Introduction

Estrogen Reconsidered: Exploring the Evidence for Estrogen's Benefits and Risks

Avrum Zvi Bluming, MD

There is not enough time to reason out every decision we are obligated to make every minute of every day of every year of our lives. Shortcuts allow us to make many of these decisions quickly, even reflexively, leaving more time for those other decisions, the ones requiring thought and reason. Psychologist Robert Cialdini[1] describes one such shortcut used by the turkey hen, which responds to the *cheep cheep* sound of her chicks. Without that sound, she will not mother them and might even kill them, but she will attempt to mother a natural enemy, a polecat, if the polecat seems to be generating that sound. You have to marvel at the longevity of turkey hens until you realize that creating a *cheep cheep* sound from a polecat is possible only in an artificial environment engineered by human beings.

Like the chirping sound to the turkey hen, the words *breast cancer* trigger an automatic response in most women: Take the shortcut and avoid anything that may give you breast cancer. Of all those "anythings," the leading assumption, the one that generates the most fear, is estrogen. Although we do not yet understand exactly what breast cancer is, accepting the claim that estrogen causes it allows us to reflexively discourage its use in anyone believed to be at increased risk of developing a primary breast tumor or a recurrence after treatment.

In this issue, we will consider the validity of the arguments that estrogen (+/− progestogen) causes breast cancer *in vitro*, in laboratory animals (Santen; Abderrahman) and in humans, the latter most prominently disseminated by the Women's Health Initiative (WHI) (Chlebowski). We will review data on its role in prevention and treatment of breast cancer (Abderrahman; Santen) and the major benefits of estrogen as part of hormone replacement therapy (HRT), including reduction of heart disease and all-cause mortality (Hodis), prevention of hip fracture (Rozenberg), and treatment of the genitourinary syndrome of menopause (Liang). We will present concerns about the widespread use and promotion of compounded bioidentical hormones, including a review of the role of testosterone in the management of menopausal symptoms (Pinkerton) and the pronounced absence of menopause management teaching as part of medical training programs (Faubion). We will offer a form of graphic imaging to communicate the benefits and risks of HRT (Rifkin), discuss the safety of pregnancy following primary breast cancer treatment (Perachino), and report on current data evaluating the risk of HRT administration to breast cancer survivors (Bluming).

Because breast cancer develops 100 times more frequently among women than among men, and because estrogen is primarily responsible for breast development in women, it has long been assumed that estrogen is implicated in the development of female breast cancer (see Santen and Abderrahman for supporting preclinical studies). That belief originated in 1882, when Thomas William Nunn[2] reported the case history of a perimenopausal women with breast cancer, whose disease regressed 6 months after her menstruation ceased. Shortly thereafter, as described by Love and Philips,[3] the German physician Albert Schinzinger[4,5] first proposed oophorectomy both as treatment for advanced breast cancer and as prophylaxis against local recurrence, although he never performed the surgery himself. But in 1895, Beatson[6] performed a bilateral oophorectomy on a woman with extensive soft tissue recurrent breast cancer; the patient had a complete remission and survived for 4 years after the surgery.[6,7] In 1896, Gould[8] reported the case history of another woman going through menopause who experienced a spontaneous remission of her metastatic breast cancer as her estrogen levels declined. Also that year, the English surgeon Boyd[9] performed a bilateral oophorectomy as treatment for a woman with metastatic breast cancer. Years later, he commented that this patient had survived 12 years after her oophorectomy.[10] Boyd[11] championed oophorectomy as an effective, although not curative, treatment and provided summary data in 1900, indicating that 19 (35%) of 54 breast cancer patients clearly benefitted from this approach.

In the ensuing century, prophylactic oophorectomy to prevent breast cancer development yielded inconsistent results. The procedure has been reported as reducing the risk of breast cancer when performed on women with deleterious BRCA1 mutations,[12] although there are conflicting study results

From the University of Southern California, Los Angeles, CA.
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Reprints: Avrum Zvi Bluming, MD, University of Southern California, 25095 Thousand Peaks Road, Calabasas, CA 91302. E-mail: Avrumzbluming@yahoo.com.

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even on this point.[13] Other observations consistent with the concern that estrogen is implicated in the development of female breast cancer include experimental experience with the natural hormone 17β-estradiol in animals; the administration of estradiol to mice and rats, for example, will increase the incidence of mammary and pituitary tumors.[14] As Clemons and Goss[15] asserted, "Estrogens promote the development of mammary cancer in rodents and exert both direct and indirect proliferative effects on cultured breast cancer cells…," but then added: "…although the exact mechanisms of this tumorigenic effect remain to be fully elucidated."

Another often used argument for the role of estrogen in breast cancer risk is that tamoxifen, a selective estrogen receptor (ER) modulator, and aromatase inhibitors, which prevent estrogen production in postmenopausal women, have demonstrated benefit in both preventing and treating breast cancer.

