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Menopausal hormone therapy (HT) in patients with breast cancer

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Abstract

Objectives: To assess the effect of menopausal hormone therapy (HT) on reoccurrence, cancer-related mortality, and overall mortality after a diagnosis of breast cancer.
Methods: We performed a quantitative review of all studies reporting experience with menopausal HT for symptomatic use after a diagnosis of breast cancer. Rates of reoccurrence, cancer-related mortality, and overall mortality were calculated in this entire group. A subgroup analysis was performed in studies using a control population to assess the odds ratio of cancer reoccurrence and mortality in hormone users versus non-users.
Results: Fifteen studies encompassing 1416 breast cancer survivors using HT were identified. Seven studies included a control group comprised of 1998 patients. Among the 1416 HT users, reoccurrence was noted in 10.0% (95% CI: 8.4–11.6%). Cancer-related mortality occurred at a rate of 2.6% (95% CI: 1.8–3.7%), while overall mortality was 4.5% (95% CI: 3.4–5.8%). Compared to non-users, patients using HT had a decreased chance of reoccurrence and cancer-related mortality with combined odds ratio of 0.5 (95% CI: 0.2–0.7) and 0.3 (95% CI: 0.0–0.6), respectively.
Conclusions: In our review, menopausal HT use in breast cancer survivors was not associated with increased cancer reoccurrence, cancer-related mortality or total mortality. Despite conflicting opinions on this issue, it is important for primary care physicians to feel comfortable medically managing the increasing number of breast cancer survivors. In the subset of women with severe menopausal symptoms, HT options should be reviewed if non-hormonal methods are ineffective. Future trials should focus on better ways to identify breast cancer survivors who may safely benefit from HT versus those who have a substantial risk of reoccurrence with HT use.

Keywords: Breast cancer; Hormone therapy; Hormone replacement therapy; Estrogen therapy; Estrogen replacement therapy; Menopause

1. Introduction

In the United States, 212,600 women are expected to be diagnosed with breast cancer this year with a 12.6% lifetime risk of breast cancer for the average woman [1]. More than 86% of those diagnosed with invasive breast cancer can expect to survive for at least 5 years

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after their diagnosis. With an average age at diagnosis of 60 years, the current number of breast cancer survivors approach 2.5 million women. An increasing number of cases are now being detected at an earlier stage, with many young women going through premature menopause due to adjuvant chemotherapy-induced ovarian failure. Premature menopause can cause bothersome menopausal symptoms, including hot flashes, irritability, sleep disturbance, urogenital atrophy (causing dyspareunia and frequent urinary tract infections), as well as worsening of bone density and lipid levels. Use of menopausal hormone therapy (HT) has been approved for relief of the vasomotor symptoms, vulvar and vaginal atrophy, and osteoporosis prevention.

There has been much debate in recent years regarding the role of menopausal HT in increasing the chance of breast cancer development. Although 50 years of observational studies in this area showed conflicting results, the Women's Health Initiative (WHI), a recent randomized placebo-controlled trial, showed a 26% increase in the risk of breast cancer diagnosis after 5.2 years (if estrogen and progestin were used together) [2]. However, the estrogen-only arm of the WHI showed that there is no increased risk of breast cancer, and a possibility for reduction in breast cancer risk; though to prove this would require further investigation [3]. Because of this controversy, a prior diagnosis of breast cancer has been thought of as a contraindication for the use of HT. In the case of established breast cancer, there are concerns that estrogen may stimulate tumor growth, and that the stimulation may be dose-dependent. It is feared that HT use in patients with a history of breast cancer may lead to the potential reactivation of any residual cancer cells, or stimulation of breast tissue which may be susceptible to malignant transformation. However, surveys of patients with breast cancer show that one out of three patients were prepared to use HT to alleviate their symptoms [4]. The increasing number of breast cancer survivors, many with severe menopausal symptoms, has led to observational studies of HT use after breast cancer for symptom control. The goal of this study is to systematically review all of these studies, with specific attention to cancer-related mortality and reoccurrence rates. Compared to a prior review of studies on this topic, this study more than doubles the clinical experience of breast cancer survivors taking menopausal HT ($N = 1416$ versus 669) [5].

2. Methods

The entire MEDLINE, CINHL, and Healthstar databases were searched between the years 1967 and 2001 to identify all studies that included the search terms: estrogen replacement, hormone replacement, hormone therapy (HT), estrogen therapy (ET), hormone replacement therapy (HRT), estrogen replacement therapy (ERT), breast cancer, and breast carcinoma. Both studies with and without control groups were included in the review. Existing reviews of menopausal HT and breast cancer risk were used to identify relevant references, while records of conference proceedings were hand-searched to identify abstracts. Non-English language studies were included with the help of translating services. Data points reviewed in each study included patient population, type of estrogen used, method of estrogen delivery, use of concurrent progestin, interval between cancer diagnosis and initiation of HT, length of time on HT, cancer stage, age at diagnosis, and follow-up period. The outcomes searched were those considered most clinically relevant: breast cancer reoccurrence, symptom control, breast cancer mortality, and all cause mortality.

