HRT after Breast Cancer

General Review

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Breast cancer risk with postmenopausal hormonal treatment

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This review was designed to determine from the best evidence whether there is an association between postmenopausal hormonal treatment and breast cancer risk. Also, if there is an association, does it vary according to duration and cessation of use, type of regimen, type of hormonal product or route of administration; whether there is a differential effect on risk of lobular and ductal cancer; and whether hormone treatment is associated with breast cancers that have better prognostic factors? Data sources for the review included Medline, the Cochrane Database of Systematic Reviews (Cochrane Library, 2005) and reference lists in the identified citations. Eligible citations addressed invasive breast cancer risk among postmenopausal women and involved use of the estrogen products with or without progestin that are used as treatment for menopausal symptoms. Abstracted data were demographic groupings, categories of hormone use, categories of breast cancer, two-by-two tables of exposure and outcome and adjusted odds ratios, relative risks (RRs) or hazard rates. Average estimates of risk were weighted by the inverse variance method, or if heterogeneous, using a random effects model. The average risk of invasive breast cancer with estrogen use was 0.79 [95% confidence interval (95% CI) = 0.61–1.02] in four randomized trials involving 12 643 women. The average breast cancer risk with estrogen–progestin use was 1.24 (95% CI = 1.03–1.50) in four randomized trials involving 19 756 women. The average risks reported in recent epidemiological studies were higher: 1.18 (95% CI = 1.01–1.38) with current use of estrogen alone and 1.70 (95% CI = 1.36–2.17) with current use of estrogen–progestin. The association of breast cancer with current use was stronger than the association with ever use, which includes past use. For past use, the increased breast cancer risk diminished soon after discontinuing hormones and normalized within 5 years. Reasonably adequate data do not show that breast cancer risk varies significantly with different types of estrogen or progestin preparations, lower dosages or different routes of administration, although there is a small difference between sequential and continuous progestin regimens. Epidemiological studies indicate that estrogen–progestin use increases risk of lobular more than ductal breast cancer, but the number of studies and cases of lobular cancer remains limited. Among important prognostic factors, the stage and grade in breast cancers associated with hormone do not differ significantly from those in non-users, but breast cancers in estrogen–progestin users are significantly more likely to be estrogen receptor (ER) positive. In conclusion, valid evidence from randomized controlled trials (RCTs) indicates that breast cancer risk is increased with estrogen–progestin use more than with estrogen alone. Epidemiological evidence involving more than 1.5 million women agrees broadly with the trial findings. Although new studies are unlikely to alter the key findings about overall breast cancer risk, research is needed, however, to determine the role of progestin, evaluate the risk of lobular cancer and delineate effects of hormone use on receptor presence, prognosis and mortality in breast cancer.

Key words: breast cancer/duration of use/estrogen/progestin/recency/relative risk

Introduction

A serious adverse event associated with treatment of a common disorder has public health significance. The incidence of breast cancer, which is the most common cancer in women, is highest after the menopause. Menopausal symptoms affect more than 50% of women, and estrogen treatment (E) with or without a progestin is the most effective therapy (Greendale *et al.*, 1998). After years of uncertainty, a 1997 review defined the association between hormonal treatment and breast cancer risk based on data from 51 epidemiological studies (Collaborative Group on Hormonal Factors in Breast Cancer, 1997). Breast cancer risk increased by 2.3% per

HRT after Breast Cancer

For HRT

J Clin Oncol. 1999 May;17(5):1482-7. Full Text J Clin Oncol Links

Estrogen replacement therapy after localized breast cancer: clinical outcome of 319 women followed prospectively.

Vassilopoulou-Sellin R, Asmar L, Hortobagyi GN, Klein MJ, McNeese M, Singletary SE, Theriault RL.

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PURPOSE: To determine whether estrogen replacement therapy (ERT) alters the development of new or recurrent breast cancer in women previously treated for localized breast cancer. PATIENTS AND METHODS: Potential participants (n = 319) in a trial of ERT after breast cancer were observed prospectively for at least 2 years whether they enrolled onto the randomized trial or not. Of 319 women, 39 were given estrogen and 280 were not given hormones. Tumor size, number of lymph nodes, estrogen receptors, menopausal status at diagnosis, and disease-free interval at the initiation of the observation period were comparable for the trial participants (n = 62) versus nonparticipants (n = 257) and for women on ERT (n = 39) versus controls (n = 280). Cancer events were ascertained for both groups. RESULTS: Patient and disease characteristics were comparable for the trial participants versus nonparticipants, as well as for the women on ERT versus the controls. One patient in the ERT group developed a new lobular estrogen receptor-positive breast cancer 72 months after the diagnosis of a ductal estrogen receptor-negative breast cancer and 27 months after initiation of ERT. In the control group, there were 20 cancer events: 14 patients developed new or recurrent breast cancer at a median time of 139.5 months after diagnosis and six patients developed other cancers at a median time of 122 months. CONCLUSION: ERT does not seem to increase breast cancer events in this subset of patients previously treated for localized breast cancer. Results of randomized trials are needed before any changes in current standards of care can be proposed.

