Clinical practice guidelines for the care and treatment of breast cancer: 14. The role of hormone replacement therapy in women with a previous diagnosis of breast cancer

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Abstract

Objective: To provide information and recommendations to women with a previous diagnosis of breast cancer and their physicians regarding hormone replacement therapy (HRT).

Outcomes: Control of menopausal symptoms, quality of life, prevention of osteoporosis, prevention of cardiovascular disease, risk of recurrence of breast cancer, risk of death from breast cancer.

Evidence: Systematic review of English-language literature published from January 1990 to July 2001 retrieved from MEDLINE and CANCERLIT.

Recommendations:

- Routine use of HRT (either estrogen alone or estrogen plus progesterone) is not recommended for women who have had breast cancer. Randomized controlled trials are required to guide recommendations for this group of women. Women who have had breast cancer are at risk of recurrence and contralateral breast cancer. The potential effect of HRT on these outcomes in women with breast cancer has not been determined in methodologically sound studies. However, in animal and in vitro studies, the development and growth of breast cancer is known to be estrogen dependent. Given the demonstrated increased risk of breast cancer associated with HRT in women without a diagnosis of breast cancer, it is possible that the risk of recurrence and contralateral breast cancer associated with HRT in women with breast cancer could be of a similar magnitude.
- Postmenopausal women with a previous diagnosis of breast cancer who request HRT should be encouraged to consider alternatives to HRT. If menopausal symptoms are particularly troublesome and do not respond to alternative approaches, a well-informed woman may choose to use HRT to control these symptoms after discussing the risks with her physician. In these circumstances, both the dose and the duration of treatment should be minimized.

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Hormone replacement therapy (HRT) connotes treatment with either estrogen alone or estrogen with progesterone in postmenopausal women. Menopausal symptoms, such as hot flashes and vaginal dryness, and the potential long-term effects of estrogen deprivation are a concern to women with breast cancer, particularly those in whom menopause develops early as a result of adjuvant chemotherapy.

Traditionally, the use of HRT has been contraindicated in women with breast cancer because of the notion that the development and growth of breast cancer is

Research

Recherche

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The steering committee is part of Health Canada's Canadian Breast Cancer Initiative. A list of the committee members appears at the end of the article.

A patient version of these guidelines appears in Appendix 1.

estrogen dependent and that the introduction of HRT may increase the risk of breast cancer recurrence. The focus of this guideline is on whether it is safe to give HRT to women with breast cancer.

Methods

This guideline is based on a systematic review of the English-language literature published from January 1990 to July 2001 retrieved from MEDLINE and CANCERLIT. Medical subject headings used in the search were "breast," "breast neoplasms," "estrogen replacement therapy," "estrogens" and "hormone replacement therapy." For the purposes of this guideline we considered HRT as replacement with either estrogen alone or estrogen plus progesterone. Review articles and textbook chapters were also consulted, primarily to provide background information and to secure additional references. Rules of evidence as described by Sackett[1] were used for grading the levels of experimental studies. The initial draft was prepared by a writing committee and was revised according to feedback from several members of the Steering Committee on Clinical Practice Guidelines for the Care and Treatment of Breast Cancer. The document was then discussed by the entire steering committee at meetings in May and October 2001, and further revisions were made. The final document was approved by the steering committee.

Evidence from randomized trials (levels I and II) on the efficacy and safety of HRT in women with breast cancer is unavailable. Hence we first reviewed indirect evidence relating estrogen exposure to breast cancer and then considered the limited number of studies involving women with breast cancer who took HRT. For the suggested alternatives to HRT that can be considered by women with breast cancer, we reviewed the highest level of evidence available but did not conduct a comprehensive systematic review of the literature.

Recommendations (including evidence and rationale)

Safety of HRT in women with a previous diagnosis of breast cancer

- **Routine use of HRT (either estrogen alone or estrogen plus progesterone) is not recommended for women who have had breast cancer. Randomized controlled trials are required to guide recommendations for this group of women. Women who have had breast cancer are at risk of recurrence and contralateral breast cancer. The potential effect of HRT on these outcomes in women with breast cancer has not been determined in methodologically sound studies. However, in animal and in vitro studies, the development and growth of breast cancer are known to be estrogen dependent. Given the demonstrated increased risk of breast cancer associated with HRT in women without a diagnosis of breast cancer, it is possible that the risk of recurrence and contralateral breast cancer associated with HRT in women with breast cancer could be of a similar magnitude.**

