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The Modulation of Estrogen-Induced Apoptosis as an Interpretation of the Women's Health Initiative Trials

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Abstract

The Women's Health Initiative (WHI) consisted of two placebo controlled trials: one in women with a uterus, using Conjugated Equine Estrogen (CEE) plus medroxyprogesterone acetate (MPA), and the second trial in women without a uterus used CEE alone. The study population average age was approximately 63 years. Although the predicted rise in breast cancer occurred in the MPA plus CEE trial, the CEE alone trial, had a sustained decrease in breast cancer incidence. A unifying theory is presented that explains the decrease in breast cancer based on the new biology of estrogen-induced apoptosis in long term estrogen deprived nascent breast cancer cells. Glucocorticoids block estrogen-induced apoptosis and MPA has glucocorticoid activity. This is why MPA increases breast cancer when used with CEE as menopausal hormone replacement. A safer menopausal hormone therapy can now be designed with a more selective synthetic progestin such as norethindrone acetate.

Keywords

Conjugated equine estrogen; medroxyprogesterone acetate; menopausal hormone therapy; estrogen-induced apoptosis; breast cancer; glucocorticoid activity; inflammatory response; estrogen deprivation

A clinical result from a well-planned clinical trial trumps data from laboratory models. However, the discovery of unanticipated results from a well-planned clinical trial demands explanation. The pieces of translational research and clinical observations need to fit so that an understanding of new clinical knowledge can be used wisely. In this case, the Women's Health Initiative (WHI) presented a paradox [1–4]. Estrogen that stimulates breast cancer cell growth in the laboratory caused a decrease in breast cancer incidence in the estrogen alone trial [2]. The WHI consists of two placebo controlled trials: one uses Conjugated Equine Estrogen (CEE) alone in hysterectomized women (80% hysterectomized at less than 50 years of age), and a second used CEE plus medroxyprogesterone acetate (MPA) as menopausal hormone therapy in women with a uterus. The MPA prevents endometrial cancer that develops from unopposed estrogen stimulation of the uterine lining [5,6]. The trials recruited women with a mean age of 63 (SD 7) as the primary endpoint was to

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determine whether CEE alone or CEE plus MPA protected women from coronary heart disease. Coronary heart disease is known to increase with years after menopause. Stop rules for the trials included an increase in breast cancer incidence and the CEE plus MPA trial was stopped when an interim analysis indicated more risks than benefits [1]. The CEE trial did not stop for breast cancer or increase in coronary heart disease but was stopped 2 years later for an increase in strokes [2]. These trials have repeatedly been reanalyzed and the data remains the same; CEE alone causes a long term decrease in breast cancer incidence whereas the CEE plus MPA trial causes a consistent increase of breast cancer.

Two questions must be addressed. The first question is why does CEE alone cause a decrease in the incidence of breast cancer? The second question is, why does MPA plus CEE cause an increase in breast cancer if CEE causes a decrease in breast cancer incidence? The answer to each question will be a synthesis of the laboratory and clinical evidence in the scientific literature.

Starting a century ago, oophorectomy of premenopausal women with breast cancer produced a 30% response rate [7], and laboratory studies in animal models showed that ovariectomy prevents mouse mammary tumorigenesis and estrogen administration initiates mouse mammary tumors [8, 9]. Estrogen was clearly the culprit causing the initiation and growth of breast cancers. All the evidence emerging in the laboratory and clinic supported the dogma that estrogen was stimulating breast cancer growth. Unexpectedly, a paradoxical discovery was made. The first chemical therapy to successfully treat any cancer in clinical trial was the use of high-dose synthetic estrogens to treat metastatic breast cancer in post-menopausal women [10]. The remarkable thing about these findings was the effectiveness of estrogen to treat breast cancer was dependent upon the time after menopause when estrogen was administered after menopause. Patients who were more than 5 years following menopause had about a 30% response rate whereas those less than 5 years after menopause tended to have tumor growth [11]. High dose estrogen became the treatment of choice for breast cancer for the next 30 years despite the high incidence of thrombo-embolic events and not understanding how estrogen was an anti-cancer agent. The introduction of the anti-estrogen tamoxifen in the early 1970s [12] now conformed to the original medical dogma that estrogen drove breast cancer growth and the standard of care changed to tamoxifen which has a safer therapeutic profile with fewer thrombo-embolic events compared to high dose estrogen [12]. This anti-estrogen was used ubiquitously in all stages of breast cancer for 30 years. Tamoxifen was the only anti-estrogenic therapy proven to save lives. The dogma was further supported with the discovery of the aromatase inhibitors that block peripheral estrogen synthesis, and were subsequently introduced as a successful breast cancer treatment in postmenopausal breast cancer patients [13]. All interest in high dose estrogen therapy was forgotten despite the fact that some of the tumors just disappeared [11]! It is therefore ironic that investigations of long-term tamoxifen therapy to understand the development of acquired drug resistance to tamoxifen [14] would result in an understanding of the evolution of acquired resistance to anti-hormone therapy and lead to the new biology of estrogen-induced apoptosis [15]. This new biology of estrogen action does not replicate the use of high dose estrogen used clinically 40 years ago but occurs with low concentrations of estrogen in the physiologic range [16].