Today, however, the paradigmatic contention that estrogen causes breast cancer and that eliminating estrogen is effective in preventing and treating breast cancer has been challenged by the following findings:

- Postmenopausal women randomized to estrogen alone in the WHI's prospective, randomized, double-blind study were reported to have a persistent 23% reduced risk of breast cancer after 20 years of follow-up[16] and a 40% reduced risk of breast cancer mortality.[17] Among women with no prior HRT exposure (constituting the majority of perimenopausal women taking HRT as part of the study), the WHI reported no increased risk of breast cancer associated even with combination HRT (conjugated equine estrogen [CEE] + medroxyprogesterone acetate [MPA]) administration.[18]
- A full-term pregnancy, which floods the body with both estrogen and progestogen, before age 20 years reduces the risk of subsequent breast cancer by 70%.[19]
- Administration of replacement estrogen to BRCA mutation carriers, oophorectomized to reduce breast cancer risk,[20] does not interfere with the reduced risk.[21–24]
- *In vitro* fertilization, which greatly elevates estrogen levels, does not increase the risk of recurrence among breast cancer survivors.[25,26]
- Pregnancy among breast cancer survivors does not worsen prognosis,[27] even among BRCA mutation carriers and even among those whose breast cancer was ER–positive.[28,29]
- Estrogen has been used successfully to treat breast cancer,[30–38] as has progesterone.[39,40]

The story of tamoxifen offers an instructive case in the complexity of this issue. Tamoxifen was initially labeled an estrogen antagonist or antiestrogen. One of the arguments used to promote the theory that estrogen causes breast cancer is that tamoxifen helps to reduce or retard the growth of ER-positive breast cancer by competitively blocking the binding of estrogen to the ER on breast cancer cells.[41] But several lines of research dispute this as its major mode of action. For one thing, when tamoxifen is given to premenopausal women, their natural estrogen levels increase up to 5-fold.[42] This rise in estrogen should block any competitive binding of tamoxifen, yet tamoxifen's effect against breast cancer works as well in these premenopausal women as in postmenopausal women.[43–45] Second, approximately 40% of ER-positive patients fail to respond to tamoxifen.[46] Third, laboratory studies have shown that tamoxifen inhibits the stimulatory effects of growth factors involved in breast cancer development and progression,[47–50] even in the absence of estrogen.[51] In addition, some breast cancer cells actually acquire the ability to proliferate while under treatment with tamoxifen,[52] and low doses of estrogen have been shown capable of killing them[53–56] and indeed to be beneficial in the treatment of breast cancer that has acquired resistance to tamoxifen.[57] Tamoxifen also has a therapeutic effect on ER-negative breast cancer cells, both in laboratory studies and in human patients,[58] and ER activation has been reported in the absence of estrogen among treated women who develop ER mutations.[59,60] Finally, breast cancer regression has been reported following withdrawal of tamoxifen[61–65] and withdrawal of aromatase inhibitor therapy.[66–70]

In summary, tamoxifen works in a variety of ways that are exclusive of its action on ERs. Because the precise mechanisms responsible for its therapeutic effect remain unknown,[71,72] it seems inadequate to claim that the success of tamoxifen supports the view that estrogen causes breast cancer.

Three articles in this special issue (Abderrahman, Santen, Chlebowski) cite The Collaborative Reanalysis[73] and The Million Women Study[74] to support their contention that HRT increases the risk of breast cancer. Challenges to the validity of the increased breast cancer risk reported in these 2 widely quoted reports are listed in Tables 1 and 2, respectively.

Thomas Kuhn, author of *The Structure of Scientific Revolutions*, observed that in every scientific enterprise, there is a paradigm unquestioningly assumed to be true, which freezes criticism, discourages alternate explanations of a phenomenon, and, therefore, stifles progress. After all, why devote more funds and energy to study a question if we already know the answer? But over time, researchers eventually find what Kuhn called "anomalies" that do not fit the paradigm, and when enough of those anomalies accrue to undermine it, the paradigm collapses. Scientists then cast about for a new paradigm that explains both the old and new facts. Echoing Kuhn in a 1993 article on breast cancer as a case study of dogma in medicine, Samuel Hellman[79] noted: "Although much of medicine is empiric, basing treatment on a single paradigm becomes an extremely powerful force. It simplifies individual treatment decisions without requiring a reconsideration of the pathogenesis in each patient."

In this issue of *The Cancer Journal*, we will highlight the anomalies underlying the paradigm that estrogen causes breast cancer. Estrogen, as it relates to a patient with breast cancer, may stimulate or induce regression of breast cancer cells. Therapeutic manipulations forcing a cancer to adapt or die will most likely prove a more useful paradigm for treatment than simple elimination of estrogen. Marsden and Sacks[80] hypothesized that the response duration to endocrine therapy in women with advanced disease could be prolonged by treatments that alternately lower and increase effective estrogen levels.

