2,2} = 21$ days, $\mu_{PR} = 21$ days, $\mu_c = 1$ day, and $\mu_T = 14$), $\sigma$ is the distribution (All set to 2 days), $g_1$ and $g_2$ are coupling factors of the reduction of E2 produced by P4. The value of $g_1$ varies to denote the level of E2 modulation within the system. Therefore, $g_1 = 0.0$ represents a total decoupling of the hormonal activity which will result in a static estrogen dosing. This is essentially the effect of artificial hormones blocking the normal processes. When $g_1 = 1.0$, then maximum hormone coupling to E2 can be achieve and this produces the normal hormonal cycle.

III. CONCLUSIONS

We provide evidence that the standard of care for the treatment of breast cancers may be inherently flawed. The ablation of natural hormones from the body is not a coherent course of action for treatment based on the known endocrine action on genes controlling apoptotic and differentiation
mechanisms. Based on the physical and biological understanding of the body at the molecular receptor response level, modulated hormone treatment may be a wiser course of action, since it can provide a return of the body to its natural hormonal state. We argue that the improper understanding of hormone interactions and the mechanisms for which they work may be contributing to the increase in cancer rates, and not the hormones themselves. As shown by our mathematical model, decoupling the hormone activity can produce a static hormonal state, which, through the normal mechanisms of the body, produces negative effects in overall quality of life. Therefore, by returning the hormone cycles to a normal rhythmic series, one could provide a better quality of life and a potentially new prophylactic treatment for hormonally responsive cancers. Case studies of this methodology are currently underway for breast cancer patients and have produced promising results, where the quality of life is typically better than the normal standard of care, and no remarkable harm has yet been observed.

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