The systematic study of the anti-tumor properties of physiological estrogen levels in vivo started in 2000 [14], and subsequently in vitro models of estrogen deprived estrogen receptor (ER) + breast cancer cells [17,18] would open the door to an evaluation of estrogen induced apoptosis. Studies described a “movie” of the events that occur after estrogen triggers the molecular mechanisms that lead to an apoptotic response [19]. The ER is the target which controls estrogen induced apoptosis. It is a unique natural process where physiologic estrogen requires several days of cell growth and then triggers an inflammatory reaction before apoptosis [19, 20].

Different classes of estrogens have been studied in detail. Remarkably, it is the shape of the estrogen: ER complex that controls the time to apoptosis triggered by estrogen. A planar estrogen (eg, estradiol) fits neatly into the unoccupied ER and the protein folds around the ligand. Helix 12 of the ER now seals the ligand into the ligand binding domain (LBD). This is called “the crocodile model” where the jaws of crocodile close tightly. By contrast the triphenylethylene (TPE) - type of estrogen also bind to the ER in the LBD but the molecule is bulky and angular. When it first binds to the ER, the TPE prefers to occupy the “anti-estrogenic” conformation of the ER. Indeed, the TPE: ER complex acts as an “anti-estrogenic complex” and prevents planar estradiol from triggering apoptosis. The TPE: ER complex eventually evolves to trigger apoptosis a week later destroying the estrogen deprived breast cancer cells. These molecular concepts have been reviewed [16].

Overall, the key to the success of physiologic estrogen therapy as an anti-tumor treatment is long term estrogen deprivation that causes selection pressure to develop new surviving cell populations. Laboratory studies in vivo using immune deficient mice implanted with ER+ breast cancer cells supported the idea [14] that the surviving cell population evolve over time from acquired resistance to tamoxifen that grows with estrogen or tamoxifen, to a cell population that is killed by estrogen. In the laboratory this process takes five years [14]. Coincidentally, treatment with adjuvant tamoxifen must be more than five years in patients to produce the best decreases in mortality [21]. This treatment strategy produced survival advantages but decreases in mortality occurred *after* tamoxifen treatment had been stopped. It has been proposed that a women’s own estrogen is responsible for triggering apoptosis in vulnerable micrometastatic breast cancer that has acquired resistance to tamoxifen [14,21]. The effect is even more profound when ten years of adjuvant tamoxifen is used. The decreases in mortality were observed in the decade after tamoxifen was stopped [21, 22].

There are also current examples of estrogen therapy used in medical oncology to treat anti-hormone refractory breast tumors. Lonning and coworkers [23] obtained profound responses in 30% of patients following exhaustive antihormone treatment for metastatic breast cancer. However, these studies used high dose estrogen therapy thereby exposing patients to an increased risk of thrombo-embolic disorders. Ellis and coworkers [24] found similar 30% rates of clinical benefit for patients who had recurred following adjuvant aromatase inhibitor therapy. The trial compared high dose (30 mg) and low dose (6mg) estradiol. Response rates were the same (30%) but a lower incidence of side effects occurred with low dose estrogen. These data [24] are the clinical translation of the original laboratory studies [14] that proposed the clinical application of low dose estrogen therapy following exhaustive anti-hormone therapy. All of these data support estrogen induced apoptosis being responsible for

the decrease in breast cancer incidence observed in the WHI CEE alone trial. These concepts are described in detail elsewhere [16].

Turning now to the second question, why does MPA plus CEE cause an increase in breast cancer incidence?. This is not simply the addition of MPA to CEE as there are changing cell populations exposed to menopausal hormone therapy depending upon whether treatment starts less than or more than five years after menopause. This important dimension of breast cancer cell selection in response to estrogen deprivation, universally obeys rules based on both clinical experience and laboratory experimentation [25]. The five year rule is called “the gap time” [26].