Indirect evidence

Estrogen and progesterone in experimental studies

The basic biology of breast cancer indicates that estrogen contributes to its development. Many animal and in vitro studies have shown the development of breast cancer to be estrogen dependent.[2,3] Virtually all mouse mammary tumour models and mouse xenograft models as well as many in vitro cell lines are dependent on estrogen for their growth and spread. Data from animal and in vitro experiments concerning progesterone are less conclusive. In some studies progesterone had an inhibiting effect on breast cancer growth, whereas in other studies the reverse was true.[2–4]

Epidemiologic studies

Epidemiological data from case–control and cohort studies have shown that a number of factors related to estrogen or to estrogen and progesterone cycling are associated with increased risk of breast cancer.[5] These include the observations that early menarche and late menopause are associated with an increased risk of breast cancer and that premature menopause, whether natural or surgically induced, substantially reduces the risk of breast cancer.[6]

HRT in healthy women

More than 50 case–control and cohort studies of the association between HRT and breast cancer development have been carried out. Initially, the results seemed conflicting, but with longer use of HRT and with meta-analyses to examine these results, it has become clear that there is probably a relative risk of breast cancer of 1.3 or 1.4 associated with HRT use, particularly if the use is long term. The most recent analysis of data from 51 studies involving a total of 52 000 women with breast cancer and 108 000 women without breast cancer reported a 1.31 relative risk among long-term HRT users.[7] In addition, recent studies suggest that the addition of progesterone to estrogen increases the risk of breast cancer.[7–10]

Effect of estrogen removal in women with breast cancer

Ovarian ablation, presumably because it eliminates most estrogen production, results in a significant reduction in breast cancer recurrence and death (level I evidence).[11] Furthermore, it is felt that the enhanced effects of adjuvant chemotherapy in premenopausal women may relate, in part, to the induction of ovarian ablation by the cytotoxic drugs involved.[12]

Direct evidence

HRT in women with breast cancer

There have been 4 case series[13–16] (level V evidence) and 1 cohort study[17] (level III evidence) involving women with

early breast cancer who were given HRT to relieve menopausal symptoms (Table 1). Alleviation of these symptoms was observed in all of the patients. None of these small studies showed any obvious increase in risk of breast cancer recurrence related to HRT. In another small series, women with advanced breast cancer received a combination of estrogen and progesterone as anti-cancer therapy[18] (level V evidence).

In addition to these case series, 3 case–control studies have been conducted. In one, 25 case subjects were matched with 50 control subjects; no adverse effect of HRT on cancer-related deaths was detected.[19,20] In the second study a reduced risk of breast cancer recurrence was found in the HRT cohort, a result that may also be subject to potential bias from physician and patient selection of HRT.[21,22] In the most recent study 174 women with breast cancer who took HRT were identified from 2755 women with breast cancer enrolled in an HMO (Health Maintenance Organization).[23] Each HRT user was matched to 4 nonusers. The rates of breast cancer recurrence and death were statistically significantly lower among the HRT users than among the nonusers.

These reports show that data regarding HRT in women with breast cancer are scarce, that patients given HRT are probably highly selected and that these observations must be viewed as preliminary and uncontrolled. In addition, the mean follow-up time of published cases was relatively short, given that an increased risk of breast cancer in healthy women may be associated mainly with longer durations of HRT.

It is unknown whether the addition of tamoxifen to estrogen offers women with a history of breast cancer protection against any estrogen-induced increased risk of cancer recurrence. There are limited data on this issue. In a report by Powles and colleagues 2 of 35 women with breast cancer who took estrogen with tamoxifen experienced relapse (level V evidence).[16] Marsden and colleagues reported on a pilot study involving 100 women with menopausal symptoms and early breast cancer who were randomly assigned to receive HRT or no HRT for 6 months (level II evidence).[24,25] One of the 29 women who were also taking tamoxifen had breast cancer recurrence.

Clinical trials

In considering trials of HRT use, one must recognize that women with a previous diagnosis of breast cancer will not accept much increased risk of recurrence in order to take HRT.[26,27] Three randomized trials are now underway. The HABITS study (opened in 1996), a second Swedish study (opened in 1998) and a British study (opened in 2001) are each assigning women with breast cancer to HRT or no HRT for 2 years. Until results from these randomized trials are available increased risk related to HRT for women with a prior diagnosis of breast cancer cannot be ruled out.

