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Use of Hormonal Replacement Therapy After Treatment of Breast Cancer

This guideline has been reviewed by the Breast Disease Committee and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To review the use of hormonal replacement therapy (HRT) after treatment of breast cancer.

Options: The effect and role of estrogens on breast cancer.

Outcome: Improved health and quality of life for women with breast cancer.

Values: References were collected through MEDLINE searches up to 2002.

Evidence: The level of evidence and quality of recommendations have been determined using the criteria described by the Canadian Task Force on the Periodic Health Examination.

Benefits, Harms, and Costs: Utilization of the information to make a proper risk-benefit assessment of HRT use in women with breast cancer.

Recommendations:

1. HRT after treatment of breast cancer has not been demonstrated to have an adverse impact on recurrence and mortality. (II-2B)
2. HRT is an option in postmenopausal women with previously treated breast cancer. (II-2B)
3. Prospective, randomized clinical trial results are needed. (III-A)

Validation: Recommendations were reviewed and revised by the Breast Disease Committee of the Society of Obstetricians and Gynaecologists of Canada (SOGC) and approved by the Executive and Council of the SOGC.

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Key Words
Hormone replacement therapy, breast cancer

INTRODUCTION

Although the incidence of breast cancer increases with age, with 75% of cases occurring after the age of 50,[1] an increasing number of young women with breast cancer experience postmenopausal symptoms due to chemotherapy that causes ovarian failure.[2] These women may experience bothersome and potentially debilitating menopausal symptoms such as hot flashes, mood and sleep disturbances, memory impairment, and sexual dysfunction.[3] Early menopause also increases the risks of osteoporosis and coronary heart disease.[4] Prescribing hormone replacement therapy (HRT) relieves menopausal symptoms and protects against osteoporosis.[5] The reduction in risk of colon cancer is strongest among current users and there is a significant trend of decreasing risk with increasing years of estrogen use among all users.[6]

The level of evidence and quality of recommendations in this document have been determined using the criteria described by the Canadian Task Force on the Periodic Health Examination (Table 1).[7]

ESTROGEN AND BREAST CANCER RISK

In vitro studies imply that estrogens can act as cell-proliferating agents by acting on promoter sites of cellular regulatory genes.[8] Estrogens can stimulate the growth of breast cancer cells in tissue culture, but can inhibit growth at high doses[8]; however, a direct carcinogenic effect of estrogens has not been demonstrated.[9] Endogenous production of female sex hormones and

FOR INFORMATION ON THE SELF-DIRECTED LEARNING EXERCISE, SEE PAGE 62.

the development of breast cancer have been linked by the fact that breast cancer is 180 times more frequent in women than in men and that most risk factors associated with an increased evidence of breast cancer relate to reproductive processes such as early menarche, late menopause, having a first child at a late age, and being nulliparous.[10]

Tamoxifen, a non-steroidal that has anti-estrogenic effects on the breast, reduces the risk of contralateral breast cancers in women with a history of breast cancer and decreases the risk of breast cancer in women at high risk for the disease by 50%.[11]

Prophylactic oophorectomy has been shown to reduce the risk of breast cancer.[12] A randomized, prospective study, however, suggested that the use of HRT did not affect the reduction in breast cancer risk after bilateral oophorectomy surgery among carriers of BRCA1 mutations.[13]

A reanalysis of 54 epidemiological studies on oral contraceptives (OCs) and breast cancer demonstrated a small increase in the relative probability of having breast cancer diagnosed in current users of OCs.[14] Some association was found between an increased probability for breast cancer diagnosis and OC use at an early age before the first pregnancy.[14] The breast cancers diagnosed in current or past OC users (up to 20 years after the use of OCs) were more likely to remain localized to the breast, show fewer metastases, and be clinically less advanced with increased survival, than those diagnosed in women who have never used OCs. A recent study showed an increase in breast cancer among OC users who have a first-degree relative with breast cancer.[15]

It has also been reported that pregnancy transiently increased the probability for breast cancer diagnosis after giving birth, with a reduced risk later in life.[16] Women who had been pregnant 1 to 2 years before or are pregnant at the time of their breast cancer diagnosis do not appear to have a worse prognosis than nonpregnant women, when matched for age and stage.[17] An increased mortality from breast cancer, diagnosed during pregnancy in young women (20 to 29 years of age), has been reported.[18] Women becoming pregnant after treatment for their breast cancer have been reported to have similar or even improved prognosis, in comparison with breast cancer survivors who subsequently never become pregnant.[19] Further information can be found in the guidelines entitled *Breast Cancer, Pregnancy, and Breastfeeding*, developed by the Breast Disease Committee of the Society of Obstetricians and Gynaecologists of Canada.[20]

Reanalysis of the individual data from 51 epidemiological studies demonstrated that the probability of having breast cancer diagnosed is increased by 2.3% per year of HRT use.[21] For each year that the menopause is delayed, a similar increase in probability has been found to be 2.8%.[21] The number of extra cases of breast cancer associated with risk factors beyond baseline risk[21,22] are outlined in Table 2.