To ensure accuracy, the literature was searched by two individuals and then, the data from the studies were independently extracted by two investigators. We spoke with experts in the field in attempts to identify any ongoing studies. When multiple publications from the same author or institution were noted, the authors were contacted to ensure that the same patient population was not included in duplicate. In addition, pharmaceutical companies were contacted regarding any ongoing trials.

The patients were classified as being low or high risk for cancer reoccurrence based on the stage of the cancer at diagnosis. Because the time span of the studies involves two common staging systems (Manchester and TNM), patients were considered low risk for reoccurrence if they were node-negative by the TNM staging system, or stage 0 and I by the Manchester system. Conversely, high risk was defined as presence of axillary lymph node involvement or stages II and III, as well as rare stage IV patients included in these trials. Patients were defined as having hormone receptor-positive disease if either estrogen or progesterone receptors were expressed. Patients negative for both estrogen and progesterone

receptors were classified as receptor negative. Patients with unknown receptor status were excluded from calculations of prevalence involving receptor status.

We calculated the estimates of combined reoccurrence, cancer-related mortality, and overall mortality rates when combining the studies. Proportions and 95% confidence intervals were given for each outcome when combining all of the studies together. Using the Mantel–Haenszel method, we also estimated the odds ratio of having reoccurrence and cancer-related mortality when all of the studies using control groups (no HT use) were combined. Odds ratio was used instead of relative risk to compare the likelihood of an event between two groups since two of the studies were case-control studies.

Since the Mantel–Haenszel methods for estimating the common odds ratio are based on the assumption that the odds ratios are constant across studies, we first performed the heterogeneity test of the odds ratios to ensure that the odds ratios are constant across the studies. For reoccurrence and cancer-related mortality, the heterogeneity test results were not statistically-significant, which means that the odds ratios were homogeneous amongst the studies. For the overall mortality, the test result was significant, which means the odds ratios were not constant across studies. Two of the studies using a control group did not report the overall mortality; therefore, we did not calculate the common odds ratio of overall mortality. SAS software was used for all statistical calculations.

3. Results

By the year 2001, there were 29 publications that studied the effects of menopausal HT use after a diagnosis of breast cancer. Of these 29 studies, 14 were excluded from our review since they represented the same group of patients that were re-evaluated at a later date and republished [6–19]. In these cases, the authors were contacted to ensure that indeed these were the same patients, and the most updated publication was used in our endpoint calculations. The remaining 15 studies of menopausal HT use after breast cancer included 1416 patients using HT [20–34]. Six of these were prospective [21,25,27,28,30,33] and nine retrospective [20,22–24,26,29,31,32,34]. Of the 15 included

Table 1
Demographic summary for patients with HT treatment in all studies

Paper	Total patients	Age at diagnosis[a]	Treatment length (month)[a]	Follow-up (month)[a]	Low risk		ER positive	
					N^b	Percentage (95% CI)	N^b	Percentage (95% CI)
Powles	35	NR	14.6	43	12/22	54.5 (32.2, 75.6)	NR	
Wile	25	51	35.2	35.2	15/25	60.0 (38.7, 78.9)	13/16	81.3 (54.4, 96.0)
Decker	61	52	26.4	26.4	39/61	63.9 (50.6, 75.8)	19/34	55.9 (37.9, 72.8)
Ursic	21	42	28	100	14/21	66.7 (43.0, 85.4)	13/21	61.9 (38.4, 81.9)
Natrajan	50	57.6	NR	83	47/50	94.0 (83.4, 98.8)	19/19	100 (82.4, 100)
Brewster	145	50	40	30	79/121	65.3 (56.1, 76.7)	NR	
Espie	120	44.5	28.8	NR	72/120	60.0 (50.7, 68.8)	79/120	65.8 (56.6, 74.3)
Guidozzi	24	48	32	68	6/14	42.9 (17.7, 71.1)	2/4	50.0 (6.8, 93.3)
Bluming	211	NR	63	NR	162/211	76.8 (70.5, 82.3)	NR	
Beckmann	64	NR	32	37	44/64	68.8 (55.9, 79.8)	31/64	48.4 (35.7, 61.3)
Marttunen	88	49.2	30	30	72/82	87.8 (78.7, 94.0)	57/72	79.2 (68.0, 87.8)
O'meara	174	NR	15	228	91/174	52.3 (44.6, 59.9)	84/123	68.3 (59.3, 76.4)
Peters	56	49	76.8	153.6	42/56	75.0 (61.6, 85.6)	28/38	73.7 (56.9, 86.6)
Vassilopoulou	56	NR	NR	71	35/54	64.8 (50.6, 77.3)	0/37	0 (0, 9.5)
Durna	286	55.8	21	69.6	180/266	67.7 (61.7, 73.2)	NR	
Combined	1416	51[c]	34[c]	86[c]	910/1341	67.9 (65.3, 70.4)	345/548	63.0 (58.8, 67.0)

Abbreviations: NR, not reported.

