

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

(*Cancer J* 2022;28: 183–190)

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.

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 flashes, 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 for 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

From the Department of Medicine, University of Southern California, Los Angeles, CA.

The author has disclosed that he has no significant relationships with, or financial interest in, any commercial companies pertaining to this article.

Reprints: Avrum Zvi Bluming, MD, University of Southern California, 25095 Thousand Peaks Road, Calabasas, CA 91302.

E-mail: avrumzbluming@yahoo.com.

Supplemental digital contents are available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.journalppo.com).

Copyright © 2022 Wolters Kluwer Health, Inc. All rights reserved.

ISSN: 1528-9117

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.^{40–43} 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 woman 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 world⁵⁵; 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*, Lobo⁵⁷ 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.^{61–85} 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 Study⁸⁶—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. Blumling	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 colleagues⁸¹ 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 Vogl¹¹³ 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 cancer¹¹⁹ 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.

ACKNOWLEDGMENTS

The authors thank Dr. Carol Tavris for her many suggestions and critical editing and research librarian, Pamela Gay, for rapidly supplying full-text articles whenever requested.

REFERENCES

1. Avis NE, Crawford SL, Greendale G, et al. Duration of menopausal vasomotor symptoms after the menopause transition. *JAMA Intern Med.* 2015; 175:531–539.

2. Pines A. Guidelines and recommendations on hormone therapy in the menopause. *J Midlife Health.* 2010;1:41–42.
3. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288:321–333.
4. British Medical Association. Challenging the culture on menopause for working doctors. 2020. Available at: <https://www.bma.org.uk/media/2913/bma-challenging-the-culture-on-menopause-for-working-doctors-report-aug-2020.pdf>.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin.* 2018;68:7–30.
6. Cushman M, Shay CM, Howard VJ, et al. Ten-year differences in women's awareness related to coronary heart disease: results of the 2019 American Heart Association National Survey: a special report from the American Heart Association. *Circulation.* 2021;143:e239–e248.
7. Assessing the odds. *Lancet.* 1997;350:1563.
8. Berkman A, F Cole B, ADES PA, et al. Racial differences in breast cancer, cardiovascular disease, and all-cause mortality among women with ductal carcinoma in situ of the breast. *Breast Cancer Res Treat.* 2014;148:407–413.