Which brings me to the primary research that investigators still cite in support of the idea that HRT causes breast cancer: the WHI. During the 20 years since its initial publication, the WHI investigators have walked back almost all the negative conclusions of their initial press conference on July 7, 2002[81] and the *JAMA* article that was unavailable for another 10 days, eventually released on July 17.[82] That press conference generated international alarm, with women flooding their doctors' offices in a panic.

TABLE 1. The Collaborative Reananalysis (Challenges)

1. Increase in breast cancer risk was found by including only the women who were current users, still on HRT at the time they were interviewed, and who had been on it for 5 or more years. But no increase in breast cancer was observed among women who had taken HRT in the past, no matter how long they had taken it.
2. The reported increase was 0.6 per 100 women taking estrogen for 10 or more years.
3. More than 80% of analyzed subjects were on estrogen (CEE) alone, and yet were reported to have an increased risk of breast cancer—precisely the opposite finding reported by the WHI of the decreased risk.[75]

TABLE 2. The Million Women Study (Challenges)

1. Although called a study, it consisted of only 2 questionnaires, separated by approximately 3 years and sent to a million women, of whom fewer than half (only 44%) responded to both surveys.
2. Total incidence of breast cancer was 1% among estrogen-only users (969/113,206) and 1.4% among estrogen/progestin users (1891/139,596). For every 1000 women taking estrogen alone for 5 years, there would be an extra 1.5 cases of breast cancer. For every 1000 women taking combination estrogen/progestin for 5 years, there would be an extra 6 cases of breast cancer.
3. Of that 1% to 1.4%, the increased risk was identified in only current, but not past, users even if past use had exceeded 15 years.
4. Perimenopausal or postmenopausal women who had never used HRT had significantly reduced risks of breast cancer when compared with premenopausal women. This is a puzzle because the risk of breast cancer is known to increase with age.[76]
5. The authors of The Million Women Study did not discuss the possibility that in a significant number of their identified cases, breast cancer may have been present, but unidentified, before these women joined the study. Women who responded to the original questionnaire may have been aware of a problem in the breast, prompting their participation.[77,78] In support of that interpretation, the average time from joining the study to diagnosis of breast cancer was only 1.2 years; the median time from diagnosis to death from breast cancer was only 1.7 years.

No wonder. The WHI had announced in 2002 and subsequent early articles:

- HRT increased the risk of breast cancer. After almost 20 years of follow-up, they now report that estrogen alone decreases the risk of breast cancer, decreases the risk of death from breast cancer, and decreases the risk of death from all causes.[83]
- HRT "did not have a clinically meaningful effect on health-related quality of life" for women in menopause.[84] They have subsequently reported that it is the most effective treatment for managing menopausal vasomotor symptoms.[85,86]
- HRT increased the risks of cardiac events, strokes, and cognitive decline and that it even increased "all-cause mortality." Those conclusions have been rescinded as well especially when HRT is initiated within 10 years of a woman's final menstrual period.[87]

But on one key point the leading WHI investigators have not changed their belief: that combination HRT increases the risk of developing breast cancer, although not of dying of it. Three arguments they call on to support their conclusion have proved inadequate or faulty. One is that early menarche and late menopause, by increasing a woman's lifetime exposure to estrogen + progestogen, increases the risk of breast cancer. The problems with this claim are that nulliparous women, who avoid the very high levels of endogenous estrogen and progestogen associated with pregnancy, have an increased risk of breast cancer compared with multiparous ones[88]; as already noted, pregnancy before age 20 years decreases the lifetime risk of breast cancer by 70%[19]; and women with a history of progesterone deficiency have a five-fold increased risk of breast cancer.[89]

Second, the WHI investigators continue to claim credit for the rapid fall in rates of invasive breast cancer, attributing that drop to their having scared women off HRT following publication of their first article in 2002. However, the national decline in cases of *invasive* breast cancer began in 1999, after a brief rise from 1995.[90] Based on our current understanding of breast cancer initiation and development,[91] we know that invasive breast cancers take up to 10 years to develop. How could a significant decline have occurred within 6 months of that first *JAMA* article?[92] Dr. Chlebowski was quoted in the *Wall Street Journal* as saying, "There's great benefit to women for stopping [HRT] because the risk [of breast cancer]