J Clin Oncol. 2001 Apr 15;19(8):2357-63. Full Text J Clin Oncol Links

Hormone replacement therapy after breast cancer: a systematic review and quantitative assessment of risk.

Col NF, **Hirota LK**, **Orr RK**, **Erban JK**, **Wong JB**, **Lau J**.

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PURPOSE: Hormone replacement therapy (HRT) is typically withheld from women with breast cancer because of concern that it might increase the risk of recurrence. The purpose of this study was to quantify the risk of recurrent breast cancer associated with HRT among breast cancer survivors. METHODS: We performed a systematic literature review through May 1999, calculating the relative risk (RR) of breast cancer recurrence in each study by comparing the number of recurrences in the HRT group to those in the control group. In studies that did not contain a control group, we constructed one by estimating the expected number of recurrences based on data from the Early Breast Cancer Trialists' Collaborative Group, adjusting for nodal status and disease-free interval. RRs across all studies were combined using random-effects models. RESULTS: Of the 11 eligible studies, four had control groups and included 214 breast cancer survivors who began HRT after a mean disease-free interval of 52 months. Over a mean follow-up of 30 months, 17 of 214 HRT users experienced recurrence (4.2% per year), compared with 66 of 623 controls (5.4% per year). HRT did not seem to affect breast cancer recurrence risk (RR = 0.64, 95% confidence interval [CI], 0.36 to 1.15). Including all 11 studies in the analyses (669 HRT users), using estimated control groups for the seven uncontrolled trials, the combined RR was 0.82 (95% CI, 0.58 to 1.15). CONCLUSION: Although our analyses suggest that HRT has no significant effect on breast cancer recurrence, these findings were based on observational data subject to a variety of biases.

Oncology. 2001;60(3):199-206. KARGER Full Text Links

Hormone replacement therapy after treatment of breast cancer: effects on postmenopausal symptoms, bone mineral density and recurrence rates.

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PURPOSE: Breast cancer (BC) is the most frequent female carcinoma and the major cause of death in women aged 35--50 years. The total number of patients surviving BC and especially the morbidity rate of patients below the age of 55 years has increased significantly in the last several years. As a consequence, the number of BC patients suffering from the long-term effects of estrogen deficiency due to adjuvant treatment is increasing. At present, hormone replacement therapy (HRT) following BC treatment is applied individually and mainly depends on the severity of postmenopausal symptoms (PMS) experienced by these patients. PATIENTS AND METHODS: In a retrospective study (total n = 185 BC patients, 64 with and 121 without HRT), the effect of HRT during or after adjuvant therapy [chemotherapy and/ or (anti-) hormonotherapy] has been investigated. The surveillance period was up to 60 months. Evaluated were HRT effects on (1) PMS measured by a comprehensive life quality questionnaire, (2) bone mineral density (BMD) measured by osteodensitometry and (3) morbidity as well as mortality rates. RESULTS: Both groups did not differ with regard to tumor stage, lymph node involvement, metastasis, grading, and steroid hormone receptor status. A reduction in PMS was significant in women taking HRT ($p < 0.001$), especially in the subgroup of women < or =50 years ($p < 0.0001$). For both age groups, the median reduction in BMD (z-score) was less in women receiving HRT (< or =50 years: without HRT -1.99 vs. with HRT -0.95, $p < 0.05$; >50 years: without HRT -2.29 vs. with HRT -1.19, $p < 0.01$). There were no statistically significant differences regarding morbidity and mortality ($p = 0.29$). CONCLUSION: In this study of BC patients, the use of HRT shows positive effects on PMS and BMD. There was no significant influence on morbidity or mortality. However, a reevaluation of HRT in the routine management of BC patients should await the results of prospective randomized trials.

J Natl Cancer Inst. 2001 May 16;93(10):754-62. FREE FINAL TEXT Links
Comment in:
J Natl Cancer Inst. 2001 May 16;93(10):733-4.

Hormone replacement therapy after a diagnosis of breast cancer in relation to recurrence and mortality.

