Hormone Replacement Therapy After Breast Cancer It Is Time

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Hormone Replacement Therapy After Breast Cancer
It Is Time

Avrum Zvi Bluming, MD

Abstract: This article reviews the decades of evidence supporting the reproducible benefits of HRT for menopausal symptom control, improved cardiac health, prevention of hip fracture, reduction in the risk and pace of cognitive decline, and enhanced longevity. It quantifies the increased risk of thromboembolism associated with oral, though not transdermal, HRT. It evaluates the repeated claims that HRT is associated with an increased risk of breast cancer development, and, when administered to breast cancer survivors, an increased risk of breast cancer recurrence. Twenty-five studies of HRT after a breast cancer diagnosis, published between 1980 and 2013, are discussed, as are the 20 reviews of those studies published between 1994 and 2021. Only 1 of the 25 studies, the HABITS trial, demonstrated an increased risk of recurrence, which was limited to local or contralateral, and not distant, recurrence. None of the studies, including HABITS, reported increased breast cancer mortality associated with HRT. Even in the HABITS trial, the absolute increase in the number of women who had a recurrence (localized only) associated with HRT administration was 22. It is on the basis of these 22 patients that HRT, with its demonstrated benefits for so many aspects of women's health, is being denied to millions of breast cancer survivors around the world.

Key Words: Breast cancer, breast cancer survivors, hormone replacement therapy, menopause hormone therapy

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The British polymath Dr. Thomas Young died at age 55 years on May 10, 1829. According to his biographer, Andrew Robinson, he was "the last man who knew everything." In 1829, that might nearly have been true, but today a secondary school student has access to information that dwarfs the totality of everything that Dr. Young knew, many times over. Yet, our ability to distill reliable answers from this web of abundant information is often stymied by misleading assumptions and incorrect interpretations. Knowledge is not only a matter of facts, but of their wisest interpretation. As the statistician John Allen Paulos once lamented, "Data, data everywhere but not a thought to think."

The benefits and risks of estrogen therapy (ERT) and estrogen + progestogen (HRT) administration to postmenopausal breast cancer survivors illustrate this problem and require us to rethink beliefs many have held as beyond dispute. Let us begin by reviewing the evidence for the benefits of estrogen for menopausal and postmenopausal women, not only for the familiar symptoms of menopause but also for the most common causes of morbidity and mortality that afflict women in their later years. Let us then consider the risks of offering those benefits of estrogen to women who are survivors of breast cancer—obviously a contentious idea.

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MENOPAUSAL SYMPTOMS

Estrogen therapy/HRT have been reproducibly found to improve quality of life in the 80% of women who experience perimenopausal and postmenopausal symptoms, which could include hot flushes, night sweats, insomnia, difficulty concentrating, decreasing recent memory, bladder/urinary discomfort, frequent urinary tract infections, mood swings, arthralgias, and palpitations and which will last a median of 7.4 years.[1] Estrogen therapy/HRT are the most effective treatments for these symptoms, relieving most of them in the great majority of treated patients. Nothing else comes close.[2] And yet, as a result of widely circulated misinformation stemming largely from the Women's Health Initiative (WHI) in 2002,[3] these treatments are not widely used even among eligible women with no history of treated breast cancer. Indeed, in 2020, the British Medical Association published a report showing that a third of female general practitioners were considering cutting back their working hours or retiring prematurely due to untreated menopausal symptoms.[4]

HEART DISEASE

The number of American women who die of heart disease annually, approximately 300,000, is more than 7 times the number who die of breast cancer.[5,6] Not widely appreciated is the finding that in every decade of life older than 40 years, more women die of heart disease than die of breast cancer.[7,8] Given that the cure rate for newly diagnosed breast cancer is currently approximately 90%, breast cancer survivors are at far greater risk of dying of heart disease than of breast cancer,[9] a difference that grows as they age. Repeated studies have found that estrogen decreases the risk of heart disease by 40% to 50%[10,11]—more reliably than statins.[12–16]