The Women's Health Initiative (WHI) trial after 5.2 years observed a 26% increase (38 vs 30 per 10 000 person-years) in invasive breast cancers in the estrogen plus progestin group, which almost reached nominal statistical significance. No significant difference was observed for in situ breast cancers.

TABLE 1

QUALITY OF EVIDENCE ASSESSMENT[7]	CLASSIFICATION OF RECOMMENDATIONS[7]
The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Examination. I: Evidence obtained from at least one properly randomized controlled trial. II-1: Evidence from well-designed controlled trials without randomization. II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group. II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category. III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.	Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Canadian Task Force on the Periodic Health Examination. A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination. B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination. C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds. D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination. E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.

TABLE 2

BREAST CANCER RISK AND HRT: RESULTS FROM THE REANALYSIS OF EPIDEMIOLOGICAL STUDIES BY THE COLLABORATIVE GROUP ON HORMONAL FACTORS IN BREAST CANCER (1997) AND THE CANADIAN CONSENSUS ON MENOPAUSE AND OSTEOPOROSIS[21,22*]

Risk Factor	Breast Cancers Diagnosed Over the 20 Years from Ages 50 to 70	Extra Breast Cancers
Never used HRT	45/1000	—
>5 years' HRT use	47/1000	2/1000
>10 years' HRT use	51/1000	6/1000
>15 years' HRT use	57/1000	12/1000
Late menopause (age 60)	59/1000	14/1000
Alcohol (2 drinks/day)	72/1000	27/1000
No daily exercise	72/1000	27/1000
Weight gain (>20 kg)	90/1000	45/1000

*Data from V. Beral and the Collaborative Group on Hormonal Factors in Breast Cancer.[21] Table was adapted from Table 1, Bélisle and Derzko, *Hormone Replacement Therapy and Cancer*,[22] and appears by permission of the Society of Obstetricians and Gynaecologists of Canada.

The estrogen-only arm of WHI is still continuing.[23]

In the Heart and Estrogen/progestin Replacement Study (HERS), there was no significant difference between the treatment groups in the rates of breast cancer, but the power was limited.[24]

The Breast Cancer Demonstration Project[25] stated that the relative risk (RR) of developing breast cancer on estrogen plus progestin (RR = 1.3) was greater than that with estrogen alone (RR = 1.1). This breast cancer report was retrospectively derived from a mammography screening database, and the single point that had statistical significance that led to the conclusion of the paper was based on only 22 cases. A case-controlled study[26] reported intriguing but nonsignificant trends toward a lower relative risk with continuous progestin addition than with intermittent addition; this positive conclusion was based on 20 cases only.

In intent-to-treat analysis from WHI, it was found that the breast cancers diagnosed in the estrogen plus progestin group were similar in the histology and grade but were larger and at a more advanced stage compared with those diagnosed in the placebo group.[27] After one year, the percentage of women with abnormal mammograms was substantially greater in the estrogen plus progestin group compared with the placebo group, a pattern which continued for the study duration.[27]

Women using unopposed estrogen replacement therapy (ERT), that is, exclusive ERT use, even for 25 years or longer, had no appreciable increase in risk of breast cancer.[28] However, the meta-analysis by the Collaborative Group on Hormonal Factors in Breast Cancer did find that current use of ERT for 5 years or longer was associated with a 1.34-fold increased risk of breast cancer.[21] This meta-analysis was limited, though, in that data on the type of HRT used were only available for 39% of the eligible women, and because the analysis was not restricted to women who were exclusive users of ERT. As a result, some of the association that was observed may have been due to mixing of the effects of ERT use with combined HRT use (CHRT).

Evidence is mounting regarding the adverse impact on breast cancer risk of adding progestin to HRT. This adverse impact appears to be manifest within several years of initiating use of CHRT, and to be similar in magnitude irrespective of the pattern of CHRT (continuous or sequential).[28]

HRT AND BREAST CANCER

A woman who has been treated for breast cancer and is thinking about taking HRT should understand the likelihood of recurrence over time. The data from the Eastern Co-operative Oncology Group showed that women with positive axillary nodes had a very high risk of recurrence between years 1 and 2, with a gradual drop-off between years 4 and 5. There was a 5% annual risk of recurrence even up to 9 years. In the population of women with negative nodes, however, the annual risks decreased to as low as 0% after 5 years.[29]

Canney and Hatton[30] surveyed 108 women successfully treated for breast cancer to discover the prevalence of menopausal symptoms, using the Greene Climacteric Scale. During the first year after treatment, 70% of women suffered from menopausal symptoms, and overall, 60% of the women surveyed were affected. The challenge for physicians involved in the care of women with breast cancer is to develop treatment strategies that reduce not only the risk of tumour recurrence but also the risk of cardiovascular and osteoporotic disease, while preserving the quality of life.

