

Hormone replacement therapy after cancers

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Purpose of review

The role of female hormones in estrogen-dependent cancers has been debated for years. This is particularly true of breast cancer. Retrospective, case, and cohort control studies usually have suggested no influence. The Women's Health Initiative study in 2002, a prospective double-blind study, noted an increased risk of breast cancer if estrogen plus progesterone was given. In the estrogen-only arm of that study, a decreased (not significant) risk of breast cancer was noted. With this controversy, can estrogen be given safely to a woman who has been treated for breast cancer? The relation between endometrial cancer and unopposed estrogen is well established. With clear-cut evidence of this relation, is there evidence to suggest a role for replacement therapy in women who have been treated for endometrial cancer?

Recent findings

Several case-control and cohort studies have noted either no increased risk or actually less risk of recurrence in women taking estrogen after therapy after breast cancer. Although the general consensus is that such a recommendation is contraindicated, the data do not support this admonition. The current data suggest that replacement therapy can be given to the woman who has been treated for endometrial cancer.

Summary

There seems to be little if any risk in giving hormone replacement therapy to women who have had breast or endometrial cancer. There are no data to suggest that hormone replacement therapy is contraindicated in women who have been treated for cervical or ovarian cancer.

Keywords

breast cancer, endometrial cancer, estrogen, progesterone

Introduction

Can hormone replacement therapy (HRT) be given to patients who have had previous breast cancer? Many would say it is contraindicated, although data to support that admonition is lacking.

Breast cancer

A tremendous amount of data has been accumulated over the past couple of decades, both *in vitro* and *in vivo*, in an attempt to answer this question [1–3]. Epidemiologic studies, including both large and small studies, mostly observational in nature, have been reported as well as meta-analysis and re-analysis (and re-analysis of the re-analysis) [4,5,6*]. The results of these studies suggest that there is probably no benefit or risk with regard to the role of estrogen and its association with breast cancer [7]. Most of these data were based on estrogen alone, and although patients receiving estrogen plus progesterone were included, their numbers were small. The recently reported Women's Health Initiative (WHI) study (a prospective randomized double-blind study) suggested that estrogen plus progesterone does increase the risk of breast cancer. This was just statistically significant at the nominal level but lost its significance on adjusted analysis. This was heralded as the first prospective randomized double study, and even though it was not statistically significant, the increased risk ratio of 1.26 was widely publicized and caused considerable questions and anxiety by patients and physicians alike. An earlier double-blind randomized study found no increased risk of breast cancer – breast cancer was a secondary objective in patients with previous adverse cardiac events [8]. Several other studies of estrogen plus progesterone have shown mixed results, although in the literature evaluation of Bush *et al.* [4] from the last quarter of the 20th century, those studies that did evaluate estrogen plus progesterone separately had the same results as did the estrogen-alone study, which showed no increased risk of breast cancer in women taking estrogen [4]. In the WHI study on estrogen alone, the risk of breast cancer showed a risk ratio of 0.77 – not quite statistically significant – with a risk ratio of 0.72 in women 50 to 59 years of age [9**].

Clinical data from two similar but pertinent clinical situations seem applicable to this discussion. For many years, it was thought that if a woman received a diagnosis of breast cancer while she was pregnant, she was doomed to death. It was suggested that termination of pregnancy was warranted. Today, on the basis of clinical information, pregnancy has no effect on survival from breast cancer one way or the other. Termination of the pregnancy does not increase survival,

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Abbreviations

ERT estrogen replacement therapy
HRT hormone replacement therapy
NHT non-hormone therapy
WHI Women's Health Initiative

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and carrying the pregnancy to term is not detrimental. Likewise, it was thought that a woman with breast cancer should never have a subsequent pregnancy. Current data indicate that women who have had a subsequent pregnancy do not have a worse prognosis than do those who choose to not have future pregnancies [10]. The rationale for the original recommendations was based on the fear that the very high levels of hormones secondary to the pregnancy would increase the risk of rapid tumor growth or recurrence. This admonition seems unjustified today.