[a] Mean value.

[b] This information may not be available for all patients in the study.

[c] Weighted average.

Table 2
Outcome summary for patients with HT treatment in all cases

Paper	Total patients	Recurrence		Cancer-related mortality		Overall mortality	
		N	Percentage (95% CI)	*N*	Percentage (95% CI)	*N*	Percentage (95% CI)
Powles	35	2	5.7 (0.7, 19.2)	NR		NR	
Wile	25	3	12.0 (2.5, 31.2)	1	4.0 (0.1, 20.4)	1	4.0 (0.1, 20.4)
Decker	61	6	9.8 (3.7, 20.2)	2	3.3 (0.4, 11.3)	2	3.3 (0.4, 11.3)
Ursic	21	4	19.0 (5.4, 41.9)	0	0 (0, 16.1)	0	0 (0, 16.1)
Natrajan	50	3	6.0 (1.3, 16.6)	3	6.0 (1.3, 16.6)	3	6.0 (1.3, 16.6)
Brewster	145	13	9.0 (4.9, 14.8)	3	2.1 (0.4, 5.9)	3	2.1 (0.4, 5.9)
Espie	120	5	4.2 (1.4, 9.5)	NR		NR	
Guidozzi	24	0	0 (0, 14.3)	0	0 (0, 14.3)	NR	
Bluming	211	28	13.3 (9.0, 18.6)	0	0 (0, 1.7)	2	0.9 (0.1, 3.4)
Beckmann	64	6	9.4 (3.5, 19.3)	4	6.3 (1.7, 15.2)	4	6.3 (1.7, 15.2)
Marttunen	88	7	8.0 (3.3, 15.7)	2	2.3 (0.3, 8.0)	2	2.3 (0.3, 8.0)
O'meara	174	16	9.2 (5.3, 14.5)	5	2.9 (0.9, 6.6)	17	9.8 (5.8, 15.2)
Peters	56	2	3.6 (0.4, 12.3)	0	0 (0, 6.4)	3	5.4 (1.1, 14.9)
Vassilopoulou	56	2	3.6 (0.4, 12.3)	0	0 (0, 6.4)	NR	
Durna	286	44	15.4 (11.4, 20.1)	13	15.4 (11.4, 20.1)	16	5.6 (3.2, 8.9)
Combined	1416	141	10.0 (8.4, 11.6)	33	2.6 (1.8, 3.7)	53	4.5 (3.4, 5.8)

studies, only seven had a control group comprised of 1998 patients [23,24,29–32,34].

Including all 15 studies, there was reoccurrence in 10.0% of patients using HT after approximately 7 years of follow-up (141/1416, 95% CI: 8.4–11.6%). Cancer-related mortality occurred at a rate of 2.6% (33/1261, 95% CI: 1.8–3.7%), while overall mortality was 4.5% (53/1181, 95% CI: 3.4–5.8%). Tables 1 and 2 review the demographics and outcome summaries of the patients in all 15 studies. When only the seven studies with control groups were evaluated, patients using HT had a decreased chance of reoccurrence and cancer-related mortality compared to the control groups with a combined odds ratio of 0.5 (95% CI: 0.2–0.7) and 0.3 (95% CI: 0.0–0.6), respectively. Tables 3 and 4 review the demographics and outcome summaries of the patients in all seven case-controlled studies.

The populations of women included those from the US, Europe, Australia, Africa, and Scandinavian countries. The weighted average age of the women at breast cancer diagnosis was 51 years (range of averages 44.5–57.6 years). Cancer stage was defined as low risk for reoccurrence in 67.9% of the patients (910/1341, 95% CI: 65.3–70.4%). Of those patients with known hormone receptor status, a hormone receptor-positive tumor was noted in 63.0% (345/548, 95% CI: 58.8–67.0%). Unfortunately, data on stage or hormone receptor status was not available on all of the patients in some studies. Table 3 summarizes these characteristics in the HT users and controls.

The hormones used varied amongst the studies, but were mostly composed of standard dose conjugated estrogen (0.625 mg), or its equivalent (0.05 mg transdermal estradiol patch, 1 mg oral 17β-estradiol, 0.625 mg esterified estrogen). All but one of the studies included women using progestins in varied doses and regimens, mostly consisting of medroxyprogesterone acetate. The mean time interval between the diagnosis and start of HT was anywhere from 26–108 months, with the majority of the patients starting HT 2–5 years after their diagnosis. The weighted average treatment length was 34 months (range of averages 14.6–76.8 months), with 86 months of follow-up (range of averages 26.4–228 months). Relief of symptoms with HT use was not consistently reported throughout the studies. Similarly, most studies did not report the use of tamoxifen. Of the studies providing this data, the percentage of patients using tamoxifen varied mostly between 10 and 13%, with a high of 22% in one study.