HIP FRACTURE

The number of American women who die during the first year following a hip fracture is similar to the number who die each year due to breast cancer,[17,18] and this is not as a result of whatever illness was responsible for the hip fracture.[19,20] Calcium and vitamin D administered to postmenopausal women not on HRT do not decrease the risk of these fractures,[21] but estrogen does; it decreases the risk of hip fracture by 30% to 50%. Long-term HRT is more effective than bisphosphonates (like pamidronate disodium [Aredia], zoledronate [Zometa], or denosumab [Prolia]) in preventing femoral fractures.[22]

ALZHEIMER DISEASE AND DEMENTIAS

Alzheimer disease annually affects twice as many women as does breast cancer, but the cure rate for Alzheimer disease is 0%. While research scientists are looking at clues that might help prevent or treat Alzheimer disease, none has yet yielded promising clinical results.[23] Admittedly, it is difficult to measure and trace the course of dementia, let alone to conduct randomized controlled

trials, but the most effective available preventive therapy for dementia is estrogen. A series of uncontrolled studies has demonstrated a 45% to 70% decreased risk,[24–32] although this conclusion is not supported by all studies.[33]

OTHER DISEASES

Postmenopausal estrogen has been reported to reduce the risk of colon cancer[34–39] and to improve the prognosis for women diagnosed with colon cancer.[40–44] It has also been reported to reduce the risk of developing diabetes.[45,46]

LONGEVITY

Largely because of estrogen's benefits on heart, bone, and brain, women taking estrogen have been projected to live an additional 3 to 4 years compared with those who do not take it.[47–49] Even the WHI reported, as early as 2012, that women randomized to postmenopausal estrogen were less likely to die of breast cancer —and less likely to die of all causes after a breast cancer diagnosis —than women taking a placebo.[50]

WHAT ARE THE RISKS?

Estrogen replacement therapy does have a twofold increased risk of venous thrombosis and, more seriously, of pulmonary embolism, a risk similar to that of oral contraceptives. "Twofold" sounds alarming and indeed is a primary reason that a position paper on HRT published by the US Preventive Services Task Force concluded that the risks of HRT for menopausal and postmenopausal women outweigh the benefits.[51] What are the absolute numbers? The baseline risk of pulmonary embolism in women aged 50 to 60 years is approximately 10 to 20 events/100,000 woman-years; thus, with HRT, the 2-fold increase may result in 40 events/100,000 woman-years. This is lower than the rate in normal pregnancy, which is approximately 60/100,000 women years. Moreover, most embolic events occur within the first year of HRT administration and decrease thereafter.[52] Clinical studies suggest that this risk is not increased among women receiving transdermal estrogen.[53,54]

These statistics apply to women who have never had breast cancer. But given the clear benefits of estrogen in so many health domains, especially those that affect quality of life and longevity, how shall we think about treating breast cancer survivors, so many of whom are thrown into debilitating symptoms of menopause usually due to chemotherapy?

Every year, 2.3 million women are diagnosed with breast cancer throughout the world[55]; 330,840 of them among American women.[56] A projected 90% cure rate would result in approximately 300,000 women added each year to the existing number of breast cancer survivors. Should we continue to deny them the benefits of ERT? Is it time to replace the categorical refusal of many physicians to consider ERT for their patients who have survived breast cancer?

Before publication of the WHI's conclusions, investigators were not only open to the question but also thought the time had come to consider estrogen for breast cancer survivors. In a 1993 editorial in *Lancet*, Lobo[57] wrote: "There may be a place for estrogen in women who have been treated for breast cancer. For a definitive clinical trial, the time is now." In a Special Communication from the Eastern Cooperative Oncology Group, published in 1994, Cobleigh et al.[58] concluded: "We believe it is time for a change and the time is right to study the effects of ERT in breast cancer survivors." They continued: "Clinical trials of ERT in breast cancer survivors have been hindered in part by the maxim *primum non nocere* (first do no harm). In light of the lack of evidence of a detrimental effect of ERT in breast cancer survivors and in light of the potential positive effects of ERT on the health of women, we suggest a new maxim, *primum certior fi, tunc mone* (first understand, then advise)."[58]