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BACKGROUND: Hormone replacement therapy (HRT) is typically avoided for women with a history of breast cancer because of concerns that estrogen will stimulate recurrence. In this study, we sought to evaluate the impact of HRT on recurrence and mortality after a diagnosis of breast cancer. METHODS: Data were assembled from 2755 women aged 35-74 years who were diagnosed with incident invasive breast cancer while they were enrolled in a large health maintenance organization from 1977 through 1994. Pharmacy data identified 174 users of HRT after diagnosis. Each HRT user was matched to four randomly selected nonusers of HRT with similar age, disease stage, and year of diagnosis. Women in the analysis were recurrence free at HRT initiation or the equivalent time since diagnosis. Rates of recurrence and death through 1996 were calculated. Adjusted relative risks were estimated by use of the Cox regression model. All statistical tests were two-sided. RESULTS: The rate of breast cancer recurrence was 17 per 1000 person-years in women who used HRT after diagnosis and 30 per 1000 person-years in nonusers (adjusted relative risk for users compared with nonusers = 0.50; 95% confidence interval [CI] = 0.30 to 0.85). Breast cancer mortality rates were five per 1000 person-years in HRT users and 15 per 1000 person-years in nonusers (adjusted relative risk = 0.34; 95% CI = 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years in HRT users and 30 per 1000 person-years in nonusers (adjusted relative risk = 0.48; 95% CI = 0.29 to 0.78). The relatively low rates of recurrence and death were observed in women who used any type of HRT (oral only = 41% of HRT users; vaginal only = 43%; both oral and vaginal = 16%). No trend toward lower relative risks was observed with increased dose. CONCLUSION: We observed lower risks of recurrence and mortality in women who used HRT after breast cancer diagnosis than in women who did not. Although residual confounding may exist, the results suggest that HRT after breast cancer has no adverse impact on recurrence and mortality.

Maturitas. 2001 Sep 28;39(3):217-25. ELSEVIER FULL-TEXT ARTICLE Links

A prospective study on women with a history of breast cancer and with or without estrogen replacement therapy.

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OBJECTIVE: Because a categorical refusal of estrogen replacement therapy (ERT) from postmenopausal patients with a history of breast cancer is not based on any research evidence and may be more harmful than beneficial, we evaluated the safety and efficacy of ERT in these women. METHODS: We recruited 131 patients who had been treated for breast cancer for a mean of 4.2 years (range 1 month to 20 years) before. Eighty-eight decided to use ERT, whereas 43 refused or had no need for ERT. At recruitment, the patients were carefully examined for breast and gynaecologic findings. Non-hysterectomized patients wishing to receive ERT (n=54) then started using estradiol as oral tablets (2 mg/day) (n=44) or as transdermal gel (1.5 mg/day) (n=10) in combination with 10-day courses of oral medroxyprogesterone acetate at 4-week intervals, whereas hysterectomized patients (n=34) used only estradiol, orally (2 mg/day) (n=31) or transdermally (1.5 mg/day) (n=3). The patients using ERT were carefully examined 6 and 12 months later, and then annually at a specific outpatient department, and the mean follow-up time is now 2.5 years (range from 1 month to 5.2 years, 216 woman-years). The 43 patients not wishing to receive ERT were followed annually at the oncologic department for a mean of 2.6 years (range from 1 month to 4.7 years), and served as a control group. RESULTS: ERT significantly reduced climacteric symptoms, and the Kupperman score fell by 63%, from 26.9+/-8.6 to 9.9+/-6.7 (mean+/-SD). In non-hysterectomized women, medroxyprogesterone acetate triggered withdrawal bleeding in all except seven women. Seven patients (13%) experienced spotting during ERT. In 27 women, endometrial thickness exceeded 10 mm, and two of the total of 54 patients (3.7%) had simple hyperplasia. This vanished spontaneously in 3-6 months. Ten patients terminated the use of ERT within the first 12 to 39 months due to the lack of severe vasomotor symptoms (n=4) or due to the recurrence of breast cancer or to cancer of the contralateral breast (n=6). Eighty-one of the 88 patients (92%) using ERT showed no evidence of recurrence, whereas five patients (5.7%) had recurrence in 12-36 months and two patients (2.3%) developed a cancer of the contralateral breast in 14-24 months; another one of those wanted to continue with ERT. Thus the combined risk of recurrence or a new cancer of the contralateral breast in ERT users was 7/216 woman-years (3% per year). In the control group, 38 of 43 patients (88.4%) showed no evidence of recurrence or contralateral cancer, whereas four patients

had recurrence and one developed a contralateral breast cancer (5/112 woman-years, 4% per year). CONCLUSIONS: Symptomatic climacteric patients with a history of breast cancer benefited from ERT without increasing their risk of recurrence, but the short follow-up and the small number of patients limit any definitive recommendations.