4. Discussion

We found that reoccurrence and mortality rates in women using menopausal HT after a diagnosis of breast cancer were low. Reoccurrence was noted in

Table 3
Demographic summary for cases with controls

Paper	Total	Age at diagnosis[a]	Low risk		ER positive	
			N[b]	Percentage (95% CI)	N[b]	Percentage (95% CI)
Ursic						
Treatment	21	42	14/21	66.7 (43.0, 85.4)	13/21	61.9 (38.4, 81.9)
Control	42	43	14/42	33.3 (19.6, 50.0)	40/42	95.2 (83.8, 99.4)
Natrajan						
Treatment	50	57.6	47/50	94.0 (83.4, 98.8)	19/19	100 (82.4, 100)
Control	18	64.7	NR		NR	
Beckmann						
Treatment	64	NR	44/64	68.8 (55.9, 79.8)	31/64	48.4 (35.7, 61.3)
Control	121	NR	76/121	62.8 (53.6, 71.4)	48/121	40.0 (30.9, 49.0)
Marttunen						
Treatment	88	49.2	72/82	87.8 (78.7, 94.0)	57/72	79.2 (68.0, 87.8)
Control	43	48.6	30/43	70.0 (53.9, 82.8)	29/38	76.3 (59.8, 88.6)
O'Meara						
Treatment	174	NR	91/174	52.3 (44.6, 59.9)	84/123	68.3 (59.3, 76.4)
Control	695	NR	403/695	60.0 (54.2, 61.7)	409/546	74.9 (71.0, 78.5)
Vassilopoulou						
Treatment	56	NR	35/54	64.8 (50.6, 77.3)	0/37	0 (0, 9.5)
Control	243	53	133/236	56.4 (49.8, 62.8)	0/243	0 (0, 1.5)
Durna						
Treatment	286	55.8	180/266	67.7 (61.7, 73.2)	NR	
Control	836	63.7	470/781	60.2 (56.6, 63.6)	NR	

Abbreviations: NR, not reported.
[a] Mean value.
[b] This information may not be available for all patients in the study.

10.0%, cancer-related mortality occurred at a rate of 2.6%, while overall mortality was 4.5%. Although no direct statistical comparisons can be made with our study outcomes, there are several resources available for baseline data on reoccurrence, overall and cancer-related mortality rates in those not using menopausal HT after their cancer diagnosis. For example the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute is an authoritative source of information on cancer incidence and survival in the United States. Based on the most recently available data, the 7-year cancer-related mortality rate for invasive breast cancer is 17.9% [1]. Similarly, The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) performed a meta-analysis of randomized studies of adjuvant tamoxifen use in early breast cancer, comprising about the 87% of the worldwide experience at that time [35]. In women with early breast cancer followed for 10 years, reoccurrence occurred at a rate of 42.1% of controls and 34.7% of those allocated to 5 years of tamoxifen. Death from any cause occurred at a rate of 37.9% in controls and 34.2% in tamoxifen users. Table 5a and b report the reoccurrence and all-cause mortality rates from the EBCTCG meta-analysis in women with estrogen-positive tumors, categorized by nodal status. The reoccurrence and mortality rates found in our review are significantly lower than those reported amongst the 55 randomized trials reviewed by the EBCTCG, as well as the SEER data which covers approximately 26% of the US population.

This study is significant because it combines and quantitates information obtained from individual smaller studies of breast cancer survivors using HT. It is important for primary care physicians to educate themselves on the health concerns of breast cancer survivors since they often become the principal providers to care for these patients after their diagnosis. This may be a difficult task, however, given that most of these