If estrogen replacement therapy (ERT) or HRT is a risk factor for breast cancer, one dichotomy that multiple studies have noted is a reduced mortality in breast cancer patients who have used replacement therapy prior to the diagnosis of breast cancer. These include data from large cohort studies (Nurses Health Study) and the Iowa Women's Study [11,12]. Nevertheless, conventional wisdom suggests that to offer women replacement therapy after breast cancer would be detrimental. In fact, the *Physicians Desk Reference* notes that breast cancer is a contraindication to replacement therapy, although it states as late as the 2003 edition that 'most studies have not shown a higher risk of breast cancer in women who have used estrogen at some time in their lifetime. Some studies do show an increased risk of breast cancer if taken for 10 years or more' [13]. This statement was dropped in the 2005 edition and was replaced with the WHI data (2002). Why the data from the original article were presented when the WHI has published scores of subsequent articles that in some instances change the original article's finding is unknown. Nevertheless, data to substantiate that replacement therapy is a contraindication in a woman who has had breast cancer are lacking in the *Physicians Desk Reference* or other literature.

It is interesting to note that there are at least six prospective randomized studies comparing tamoxifen with estrogen in the postmenopausal patient with advanced breast cancer [14,15]. All six studies note that the response rates and duration between tamoxifen and estrogen are similar. In three of the studies, those women who took estrogen had a considerably longer survival than did those who were taking tamoxifen, with one study noting 13.5 months longer survival. About a dozen studies have evaluated progestins in the treatment of metastatic breast cancer, and those results are equivalent to the overall response rate with tamoxifen [16,17]. Even when used in an adjuvant setting, estrogen did as well as tamoxifen and considerably better than a placebo with regard to the length of progression-free survival. It should be remembered that not very long ago, if a postmenopausal breast cancer patient had advanced disease or had experienced recurrence, estrogen was the first-line therapy. Many of these patients responded to estrogen. This was before we knew about estrogen receptor-positive and -negative tumors. The response rate probably correlated

with receptor status; therefore, the results of randomized studies between estrogen and tamoxifen should not be a surprise.

In several retrospective studies, HRT has been used after breast cancer (Table 1) [18–27]. These studies have demonstrated that ERT/HRT in patients after breast cancer can be given without a negative impact on survival. Hormones were given to these women mainly because of significant vasomotor symptoms that were having a major impact on their quality of life. Studies in patients after breast cancer have suggested that women are concerned about a possible recurrence if they take estrogen; nevertheless, a considerable number of them are using ERT or would consider such use for the treatment of considerable vasomotor symptoms. These retrospective studies have shown very low rates of recurrence or death. It is certainly appreciated that retrospective studies can be influenced by unintentional bias. To a large degree, these retrospective studies have a selection bias, but the selection bias is by the patients themselves.

In several case controlled/match controlled studies, recurrence and death in breast cancer patients taking replacement therapy after diagnosis was not different from those in the non-estrogen user (Table 2) [28–35].

In a cohort study by DiSaia and associates [36], there were 125 breast cancer patients identified who received HRT after the diagnosis of breast cancer. These were matched with 362 control individuals from the same geographic area (Table 3). Almost three fourths of the patients were taking estrogen plus progesterone. The risk of death was considerably lower in the estrogen users than in the non-estrogen users, with an odds ratio of 0.28 (CI = 0.11–0.71, $P = 0.01$). A study from a large health maintenance organization evaluated the conditions of 2755 women with breast cancer. Medical and pharmacy records were reviewed with regard to hormone use after the diagnosis of breast cancer [30]. Of these women, 173 eligible ERT/HRT users were identified for analysis. Four matched control individuals were identified for each of the breast cancer patients taking ERT/HRT. Both estrogen alone and estrogen plus progesterone were used. Breast cancer recurrences

Table 1. Hormone replacement therapy in women with breast cancer

Study	Recurrence no. (%)	Deaths
Stoll [18]	0/65 (0)	
Powles <i>et al.</i> [19]	2/35 (8)	0
Vassilopoulou-Sellin <i>et al.</i> [20]	1/49 (2)	0
Bluming <i>et al.</i> [21]	10/189 (5)	1 (1%)
Brewster <i>et al.</i> [22]	13/145 (9)	3 (2%)
Natrajan <i>et al.</i> [23]	2/50 (4)	3 (6%)
Wile <i>et al.</i> [24]	3/25 (12)	
Decker <i>et al.</i> [25]	6/61 (10)	
Guidozzi [26]	0/24 (0)	
Espie <i>et al.</i> [27]	5/120 (4)	

