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Estrogen for the Treatment and Prevention of Breast Cancer: a Tale of Two Karnofsky Lectures

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Abstract

In 1971, Sir Alexander Haddow delivered the inaugural David A. Karnofsky lecture at the American Society for Clinical Oncology (ASCO). This award was designated ASCOs highest, as he had used translational research to identify the first clinical therapy i.e.: synthetic estrogens to treat breast cancer. His lecture was entitled “Thoughts on Chemical Therapy.” For 40 years, high dose synthetic estrogens were used as palliative therapy, for some advanced breast cancer patients five years following menopause. Mechanisms were unknown. Tamoxifen, a failed “morning after pill” is an anti-estrogen in estrogen receptor (ER) positive breast cancer which subsequently became used to treat all stages of breast cancer and to prevent breast cancer. In 2008, Jordan was selected to present the 38th Karnofsky lecture entitled: “The paradoxical action of estrogen in breast cancer - survival or death?” Unexpectedly, through a study of acquirements to long-term tamoxifen therapy, estrogen- induced apoptosis in long-term estrogen deprived breast cancer was deciphered in Jordan laboratory. These data and the biological rules established under laboratory conditions, provided molecular mechanisms to aid in the interpretation of the Women's Health initiative in the USA and the Million Women Study in the UK. Additionally, by establishing laboratory models to understand mechanisms of estrogen-induced apoptosis, new estrogen derivatives were successfully evaluated in the laboratory and tested as candidates for women after the therapeutic failure of anti-estrogenic strategies to treat breast cancer. For the future, the knowledge obtained about estrogen-induced apoptosis in cancer holds the promise of discovering new therapies to control or cure cancer in general.

By looking back we can see the way forward.

On the cusp of the 20th century (1), Beatson reported the first case of an oophorectomy as a treatment for breast cancer. The procedure rapidly gained traction as the only method of producing any hope of causing breast tumor regression. Boyd (2) subsequently gathered the reports of all known cases of oophorectomy to treat breast cancer around Britain and discovered a 30% response rate.

The discovery that the ovaries contained a substance that caused responses in reproductive organs (3) is key to focusing on estrogen action and breast cancer. Allen and Doisy,

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ovariectomized mice, thereby stopping the estrous cycle. They extracted pig ovaries and inoculated the mice. The vaginal epithelium changed, and mice became more receptive to males. They named their new extracted material “estrogen” *(latin for frenzy)* and the Allen-Doisy test was born to identify all further estrogens and eventually synthetic anti-estrogens. Parenthetically one of the authors (VCJ) used the Allen-Doisy test throughout his PhD (1969-1972) to quantify the estrogenicity of newly synthesized non-steroidal antiestrogens (4). The explosion of new synthetic non-steroidal estrogens in the 1930s (5) now turned attention to finding a practical use for the synthetic estrogens in medicine.

During the 1940’s, Haddow discover that carcinogenic polycyclic hydrocarbons caused tumor regression in laboratory animals. Naturally these compounds could not be used in patient cancer care, but he reasoned that the new polycyclic synthetic estrogens could be used in patients. Prostate and breast cancer had a 30% response rate in patients (6). Today we know that prostate cancer progresses because of estrogens action at the hypothalamo-pituitary axis to prevent gonadotrophin secretion. The elucidate of the mechanism of estrogen action to treat breast cancer through apoptosis had to wait until the development of animal models to study breast cancer in the 1980’s (7).

To advance the clinical utility of high does synthetic estrogen treatment, Haddow organized a clinical trial with a dozen centers administered by the Royal Society of Medicine (Section of Oncology, of which he was the head).

During his Karnofsky lecture he stated:

When the various reports were assembled at the end of that time, it was fascinating to discover the rather general impression, not sufficiently strong from the relatively small numbers in a single site, became reinforced to the point of certainty; namely, the beneficial responses were three times more frequent in women over the age of 60 years than in the women under that age; that oestrogen may, on the contrary, accelerate the course mammary cancer in younger women, and that their therapeutic use should be restricted to cases 5 years beyond the menopause. Here was an early example of the advantages which may accrue from cooperative clinical trials (8).