Climacteric. 1998 Jun;1(2):137-42. Links

Comment in:
Climacteric. 1998 Jun;1(2):89-90.

A cohort study of hormone replacement therapy given to women previously treated for breast cancer.

Dew J, **Eden J**, **Beller E**, **Magarey C**, **Schwartz P**, **Crea P**, **Wren B**.

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Women who have been previously treated for breast cancer are usually advised to avoid hormone therapy for fear of increasing their risk of tumor recurrence. However, for some women, menopausal symptoms are so severe that their quality of life is poor. Because ethic committees are reticent to permit a double-blind randomized trial, we performed a cohort study of hormone therapy after breast cancer. METHODS: The study group comprised 1472 women with breast cancer. A total of 167 subjects had used an oral or transdermal estrogen after their treatment for breast cancer. Amongst these estrogen users, 152 (91%) had also used a progestin. In total, 106 other women had used a progestin alone as a treatment for menopausal flushes and not as a treatment for breast cancer. Cox regression analysis was performed using estrogen as a time-dependent covariate with disease-free interval as the outcome. RESULTS: The uncorrected hazard ratio for the estrogen-progestin users was 0.67 (95% confidence interval (CI) 0.38-1.16) and for the progestin alone users was 0.85 (95% CI 0.44-1.65). CONCLUSIONS: This study was unable to demonstrate a significant increase in risk of breast cancer recurrence for women who used HRT and suggests that the time is now appropriate for a randomized prospective trial of hormone therapy after breast cancer.

Am J Obstet Gynecol. 2002 Aug;187(2):289-94; discussion 294-5.

Estrogen replacement therapy in patients with early breast cancer.

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OBJECTIVE: Most physicians believe that estrogen replacement therapy is contraindicated once a patient is diagnosed with breast cancer. Recently, several studies have shown that estrogen replacement therapy may be safely used in patients with early breast cancer that has been treated successfully. These women can have severe menopausal symptoms and are at risk for osteoporosis. We reviewed the current status of women in our practice with breast cancer who received estrogen replacement therapy, who did not receive hormone replacement therapy, and who did not receive estrogenic hormone replacement therapy.
STUDY DESIGN: The study group consisted of 123 women (mean age, 65.4 +/- 8.85 years) who were diagnosed with breast cancer in our practice, including 69 patients who received estrogen replacement therapy for < or = 32 years after diagnosis. The comparative groups were 22 women who used nonestrogenic hormones for < or = 18 years and 32 women who used no hormones for < or = 12 years. The group who did not receive estrogenic hormone replacement therapy received androgens with or without progestogens (such as megestrol acetate). Of the 63 living hormone users, 56 women are still being treated in our clinic, as are 15 of the 22 subjects who receive nonestrogenic hormone replacement therapy. Follow-up was done through the tumor registry at University Hospital; those patients whose tumor records were not current were contacted by telephone.
RESULTS: There were 18 deaths in the 123 patients: 6 patients who received estrogen replacement therapy (8.69%), 2 patients who received nonestrogenic hormone replacement therapy (9.09%), and 10 patients who received no hormone replacement therapy (31.25%). Of the 18 deaths, 9 deaths were from breast cancer (mortality rate, 7.3%); 3 deaths were from lung cancer; 1 death was from endometrial cancer; 1 death was from myocardial infarction; 1 death was from renal failure; and 3 deaths were from cerebrovascular accidents. The 9 deaths from breast cancer included one patient who received nonestrogenic hormone replacement therapy (mortality rate, 4.5%), 6 patients who received no hormone replacement therapy (mortality rate, 11.3%), and 2 patients who received estrogen replacement therapy (mortality rate, 4.28%). The 9 non-breast cancer deaths included 4 patients who received estrogen replacement therapy (endometrial cancer [1 death], lung cancer [1 death], cerebrovascular accident [1 death], and renal failure [1 death]), 1 patient who did not receive estrogenic hormone replacement therapy group (myocardial infarction), and 4 patients who used no hormones (lung cancer, 2 deaths; stroke, 2 deaths). Carcinoma developed in one

patient in the estrogen replacement therapy group in the contralateral breast after 4 years of hormone replacement therapy; she is living and well 2.5 years later with no evidence of disease. Metastatic breast cancer developed in one patient after 8 years of hormone replacement therapy; she is living with disease. CONCLUSION: Estrogen replacement therapy apparently does not increase either the risk of recurrence or of death in patients with early breast cancer. These patients may be offered estrogen replacement therapy after a full explanation of the benefits, risks, and controversies.