9. Mehta LS, Watson KE, Barac A, et al. Cardiovascular disease and breast cancer: where these entities intersect: a scientific statement from the American Heart Association. *Circulation.* 2018;137:e30–e66.
10. Schierbeck LL, Rejnmark L, Tofteng CL, et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomised trial. *BMJ.* 2021;345:e6409.
11. Manson JE, Chlebowski RT, Stefanick ML, et al. Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials. *JAMA.* 2013; 310:1353–1368.
12. Kendrick M. Should women be offered cholesterol lowering drugs to prevent cardiovascular disease? No. *BMJ.* 2007;334:983.
13. Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA.* 2004;291:2243–2252.
14. Brugs JJ, Yetgin T, Hoeks SE, et al. The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials. *BMJ.* 2009;338:b2376.
15. Petretta M, Costanzo P, Perrone-Filardi P, et al. Impact of gender in primary prevention of coronary heart disease with statin therapy: a meta-analysis. *Int J Cardiol.* 2010;138:25–31.
16. Yusuf S, Bosch J, Dagenais G, et al. Cholesterol lowering in intermediate-risk persons without cardiovascular disease. *N Engl J Med.* 2016;374:20212–20231.
17. Wilson JF. New treatments for growing scourge of brittle bones. *Ann Intern Med.* 2004;140:153–156.
18. Brauer CA, Coca-Perrillon M, Cutler DM, et al. Incidence and mortality of hip fractures in the United States. *JAMA.* 2009;302:1573–1579.
19. Vestergaard P, Rejnmark L, Mosekilde L. Increased mortality in patients with a hip fracture—effect of pre-morbid conditions and post-fracture complications. *Osteoporos Int.* 2007;18:1583–1593.
20. Vestergaard P, Rejnmark L, Mosekilde L. Loss of life years after a hip fracture: effects of age and sex. *Acta Orthop.* 2009;80:525–530.
21. Zhao JG, Zeng XT, Wang J, et al. Association between calcium or vitamin D supplementation and fracture incidence in community-dwelling older adults: a systematic review and meta-analysis. *JAMA.* 2017;318:2466–2482.
22. Langer RD, Simon JA, Pines A, et al. Menopausal hormone therapy for primary prevention: why the USPSTF is wrong. *Climacteric.* 2017;20:402–413.
23. Schneider LS, Mangialasche F, Andreassen N, et al. Clinical trials and late-stage drug development for Alzheimer's disease: an appraisal from 1984 to 2014. *J Intern Med.* 2014;275:251–283.
24. Kampen DL, Sherwin BB. Estrogen use and verbal memory in healthy postmenopausal women. *Obstet Gynecol.* 1994;83:979–983.
25. Paganini-Hill A, Henderson VW. Estrogen replacement therapy and risk of Alzheimer disease. *Arch Intern Med.* 1996;156:2213–2217.
26. Tang MX, Jacobs D, Stern Y, et al. Effect of oestrogen during menopause on risk and age at onset of Alzheimer's disease. *Lancet.* 1996;348:429–432.
27. Rice MM, Graves AB, McCurry SM, et al. Estrogen replacement therapy and cognitive function in postmenopausal women without dementia. *Am J Med.* 1997;103:26–35S.