A similar conclusion was noted by Stoll (9) through a review of his lifelong experience with 407 postmenopausal patients with Stage IV breast cancer treated with high dose estrogen (Table 1).

High-dose synthetic estrogen therapy became the standard of care for Stage IV breast cancer patients until the approval of tamoxifen in the United Kingdome (1973) and the United States of America (1977). This clinical decision was based on fewer side effects observed with tamoxifen as the clinical response rate was the same for tamoxifen and estrogen at around 30% (10, 11). During the 30 years that high dose estrogen use was the standard of care, there was no progress in understanding the anticancer action of high dose estrogen in long-term estrogen deprived patients (5 years post-menopause). By contrast, if surgical removal of organs that synthesize estrogen precursors or hormones that stimulate estrogen synthesis caused breast cancer regression then some breast tumors depended on estrogen to grow (12). This made the mechanism of action of tamoxifen, a nonsteroidal, anti-estrogen

self-evident once the estrogen receptor (ER) was identified in estrogen target tissues and about 2/3 of human breast cancers (13).

Long Term Adjuvant Tamoxifen Therapy as a lifesaving strategy in ER positive breast cancer patients.

Once the translational research strategy of long-term adjuvant therapy (14) was proven in the Oxford Overview Analysis (15) the major challenge, for translational research, was to create models to discover mechanisms to develop new medicines. The previous DMBA-induced rat mammary carcinoma model was inappropriate. By contrast, the human derived MCF-7 cell line was relevant as it is an ER positive breast cancer cell line and transplantable into ovariectomized athymic mice. Subsequently tamoxifen resistant tumors can be retransplanted for years i.e.: the actual time course for the treatment of human disease. Several surprises were in store.

Tamoxifen-stimulated MCF-7 tumors started to grow after about 6 months of tamoxifen therapy so tamoxifen was not killing the MCF-7 cells. The unique feature was the discovery that tamoxifen was the first treatment for cancer to cause the growth of resistant breast cancers cells (16). Indeed, either tamoxifen or estradiol caused ER positive breast cancers to grow (16, 17). Early clinical case reports documented a withdrawal response of tumor regression for metastatic breast cancer that occurred on stopping SERMs and the drug was cleared from the patient (18, 19). However, in the laboratories after tamoxifen stimulated tumors had been transplanted for 5 years, estrogen no longer stimulated tumor growth, but killed tumor cells with rapid tumor regression. Haddow was speaking to us from his Karnofsky lecture (8) *the extraordinary extent of tumor regression observed in the 1% of post-menopausal cases (with oestrogen) has always been regarded as a major theoretical importance and it is a matter for some disappointment that so much of the underlying mechanism continues to illude us.*

In the laboratory we develop the first reproducible *in vivo* transplantable ER positive breast cancer (MCF-7) tumor model that responded to estrogen with tumor regression (20, 21). The tamoxifen resistant model was expanded to a model using the selective estrogen receptor modulator (SERM) raloxifene (22, 23) once it was clear that raloxifene would be marketed to treat osteoporosis (24) with the added advantage of reducing the risk of breast cancer at the same time (25). Additionally, raloxifene was found to reduce the risk of breast cancer in high risk post-menopausal women (26).

The aromatase inhibitors were attracting attention in clinical trials in the early 1990s, so it was essential to develop appropriate long-term estrogen deprived (LTED) cells *in vitro* to study molecular mechanisms of estrogen-induced apoptosis ( ). Although we developed cell lines *in vitro* (27, 28), results were disappointing. These went back in the freezer for nearly a decade until the Santen group (29) described the final stages of estrogen-induced apoptosis using an extrinsic mechanism. What they reported was 1) estrogen binds to the ER 2) a week later, something happens, and 3) the extrinsic mechanism occurs via feed back to the cell membrane to trigger cell death.