Med J Aust. 2002 Oct 7;177(7):347-51. eMJA free text Links
Comment in:
Med J Aust. 2002 Oct 7;177(7):340-1.
Med J Aust. 2003 Apr 21;178(8):412-3; author reply 413.

Hormone replacement therapy after a diagnosis of breast cancer: cancer recurrence and mortality.

Durna EM, **Wren BG**, **Heller GZ**, **Leader LR**, **Sjoblom P**, **Eden JA**.

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OBJECTIVE: To determine whether hormone replacement therapy (HRT) after treatment for breast cancer is associated with increased risk of recurrence and mortality. DESIGN: Retrospective observational study. PARTICIPANTS AND SETTING: Postmenopausal women diagnosed with breast cancer and treated by five Sydney doctors between 1964 and 1999. OUTCOME MEASURES: Times from diagnosis to cancer recurrence or new breast cancer, to death from all causes and to death from primary tumour were compared between women who used HRT for menopausal symptoms after diagnosis and those who did not. Relative risks (RRs) were determined from Cox regression analyses, adjusted for patient and tumour characteristics. RESULTS: 1122 women were followed up for 0-36 years (median, 6.08 years); 154 were lost to follow-up. 286 women used HRT for menopausal symptoms for up to 26 years (median, 1.75 years). Compared with non-users, HRT users had reduced risk of cancer recurrence (adjusted relative risk [RR], 0.62; 95% CI, 0.43-0.87), all-cause mortality (RR, 0.34; 95% CI, 0.19-0.59) and death from primary tumour (RR, 0.40; 95% CI, 0.22-0.72). Continuous combined HRT was associated with a reduced risk of death from primary tumour (RR, 0.32; 95% CI, 0.12-0.88) and all-cause mortality (RR, 0.27; 95% CI, 0.10-0.73). CONCLUSION: HRT use for menopausal symptoms by women treated for primary invasive breast cancer is not associated with an increased risk of breast cancer recurrence or shortened life expectancy.

J Fam Pract. 2002 Dec;51(12):1056-62. Links

Cancer recurrence and mortality in women using hormone replacement therapy: meta-analysis.

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OBJECTIVES: We compared the risk of cancer recurrence and all-cause mortality among users and nonusers of estrogen replacement therapy (ERT) after the diagnosis of breast cancer. STUDY DESIGN: This was a systematic review of original research. Eligible studies were reviewed by 2 investigators who independently extracted data from each study according to a predetermined form and assessed each study for validity on standard characteristics. Meta-analyses were performed with Review Manager 4.1 to provide a summary of relative risks of cancer recurrence and mortality. POPULATION: Studies included 717 subjects who used hormone replacement therapy (HRT) at some time after their diagnosis of breast cancer, as well as 2545 subjects who did not use HRT. OUTCOMES MEASURED: Outcomes included breast cancer recurrence and all-cause mortality. RESULTS: Nine independent cohort studies and one 6-month pilot randomized controlled trial were identified. Studies were of variable quality. Breast cancer survivors using ERT experienced no increase in the risk of recurrence compared with controls (relative risk, 0.72; 95% confidence interval, 0.47-1.10) and had significantly fewer deaths (3.0%) than did the nonusers (11.4%) over the combined study periods (relative risk, 0.18; 95% confidence interval, 0.10-0.31). All tests for heterogeneity were nonsignificant. CONCLUSIONS: Although limited by observational design, existing research does not support the universal withholding of ERT from well-informed women with a previous diagnosis of low-stage breast cancer. Long-term randomized controlled trials are needed.

Climacteric. 2003 Mar;6(1):45-52. Links

A cohort study of topical vaginal estrogen therapy in women previously treated for breast cancer.