And in 2002, shortly before the WHI's first reports, Ylikorkala and Metsä-Heikkilä,[59] gynecological researchers at Helsinki University Central Hospital observed that because the number of women surviving breast cancer has been increasing steadily, health professionals need to face the issue of how best to treat their symptoms of menopause and improve their health in general. The "categorical refusal [to prescribe HRT] is a double-edged sword," they wrote, "because it also denies these women all the indisputable health benefits HRT provides… This refusal is not, however, supported by the observational data available so far on this question, because HRT has not increased the risk for breast cancer recurrence."[59]

Even after the WHI, some physicians concurred. Writing for the Council of the Society of Obstetricians and Gynecologists of Canada in 2004, Robert Lea stated: "HRT after treatment of breast cancer has not been demonstrated to have an adverse impact on recurrence and mortality. HRT is an option in postmenopausal women with previously treated breast cancer. Prospective, randomized clinical trial results are needed."[60]

Regrettably, the WHI's claims of HRT's purported dangers largely shut these trials down. To date, 25 studies of this important question have been published between 1980 and 2013.[61–88] These are listed in Table 1.

Of these, 5 reported *fewer* breast cancer events among those survivors receiving HRT,[62,65,78,80,87] and 4 reported *reduced* mortality from breast cancer.[62,73,78,80] Four of the 5 prospectively randomized trials—those of Palshof et al[62] and Marsden et al[74] and Vassilopoulou-Sellin et al[79] and the Stockholm Study[86]—reported *no* increase in breast cancer events among survivors randomized to HRT. In the Stockholm trial, the 10-year follow-up report identified an increased risk of contralateral cancer (14 of 188 = 7% vs 4 of 190 = 2%) with no significant overall increase in breast cancer events, distant metastases, or mortality.[86]

Thus, of the 25 studies, only one, the HABITS study, the fourth prospectively randomized one,[83,84] reported an increased risk of breast cancer events following the administration of HRT to breast cancer survivors. This is the one that has gotten all the attention, so physicians should consider its findings closely.

The HABITS trial was prematurely terminated on December 17, 2003, after only 2 years of median follow-up and after only 434 women of the proposed 1300 had been enrolled. The reason for the sudden termination, according to the initial paper, was the disproportionate number of women randomized to HRT who developed another breast cancer (26 of 174 = 15%), compared with only 7 of the 171 (5%) randomized to no HRT.[83] The increase was seen only as local recurrences or contralateral tumors. There was no increase in the development of distant metastases, nor was there an increase in the risk of death. Further, there was no increase among women randomized to estrogen alone; there was no increase when Premarin (conjugated estrogens) was used as the source of estrogen; there was no increase among women who had been initially diagnosed with lymph node involvement, and the increase was noted only among women who were taking tamoxifen in conjunction with HRT. In the contemporaneous Stockholm study, a larger percentage of women randomized to HRT were also taking tamoxifen (52% vs 34%) but that study reported no increase in breast cancer events.[85,86] It is particularly noteworthy that the HABITS study, which ultimately reported an increase of only local or contralateral recurrence among patients randomized to HRT, required no baseline breast imaging, such as a mammogram, prior to entry. Participating patients were recruited from more than 10 different institutions; the HRT regimen was determined by the individual treating