28. Jacobs DM, Tang MX, Stern Y, et al. Cognitive function in nondemented older women who took estrogen after menopause. *Neurology*. 1998;50:368–373.
29. Baldereschi M, Di Carlo A, Lepore V, et al. Estrogen-replacement therapy and Alzheimer's disease in the Italian Longitudinal Study on Aging. *Neurology*. 1998;50:996–1002.
30. LeBlanc ES, Janowsky J, Chan BK, et al. Hormone replacement therapy and cognition: systematic review and meta-analysis. *JAMA*. 2001;285:1489–1499.
31. Bagger YZ, Tanko LB, Alexandersen P, et al, For the PERF study group. Early postmenopausal hormone therapy may prevent cognitive impairment later in life. *Menopause*. 2005;12:12–17.
32. Matyi JM, Rattinger GB, Schwartz S, et al. Lifetime estrogen exposure and cognition in late life: the Cache County study. *Menopause*. 2019;26:136–174.
33. Gleason CE, Dowling NM, Wharton W, et al. Effects of hormone therapy on cognition and mood in recently postmenopausal women: findings from the randomized, controlled KEEPS-cognitive and affective study. *PLoS Med*. 2015;12:e1001833.
34. Newcomb PA, Storer BE. Postmenopausal hormone use and risk of large-bowel cancer. *J Natl Cancer Inst*. 1995;87:1067–1071.
35. Grodstein F, Martinez ME, Platz EA, et al. Postmenopausal hormone use and risk for colorectal cancer and adenoma. *Ann Intern Med*. 1998;128:705–720.
36. Hildebrand JS, Jacobs EJ, Campbell PT, et al. Colorectal cancer incidence and postmenopausal hormone use by type, recency, and duration in cancer prevention study II. *Cancer Epidemiol Biomarkers Prev*. 2009;18:2835–2841.
37. Rennett G, Rennett HS, Pinchev M, et al. Use of hormone replacement therapy and the risk of colorectal cancer. *J Clin Oncol*. 2009;27:4542–4547.
38. Green J, Czanner G, Reeves G, et al. Menopausal hormone therapy and risk of gastrointestinal cancer: nested case-control study within a prospective cohort, and meta-analysis. *Int J Cancer*. 2012;130:2387–2396.
39. Barzi A, Lenz AM, Labonte MJ, et al. Molecular pathways: estrogen pathway in colorectal cancer. *Clin Cancer Res*. 2013;19:5842–5848.
40. Calle EE, Miracle-McMahill HL, Thun MJ, et al. Estrogen replacement therapy and risk of fatal colon cancer in a prospective cohort of postmenopausal women. *J Natl Cancer Inst*. 1995;87:517–523.
41. Persson I, Yuen J, Bergkvist L, et al. Cancer incidence and mortality in women receiving estrogen and estrogen-progestin replacement therapy—long-term follow-up of a Swedish cohort. *Int J Cancer*. 1996;67:327–332.
42. Slattery ML, Anderson K, Samowitz W, et al. Hormone replacement therapy and improved survival among postmenopausal women diagnosed with colon cancer (USA). *Cancer Causes Control*. 1999;10:467–473.
43. Mandelson MT, Miglioretti D, Newcomb PA, et al. Hormone replacement therapy in relation to survival in women diagnosed with colon cancer. *Cancer Causes Control*. 2003;14:979–984.
44. Chan JA, Meyerhardt JA, Chan AT, et al. Hormone replacement therapy and survival after colorectal cancer diagnosis. *J Clin Oncol*. 2006;24:5680–5686.
45. Bonds DE, Lasser N, Qi L, et al. The effect of conjugated equine oestrogen on diabetes incidence: the Women's Health Initiative randomised trial. *Diabetologia*. 2006;49:459–468.
46. Lobo RA, Davis SR, De Villiers TJ, et al. Prevention of diseases after menopause. *Climacteric*. 2014;17:540–556.
47. Gorsky RD, Koplan JP, Peterson HB, et al. Relative risks and benefits of long-term estrogen replacement therapy: a decision analysis. *Obstet Gynecol*. 1994;83:161–166.
48. Col NF, Eckman MH, Karas RH, et al. Patient-specific decisions about hormone replacement therapy in postmenopausal women. *JAMA*. 1997;277:1140–1147.
49. Lobo RA. Hormone replacement therapy: current thinking. *Nat Rev Endocrinol*. 2017;13:220–231.
50. Anderson GL, Chlebowski RT, Aragaki AK, et al. Conjugated equine oestrogen and breast cancer incidence and mortality in postmenopausal women with hysterectomy: extended follow-up of the Women's Health Initiative randomised placebo-controlled trial. *Lancet Oncol*. 2012;13:476–486.