Clearly, our *in vivo* model was not suited to document the subcellular steps leaving to apoptosis. The cells in our freezer were waiting to describe those mechanisms. The cloned cell line MCF-7:5C fully documented the mitochondrial pathway to trigger estrogen-induced apoptosis (30).

The practical value of a laboratory investigation of estrogen-induced apoptosis and its modulation.

There have been two practical benefits to creating models in the laboratory 1) to decipher mechanisms of the modulation of breast cancer incidence in post-menopausal women in trials focused of the incidence of heart disease i.e.: The Women's Health Initiative and the Million Women Study 2) to discover mechanisms of estrogen-induced apoptosis with the goal of designing new estrogen-like molecules to treat patients who eventually fail long term adjuvant aromatase inhibitor therapy.

The Women's Health Initiative

The 30-year clinical trial (recruitment 1993-1998) referred to as the Women's Health Initiative (WHI) consisted of two trials: women with an intact uterus who were randomized to either placebo (8,102) or 2.5 mg daily medroxy progesterone acetate (MPA) (8,506) and 0.625mg conjugated equine estrogen (CEE). In the second trial hysterectomized women randomized to placebo (5,429) or 0.625 (CEE) (5,310). The CEE plus MPA trial was stopped after 6.8 years in 2002 because of the expected increase in breast cancer. The CEE trial was stopped after 6.8 years of treatment because of the elevation of strokes (31, 32).

It is important to note that the mean age of screening to enter the two placebo-controlled trials was 63.3 years old i.e.: more than a dozen years after women would normally considering using hormone therapy at menopause. This gap was intentional to build in an increased risk of cardiovascular disease in older women. There was no benefit for women taking hormone therapy with regard to a cardiovascular end point.

A recent review (33) fully documents the WHI and the conclusion of estrogen-induced apoptosis as the reason for prolonged decrease in breast cancer incidence in the women taking CEE. Additionally, those women with a uterus who took CEE/MPA for 7.2 years, at the anticipated rise in the incidence of breast cancer.

With regard to the breast cancer safety of combined CEE/MPA treatment for 7.2 years it was concluded in 2020 (34), 27 years after the start of combination therapies, that although there was a higher risk of breast cancer hazard ratio 1.28, there was no significant difference in breast cancer mortality (treatment 73 deaths, control 53 deaths). Bearing in mind the trial only included 8,506 women randomized with a uterus the calculation should be revisited using the national statistic of women with a uterus on combination HRT. Only then, can realistic claims be made on deaths from breast cancer. Additionally, as most women who volunteered were more than a decade post-menopause, to ensure sufficient cardiovascular events would occur, the results for breast cancer are skewed as most women go on post-

menopausal HRT at menopause, arbitrarily considered to be 50 years of age by most clinical trials groups.

The final breast cancer report of the WHI study ( ) had a sustained increase in breast cancer incidence for the CEE/MPA trials out to 22 years and the CEE alone trial had a sustained decrease in breast cancer incidence out to 22 years.

Mechanisms of ERT and combination MPA, +ERT therapy.

The molecular mechanism of action of CEE to trigger apoptosis is summarized Figure 1 and the effect of MPA to neutralize estrogen-induced apoptosis is summarized in Figure 2. The molecular mechanisms on hormonal responses of long-term estrogen-deprived breast cancer have been studied and published in the refereed literature over the past two decades (35-38). The molecular mechanism of MPA to block estrogen-induced apoptosis has emerged with the demonstration that the glucocorticoid properties of MPA suppressed estrogen-induced inflammation critical to trigger apoptosis (39-42). This explains how MPA reverses the reduction of breast cancer incidence by CEE in the WHI.