Based on laboratory work, short-term estrogen deprivation does not change cell population dramatically and re exposure to estrogen rapidly initiates cell growth. By contrast, prolonged estrogen deprivation for years in the laboratory creates new surviving cell populations where estrogen triggers tumor regression or apoptosis [14, 17–18].

Prentice and coworkers [27] have analyzed the WHI trials and concluded for the CEE alone trial that those hysterectomized women who initiate a daily 0.625 mg regimen soon after menopause have little indication of a reduction in breast cancer. However, there is a reduction of breast cancer risk in those women who initiate CEE more than 5 years after menopause [27]. In the Million Women’s study in the UK, Beral and coworkers [26] noted that women currently taking an estrogen alone preparation starting more than 5 years after menopause had no increase in breast cancer risk (RR 1.05), but if estrogen was started immediately after menopause there was an increase in breast cancer incidence (RR 1.43). Prentice and coworkers [28] analyzed the impact of CEE and MPA and noted that those women who initiated menopausal hormone therapy soon after menopause and continued for many years, were at particularly high risk for breast cancer with an estimated hazard ratio of 1.64 after 5 years and 2.19 after 10 years of treatment. Beral and coworkers [26] in the Million Women’s study noted that women who started menopausal hormone therapy immediately after menopause had a RR 2.04 but if they started more than 5 years post menopause the RR was 1.53. Thus, both of these clinical data sets point to the potential of MPA neutralizing the effectiveness of estrogen-induced apoptosis that occurs after more than five years of estrogen deprivation. However, menopausal hormone therapy clearly immediately following menopause enhances estrogen stimulated tumorigenesis.

Prentice and coworkers [29] have taken their analyses of the WHI trials one step further to discover an association between baseline sex steroids and future disease risk. They compared and contrasted total and bioavailable estradiol, estrone, and sex hormone binding globulin (SHBG) in representative samples from both trials with an average participant age of 64 years old. Estrogenic steroids and SHBG were measured before and one year after relevant trial treatments. Following CEE, breast cancer risk was associated with higher baseline serum bioavailable estradiol and lower SHBG. This is consistent with higher SHBG (and therefore lower bioavailable estradiol) being protective for breast cancer risk (30). However, the association of higher baseline estrogen with breast cancer risk in the CEE trial does not appear to consider gap time from menopause. Nevertheless, the conclusion is that SHBG is responsible for the reduced bioavailability of estradiol to decrease breast cancer

incidence in the CEE trial but this does not apply to the increase in breast cancer incidence in the CEE/MPA trial. MPA is having an independent role in the prediction of tumorigenesis. We now consider it is important to integrate mechanisms of subcellular action as an important new dimension that impacts on tumorigenesis.

A recent Editorial by Joshi et al. [31] suggested that progesterone or a synthetic progestin would cause a sustained clonal expansion in stem cells or progenitor cells, thereby stimulating breast cancer cell growth in the CEE/MPA trial. These data [31] inform about a role for the synthetic progestin in tumorigenesis in women. However, the proposition does not explain the decrease in breast cancer incidence with physiologic estrogen in postmenopausal women with a mean age of 63 years [2–4, 32]. Perhaps the key to understanding how MPA reverses the anti-tumor action of CEE, is the observation that estrogen-induced apoptosis is presaged by an inflammatory response [19]. Glucocorticoids inhibit estrogen-induced apoptosis [33], and MPA is known to also have glucocorticoid activity [34]. Recent laboratory studies demonstrate that MPA not only blunts estrogen-induced apoptosis but also, over time, new populations of breast cancer cells develop and grow [35]. The WHI trial certainly has the dimension of time with six years of treatment [1–4]. It has been suggested [35] that the selection of a synthetic progestin with no glucocorticoid activity but with estrogen-like activity would provide benefits to protect the uterus through progestational activity but the estrogen-like activity would reinforce the natural estrogen-induced apoptosis in breast cancer. The 19 nortestosterone derivative with known estrogenic activity [36] would be a safer alternative, as the available synthetic progestins such as: norethindrone acetate, norethynodrel and norgestrel, have been used by women for more than half a century in oral contraceptives [35]. Nevertheless, rigorous clinical studies are required in healthy postmenopausal women with monitoring of multiple clinical outcomes before wide spread use is approved.