Table 4
Outcome summary for cases with controls

Paper	Total	Recurrence			Cancer-related mortality			Overall mortality		
		N	Percentage (95% CI)	Odds ratio	*N*	Percentage (95% CI)	Odds ratio	*N*	Percentage (95% CI)	Odds ratio
Ursic										
Treatment	21	4	19.0 (5.4, 41.9)	1.7 (0.4, 7.3)	0	0 (0, 16.1)	0.6 (0.03, 16.5)	0	0 (0, 16.1)	
Control	42	5	11.9 (4.0, 25.6)		1	2.4 (0.1, 12.6)		NR		
Natrajan										
Treatment	50	3	6.0 (1.3, 16.6)	0.1 (0.03, 0.6)	3	6.0 (1.3, 16.6)	0.2 (0.03, 0.8)	3	6.0 (1.3, 16.6)	0.1 (0.03, 0.6)
Control	18	6	33.3 (13.3, 59.0)		5	27.8 (9.7, 53.5)		6	33.3 (13.3, 59.0)	
Beckmann										
Treatment	64	6	9.4 (3.5, 19.3)	0.6 (0.2, 1.7)	4	6.3 (1.7, 15.2)	0.5 (0.1, 1.5)	4	6.3 (1.7, 15.2)	0.5 (0.1, 1.5)
Control	121	17	14.1 (8.4, 21.5)		15	12.4 (7.1, 19.6)		15	12.4 (7.1, 19.6)	
Marttunen										
Treatment	88	7	8.0 (3.3, 15.7)	0.7 (0.2, 2.2)	2	2.3 (0.3, 8.0)	0.3 (0.05, 1.9)	2	2.3 (0.3, 8.0)	0.3 (0.05, 1.9)
Control	43	5	11.6 (3.9, 25.1)		3	7.0 (1.5, 19.1)		3	7.0 (1.5, 19.1)	
O'meare										
Treatment	174	16	9.2 (5.3, 14.5)	0.6 (0.3, 1.0)	5	2.9 (0.9, 6.6)	0.3 (0.1, 0.8)	17	9.8 (5.8, 15.2)	0.5 (0.3, 0.9)
Control	695	101	14.5 (12.0, 17.4)		59	8.5 (6.5, 10.8)		115	16.5 (13.9, 19.5)	
Vassilopoulou										
Treatment	56	2	3.6 (0.4, 12.3)	0.2 (0.05, 1.0)	0	0 (0, 6.4)	1.4 (0.06, 35.6)	NR		
Control	243	33	13.6 (9.5, 18.5)		1	0.4 (0, 2.3)		1	0.4 (0, 2.3)	
Durna										
Treatment	286	44	15.4 (11.4, 20.1)	0.4 (0.3, 0.6)	13	15.4 (11.4, 20.1)	0.3 (0.2, 0.5)	16	5.6 (3.2, 8.9)	0.1 (0.06, 0.2)
Control	836	247	29.5 (26.5, 32.8)		122	14.6 (12.3, 17.2)		199	23.8 (20.9, 26.8)	
Combined Odds ratio		0.5 (0.2, 0.7)			0.3 (0.0, 0.6)					

Table 5
Early Breast Cancer Trialists' Group

	Control	Tamoxifen
(a) Percentage reoccurrence at 10-year follow-up for ER+ patients		
Node (−)	35.7	20.8
Node (+)	55.5	40.3
(b) Percentage all-cause mortality at 10-year follow-up for ER+ patients		
Node (−)	26.7	21.1
Node (+)	49.5	38.6

ER+: estrogen receptor-positive.

prior studies have been presented in forums geared to the oncology specialist. Greater understanding of medical options for these women will undoubtedly improve patient care.

4.1. Magnitude of menopausal symptoms in breast cancer survivors

An increase in breast cancer incidence has been noted in the United States, potentially due to inereased screening [36]. With more breast cancer survivors now than ever before, the non-oncologic health problems of these women has become a significant health issue. The incidence of amenorrhea from adjuvant chemotherapy is high. For example with CMF (Cytoxan, Methotrexate and 5-FU), a commonly prescribed regimen, amenorrhea occurs in 40% of women younger than age 40, and 70% of women over age 40 [37]. Similar to the side effects of chemotherapy-induced premature menopause, tamoxifen can precipitate or worsen vasomotor and vaginal symptoms, causing some women to stop therapy for this reason alone. By discontinuing this drug, patients are denying themselves the 50% decreased risk of cancer reoccurrence with 5 years of tamoxifen use; and yet, this is a risk some women are willing to accept [38].

Breast cancer survivors with severe hot flashes report significantly greater mood disturbances, higher negative affect, more interference with daily activities (sleep, concentration, sexuality), and poor overall quality of life in comparison to breast cancer survivors with no or mild hot flashes [39]. Compared to controls, breast cancer survivors are 5.3 times more likely to experience menopausal symptoms and 7.4 times more likely to try alternative agents, such as vitamins, herbs, and soy products [40]. Unfortunately, the efficacy, safety, or purity of many of these over-the-counter treatments is still unclear. Due to the above, women who are experiencing refractory postmenopausal symptoms may be willing to accept the potential risks of HT to alleviate their symptoms. In fact, a survey of patients with breast cancer showed that one out of three patients was prepared to use HT to alleviate their symptoms and improve quality of life [41]. Therefore, HT after breast cancer has become increasingly used in clinical practice. Because the opinions of many professional societies are ambiguous or hesitant to approve of such treatment, the physician taking care of breast cancer survivors currently has no official justification for this use of HT.