The Million Women Study (MWS)

The Million Women Study was established to start recruitment between 1996 and 2001. Specific types of HRT were compared and contrasted, but unlike the WHI study where the average age of starting HRT was 63 years, the average age of the MWS was 50. There were several notable conclusions: results for different estrogens or progestin did not influence the incidence of breast cancer, but increased duration of treatment, increased breast cancer. Women who had used HRT but not developed breast cancer had the same relative risk as never users. Only current users of HRT or tibolone had an increased risk of breast cancer (43). However, the most notable deviation between the WHI and the MWS, was that in the WHI there was consistent and prolonged reduction of breast cancer in the WHI with estrogen alone (34) that was not observed in the MWS (43).

In the MWS, estrogen alone was consistently lower at increasing the relative risk of breast cancer compared to current user of HRT (43). These data are consistent with the requirement, discovered in the laboratory, that breast cancer cells need at least five years of an estrogen free environments to create clones that undergo apoptosis with estrogen. Current estrogen users alone never had a lower relative risk of breast cancer compared with never users which contrast dramatically with the WHI (43).

The creation of cellular models of LTED ER positive breast cancer to screen structure function relationships of molecules to treat aromatase resistant breast cancer.

Cheap and effective treatments for breast cancer are essential to prevent the fracture of the family following death from breast cancer. To this end investigators are advancing novel agents to clinical trial.

Clearly the target for estrogen-induced apoptosis is the ER in LTED breast cancer cells. Early structure function studies using estrogen-induced prolactin synthesis in primary cultures of immature mouse pituitary cells (44-49) and cultured breast cancer cells (50, 51) mapped out the ligand-induced functional changes that occur with synthetics molecules that bind to the ER. With the discovery of estrogen-induced apoptosis in LTED breast cancer cells (27, 29, 30, 52) renewed efforts in medicinal chemistry focused on new ligands for clinical applications. One such effort, resulted in the synthesis (52) and identification of candidates (53-56) to be validated in clinical trials. The compound TTC-352 has completed a phase one trial (57). Additionally, estretrol, produced by the fetal liver during pregnancy, is of interest for the treatment of advanced breast cancer (58-60).

Interestingly enough, a recent report (61) of a non-steroidal compound called ErSO demonstrated the strong and cytotoxic activation of the unfolded protein response in wild-type and ER mutant-positive breast cancer cells. Clearly this compound creates a unique conformation in the ErSO receptor complex that kills breast cancer through inappropriate triggering of the unfolded protein response. There is clearly much that remains to be discovered in this novel area of therapeutic research.

Conclusions.

The clinical description (8) and discovery of estrogen-induced apoptosis with further clinical application (7) in two Karnofsky lectures, separated by 38 years, has now provided a mechanistic insight into the adjuvant treatment of breast cancer (62), an insight into the “unexpected” results of the Women’s Health Initiative investigation of estrogen and estrogen/progestin given to women as hormone replacement at the age of 60 vs the Million Women Study of hormone replacement therapies in the general population. The results of the two epidemiological interventional studies were not comparable but instructive about mechanisms of hormone action in the real world if long-term estrogen deprivation occurs at menopause prior to HRT administration of estrogen alone produces a sustained decrease in breast cancer and the addition of medroxyprogesterone acetate not only reverses but increases breast carcinogenesis. Mechanisms are documents in the laboratory (42).

The enormous advances made in the understanding and development of estrogen-induced apoptosis, leads to the idea that if the key triggers of ER-regulated estrogen-induced apoptosis, are deciphered, then new approaches to tumor cell killing could be found by the discovery of novel agents to switch on cancer cell apoptosis without the need for an estrogen receptor trigger.