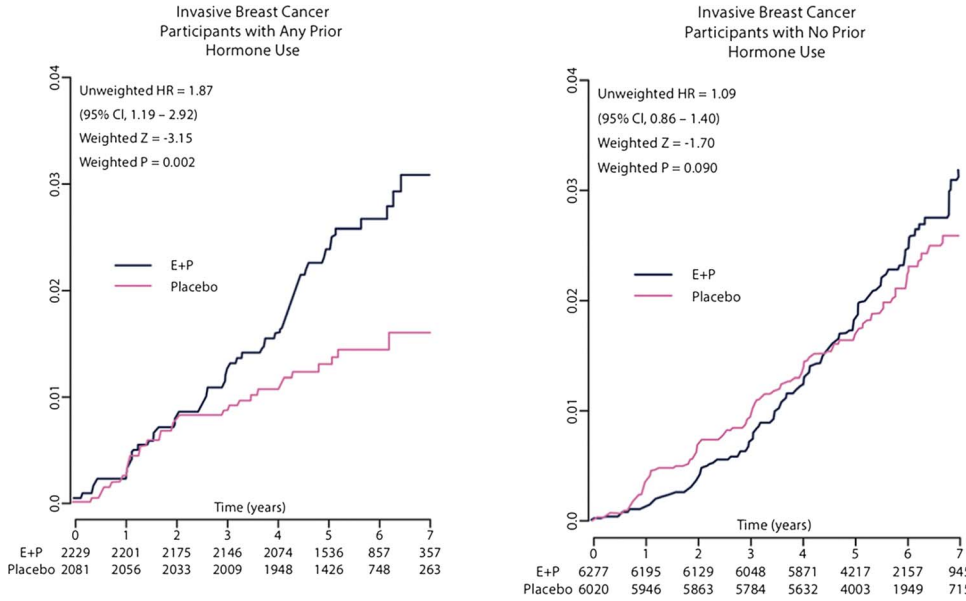

FIGURE 1. Breast cancer incidence in the Women's Health Initiative trial of CEE plus MPA (E + P) versus placebo, stratified by prior use of hormone therapy, showing similar trends for all subgroups except for women with prior hormone therapy use randomized to placebo where breast cancer incidence unexpectedly sharply diverges without explanation. It is the divergence in the trend line for women with prior hormone therapy use randomized to placebo that accounts for the elevated HR for breast cancer, falsely giving the impression that breast cancer incidence was increased in the trial due to CEE plus MPA, where in fact the elevated HR was due to a decreased breast cancer incidence in the placebo-treated group. CI indicates confidence interval.

goes down almost immediately."[93] Yet in his article for this issue, and elsewhere, he maintains that the elevated risk persists for years after cessation of HRT. He has not yet resolved this contradiction.

Third, in addition to citing The Collaborative Reanalysis[73] and The Million Women Study[74] as support for their view, Chlebowski et al. cite a Swedish study by Bergkvist et al.,[94] which reported a 440% increased risk of breast cancer associated with HRT. This finding would indeed be impressive and incontrovertible—if only it were based on impressive numbers. Bergkvist et al.[94] found 10 additional cases of breast cancer when only 2.2 were expected. That is the "440% increased risk," which they extrapolated to apply to the entire population of Sweden. Such statistical shenanigans were criticized over 30 years ago in a *Lancet* editorial[95] and by the Harvard Medical School Letter.[96] These criticisms were known to Dr. Chlebowski, given that he cited them in an article he published in 2012.[92]

I had hoped the WHI investigators would wish to reflect on how the research of the past 20 years—their own and that of many others—has modified or even eliminated the early fears about the dangers of estrogen, on its own or as HRT. In particular, I requested that they address one specific, crucial criticism in their invited manuscript: Hodis and Sarrel's[97] 2018 article challenging the WHI's interpretation of their data purporting to show that combination CEE + MPA increases breast cancer risk (Fig. 1). Take a look at the graph on the left, which seems to show clearly that the HRT group (blue line) had higher rates of invasive breast cancer than the placebo group (red line). But then Hodis and Sarrel[97] noticed something odd about the placebo group: their rates of breast cancer were lower than would have been expected. Why? On closer examination, they saw the reason was that many of them had been on estrogen before entering the study. When women who had taken HRT before being randomized to placebo or to combination HRT were removed from the analysis, there was no longer a significant difference between them in breast cancer risk.

In short, the original control group had lower rates of breast cancer not because they weren't taking HRT, but, possibly, because many of them had been on hormones previously.

Chlebowski, Pan, and Manson read my concerns carefully and respectfully, and after studied reflection, decided to keep their article unmodified. They believe that Hodis and Sarrel's interpretation is wrong, and that they have made their case persuasively. Science teaches us to doubt, basing our medical decisions on the best information available, and changing our minds when new information dictates. As Richard Feynman said: "I can live with doubt and uncertainty. I think it's much more interesting to live not knowing than to have answers which might be wrong." For me, it is time to reject the prevailing paradigm that estrogen +/− progestogen causes breast cancer. Understanding HRT's benefits and risks, as set out in this issue, should, I hope, encourage additional research in the future while, in the present, enhancing our ability to treat the menopausal women under our care.

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