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OBJECTIVE: To estimate the risk of recurrence of breast cancer associated with the use of topical vaginal estrogen therapy in the management of vaginal atrophy in women previously treated for breast cancer. METHODS: The study group comprised 1472 women with histologically confirmed breast cancer. In 69 of these subjects (4.7%) their only bothersome menopausal problems were vaginal symptoms. In these women, poorly absorbed topical vaginal estrogen cream or tablets were used. The response of these patients was compared with that of the rest of the database. A Cox regression analysis was performed using sex hormone usage after diagnosis as a time-dependent covariate. Disease-free interval was the outcome measured. Results are expressed as a hazard ratio with 95% confidence intervals. The hazard rate is defined as the probability of disease recurrence or of a subject dying from breast cancer over the study period. A second analysis was performed adjusting for factors known to affect breast cancer prognosis. RESULTS: Hormone usage was entered as a time-dependent covariate with disease-free interval as the outcome. Subjects who used a topical estrogen alone for menopausal symptoms had an uncorrected hazard ratio of 0.30 (95% confidence interval (CI) 0.11-0.80, $p = 0.02$). The corrected hazard ratio was 0.57 (95% CI 0.20-1.58, $p = 0.28$). The hazard rate for a subject dying was not analyzed, as there were too few numbers. CONCLUSIONS: Although the small numbers of this study preclude a definitive result, topical estrogen usage does not appear to be associated with an increased risk of recurrence of breast cancer.

Ann Surg Oncol. 2001 Dec;8(10):828-32. Links

Estrogen replacement therapy after breast cancer: a 12-year follow-up.

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BACKGROUND: In the United States, estrogen replacement therapy (ERT) is discouraged in breast cancer survivors because of concerns that hormones may reactivate the disease. Because ERT can improve quality of life and decrease morbidity from osteoporosis and cardiovascular disease, however, this policy is increasingly being challenged. METHODS: From February to August 1995, 607 breast cancer survivors were interviewed concerning ERT usage. Sixty-four patients indicated they received some form of ERT after their breast cancer diagnosis. Medical records for these patients were analyzed for disease stage, surgical treatment, adjuvant treatment, estrogen and progesterone receptor status, date of initiation of ERT, type of ERT, recurrence, and final outcome. Patients receiving ERT were followed prospectively. RESULTS: Eight patients were excluded because they had used only vaginal cream ERT. The remaining 56 received ERT as conjugated estrogens, an estradiol patch, estropipate, or birth control pills. The median follow-up from diagnosis was 12.8 years (range, 4.7-38.9 years). The median time on ERT since diagnosis was 6.4 years (range, 1.0-20.9 years); 38% of the patients initiated ERT within 2 years of diagnosis. Estrogen receptors were positive in 28 (74%) of the 38 cases with available information. Pathological disease stage at time of diagnosis and treatment was 0 in 15 cases (27%), I in 27 (48%), and II in 14 (25%). Twenty-six patients (47%) received adjuvant chemotherapy or hormonal therapy. One local recurrence and one contralateral breast cancer occurred during the follow-up period (13.5 and 9.6 years, respectively), with no regional or distant recurrences, for a 15-year actuarial disease-free survival rate of 92.5%. There were no breast cancer deaths. CONCLUSIONS: Use of ERT in a cohort of breast cancer survivors with tumors of generally good prognosis was not associated with increased breast cancer events compared with non-ERT users, even over a long follow-up period.

Menopause. 2003 Jul-Aug;10(4):277-85. Links
Comment in:
Menopause. 2003 Jul-Aug;10(4):269-70.

Estrogen replacement therapy in breast cancer survivors: a matched-controlled series.

Decker DA, **Pettinga JE**, **VanderVelde N**, **Huang RR**, **Kestin L**, **Burdakin JH**.

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OBJECTIVE: We prospectively administered estrogen replacement therapy (ERT) to control estrogen deficiency symptoms in breast cancer survivors as part of our clinical practice. We report the consequences of ERT compared with a historical matched-control group. DESIGN: Two hundred seventy-seven disease-free survivors received ERT. Controls were matched for exact stage, a recurrence-free period similar to the period to ERT initiation in the ERT group, approximate age, and duration of follow-up. The mean time from breast cancer diagnosis to initiation of ERT was 3.61 (+/- 0.25) years, with a median of 1.88 years. The mean duration of ERT was 3.7 (+/- 3.01) years, with a median of 3.05 years. RESULTS: Hot flashes were relieved in 206 of 223 women (92%), dyspareunia/vaginal dryness in 149 of 167 women (89%), and reactive depression/anxiety/mood change in 111 of 126 women (88%). Univariate analysis demonstrated no statistical differences between the groups for age, stage, pathology at diagnosis, progesterone receptor status, local therapy, breast at risk, prior chemotherapy, and duration of follow-up. The ERT group was more likely to be estrogen receptor negative ($P = 0.01$), to have received prior ERT ($P < 0.001$), and to have received no adjuvant tamoxifen ($P < 0.001$). There was no significant difference between the ERT and control groups in ipsilateral primary/recurrence (5/155 v 5/143; $P = 0.85$), contralateral breast cancers (10/258 v 9/260; $P = 0.99$), or systemic metastasis (8/277 v 15/277; $P = 0.13$). Noncause-specific deaths in the control group numbered 15 (of 277), and in the ERT group, 7 (of 277) ($P = 0.03$). Overall survival favored the ERT group ($P = 0.02$). CONCLUSIONS: In these selected patients, ERT relieved estrogen deficiency symptoms and did not increase the rate or time to an ipsilateral recurrence/new primary, contralateral new primary, local-regional recurrence, or systemic metastases.