Table 2. Recurrence rates in breast cancer survivors treated with estrogen replacement therapy (ERT) or hormone replacement therapy

Study	Recurrences	
	ERT	Controls
DiSaia <i>et al.</i> [28]	6/41	6/82
Ursic-Vrscaj and Bebar [29]	4/21	5/42
O'Meara <i>et al.</i> [30]	16/174	101/695
Bluming <i>et al.</i> [31]	3/95	5/64
Beckmann <i>et al.</i> [32]	6/64	17/121
Natrajan and Gambrell [33]	4/69	6/32
Durna <i>et al.</i> [34]	44/286	247/836
Dew <i>et al.</i> [35]	6/69	330/1403
Total	89/662 (13.4%)	717/3275 (21.9%)

Retrospective, case-controlled, or matched controlled studies.

were diagnosed in 16 hormone users (9%) compared with 101 (15%) nonusers. The rate of recurrence was 17 per 1000 and 30 per 1000 women-years in users and nonusers, respectively. Comparisons of rates adjusted for multiple factors noted an RR of 0.50 (CI = 0.30–0.85). Five users (3%) and 59 nonusers (8%) died of their disease, with an adjusted RR of 0.34 (CI = 0.13–0.91). The total mortality noted an adjusted RR of 0.48 (CI = 0.29–0.78).

In a study from Australia, Durna and associates [34] monitored 1122 women with breast cancer for as long as 36 years (median 6.08 years). There were 286 women who used HRT for menopausal symptoms for as long as 6 years. Approximately half of the HRT users were taking continuous combined estrogen plus progesterone. More than half of the women (both users and nonusers) took tamoxifen. After adjustment for multiple variables that were found to be significantly associated with outcome, such as tumor size, age at diagnosis, and stage of disease, the group that used HRT after diagnosis had a significantly lower risk of recurrence or new breast cancer than did the nonusers (adjusted RR 0.62; CI = 0.43–0.87). The HRT group also had a significant lower risk of death due to breast cancer (RR = 0.40; CI = 0.22–0.72) and deaths due to all causes (RR = 0.34; CI = 0.19–0.59). The subanalysis of women who used combined HRT noted a significant lower risk of breast cancer deaths as well as deaths due to all causes.

A study by Decker *et al.* [37] identified 277 disease-free survivors of breast cancer who received ERT. Control individuals were matched for exact stage, recurrence-free periods similar to the period of ERT initiation, approximate age, and duration of follow-up. The mean time for breast cancer diagnosis to initiation of ERT was 3.61 years, and the mean duration of ERT was 3.7 years. These patients took ERT mainly for vasomotor symptoms. The type of symptom was identified prior to the commencement of ERT and evaluated for the effectiveness of ERT. Hot

Table 3. Hormone replacement therapy following breast cancer

Study	RR (CI)	
	Recurrence	Deaths
DiSaia <i>et al.</i> [36]		0.28 (0.11–0.71)
O'Meara <i>et al.</i> [30]	0.5 (0.30–0.85)	0.34 (0.13–0.91)

flashes were relieved in 92% of women, dyspareunia/vaginal dryness in 89%, and reactive depression/anxiety/mood change in 88%. A control group of 271 women were monitored for comparison and matched for stage of disease at the time of diagnosis, age and free of recurrent cancer for an interval of time that was at least the same interval as their ERT match. The clinical characteristics between the ERT group and the control groups were similar except that a larger number of estrogen receptor-positive patients was in the control group, and a significantly larger number received prior tamoxifen, also in the control group. Those taking ERT used prior ERT to a greater number than did the control women. With regard to ipsilateral primary/recurrence, contralateral breast cancer recurrence with systemic metastasis, there was no significant difference between the ERT and the control group. There were, however, significantly more deaths in the control group (6% compared with 3%, $P = 0.03$). There were 9 breast cancer deaths in the control group and 5 in the ERT group. The difference of survival time between the control and ERT groups was statistically significant ($P = 0.02$).