Alternatives to HRT

- **Postmenopausal women with a previous diagnosis of breast cancer who request HRT should be encouraged to consider alternatives to HRT. If menopausal symptoms are particularly troublesome and do not respond to alternative approaches, a well-informed woman may choose to use HRT to control these symptoms after discussing the risks with her physician. In these circumstances, both the dose and the duration of treatment should be minimized.**

If HRT is to be considered, factors that may be included in the decision-making process include low-risk disease and long disease-free interval.

There are alternatives to the use of HRT in women with a previous diagnosis of breast cancer to relieve menopausal symptoms and to prevent osteoporosis.[28–30] Strategies to deal with menopausal symptoms and osteoporosis are briefly discussed here. In addition to describing approaches that are effective, some strategies that are of no benefit are also mentioned.

Menopausal symptoms

Vaginal dryness and local menopausal symptoms can be significantly reduced with the use of K-Y Jelly and Replens (level II evidence).[31]

Urogenital atrophy in women without breast cancer has been treated safely and effectively with estriol creams and estradiol vaginal rings (e.g., Estring) (level I evidence).[32–34] In the case of creams, bolus systemic absorption of higher estrogen concentrations may occur from intermittent applications. Vaginal rings provide more controlled local delivery with their continuous release of very low doses of estradiol (< 10 mg/24 h), and the observed steady-state levels of systemic plasma concentrations have been found to

Table 1: Studies of the treatment of menopausal symptoms in women with breast cancer*

Study	Treatment	No. of patients	% of patients with outcome†
DiSaia et al[13]	HRT	41	6
	No HRT	82	7
Decker et al[14]	HRT	61	7
Bluming et al[15]	HRT	171	8
Powles et al[16]	HRT	35	2
Vassilopoulou-Sellin et al[17]	HRT	39	1
	No HRT	280	14
Stoll[18]	Combined estrogen/progesterone oral contraceptive	53	Remission of tumour growth in 22% of cases

*All studies were case series except for reference 17, which was a prospective cohort design. All patients had early breast cancer except those in reference 18, who had metastatic breast cancer.
†Systemic or ipsilateral recurrence of breast cancer or new contralateral breast cancer.

be within the upper limits of those seen in untreated postmenopausal women.[35]

Hot flashes can be treated with a variety of nonhormonal therapies:

- *Vitamin E:* A placebo-controlled trial demonstrated that vitamin E (800 IU/d) achieved a statistically significant reduction in hot flashes over placebo (level I evidence).[36] However, this reduction may have been due in part to a placebo effect, since the decrease amounted to 1 hot flash per person per day.
- *Clonidine:* In a placebo-controlled trial, clonidine reduced the frequency of hot flashes by about 15% compared with placebo (level I evidence),[37] but it was associated with a statistically significant amount of toxicity. At the study's end patients did not prefer clonidine over placebo.
- *Venlafaxine (Effexor):* Low doses of venlafaxine (37.5 mg in a sustained-release preparation) substantially reduced the frequency of hot flashes and was well tolerated in a randomized trial (level I evidence).[38]
- *Soy phytoestrogens:* A recently completed placebo-controlled trial did not show that soy protein significantly reduced the severity or frequency of hot flashes when compared with placebo (level I evidence).[39]
- *Other compounds:* Compounds such as black cohash and Bellergal (a combination of belladonna, ergotamine and phenobarbital) have been used, but these have not undergone placebo-controlled trials to illustrate benefits and toxicities.
- *Megestrol acetate:* A placebo-controlled trial that evaluated a low dose of the progestational agent megestrol acetate demonstrated a reduction in the frequency of hot flashes by about 80% (level I evidence).[40] The therapy was well tolerated in this short-term double-blind, crossover clinical trial, and women significantly preferred megestrol acetate over the placebo. However, many animal and in vitro studies have shown that progestational agents may increase or accelerate breast cancer development or progression, and progesterone has been clearly identified as a cause of breast cancer in women.[2–4] As with estrogen, there are no good data to demonstrate whether low doses of megestrol acetate in women with a previous diagnosis of breast cancer increase or decrease the risk of recurrence, or have no effect. Progestational agents should be regarded with the same degree of caution as estrogen when recommending treatment to patients with a previous diagnosis of breast cancer.