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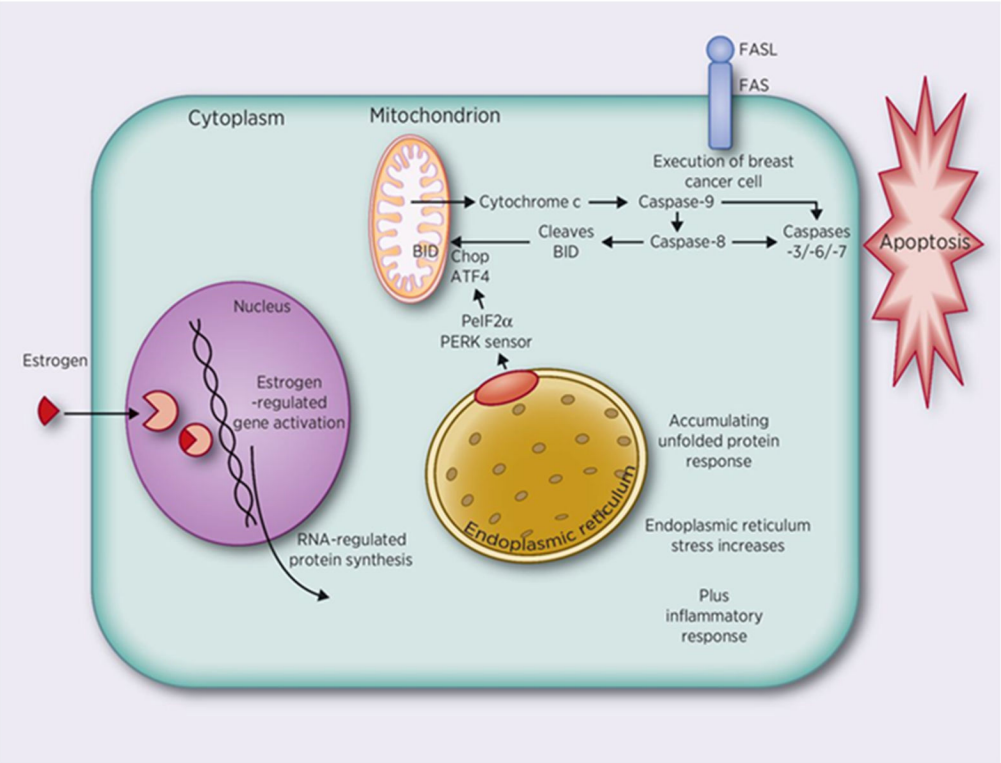

Figure 1.

Under normal circumstances, the ER-responsive breast cancer binds estrogen to increase replication of the cell population. In contrast, during long-term (5 years) estrogen deprivation following menopause, during aromatase inhibitors or SERMs treatment, the breast cancer cell survival mechanisms are reconfigured to favor estrogen-independent growth. Estrogen now binds to the nuclear ER to activate gene-specific mRNA synthesis in the endoplasmic reticulum. However, this overproduction of new proteins creates an UPR that is monitored by the PERK sensor to elevate eukaryotic initiating factor 2 alpha. This event blocks global protein translation. However, the preferential high expression of proteins, for example, activating transcription factor 4 (ATF4) and C/EBP homologous protein enables apoptosis (63). It has been reported (30) that there is an increase in the proapoptotic B-cell lymphoma 2 (BCL-2) proteins (BAX, BAK, and BIM) that in turn disrupt the mitochondrial membrane to allow the translocation of cytochrome C out of the organelle with caspase 9 activation and PARP cleavage. Further experimental details are reported in (30). Global gene expression across time has identified stress responses and massive increases in inflammatory responses to be the trigger for estrogen-induced apoptosis (39). The NF-kB noncanonical pathway was suggested (64) to be essential for cell growth that is closed down by estrogen. This was proven subsequently (41). Finally, cell execution occurs through the FAS/FASL extrinsic pathway (23, 29, 65). Reproduced with permission from (33).