At least four prospective randomized studies have evaluated hormone therapy in women who have had breast cancer. In the 1990s, two randomized studies were started in the hope of answering the question whether HRT could safely be given to women who are breast cancer survivors. Interestingly, both of these studies originated in Sweden (the Hormonal Replacement Therapy After Breast Cancer—Is It Safe? (HABITS) study and the Stockholm study). The HABITS study was stopped and the initial report published as a letter in *Lancet* [38•]. The initial objective of the study was to investigate the safety of hormone therapy in the management of postmenopausal symptoms in breast cancer survivors. The study was directed only at women with climacteric symptoms, and they could be either premenopausal or postmenopausal. The secondary aims were to look at quality of life and risk of breast cancer deaths. The letter's main endpoint was any new breast cancer event. The study was stopped early (December 2003) because of an increased incidence of breast cancer events (recurrence/contralateral breast) in the hormone therapy group.

Although the HABITS study was a prospective randomized trial, there is much to be desired in the report. It was an open study, not a placebo-controlled non-blinded study. In fact, treatment was not prescribed in either the

hormone therapy arm or the non-hormone therapy (NHT) arm. Hormone therapy was suggested to be estrogen with or without progestogen of 'median potency,' which was not defined, and what was 'commonly given in the environment where the patient lives and the clinician works.' In the NHT arm, 'best symptomatic treatment without hormones should be used and could include clonidine, beta blockers, psychologic support, physical exercise, and acupuncture.' Local estrogens could be used, but 'natural products' should not. In 2002, because of the slow recruitment, the Stockholm study joined the HABITS study. At the time of evaluation, a total of 434 women had been randomized, but only 345 were reported because 89 (20%) had not had a single follow-up visit. After a median follow-up time of 2.1 years, there were 26 women in the hormone therapy group and 7 (as noted in the abstract, although the text states 8) in the NHT group with a new breast cancer event: HR 3.5 (CI = 1.5–8.1). The authors noted an HR of 1.8 (CI = 1.03–3.1) when both the HABITS and Stockholm studies were combined. This was above the original HR 1.36, which was thought to be the level at which the study should be stopped, on the basis of a non-inferiority study concept. It was originally thought that 1300 women were needed to test this hypothesis. The letter states that they were reporting only the HABITS enrollment, which had an HR of 3.3 (CI = 1.5–7.4). They removed the Stockholm enrollment but stated that the HR for that study was 0.82 (CI = 0.35–1.9). Given that most of the HABITS women were from Sweden, one wonders why there was such a different result from apparently the same population base. Unfortunately, the Stockholm study was also terminated at the same time as the HABITS study. The data above differ slightly in that Table 2 of the letter states that the HR was 3.5; however, the text notes it at 3.3.

Many problems occur in attempts to analyze the HABITS report. More than 20% of the women randomized were not included in this analysis because they had not had at least one follow-up visit. Mammograms and follow-up visits were suggested but apparently not required. Were those items equal in both groups? Did the hormone therapy group have better compliance with regard to mammograms than the NHT group? Compliance therapy was not detailed. Approximately one fifth of the women taking hormone therapy who experienced recurrence were not taking hormone therapy at the time of recurrence. How long did these women take hormone therapy before discontinuation, and what was the time relation to the time of recurrence? With very short follow-up times (2.1 years) knowledge about the length of hormone therapy in relation to randomization time and recurrence is important. Given that breast cancer can be in the breast for as long as 10 years or longer before diagnosis, it is reasonable to assume that the recurrence/contralateral breast cancers were present at the time of randomization.

Two of the most important risk factors in breast cancer are stage and lymph node status. These two items were not stratified at the time of randomization. Were they equal in the two groups? What was the receptor status in each group? Were they equal? Tamoxifen could be used and was stratified at randomization. Given that tamoxifen can have an impact on climacteric symptoms, was compliance the same in the two groups? The authors noted that the Cox proportion hazard model would be used in their analysis. No such data were given. Once this is done, the results could be different when presented. It is interesting to note that with four times the number of recurrences identified in the HRT group, there were more breast cancer deaths in the NHT group (3 and 4, respectively).

It is appreciated that such a study is difficult with low accrual, lenient guidelines for treatment, prognostic variables, and compliance. Still, this preliminary letter must be evaluated in that light and awaits thorough and final evaluation before credence can be given to it. Certainly, the commentary that accompanied this letter, which stated that this study 'can reasonably guide clinical practice of women with breast cancer' seems premature and without merit.