51. US Preventive Services Task Force, Grossman DC, Curry SJ, Owens DK, et al. Hormone therapy for the primary prevention of chronic conditions in postmenopausal women: US Preventive Services Task Force recommendation statement. *JAMA*. 2017;318:2224–2233.
52. Lobo RA. Where are we 10 years after the Women's Health Initiative? *J Clin Endocrinol Metab*. 2013;98:1771–1780.
53. Canonico M, Plu-Bureau G, Lowe GD, et al. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. *BMJ*. 2008;336:1227–1231.
54. Olie V, Plu-Bureau G, Conard J, et al. Hormone therapy and recurrence of venous thromboembolism among postmenopausal women. *Menopause*. 2011;18:488–493.
55. Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71:209–249.
56. Breast Cancer Facts and Statistics. Updated March 11, 2022. Available at: https://www.breastcancer.org/symptoms/understand_bc/statistics.
57. Lobo RA. Oestrogen replacement after treatment for breast cancer. *Lancet*. 1993;341:1313–1314.
58. Cobleigh MA, Berris RF, Bush T, et al, for the breast Cancer Committee of the Eastern Cooperative Oncology Group. Special communication: estrogen replacement therapy in breast cancer survivors. A time for change. *JAMA*. 1994;272:540–545.
59. Ylikorkala O, Metsä-Heikkilä M. Hormone replacement therapy in women with a history of breast cancer. *Gynecol Endocrinol*. 2002;16:469–478.
60. Lea R. Use of hormonal replacement therapy after treatment of breast cancer. *J Obstet Gynaecol Can*. 2004;26:49–60.
61. Palshof T, Mouridsen HT, Daehnfeldt JL. Adjuvant endocrine therapy of breast cancer—a controlled clinical trial of oestrogen and anti-oestrogen: preliminary results of the Copenhagen breast cancer trials. *Recent Results Cancer Res*. 1980;71:185–189.
62. Palshof T, Carstensen B, Mouridsen HT, et al. Adjuvant endocrine therapy in pre- and postmenopausal women with operable breast cancer. Reviews on. *Endocr Relat Cancer*. 1985;(suppl 17):43–50.
63. Stoll BA, Parbhoo S. Treatment of menopausal symptoms in breast cancer patients. *Lancet*. 1988;1:1278–1279.
64. Powles TJ, Hickish T, Casey S, et al. Hormone replacement after breast cancer. *Lancet*. 1993;342:60–61.
65. Eden JA, Bush T, Nand S, et al. A case-controlled study of combined continuous estrogen-progestin replacement therapy amongst women with a personal history of breast cancer. *Menopause*. 1995;2:67–72.
66. Vassilopoulou-Sellin R, Theriault R, Klein MJ. Estrogen replacement therapy in women with prior diagnosis and treatment for breast cancer. *Gynecol Oncol*. 1997;65:89–93.
67. Dew J, Eden J, Beller E, et al. A cohort study of hormone replacement therapy given to women previously treated for breast cancer. *Climacteric*. 1998;1:137–142.
68. Espie M, Gorins A, Perret F, et al. Hormone replacement therapy (HRT) in patients treated for breast cancer: analysis of a cohort of 120 patients. *Proc ASCO*. 1999(abstract);18:2262.
69. Guidozzi F. Estrogen replacement therapy in breast cancer survivors. *Int J Gynecol Obstet*. 1999;64:59–63.
70. Natrajan PK, Soumakis K, Gambrell RD Jr. Estrogen replacement therapy in women with previous breast cancer. *Obstet Gynecol*. 1999;181:288–295.
71. Uršič-Vrščaj M, Bebar S. A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. *Eur J Surg Oncol*. 1999;25:146–151.
72. Vassilopoulou-Sellin R, Asmar L, Hortobagyi GN, et al. Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively. *J Clin Oncol*. 1999;17:1482–1487.
73. Disaia PJ, Brewster WR, Ziogas A, et al. Breast cancer survival and hormone replacement therapy. A cohort analysis. *Am J Clin Oncol*. 2000;23:541–545.
74. Marsden J, Whitehead M, A'Hern R, et al. Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? *Fertil Steril*. 2000;73:292–299.
75. Peters GN, Fodera T, Sabol J, et al. Estrogen replacement therapy after breast cancer: a 12-year follow-up. *Ann Surg Oncol*. 2001;8:828–832.
76. Marttunen MB, Hietanen P, Pyrhonen S, et al. A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy. *Maturitas*. 2001;39:217–225.
77. Beckmann MW, Jap D, Djahansouzi S, et al. Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates. *Oncology*. 2001;60:199–206.