4.2. Current non-hormonal treatments for menopausal symptoms

Currently, women with a history of breast cancer who complain of hot flashes and sweating are given a trial of Vitamin E, Vitamin B_6, clonidine, gabapentin, or select antidepressants. Of these therapies, the antidepressants paroxetine and venlafaxine have shown greatest efficacy with a reduction in symptoms by 27–61%, depending on the dose used [42,43]. Although higher doses have greater efficacy, they are also associated with more side effects. For women with significant symptoms, these non-hormonal regimens are often not sufficient. A review of double-blind, placebo-controlled trials of oral HT therapy used for reduction of hot flashes showed that estrogen provided a 77% reduction of symptoms, by far the most efficacious regimen [44]. Interestingly, this review also showed a 50% reduction in hot flashes in the placebo group; therefore, studies of non-hormonal treatments for hot flashes must be interpreted with caution if a placebo control group is not included.

4.3. The unknown regarding HT

Women may survive their breast cancer only to succumb to other diseases, such as coronary artery disease, the risk of which may be increased in premature menopause. In fact, cardiovascular disease is the most common cause of death among node-negative breast cancer survivors. However, a 60% decreased risk of cardiovascular events in women who use HT

after surgical menopause has been demonstrated by the Harvard Nurse's Health Study [45]. The WHI showed a 29% increased risk of cardiovascular disease in postmenopausal women with an average age of 63 (using estrogen with progestin); however, this study did not address the cardiovascular effects of HT in women who undergo premature menopause (age <50). The WHI did not reveal any increased risk of cardiovascular disease in patients taking only estrogen [3]. Whether HT may offer a cardiovascular benefit in this subset of young menopausal women has not yet been studied in prospective trials.

Similarly, osteoporotic fractures not only result in loss of independence but cause a 20% increased mortality after 5 years, with the greatest risk within the first year [46]. HT decreases the risk of osteoporotic fractures at all sites by 37%. When deciding on a treatment for osteoporosis, it is important to remember that all of the newer treatments have been used within the last decade compared to HT, which has been in use for over 60 years. Given the long half-life of the bisphosphonates, it is not yet clear what the long-term effects of these medicines will be. Though current indications limit the use of HT for protection from these chronic diseases in both the general population and breast cancer survivors, it is clear that many unanswered questions remain regarding the overall risks and benefits of HT in younger women.

5. Limitations

The biggest limitation of the data available to date is the lack of delineation between combination HT versus unopposed estrogen therapy (ET), and their individual effects on the risk of breast cancer reoccurrence. In a recent review of 29,508 women followed for approximately 10 years, long-term use of combined HT significantly increased the risk of breast cancer compared to non-users, but ET did not significantly increase the risk of first breast cancer occurrence [47]. This is consistent with findings from the WHI. Other limitations of the available literature include a limited number of women in many of these studies (10 of the 15 studies involved less then 100 women), relatively short follow-up periods, and a long interval between cancer diagnosis and starting HT (Table 1). In the studies employing control groups, one showed a large difference between the number of patients at lower risk for reoccurrence in the HT-treated group in comparison to the controls (Table 3). Future studies should take these variables into account when evaluating outcomes.

After data collection for our study was completed, HABITS, a study of 345 breast cancer survivors randomized to HT versus placebo, was stopped early due to increased risk of breast cancer events for those on HT [48]. It is important to note that the breast cancer of half of the patients in this study was hormone receptor-positive. As expected, the patients who were hormone receptor-positive had a much higher relative hazard for new breast cancer events compared to those who tested receptor-negative. Unfortunately, not enough women were studied to determine whether there was any difference in outcomes amongst those taking ET and HT in this study population. Although the trial was stopped at 2.1 years, these patients will be followed for at least 5 years for additional outcomes data. This study represents the first study showing negative outcomes of HT use in breast cancer survivors, and stands in contrast to prior published studies. If included in our end-point calculations, it is likely that this large study would have altered our findings. These controversies remind us that we have now created more questions than answers with regards to HT, especially in the case of breast cancer survivors. Focus of further research should be on how hormone receptor status will affect outcomes in patients wishing to use HT after a diagnosis of breast cancer. The HABITS study suggests that in a high-risk population (node-positive patients) there may be a substantial risk to HT use. However, there may be a select group of patients in whom HT is safe despite a prior diagnosis of breast cancer. The challenge for the future is to decide which patients can be treated safely. Also, since the risks of HT seem to be greater than the risk of ET, can we make HT safer by limiting the use of progestins, even in women with an intact uterus? If so, what is the minimum progestin that is safe, and how should the endometrium be monitored with this regimen?

Limitations of any retrospective review need to be acknowledged, including the risk of bias and confounding variables. Different hormonal formulations and doses, concurrent use of a progestin, type of breast cancer, time interval from diagnosis to HT, and length of therapy all impact outcomes. The role of these variables in outcomes would best be answered via future

prospective randomized studies. However, it is important to note that the variety of doses and regimens used in these studies reflects the variety of prescribing practices used clinically. Similarly, selection bias may affect outcomes since only patients with the most severe symptoms will be willing to take the potential risks of treatment. It is important to remember that selection bias routinely occurs in everyday clinical practice (since patients with the most severe symptoms come to us for help). It is important to note that HT use has not been studied in patients using aromatase inhibitors; therefore, HT use would not be recommended in these patients given the mechanism of action of these medications. Given the recent controversies surrounding the role of HT in breast cancer and cardiovascular disease, large randomized prospective studies of HT's role in breast cancer survivors is now more unlikely than ever before. It is important for practitioners to manage patients with data they currently have, despite the acknowledged limitations.