The other prospective studies noted in Table 4, although individually small, collectively had more women randomized than did the HABITS and Stockholm studies [39,40,41]. In these three studies, the recurrence was 6% in both the hormone and control groups.

In the United States this year, almost 50 000 women 50 years of age or younger will experience breast cancer. As part of their therapy, most will undergo cytotoxic chemotherapy. The vast majority will experience chemotherapy-induced amenorrhea. Although this is age related, the vast majority of those who do become amenorrheic never resume menstruation and therefore undergo premature chemotherapy-induced menopause. It is well recognized that premature surgical menopause usually results in more significant vasomotor symptoms than a natural menopause and that these symptoms last longer. There is no reason to believe that this would not also occur in chemotherapy-induced menopause. Although the admonition is that HRT in the post-cancer patient is contraindicated, this

Table 4. Recurrence rates in breast cancer survivors treated with estrogen replacement therapy (ERT) or hormone replacement therapy

Study	Recurrences	
	ERT	Controls
Vassilopoulou-Sellin <i>et al.</i> [39]	2/56	33/243
Marsden <i>et al.</i> [40]	2/51	1/49
Marttunen <i>et al.</i> [41]	7/88	5/43
Total	11/195 (6%)	39/435 (6%)

Prospective case-control studies.

observer is unaware of any data to substantiate that belief except for the HABITS study, which is believed to contain numerous flaws. The belief that HRT is absolutely contraindicated in this group of women who want replacement therapy because of significant symptoms may not be in their best interest. All the reported data except HABITS evaluating the post-breast cancer patient taking replacement therapy have either noted a benefit with regard to decreased breast cancer recurrence, breast cancer deaths, and total mortality or noted a neutral impact on these parameters. With the exception of the HABITS study, all the other data do not identify the deleterious effects of replacement therapy in the post-cancer patient. To deny such therapy for life-disturbing symptoms does not seem to be in their best interest. Today, survival from breast cancer is 80%; in women with stage I disease, 97% longtime survival is expected.

Unfortunately, with termination of the HABITS and the Stockholm study, a prospective double-blind randomized study with a large cohort monitored for an adequate period of time will probably never be done. Given the data presented, should HRT be denied to patients only on the basis of opinion? Many women who have had breast cancer may be interested in HRT. To not even discuss this and reject it out of hand for a patient who may be having significant vasomotor symptoms or who is several years beyond breast cancer therapy and may be interested in the preventive measures for bone and cancer that HRT can provide is unrealistic and not in the patient's best interest. As health care providers we should provide the known data to our patients and reject unproved opinions so that our patients may make the appropriate choices for themselves. Once those choices are made, we must be sensitive to their desires and be supportive of their decisions.

Endometrial cancer

It is well recognized that endometrial cancer is an estrogen-dependent neoplasm. Numerous studies in the literature have shown that unopposed estrogen significantly increases the risk for the development of endometrial cancer [42]. If progestin is added to the estrogen either continuously or for 10 days or longer of sequential therapy, this risk decreases to normal, or some studies have noted a protective effect [43]. To give replacement therapy to a woman who has been successfully treated for endometrial cancer in view of the above seems to be a contraindication. There are, however, no data to substantiate that statement. Several retrospective studies have been published. Creasman *et al.* [44] were the first to suggest in 1986 that HRT could be given to patients who had been previously treated for endometrial cancer (Table 5) [45–48]. The indication for this therapy was mainly to control vasomotor symptoms. There has been one match-controlled study in which 75 women with endometrial cancer who received replacement therapy after treatment were given replacement therapy

Table 5. Hormone replacement therapy (HRT) in patients with previous endometrial cancer

Study	Recurrences	
	HRT	No HRT
Creasman <i>et al.</i> [44]	1/47 (2%)	26/174 (15%)
Bryant [45]	0/20	
Baker [46]	0/31	
Lee <i>et al.</i> [47]	0/44	8/99 (8%)
Chapman <i>et al.</i> [48]	2/62 (3%)	6/61 (10%)

and were compared with a like number of individuals who did not receive hormone therapy [49]. The duration of hormone therapy was 83 months in the users and 63 months in the nonusers. The recurrence rate was 1% in the users and 15% in the nonusers ($P = 0.006$).