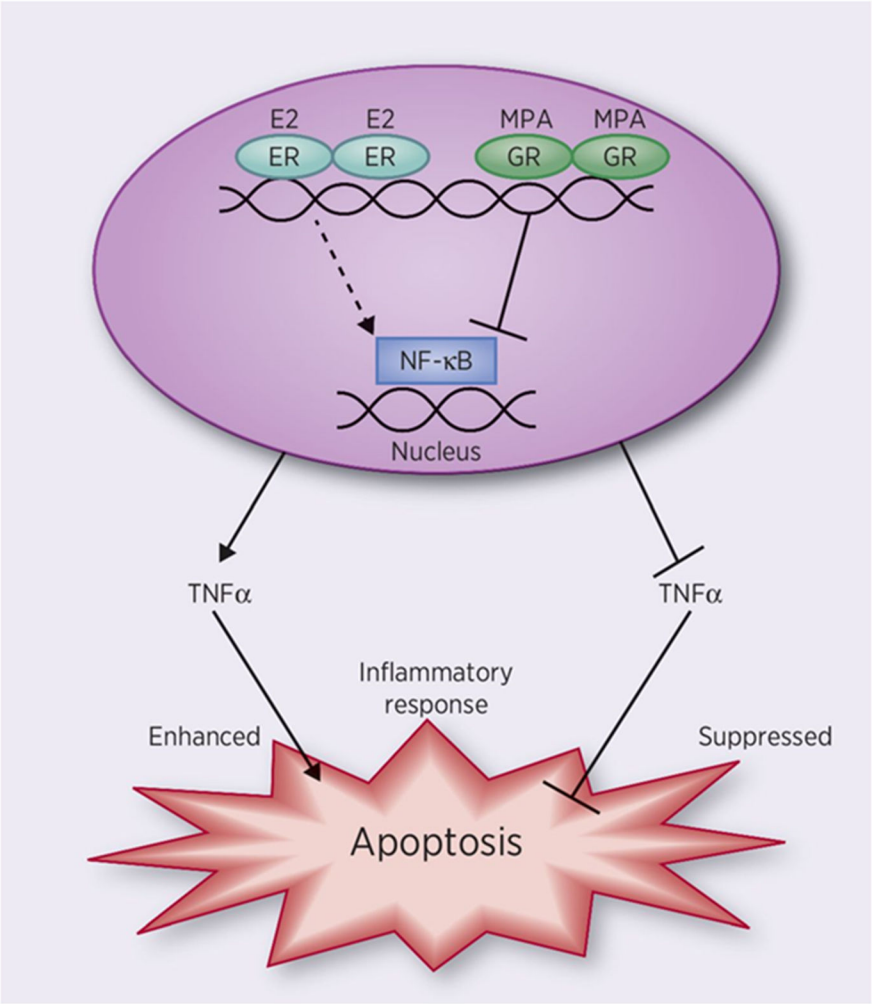

Figure 2.

Estrogen, through PERK, activates lipid metabolism–associated transcription factor CCAAT/enhancer-binding protein beta (c/EBP beta), which is responsible for suppressing NF-kB in LTED MCF7-5C cells. However, NF-kB binding activity increases when E2 treatment is prolonged. The mechanism is to increase STAT3. This enhancement of stress responses results in the release of NF-kB–dependent TNFa. This stress and inflammation response can be blocked by glucocorticoids. MPA (synthetic progestin) is not a pure progestin, but has significant glucocorticoid activity (42). The synthetic progestin, dexamethasone, through the glucocorticoid receptor, prevents stress responses and inflammation by blocking NF-kB DNA-binding activity with a blockade of TNFa production (66). This process blocks apoptosis and breast cancer cells grow. Reproduced with permission from (33).

Table 1.

Objective response rates in postmenopausal women with metastatic breast cancer using high-dose estrogen therapy.

Age since menopause	Numbers of patients	Percentage responding
Postmenopausal		
0–5 years	63	9
>5 years	344	35

Note: A total of 407 patients were classified on the basis of the time from menopause (9).