For the future it would be valuable to enhance the killing of cancer cells and improve response rates in menopausal hormone replacement and cancer therapeutics from 30% responses as seen in the CEE alone WHI trial [3] or cancer therapy [24], to 100%. The question now becomes “what is preventing estrogen-induced apoptosis in all estrogen-deprived breast cancer cells?”. Maybe it is the women’s own glucocorticoids that protect some tumors from the targeted treatment by estrogen. One appropriate clinical approach for the treatment of anti-hormone resistant breast cancer would be to develop a selective glucocorticoid receptor modulator to block the tumor glucocorticoid receptor during physiologic estrogen therapy. Another new strategy is to avoid MPA but use a Selective ER Modulators (SERMs) plus CEE as menopausal hormone therapy. The SERM is antiestrogenic in the uterus and breast thereby by blocking carcinogenesis by estrogen in these target sites. Again, the SERM/EE requires wide spread testing against menopausal hormone therapy to establish safety for multiple outcomes before long term use is advocated for indications other than osteoporosis. It is now clear that new innovations in menopausal hormone therapy are emerging, and physicians have a better understanding how these medicines should be deployed to improve safety in both the treatment and prevention of breast cancer.

Expert Commentary

The Women's Health Initiative (WHI) trials were designed to address whether hormone replacements could reduce coronary heart disease (CHD) in postmenopausal women. These trials provided valuable information and serious side effects, but demonstrated no benefit in controlling CHD. Nevertheless, valuable information on the decrease in breast cancer noted in the estrogen alone trial, has now been integrated with results from the Million Women's Study and the current understanding of estrogen-induced apoptosis triggered in estrogen deprived breast cancer cells. Estrogen-induced apoptosis is preceded by a cellular inflammatory response. Glucocorticoids, including synthetic progestin medroxyprogesterone acetate (MPA) used to protect the postmenopausal uterus from increases in endometrial cancer are known to blunt estrogen-induced apoptosis under laboratory conditions. These data may permit advances in menopausal hormone therapy to utilize a synthetic progestin without glucocorticoid activity, thereby retaining the benefits of estrogen-induced apoptosis to reduce the incidence of breast cancer. An alternative strategy of using a Selective Estrogen Receptor Modulator (SERM) plus estrogen has yet to be tested against traditional hormone replacement therapy.

Five Year View

The rules now established for the judicious application of menopausal hormone replacement with become the standard of care used by the gynecologic community. Additionally, a close collaboration of the translational research community with the clinical trials community will result with the gradual phasing out of synthetic progestins with glucocorticoid activity. The combination of MPA plus estrogen that reduces the beneficial effects of estrogen alone on estrogen-induced apoptosis will be replaced by new SERMs plus estrogen or synthetic progestins with enhanced estrogen-like properties. These synthetic progestins are already available for clinical trials as they are already available progestins used in oral contraceptive formulations for premenopausal women.

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Key Issues

- The Women's Health Initiative (WHI) estrogen alone menopausal hormone replacement trial demonstrated a consistent decrease in the incidence of breast cancer in women recruited, on average, over 60 years of age.
- The WHI estrogen plus medroxyprogesterone acetate (MPA) combination menopausal hormone therapy trial, demonstrated a consistent increase in the incidence of breast cancer in women recruited, on average, over 60 years of age.
- The Million Women's Study proves important complimentary data i.e.: women starting estrogen alone replacement therapy 5 years post menopause had no increase in breast cancer, but there is a 40% increase in relative risk if estrogen is started immediately at menopause. MPA plus estrogen increases relative risk for breast cancer whenever it is given relative to menopause.
- Clinical experience with the treatment of breast cancer in postmenopausal women demonstrates that estrogen therapy is only effective in causing a 30% response rate if initiated 5 years post menopause.
- Estrogen deprivation of Estrogen Receptor (ER) positive breast cancer cells under laboratory conditions requires the evolution of cell populations over 5 years. This change in acquired resistance over years to antihormone therapies eventually exposes cellular vulnerability to estrogen-induced apoptosis.
- Glucocorticoids such as dexamethasone inhibit estrogen-induced apoptosis under laboratory conditions.
- The synthetic progestin MPA is used in the majority of menopausal hormone therapy preparations to prevent endometrial cancer from unopposed estrogen therapy for postmenopausal women. However, MPA is not a pure progestin but has associated glucocorticoid activity.
- Laboratory data demonstrate that prolonged treatment of estrogen deprived ER-positive breast cancer cells with MPA plus estrogen blunts estrogen-induced apoptosis resulting in the regrowth of breast cancer cell populations.
- It is suggested that the fact that MPA plus estrogen increases the incidence of breast cancer whereas estrogen alone decreases breast cancer incidence in the WHI studies then the glucocorticoid activity of MPA prevents the beneficial effect of estrogen to induce apoptosis in occult estrogen-deprived breast cancer cells. New approaches to combination menopausal hormone therapy must be sought.