Gynecol Obstet Fertil. 2003 Jul-Aug;31(7-8):614-9. ELSEVIER FULL-TEXT ARTICLE Links

[Hormone replacement therapy in breast cancer patients: a study of 230 patients, with a case-control study]

[Article in French]

Gorins A, **Espié M**, **Bedairia N**, **Perret F**, **Tournant B**, **Novak H**, **Lucchi-Angelier E**, **Marty M**.

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OBJECTIVES: After recalling the classical contra-indication of hormone replacement therapy (HRT) concerning patients with a personal history of breast cancer (BC), and arguments that may be opposed, the authors report the present results of a prospective study undertaken in the Center of Breast Diseases in Saint-Louis hospital in Paris since February 1992. PATIENTS AND METHODS: By April 2001, 230 patients had been included. A free interval of 2 years at least since the treatment of the primary BC has been observed. The reasons for prescribing HRT were vasomotor troubles (flushes, nightly sweats) or a dyspareunia, which were severe and not controlled by non-hormonal treatments. There was also an indication of a major osteoporotic or cardiovascular danger. In fact, many of these patients had a premature, artificial, chemo-induced menopause. The HRT most often used was an estro-progestin association (estradiol + a progestin compound) given either continuously or with a 5-d interruption each month. The mean duration of treatment was 2.5 years. RESULTS: Results, concerning the improvement of menopause troubles, were remarkable in the great majority of troubles. HRT had to be stopped in 39 cases, reading as follows: 17 cases for relapses (seven local, six in the contro-lateral breast and four metastases (7%)). Also, 22 patients (9%) interrupted their HRT for serious side-effects. A case-control study did not show any significant difference between with and without HRT patients concerning the overall survival without relapse. DISCUSSION AND CONCLUSIONS: Quality of life of patients was often substantially improved, and a deleterious effect on the cancer disease was not found. Our results are in agreement with the literature from other countries. However, one must be cautious. In such circumstances, HRT must be prescribed with the informed consent of the patients and delivered in appropriate hospital and university centers. It is wished that large randomised prospective studies may be undertaken.

J Reprod Med. 2004 Jul;49(7):510-26. Links

Hormone therapy for women after breast cancer: a review.

Levgur M.

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Even though it is accepted that women with breast cancer should not receive estrogen therapy, doubts have been expressed as to the validity of this policy. In recent years opposition to this practice has been voiced more adamantly. The results of the Women's Health Initiative (WHI) study, published in July 2002, question the safety margin of estrogen therapy (ET) or hormone therapy (HT) in menopause. Whether this concern is applicable to breast cancer survivors is unclear as these women were not addressed by the study. In light of the uncertainties raised by the study and particularly the ongoing controversy about breast cancer patients, a review of the literature published prior to March 2003 was undertaken. The information gathered on the topic comes from 10 uncontrolled studies and 11 case-controlled studies, 8 retrospective and 3 prospective, carried out over the past decade. The experience encompasses 1,558 breast cancer survivors treated with ET or HT. Overall, the recurrence rate accrued from the uncontrolled studies is 7.3% (53 of 728). The average rate culminating from 11 case-controlled studies is 10.7% (99 of 830) (2.6-15.4%) in treated patients vs. 20.3% (739 of 3,640) (2.3-29.5%) in their untreated counterparts. This review revealed no increase in recurrent disease among treated patients but is not conclusive as some studies that have been flawed by biases and confounders. The fact that only 2 studies were case controlled and prospective as well as randomized, and considering concerns raised by the WHI study, it seems that many more such trials will be necessary before this controversial issue will be settled.

Curr Opin Oncol. 2005 Sep;17(5):493-9. Links

Hormone replacement therapy after cancers.

Creasman WT.

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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.

Maturitas. 2006 Jan 20;53(2):123-32. ELSEVIER FULL TEXT ARTICLE Links

Menopausal hormone therapy (HT) in patients with breast cancer.

Batur P, Blixen CE, Moore HC, Thacker HL, Xu M.

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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.