6. Recommendations

With earlier detection of cancer, in combination with more effective treatments, we can expect the number of breast cancer survivors to increase. Although non-hormonal options are available for women with significant postmenopausal symptoms, these do not approach the effectives of HT and have their own side effects. Given the findings of the WHI showing an increased risk of breast cancer in combination HT users, it is reasonable to exercise caution in women who have had breast cancer, and start first with treatments such as daily Vitamin E 500–1000 IU, 50 mg B_6, or antidepressants. However, in the subset of women with refractory symptoms affecting their quality of life, HT options should be reviewed. Patients must understand the known risks and benefits of HT, in addition to any theoretical risks on breast cancer outcomes before starting therapy [49].

References

[1] Ries LAG, Eisner MP, Kosary CL, et al., editors. SEER Cancer Statistics Review, 1975–2000. Bethesda, MD: National Cancer Institute; 2003. http://seer.cancer.gov/csr/1975_2000 (accessed 4/29/03).

[2] 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(3):321–33.

[3] WHI Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. JAMA 2004;291(14):1701–12.

[4] Marsden J, Whitehead M, A'Hern R, Baum M, Sacks N. Are randomized trials of hormone replacement therapy in symptomatic women with breast cancer feasible? Fertil Steril 2000;73(2):292–9.

[5] Col NF, Hirota LK, Orr RK, Erban JK, Wong JB, Lau J. Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk. J Clin Oncol 2001;19(8):2357–63.

[6] Stoll BA. Effect of Lyndiol, an oral contraceptive, on breast cancer. Br Med J 1967;1(533):150–3.

[7] DiSaia PJ, Odicino F, Grosen EA, Cowan B, Pecorelli S, Wile AG. Hormone replacement therapy in breast cancer. Lancet 1993;342(8881):1232.

[8] Eden JA, Bush T, Nand S, et al. A case-control study of combined continuous estrogen–progestin replacement therapy among women with a personal history of breast cancer. Menopause: J North Am Menopause Soc 1995;2(2):67.

[9] DiSaia PJ, Grosen EA, Odicino F, et al. Replacement therapy for breast cancer survivors: a pilot study. Cancer 1995;76(10, Suppl.):2075–8.

[10] Peters GN, Jones SE. Estrogen replacement therapy in breast cancer patients: a time for change? Proc ASCO 1996;15:148 [Abs].

[11] DiSaia PJ, Grosen EA, Kurosaki T, Gildea M, Cowan B, Anton-Culver H. Hormone replacement therapy in breast cancer survivors: a cohort study. Am J Obstet Gynecol 1996;174(5):1494–8.

[12] Vassilopoulou-Sellin R, Theriault R, Klein MJ. Estrogen replacement therapy in women with prior diagnosis and treatment for breast cancer. Gynecol Oncol 1997;65(1):89–93.

[13] Beckmann MW, Mohrmann T, Kuschel B. Hormone replacement therapy after breast cancer – results from an observational study. Gynakologische Tumoren 1998;58:193–6.

[14] Gorins A, Espie M, Bedairia N, et al. Hormonal replacement therapy in menopause after breast cancer: first french study. Contracept Fertil Sex 1998;26(10):696–9.

[15] 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(2):137–42.

[16] 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(5):1482–7.

[17] DiSaia PJ, Brewster WR, Ziogas A, Anton-Culver H. Breast cancer survival and hormone replacement therapy: a cohort analysis. Am J Clin Oncol 2000;23(6):541–5.

[18] Brewster WR, Ziogas A, Anton-Culver H. Breast cancer survival and hormone replacement therapy: a cohort analysis. Gynecol Oncol 2000;76:230–84 [Abs 3].