Osteoporosis

Osteoporosis can now be prevented and treated with a number of approaches that do not involve estrogen or progesterone. Diet, exercise and appropriate calcium intake are important factors in the prevention of osteoporosis,[41,42] and a wide array of bisphosphonates inhibit bone absorption and normalize bone turnover. Such agents have been used in women with breast cancer (level I evidence).[43–45]

Raloxifene, like tamoxifen, is a selective estrogen receptor modulator that has been approved recently for the treatment and prevention of osteoporosis. It provides somewhat less of a beneficial effect on bone density than HRT and does not relieve menopausal symptoms (level I evidence).[46] Given that raloxifene is a selective estrogen receptor modulator, it could potentially affect breast cancer recurrence, but the direction and magnitude of any effect is unknown. Therefore, raloxifene cannot be routinely recommended to prevent osteoporosis in a woman with breast cancer.

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A patient guide to the use of hormone replacement therapy in women who have had breast cancer appears on page 1022.

Appendix 1

Questions and answers on the use of hormone replacement therapy (HRT) by women who have had breast cancer

A guide for women and their physicians

What is hormone replacement therapy?

Hormone replacement therapy (HRT) refers to treatment with pills or skin patches that contain the hormone estrogen or the hormones estrogen and progesterone combined. Hormones are chemicals that affect the activity of certain cells or organs. For example, both estrogen and progesterone play an important role in a woman's life, regulating menstrual periods and affecting the growth of breast tissue. These hormones are produced in the ovaries, but they can also be made in a laboratory or obtained from plants and animals.

Why is HRT prescribed?

As women leave their child-bearing years behind, they begin to produce less estrogen and progesterone. Lack of estrogen can lead to unpleasant menopausal symptoms such as hot flashes and vaginal dryness. A lack of estrogen can also contribute to osteoporosis (the loss of bone tissue). HRT is often prescribed to relieve menopausal symptoms and reduce the risk of osteoporosis. HRT may also be prescribed when a woman experiences premature menopause, whether naturally or as the result of medical treatment.

I have been treated for breast cancer in the past. I am now having hot flashes and other menopausal symptoms. Should I take HRT?

Probably not. At present, too few studies of HRT use by women with breast cancer have been completed. In addition, the study results available do not indicate whether HRT is safe for women who have had breast cancer.

Why is HRT considered unsafe for women who have had breast cancer?

Researchers know that estrogen plays a role in the development of breast cancer. Studies using animals have shown that estrogen affects breast cancer growth. Other kinds of studies have shown that women exposed to more estrogen throughout life — for example, women who begin their periods at an early age or enter menopause at a late age — are at increased risk of breast cancer. Studies have also shown that women who have never had breast cancer increase their risk of the disease if they take HRT for an extended period. The risk of breast cancer increases for each year of use. A woman who has had breast cancer is at risk of having the cancer return or of developing another cancer in the opposite breast. This knowledge, combined with research findings about estrogen, has led to a concern that HRT could trigger the recurrence of breast cancer in a woman who has already had the disease.

Are there alternatives to HRT?

Yes. Several alternative treatments have been studied and found to relieve menopausal symptoms:

- *Hot flashes:* Venlafaxine, a relatively new antidepressant medication marketed as Effexor.
- *Vaginal dryness:* K Y lubricating jelly and Replens, a vaginal moisturizer.
- *Sexual and urinary problems:* Estradiol vaginal rings such as Estring, which provide controlled local delivery of very low doses of estrogen. (Creams are not recommended because the estrogen in them passes into the blood, and this can lead to high concentrations of estrogen in the body.)

Other alternative treatments have been found to improve bone mass and reduce the risk of osteoporosis:

- Exercise, a diet rich in calcium, and appropriate mineral and vitamin supplements.
- Bone-strengthening drugs called bisphosphonates.

One drug used to treat osteoporosis that is not recommended for women who have had breast cancer is raloxifene, a selective estrogen receptor modulator. Although it is similar to tamoxifen, a drug commonly used in the treatment of breast cancer, there are no studies supporting raloxifene's use in women with breast cancer.

Are there other alternatives not mentioned here?

Yes. There are alternative treatments not mentioned here, including various hormone preparations, herbs and vitamins. Some of these therapies for menopausal symptoms have been studied and found to be ineffective or potentially harmful, while others have not been studied enough and cannot be recommended yet.

What can I do if alternatives to HRT do not help?

If your menopausal symptoms are particularly troublesome and they are not relieved by any of the alternative approaches listed here, you might want to discuss HRT with your doctor. You will need to talk about many things, including when you had cancer, what kind of cancer you had and how your cancer was treated. You will need to weigh the risk of having your breast cancer return or of developing another cancer in the opposite breast against your present discomfort. If you decide to use HRT, your doctor will probably suggest a low dose and a short treatment period.