TABLE 1. Summary of 25 Studies of Breast Cancer Survivors Given HRT

Authors	Year	Study Type	No. on HRT/No. Controls	Median Duration of HRT/Range, y	Median Duration of Follow-up, y	Results	Reference
1a. Palshof et al.	1980	**Prospective randomized**	37/95	2	3	**Reduced recurrence***	61
1b. Palshof et al.	1985	Updates of the original study	51/103	2	6.5	**Reduced recurrence** **Reduced mortality**	62
2. Stoll and Parbhoo	1988	Prospective single-arm	14/	0.25–0.5	2	No recurrence	63
3. Powles et al.	1993	Retrospective observational	35/	1.2/0.1–3.7	3.6	2 of 35 developed recurrence No breast cancer deaths	64
4. Eden et al.	1995	Retrospective case-control	90/811	1.5/0.25–12	3	**Reduced recurrence**	65
5. Vassilopoulou-Sellin et al. (feasibility study)	1997	Prospective single-arm	43/	2.6/2–12	12	1 of 43 developed recurrence No breast cancer deaths	66
6. Dew et al.	1998	Retrospective cohort	167/1305	1.6/0.25–22	4	No difference†	67
7. Espie et al.	1999	Retrospective cohort	120/240	2.4/1–10.6	2.4	No difference	68
8. Guidozzi	1999	Prospective single-arm	20/	2.7/2–3.7	5.7	No recurrence	69
9. Natrajan et al.	1999	Retrospective cohort	50/26	5.5/0.5–32	7	No difference	70
10. Uršič-Vrščaj and Bebar	1999	Prospective cohort	21/42	2.3/0.25–6	2.3	No difference	71
11. Vassilopoulou-Sellin et al.	1999	Prospective cohort	39/280	4/2–6	3.8	No difference	72
12. Disaia et al.	2000	Retrospective cohort	125/362	1.8/0.1–30		**Reduced mortality**	73
13. Marsden et al.	2000	**Prospective randomized**	51/49	0.5		No difference	74
14. Peters et al.	2001	Prospective cohort	56/551	6.4/1–20.9	12.8	No difference	75
15. Marttunen et al.	2001	Prospective cohort	88/43	2.6	2.6	No difference	76
16. Beckmann et al.	2001	Retrospective cohort	64/121	3.5/3	5	No difference	77
17. O'Meara et al.	2001	Retrospective case-control	174/695	1.25	4.6	**Reduced recurrence** **Reduced mortality**	78
18. Vassilopoulou-Sellin et al.	2002	**Prospective randomized**	56/243	5	6	No difference	79
19. Durna et al.	2002	Retrospective observational	286/836	1.75/0.17–34	6	**Reduced recurrence** **Reduced mortality**	80
20. Decker et al.	2003	Prospective cohort	277/554		3.7	No difference	81
21. Gorins et al.	2003	Prospective cohort	230/	2.5		No difference	82
22a. Holmberg and Anderson (HABITS)	2004	**Prospective randomized**	174/171	2	2.1	**Increased risk of local or contralateral tumors only** **No increased risk of metastases or death**	83
22b. Holmberg et al. (HABITS)	2008	Updates of the original study	221/221	2	5	**No increased mortality**	84
23a. von Schoultz and Rutqvist (Stockholm)	2005	**Prospective randomized**	175/184	4.1/0.2–7	4.1	No difference	85
23b. Fahlén et al. (Stockholm)	2013	Updates of the original study	188/190	2.6	10.8	No difference	86
24. Bluming	2008	Prospective cohort	117/63	7.5/1–15	7.5	**Reduced recurrence**	87
25. Figueiredo et al.	2008	Retrospective case-control	708/1399			No difference	88

Boldface is employed to identify the prospective randomized trials and to identify significant positive or negative findings.

*Reduced recurrence = breast cancer survivors given HRT had *fewer* recurrences of breast cancer, or *lower* risk of death, than control group not on HRT.

†No difference in recurrence of breast cancer between survivors on HRT and the controls.

physicians, and because the final analysis was based on the intent-to-treat principle, 11 of the randomized HRT patient population did not take HRT, and 43 of those on the no-HRT arm did.

In a 2004 response to a letter to the editor in *Lancet*, Dr. Lars Holmberg,[89] principal investigator of the HABITS study, was appropriately cautious in defending the decision to stop the study prematurely. He wrote: "We agree that the results of a single randomized study should be interpreted cautiously, especially when the study is terminated early. We… have not claimed to say 'the final word.'" He added: "The HABITS study was designed to study safety. Thus, the side effect of new breast cancer events is a highly relevant endpoint." However, he continued, "mortality will also become a very important endpoint in a longer follow-up."[89] And in that longer follow-up, published in 2008, mortality was, in fact, not increased.[84] In this latter HABITS report, with a median follow-up of 4 years, 39 of 221 breast cancer survivors (18%) randomized to HRT experienced a new breast cancer event, compared with 17 of 221 (8%) randomized to no HRT. It is primarily on the basis of this difference between 39 and 17 (a total of 22 patients) that HRT is being denied to millions of breast cancer survivors around the world. Interestingly, the 2008 HABITS article amended the explanation for prematurely stopping the study, this time stating that the reason was due to reports from the WHI and the Million Women Study that hormone therapy increases the risk of breast cancer among healthy women.[84]