78. O'Meara ES, Rossing MA, Daling JR, et al. Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality. *J Natl Cancer Inst.* 2001;93:754–762.
79. Vassilopoulou-Sellin R, Cohen DS, Hortobagyi GN, et al. Estrogen replacement therapy for menopausal women with a history of breast carcinoma: results of a 5-year, prospective study. *Cancer.* 2002;95:1817–1826.
80. Duma EM, Wren BG, Heller GZ, et al. Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality. *Med J Aust.* 2002;177:347–351.
81. Decker DA, Pettinga JE, VanderVelde N, et al. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. *Menopause.* 2003;10:277–285.
82. Gorins A, Espié M, Bedairia N, et al. Hormone replacement therapy in breast cancer patients: a study of 230 patients, with a case-control study. *Gynecol Obstet Fertil.* 2003;31:614–619.
83. Holmberg L, Anderson H. HABITS (hormonal replacement therapy after breast cancer—is it safe?), a randomised comparison: trial stopped. *Lancet.* 2004;363:453–455.
84. Holmberg L, Iversen OE, Rudenstam CM, et al. Increased risk of recurrence after hormone replacement therapy in breast cancer survivors. *J Natl Cancer Inst.* 2008;100:475–482.
85. von Schoultz E, Rutqvist LE, Stockholm Breast Cancer Study Group. Menopausal hormone therapy after breast cancer: the Stockholm randomized trial. *J Natl Cancer Inst.* 2005;97:533–535.
86. Fahlén M, Fornander T, Johansson H, et al. Hormone replacement therapy after breast cancer: 10 year follow-up of the Stockholm randomized trial. *Eur J Cancer.* 2013;49:52–59.
87. Bluming AZ. Hormone replacement therapy (HRT) in women with previously treated primary breast cancer: update XIV. Proc ASCO. *J Clin Oncol.* 2008;15 s:20693.
88. Figueiredo JC, Bernstein L, Capanu M, et al. Oral contraceptives, postmenopausal hormones, and risk of asynchronous bilateral breast cancer: the WECARE study group. *J Clin Oncol.* 2008;26:1411–1418.
89. Holmberg L, Anderson H. Stopping HABITS. *Lancet.* 2004;363:1477.
90. Sands R, Boshoff C, Jones A, et al. Current opinion: hormone replacement therapy after a diagnosis of breast cancer. *J N Am Menop Soc.* 1995;2:73–80.
91. Chlebowski RT, McTiernan A. Elements of informed consent for hormone replacement therapy in patients with diagnosed breast cancer. *J Clin Oncol.* 1999;17:130–142.
92. Col NF, Hirota LK, Orr RK, et al. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. *J Clin Oncol.* 2001;19:2357–2363.
93. Meurer LN, Lena S. Cancer recurrence and mortality in women using hormone replacement therapy: meta-analysis. *J Fam Pract.* 2002;51:1056–1062.
94. Del Priore G, Hatami M. Hormone replacement therapy in breast cancer patients and survivors. *Curr Womens Health Rep.* 2003;3:165–169.
95. Batur P, Blixen CE, Moore HC, et al. Menopausal hormone therapy (HT) in patients with breast cancer. *Maturitas.* 2004;53:123–132.
96. Lea R, Bannister E, Case A, et al. Use of hormone replacement therapy after treatment of breast cancer. *J Obstet Gynecol Canada.* 2004;142:49–54.
97. Levgr M. Hormone therapy for women after breast cancer. *A review J Reprod Med.* 2004;49:510–526.
98. Col NF, Kim JA, Chlebowski RT. Menopausal hormone therapy after breast cancer: a meta-analysis and critical appraisal of the evidence. *Breast Cancer Res.* 2005;7:R535–R540.
99. Creasman WT. Hormone replacement therapy after cancers. *Curr Opin Oncol.* 2005;17:493–499.
100. Xydakis AM, Sakkas EG, Mastorakos G. Hormone replacement therapy in breast cancer survivors. *Ann N Y Acad Sci.* 2006;1092:349–360.
101. Antoine C, Liebens F, Carly B, et al. Safety of hormone therapy after breast cancer: a qualitative systematic review. *Hum Reprod.* 2007;22:616–622.
102. Mueck AO, Rabe T, Kiesel L, et al. The use of hormone replacement therapy in patients after breast cancer. *Minerva Ginecol.* 2007;59:529–541.