Breast cancer is common, and for a small number of women, menopausal symptoms are so severe that they will choose to take

HRT to improve their quality of life despite any theoretical risks. Therefore, it is important to provide them with the information we have available at present to allow the breast cancer survivor to make an informed choice about HRT use. All the previous studies have been either open, case-control, or cohort, and what is needed is a large randomized, double-blinded clinical trial. Presently, there is the Hormonal Replacement Study after Breast Cancer: Is It Safe? (HABITS), which is randomized with 1300 women enrolled in Europe and pilot studies being conducted in Britain and the United States. Despite the inherent limitations of the retrospective data, the results of most studies show that HRT after treatment of breast cancer has no adverse impact on recurrence and mortality.

An overview of some of the latest clinical studies[31-38] of breast cancer survivors who have been prescribed HRT on breast cancer prognosis is presented in Table 3. However crude, and open to treatment bias, these data do not demonstrate HRT to be associated with an increased recurrence of breast cancer. One anecdotal study[39] on 4 women with breast cancer reported that cessation of HRT halted progression of breast cancer recurrence. Reviewing the studies from the past 2 years, HRT appears to have no significant effect on breast cancer recurrence.

DiSaia *et al.*,[31] using Kaplan-Meir survival analysis for predicted survival rates at 5 and 10 years, observed no adverse effects associated with using HRT after breast cancer. Col *et al.*[36] performed a systematic literature review through May 1999, calculating relative risk of breast cancer recurrence in each study. Their analysis suggests that HRT has no significant effect on breast cancer recurrence, but these findings were based on observational data subject to a variety of biases. A study from the Group Health Co-operative of Puget Sound[37] demonstrated the rate of breast cancer recurrence to be 17 per 1000 person-years in women who used HRT after diagnosis, and 30 per 1000 person-years in non-users of HRT. Breast cancer mortality rates were 5 per 1000 person-years in HRT users and 15 per 1000 person-years in non-users. Total mortality rates were 16 per 1000 person-years in HRT users and 30 per 1000 person-years in non-users. The results suggest that HRT after breast cancer has no adverse impact on recurrence and mortality. Beckmann *et al.*,[38] in a retrospective study, demonstrated a reduction in postmenopausal symptoms, especially in the subgroup of women less than 50 years of age, and positive effect on bone mineral density with the use of HRT after breast cancer diagnosis. There was no significant influence on morbidity or mortality. When reviewing the studies, the HRT treatment group and non-users did not differ with regard to tumour stage, lymph node involvement, metastasis, tumour grading, and steroid receptor status. The mean interval between the diagnosis of breast cancer and initiation of HRT was 48 months (range, 0–114 months). The relatively low rates of recurrence and death were observed in women who used any type of HRT, and there was no increased relative risk with increased dose.[37]

An important question is whether estrogens interfere with the efficacy of cytotoxic chemotherapy in women with breast cancer, and thus, with breast cancer prognosis. Tamoxifen can

TABLE 3

HRT USE IN WOMEN WITH BREAST CANCER*

Reference	Women per Treatment	Women with Recurrence: RR (%)	No. of Deaths (%)
Eden[32]	90 HRT 180 no HRT	6/90 (7) 31/180 (19)	0/90 11/180 (6)
Vassilopoulou-Sellin[33]	38 HRT 280 no HRT	1/38 (2.4) 20/280 (7)	0 0
Ursic-Vrscaj[34]	21 HRT 42 no HRT	4/21 (19) 5/42 (12)	0 1/42 (2.4)
Brewster[35]	145 HRT	13 (9)	3 (2)
DiSaia[31]	155 HRT 446 no HRT		7%† 18%†
Col[36]	214 HRT 623 no HRT	17/214 (7.9) 66/623 (10.6)	
O'Meara[37]	916 HRT 3356 no HRT	16/916 (1.7) 101/3356 (3)	5/1050 59/3855
Beckmann[38]	64 HRT 121 no HRT	6/64 (9) 17/121 (14)	4/64 (6) 15/121 (13)

*RR: relative risk
†after 10 years

precipitate or worsen vasomotor and vaginal symptoms.[40] In the British Breast Cancer Prevention Trial, which used tamoxifen as the preventative agent, the women who experienced hot flashes were given HRT for relief.[41] The HRT and tamoxifen administered simultaneously had no ill effect.[42] In a randomized trial[43] of women with advanced breast cancer, the addition of estrogens did not adversely influence the beneficial effects of chemotherapy. The efficacy of the management of breast cancer is not negatively influenced by the presence of estrogens at concentrations considerably higher than those attained with current HRT preparations.

CONCLUSIONS

The opinion that estrogens and estrogen treatment are deleterious for breast cancer needs to be refocused. Knowing the current data, a proper risk-benefit assessment of HRT use in women with risk factors for breast cancer or in women diagnosed with a breast cancer needs to be presented. We need to wait for the prospective, randomized clinical trials that are presently ongoing to have a definitive conclusion.

RECOMMENDATIONS

1. **HRT after treatment of breast cancer has not been demonstrated to have an adverse impact on recurrence and mortality. (II-2B)**
2. **HRT is an option in postmenopausal women with previously treated breast cancer. (II-2B)**
3. **Prospective, randomized clinical trial results are needed. (III-A)**

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