In addition to the 25 reported individual studies, 20 review articles, published between 1994 and 2021, have dealt with this question. Their results are summarized in Table 2.[59,90–108]

In all these reviews, the HABITS study was the only one cited as finding an increased risk of recurrence with HRT use among breast cancer survivors. But a striking feature in several of these reviews is that some authors, apparently already convinced that HRT is harmful, misinterpret their own data. An example is found in the 2005 review by Col et al.[98] In the discussion section, Col et al. comment on "the sharp increase in risk [of breast cancer recurrence] observed even after short-term HT use in randomized trials," and they note that "the increase in risk pertained to distant as well as local recurrences." This claim references only the O'Meara study, a retrospective case-control study, but it is not at all what O'Meara actually found. The O'Meara article concluded: "We observed lower risks of recurrence and mortality in women who used HRT after breast cancer diagnosis than in women who did not… the results suggest that HRT after breast cancer has no adverse impact on recurrence and mortality."[78] As already noted, the HABITS trial reported no increase in distant recurrence associated with HRT.[83,84]

Similarly, in the 2020 article by Deli et al.,[106] the authors, who conclude that HRT is "disadvantageous and thus contraindicated" in breast cancer survivors, incorrectly report that the Stockholm trial found that HRT users had an increased risk of breast cancer recurrence compared with nonusers. But the Stockholm trial report clearly stated that "After 10.8 years of follow-up, there was no difference in new breast cancer events" and "there was no overall risk for breast cancer recurrence."*[86] In addition, the article by Deli et al.[106] incorrectly imputes "increased mortality" associated with longer periods of HRT in the HABITS,[84] Stockholm,[86] and Decker and colleagues'[81] trials. Wrong. The HABITS trial concluded that "there was no convincing evidence for a higher breast cancer mortality associated with HT exposure."[83,84] The Stockholm trial reported "no increased mortality from breast cancer or other causes from HRT."[85,86] And Decker et al.[81] wrote: "ERT relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional, or systemic metastases." In fact, they said, "Overall survival favored the ERT group."[81]

In the most recently published review of this subject, Poggio et al.[108] concluded that "use of HRT was associated with a detrimental prognostic effect in breast cancer survivors." But their review offers no new information. To reach their misleading conclusion, they selected 2 of the previously reported prospective randomized trials[84,86] and included a publication that combined a prospective cohort study with a prospective, randomized one.[79] They omitted one previously reported prospective, randomized trial from their analysis.[74] An increased recurrence was identified in only 1 of the 3 selected studies, the frequently cited HABITS trial,[84] and upon meta-analysis of these 3 studies, no significant difference in recurrence was noted when HRT patients were compared with controls. Only when the authors added another prospectively randomized trial into their meta-analysis,[109] which constituted 78% of the total 3995 patients analyzed from all 4 studies, were they able to report an observed increased recurrence rate. But that additional study did not investigate the role of estrogen but of tibolone, a compound that is not available in the United States and that has no reported estrogenic effect on breast tissue or endometrium.[110] Their conclusion is thus misleading, and their analysis adds nothing of value to the already contentious discussion of this complex issue.

In short, what we see here is the power of a paradigm and how it can blind us to disconfirming evidence. Neither estrogen alone nor estrogen and progestogen provide a sufficient condition to cause breast cancer, which develops most frequently during periods of hormonal transitions and which often responds to alterations in hormonal milieu. None of the 25 original studies provides a definitive answer to the safety of administering HRT to breast cancer survivors, and the conclusions of all are challengeable. The most serious challenges to the totality of reported studies are the short (2.5 years) median duration of HRT despite a range of 0.25 to 34 years and a median follow-up of only 5 years with a duration range of 2 to 34 years. Quantum physicist Carlo Rovelli once observed that "The search for knowledge is not nourished by certainty … It is precisely the openness of science, its constant putting of current knowledge in question, that guarantees that the answers it offers are the best so far available."