The only prospective randomized study was undertaken by the Gynecologic Oncology Group (GOG), in which patients who had been surgically staged and were found to have either a stage I or stage II cancer were eligible for randomization [50]. It was planned to have approximately 1000 patients in each arm, and approximately 1200 patients had been successfully randomized. At that time, which was about the time the WHI study was initially published, it was suggested that this study be stopped. That was done. In a preliminary report presented at the Society of Gynecologic Oncologists in 2004, it was noted that the recurrence rate in the ERT group was 2.3%, compared with 1.6% in a placebo group. Deaths due to endometrial cancer were 0.8% and 0.6%, respectively. Of interest is the fact that none of the patients in the ERT group had experienced breast cancer, whereas 3 in the placebo arm had. Currently, many gynecologic oncologists think that HRT is not contraindicated in the endometrial cancer patient who has been successfully treated for her neoplasm.

Ovarian cancer

There are no overwhelming data to suggest that HRT acts as an initiating or promoting factor in women who may experience ovarian cancer. Two recent meta-analyses have looked at HRT and subsequent ovarian cancer. One shows no increase in the RR of ovarian cancer in those women taking HRT (RR = 1.1; CI = 0.9–1.3) [51]. The other study shows a small but significant risk, with an RR of 1.15 (CI = 1.05–1.27) [52]. It was suggested in one meta-analysis that the use of estrogen for more than 10 years gives an increased RR of 1.27 (CI = 1.00–1.61), whereas the other noted no significant correlation with the duration of use. Of interest is the fact that pregnancy and the use of oral contraceptives reduce ovarian cancer. There are few studies on the use of HRT in patients with ovarian cancer, but in those few studies there are no reported differences in survival in patients treated in comparison with control individuals. The authors did note an improvement in the quality of life.

Cancer of the cervix

An association between the use of HRT and cervical cancer has never been documented. The study by Ploch [53] reported on 120 women who received HRT after treatment for stage I/II cervical cancer and showed no change in survival or disease-free interval at 5 years. HRT after treatment for cervical cancer is used quite frequently by the gynecologic oncology community.

Conclusion

The possible association of replacement therapy with regard to hormonally dependent cancers has been discussed for decades. There is general agreement that unopposed estrogen in a woman with a uterus does increase the risk of endometrial cancer severalfold. The rationale for using combined estrogen plus progesterone in such an individual is that in some studies the incidence of endometrial carcinoma is reduced to normal or even is protective against endometrial carcinoma. The data concerning its role in breast cancer are controversial. Most observational studies suggest no effect, although some show an increased risk and others note a decreased risk. Length of use and family history do not seem to be a factor. The WHI notes an increased breast cancer risk in women with a uterus who use estrogen plus progesterone, but in women without a uterus using estrogen alone, a decreased risk of breast cancer is noted.

With this background, one can understand the hesitation to use replacement therapy in patients after endometrial and breast cancers. This admonition against HRT has been very strong, although there has been a lack of data to support this view. The data presented suggest that replacement therapy can be given without detrimental effects, mainly on the basis of retrospective, case, or cohort controlled studies. One prospective double-blind study in patients with endometrial cancer enrolled approximately 1200 women of 2000 planned when the study was stopped, mainly as a result of the WHI study. Preliminary data suggest no increased risk of recurrence.

The HABITS study, which was a prospective but not double-blinded study, suggested an increased risk of recurrence, although patients were monitored for only a very short time (2.1 years). By contrast, the Stockholm study noted a decreased risk of recurrence in a small randomized study.

In the current climate it is doubtful that the definitive study will ever be done. As a result, we must rely on the published data. With regard to breast cancer, almost one fourth of females with this cancer will have their diagnoses made premenopausally. Treatment will, in most cases, result in a chemotherapy-induced menopause. In such situations, menopausal symptoms are usually more severe and may last longer than in natural menopause.

These individuals' quality of life may be severely affected, and hormones may improve that. Such women need to be made aware of the available data and not given only unsubstantiated bias. Once a woman is fully informed and her decision has been made, then we as health care providers need to support that decision.

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