[19] Dew JE, Wren BG, Eden JA. Tamoxifen, hormone receptors and hormone replacement therapy in women previously treated for breast cancer: a cohort study. Climacteric 2002;5(2):151–5.
[20] Powles TJ, Hickish T, Casey S, O'Brien M. Hormone replacement after breast cancer. Lancet 1993;342(8862):60–1.
[21] Wile AG, Opfell RW, Margileth DA. Hormone replacement therapy in previously treated breast cancer patients. Am J Surg 1993;165(3):372–5.
[22] Decker D, Cox T, Burdakin J. Hormone replacement therapy (HT) in breast cancer survivors. Proc ASCO 1996;15:136 [Abs 209].
[23] Ursic-Vrscaj M, Bebar S. A case-control study of hormone replacement therapy after primary surgical breast cancer treatment. Eur J Surg Oncol 1999;25(2):146–51.
[24] Natrajan PK, Soumakis K, Gambrell Jr RD. Estrogen replacement therapy in women with previous breast cancer. Am J Obstet Gynecol 1999;181(2):288–95.
[25] Brewster WR, DiSaia PJ, Grosen EA, McGonigle KF, Kuykendall JL, Creasman WT. An experience with estrogen replacement therapy in breast cancer survivors. Int J Fertil Womens Med 1999;44(4):186–92.
[26] Espie M, Gorins A, Perret F. Hormone replacement therapy in patients treated for breast cancer: analysis of a cohort of 120 patients. Proc ASCO 1999;18:586a [Abs 2262].
[27] Guidozzi F. Estrogen replacement therapy in breast cancer survivors. Int J Gynaecol Obstet 1999;64(1):59–63.
[28] Bluming AZ, Waisman JR, Dosik GM, et al. Hormone replacement therapy in women with previously treated breast cancer: update VIII. Proc ASCO 2002;21:65a [Abs 259].
[29] Beckmann MW, Jap D, Djahansouzi S, et al. Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and reoccurrence rates. Oncology 2001;60(3):199–206.
[30] 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(3):217–25.
[31] O'Meara ES, Rossing MA, Daling JR, Elmore JG, Barlow WE, Weiss NS. Hormone replacement therapy after a diagnosis of breast cancer in relation to reoccurrence and mortality. J Natl Cancer Inst 2001;93(10):754–62.
[32] Peters GN, Fodera T, Sabol J, Jones S, Euhus D. Estrogen replacement therapy after breast cancer: a 12-year follow-up. Ann Surg Oncol 2001;8(10):828–32.
[33] 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(9):1817–26.
[34] Durna BM, Wren BG, Heller GZ, Leader LR, Sjoblom P, Eden JA. Hormone replacement therapy after a diagnosis of breast cancer: cancer reoccurrence and mortality. Med J Aust 2002;177(7):347–51.
[35] The Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer: an overview of the randomized trials. Lancet 1998;351:1451–65.
[36] Miller BA, Feuer EJ, Hankey BF. Recent incidence trends for breast cancer in women and the relevance of early detection: an update. Cancer 1993;43:27.
[37] Goodwin PJ, Ennis M, Pritchard KI, Trudeau M, Hood N. Risk of menopause during the first year of breast cancer diagnosis. J Clin Oncol 1999;17:2365–70.
[38] Fisher B, Costantino JP, Wickerham DL. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst 1998;90(18):1371.
[39] Carpenter JS, Johnson D, Wagner L, Andrykowski M. Hot flashes and related outcomes in breast cancer survivors and matched comparison women. Oncol Nurs Forum 2002;29(3):E16–25.
[40] Harris PF, Remington PL, Trentham-Dietz A, Allen CI, Newcomb PA. Prevalence and treatment of menopausal symptoms among breast cancer survivors. J Pain Symptom Manage 2002;23(6):501–9.
[41] Couzi RJ, Helzlsouer KJ, Fetting JH. Prevalence of menopausal symptoms among women with a history of breast cancer and attitudes towards estrogen replacement therapy. J Clin Oncol 1995;13:2737.
[42] Loprinzi CL, Kugler JW, Sloan JA, et al. Venlafaxine in management of hot flashes in survivors of breast cancer: a randomised control trial. Lancet 2000;132:788.
[43] Loprinzi CL, Sloan JA, Perez EA, et al. Phase III evaluation of fluoxetine for treatment of hot flashes. J Clin Oncol 2002;20(6):1578–83.
[44] MacLennan A, Lester S, Moore V. Oral oestrogen replacement therapy versus placebo for hot flushes. Cochrane Database Syst Rev 2001;(3).
[45] Stampfer MJ, Colditz GA, Willett WC, et al. Postmenopausal estrogen therapy and cardiovascular disease: 10-year follow up from the Nurses' Health Study. N Engl J Med 1991;325:756–62.
[46] Ray NF, Chan JK, Thamer M, Melton 3rd LJ. Medical expenditures for the treatment of osteoporotic fractures in the United States in 1995: report from the National Osteoporosis Foundation. J Bone Miner Res 1997;12:24.
[47] Olsson HL, Ingvar C, Bladstrom A. Hormone replacement therapy containing progestins given continuously increases breast carcinoma risk in Sweden. Cancer 2003;97:1387–92.
[48] Holmberg L, Anderson H, for the HABITS steering and data monitoring committees. HABITS (hormonal replacement therapy after breast cancer – is it safe?), a randomized comparison: trial stopped. Lancet 2004;363:453–5.
[49] Batur P, Thacker HL, Moore HC. Discussing breast cancer and hormone replacement therapy with women. Cleve Clin J Med 2002;69(11):838–44.

in Sweden they use mostly testo-derived progestins.