In the search for an appropriate and customized balance of benefit versus risk when dealing with the administration of HRT to breast cancer survivors, the results of the Suppression of Ovarian Function Trial (SOFT) are relevant. SOFT found no significant difference in recurrence rate when premenopausal breast cancer survivors were randomized to receive either tamoxifen alone or tamoxifen plus ovarian function suppression (OFS) for 5 years.[111] In a follow-up article, among the 1353 patients who did not receive chemotherapy, the overall 8-year freedom from distant recurrence was 98.5% (98% for tamoxifen alone, 98.3% for tamoxifen plus OFS, and 99.3% for exemestane plus OFS).[112] The investigators concluded: "Given the impact on patients' quality of life from escalating endocrine therapy, clinicians need to weigh the risk of recurrence and the expected absolute improvement in disease outcomes carefully against the added adverse effects." This recommendation was supported by Steven Vogl[113] in his critical assessment of adjuvant ovarian suppression for resected breast cancer. Vogl argued that "overall survival is the definitive endpoint" and that SOFT did not include in their analyses deaths that occurred in their treated population in the absence of distant breast cancer recurrence. "The severity of life-long 'off target' toxicities," he wrote, including non–breast cancer deaths, "argues that we should require a benefit in overall survival that is both large and durable to justify the toxicities

*As noted, the Stockholm study did claim to find "a significant increase of contralateral breast cancer in the HRT group (14/188 compared with 4/190)."[86] But this finding resulted from retrospective substratification, a statistically inappropriate way of trying to eke out a finding when a main hypothesis has not been supported.

TABLE 2. Published Review Articles on HRT Administration to Breast Cancer Survivors

Authors	Year	Study Type	No. Survivors on HRT/No. Controls	Results	Reference
1. Sands et al.	1994	Review of 5 studies	277/not presented	No difference	90
2. Chlebowski and McTiernan	1999	Review of 7 studies	Not presented	No difference	91
3. Col et al.	2001	Review of 11 studies	214/623	No difference	92
4. Meurer and Lena	2002	Meta-analysis of 10 studies (9 cohort and 1 prospectively randomized)	717/2545	**Reduced mortality**	93
5. Ylikorkala and Metsä-Heikkilä	2002	Review of 9 studies	590/978	No difference	59
6. Del Priore and Hatami	2003	Review of 3 studies	Not presented	No difference	94
7. Batur et al.	2004	Review of 15 studies	1416/1998	**Reduced recurrence** **Reduced cancer related mortality**	95
8. Lea et al.	2004	Review of 8 studies	1643/5048	No difference	96
9. Levgur	2004	Review of 11 studies (2 prospectively randomized)	830/3640	No difference	97
10. Col et al.	2005	Meta-analysis of 10 studies (2 random and 8 observational)	1316/2839	No difference except for HABITS Misquotes O'Meara study	98
11. Creasman	2005	Review of 19 studies	1134/3981	No difference except for HABITS	99
12. Xydakis et al.	2006	Review of 7 studies	720/1122	No difference except for HABITS	100
13. Antoine et al.	2007	Review of 10 prospective and 2 randomized studies (HABITS and Stockholm)	Not presented	2 reported reduced recurrence 2 reported reduced BC mortality 1 reported increased recurrence (HABITS)	101
14. Mueck et al.	2007	Review of 15 studies (4 prospective randomized and 15 observational)	976/not presented	No difference except for HABITS	102
15. Liotta and Escobar	2011	Meta-analysis of 10 studies (8 observational and 2 randomized)	1316/2839	No difference except for HABITS	103
16. Garrido Oyarzún and Castelo-Branco	2017	Review of 12 studies	1384/2401	No difference except for HABITS (and Tibolone study (1556/1542)	104
17. Wang et al.	2018	Review of 4 studies, but one omitted	173/1627	**Reduced recurrence** (for women aged ≥50 y) **Reduced mortality** (for all subjects)	105
18. Deli et al.	2020	Review of 9 studies	Not presented	No difference except for HABITS But misstates results of HABITS, Stockholm, Decker regarding mortality	106
19. Ugras and Layeequr Rahman	2021	Review of 11 studies	2083/not presented	No difference except for HABITS	107
20. Poggio et al.	2021	Review of 4 studies		No difference except for HABITS (and Tibolone study)	108

Boldface is employed to identify the prospective randomized trials and to identify significant positive or negative findings.