103. Liotta M, Escobar PF. Hormone replacement after breast cancer: is it safe? *Clin Obstet Gynecol.* 2011;54:173–179.
104. Garrido Oyarzún MF, Castelo-Branco C. Use of hormone therapy for menopausal symptoms and quality of life in breast cancer survivors. Safe and ethical? *Gynecol Endocrinol.* 2017;33:10–15.
105. Wang Y, Lewin N, Qaoud Y, et al. The oncologic impact of hormone replacement therapy and premenopausal breast cancer survivors: a systematic review. *Breast.* 2018;40:123–130.
106. Deli T, Orosz M, Jakab A. Hormone replacement therapy in cancer survivors—review of the literature. *Pathol Oncol Res.* 2020;26:63–78.
107. Ugras SK, Layeequr Rahman R. Hormone replacement therapy after breast cancer: yes, no or maybe? *Mol Cell Endocrinol.* 2021;525:111180.
108. Poggio F, Del Mastro L, Bruzzone M, et al. Safety of systemic hormone replacement therapy in breast cancer survivors: a systematic review and meta-analysis. *Breast Cancer Res Treat.* 2021;191:269–275. doi:doi.org/10.1007/s10549-021-06436-9.
109. Kenemans P, Bundred NJ, Foidart JM, et al. Safety and efficacy of tibolone in breast-cancer patients with vasomotor symptoms: a double-blind, randomised, non-inferiority trial. *Lancet Oncol.* 2009;10:135–146.
110. Gompel A, Siromachkova M, Lombet A, et al. Tibolone actions on normal and breast cancer cells. *Eur J Cancer.* 2000;36:S76–S77.
111. Francis PA, Regan MM, Fleming GF, et al. For the International Breast Cancer Study Group. Adjuvant ovarian suppression in premenopausal breast cancer. *N Engl J Med.* 2015;372:436–446.
112. Pagani O, Francis PA, Fleming GF, et al. SOFT and TEXT Investigators and International Breast Cancer Study Group. Absolute improvements in freedom from distant recurrence to tailor adjuvant endocrine therapies for premenopausal women: results from TEXT and SOFT. *J Clin Oncol.* 2019;38:1293–1303.
113. Vogl SE. Adjuvant ovarian suppression for resected breast cancer: 2017 critical assessment. *Breast Cancer Res Treat.* 2017;166:1–13.
114. Manni A, Pearson OH. Antiestrogen-induced remissions in premenopausal women with stage IV breast cancer: effects on ovarian function. *Cancer Treat Rep.* 1980;54:779–785.
115. Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 5: selective estrogen receptor modulators and hormone replacement therapy. Proceedings of a conference held at the Boar's Head Inn, Charlottesville, Virginia, September 21–23, 1997. *Oncology.* 1999;13:721–735.
116. Wong ZW, Ellis MJ. First-line endocrine treatment of breast cancer: aromatase inhibitor or antiestrogen? *Br J Cancer.* 2004;90:20–25.
117. Cuzick J, Sestak I, Baum M, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 10-year analysis of the ATAC trial. *Lancet Oncol.* 2010;11:115–141.
118. Francis PA, Pagani O, Fleming GF, et al. Tailoring adjuvant endocrine therapy for premenopausal breast cancer. *N Engl J Med.* 2018;379:122–137.
119. Lambertini M, Kroman N, Ameye L, et al. Long-term safety of pregnancy following breast cancer according to estrogen receptor status. *J Natl Cancer Inst.* 2018;110:426–429.
120. Lambertini M, Ameye L, Hamy AS, et al. Pregnancy after breast cancer in patients with germline BRCA mutations. *J Clin Oncol.* 2020;10:3012–3023.
121. Bush TL, Whiteman M, Flaws JA. Hormone replacement therapy and breast cancer: a qualitative review. *Obstet Gynecol.* 2001;98:498–508.
122. Hernán MA. Methods of public health research—strengthening causal inference from observational data. *N Engl J Med.* 2021;385:1345–1348.
123. Woodcock J, Araujo R, Thompson T, et al. Integrating research into community practice—toward increased diversity in clinical trials. *N Engl J Med.* 2021;385:1351–1353.
124. Stetson PD, McCleary NJ, Osterman T, et al. Adoption of Patient-Generated Health Data in Oncology: a report from the NCCN EHR Oncology Advisory Group. *J Natl Compr Canc Network.* 2022;1–6. doi: https://doi.org/10.6004/jnccn.2021.7088.