and risks of both OFS alone and especially with an aromatase inhibitor."[113]

Finally, the reluctance to prescribe estrogen to symptomatic postmenopausal breast cancer survivors who are being treated with adjuvant tamoxifen requires an explanation in light of 2 important findings. First, tamoxifen induces a rise in circulating estradiol levels in the majority of treated premenopausal women.[114] In 1999, Craig Jordan reported that in premenopausal women, treatment with tamoxifen produces a clear-cut antitumor action despite a huge overcompensation in the production of estrogen. He concluded that in postmenopausal women, adding a small amount of estrogen "is really of no consequence with respect to safety" in light of the "huge amount of estrogen circulating endogenously in premenopausal women receiving tamoxifen."[115] Second, only a 2% to 7% absolute improvement in freedom from recurrence was reported when an adjuvant aromatase inhibitor was compared with tamoxifen in an environment of suppressed or absent ovarian function.[116–118]

Taken together with the finding that pregnancy subsequent to treated breast cancer, even ER^+ breast cancer[119] and even among those with germline BRCA mutations,[120] did not affect prognosis, what is the objection to administering ERT together with tamoxifen to perimenopausal and postmenopausal breast cancer survivors to treat incapacitating menopausal symptoms?

It is probable that no study in the future will provide the definitive answer we would all find convincing. But the fact that only 1 of the 25 studies found an increased risk of recurrence (local only)—without an increased risk of systemic recurrence or mortality[83,84]—could help us formulate a current, albeit tentative, assessment of risk and provide guidelines for how best to manage this question at our present state of knowledge. There are 2 strategies to aid researchers and clinicians approaching this challenge.

The first was suggested in 2012 by Dr. Holmberg and Anderson,[89] who proposed using national cancer registries to support clinical cancer research. This appears to offer a practical method for data collection and analysis to answer the question about the safety of this option, while offering HRT to informed patients. (Possible countries for such targeted data collection include countries with nationalized health care such as Sweden, Israel, England, and China.) In 2001, Bush et al.[121] described the benefit of this approach in a related situation, noting that "over 25 years ago, epidemiologic studies identified and subsequently confirmed that unopposed estrogen replacement therapy was associated with an increased risk of endometrial carcinoma. Despite the absence of data from clinical trials, this association has been acknowledged as causal by the medical community, in large part because it is consistent among studies, relatively strong, and more apparent at increased doses and longer duration."[121] Hernán,[122] of Harvard's T. H. Chan School of Public Health, noted in his review of carefully collected and interpreted observational data that "we cannot conduct enough target trials to answer all causal questions… and trials may take years to complete." He concluded that "Determining the effectiveness and safety of many health interventions will continue to rely on observational data because randomized trials are not always feasible, ethical, or timely."[122] The second strategy would be to offer the option of HRT to interested and informed survivors of breast cancer while prospectively collecting data from individual responsible physicians. Toward that end, an informed consent form, initially composed in 1992 with the help of Ruth Macklin, professor of Bioethics at Albert Einstein College of Medicine and an ethics consultant for the Food and Drug Administration, has been updated. This consent form is available in the online Appendix (http://links.lww.com/PPO/A37), along with a quality of life questionnaire and a serial data collection form from the author. This approach has been endorsed by Food and Drug Administration Commissioner Janet Woodcock et al.[123]; I would suggest these forms be reviewed and amended by the American Society of Clinical Oncology to be used for US data collection and by comparable organizations around the world in a continuing effort to learn more about the benefits and risks of administering HRT to breast cancer survivors. In support of this approach, the recent adoption of Patient-Generated Health Data in Oncology is a welcome sign of increasing patient-physician collaboration in health care planning and delivery.[124]

Psychologists have amply documented the human difficulty of changing our minds when the evidence says it is time to do so. The challenge for physicians is to recognize when we are stuck in an outdated paradigm, admit it, and move ahead.

ADDENDUM

Of the 25 studies reporting the risk of HRT administered to breast cancer survivors, 17, including HABITS, listed those with positive estrogen receptor assays.[62,65–67,69–72,75–79,82,84,86,88] None of those reports identified an increased risk of breast cancer recurrence associated with a positive receptor assay.

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