PMID: 16368466 [PubMed - indexed for MEDLINE]

e.g. ✓ Estrone
20H/16OH

Climacteric. 1998 Jun;1(2):137-42. Links
Comment in:
Climacteric. 1998 Jun;1(2):89-90.

A cohort study of hormone replacement therapy given to women previously treated for breast cancer.

Dew J, **Eden J**, **Beller E**, **Magarey C**, **Schwartz P**, **Crea P**, **Wren B**.

Women's Health Institute, Royal Hospital for Women, Barker Street, Randwick, NSW 2031, Australia.

Women who have been previously treated for breast cancer are usually advised to avoid hormone therapy for fear of increasing their risk of tumor recurrence. However, for some women, menopausal symptoms are so severe that their quality of life is poor. Because ethic committees are reticent to permit a double-blind randomized trial, we performed a cohort study of hormone therapy after breast cancer. METHODS: The study group comprised 1472 women with breast cancer. A total of 167 subjects had used an oral or transdermal estrogen after their treatment for breast cancer. Amongst these estrogen users, 152 (91%) had also used a progestin. In total, 106 other women had used a progestin alone as a treatment for menopausal flushes and not as a treatment for breast cancer. Cox regression analysis was performed using estrogen as a time-dependent covariate with disease-free interval as the outcome. RESULTS: The uncorrected hazard ratio for the estrogen-progestin users was 0.67 (95% confidence interval (CI) 0.38-1.16) and for the progestin alone users was 0.85 (95% CI 0.44-1.65). CONCLUSIONS: This study was unable to demonstrate a significant increase in risk of breast cancer recurrence for women who used HRT and suggests that the time is now appropriate for a randomized prospective trial of hormone therapy after breast cancer.

PMID: 11907916 [PubMed - indexed for MEDLINE]

Climacteric. 2004 Sep;7(3):284-91. Links

Breast cancer in premenopausal women: recurrence and survival rates and relationship to hormone replacement therapy.

Durna EM, Heller GZ, Leader LR, Sjoblom P, Eden JA, Wren BG.

School of Women's and Children's Health, University of New South Wales, Sydney, Australia.

OBJECTIVES: To determine any association between hormonal replacement therapy (HRT) usage and breast cancer recurrence and survival rates in women who were premenopausal at the time of diagnosis of breast cancer. METHODS: The study group comprised 524 women who were diagnosed with breast cancer when they were premenopausal. Of these, 277 women reached menopause before recurrence of the disease, being lost to follow-up, or reaching the end of the study. In this group, 119 women took HRT to control menopausal symptoms. The majority took combined continuous estrogen-progestin treatment. Times from diagnosis to cancer recurrence or new breast cancer, to death from all causes, and to death from primary tumor were compared between HRT users and non-users. RESULTS: Women who used HRT after their menopause had an adjusted relative risk of recurrence or new breast cancer of 0.75 (95% confidence interval (CI), 0.29-1.95) compared to that of non-users. The relative risk of death from all causes was 0.36 (95% CI, 0.11-1.16) and that of death from primary tumor was 0.24 (95% CI, 0.05-1.14). CONCLUSION: HRT use in women who were premenopausal at the diagnosis of primary invasive breast cancer is not associated with worse outcomes in terms of breast cancer recurrence or mortality.

Good!

PMID: 15669553 [PubMed - indexed for MEDLINE]

Minerva Ginecol. 2007 Oct;59(5):529-41. Links

The use of hormone replacement therapy in patients after breast cancer.

Mueck AO, **Rabe T**, **Kiesel L**, **Strowitzki T**.

University Women's Hospitals of Tuebingen, Tuebingen, Germany endo.meno@med.uni-tuebingen.de.

Four prospective randomized studies and at least 15 observational studies investigating hormone replacement therapy (HRT) after breast cancer are available. Only the Hormonal replacement therapy After Breast cancer: Is iT Safe (HABITS) study shows an increased risk of relapse. This is probably associated with the relatively high number of patients with HRT treatment after estrogen receptor-positive cancers as well as to the preferred use of estrogen/progestin combined preparations. As is generally known, the progestin component especially seems to be mainly responsible for the probability of increased diagnosis frequency of breast cancer. However, the patient samples in all studies investigating HRT after breast cancer are small. Therefore, HRT should only be used if alternatives, such as specific not contraindicated phytopreparations or serotonin reuptake inhibitors, are not working. This is primarily due to forensic reasons. According to medical criteria, the data for the alternatives seem to be even more sparse, since many important questions remain unanswered, such as side effects and risks, or also regarding interactions with adjuvant hormone therapy.

PMID: 17912179 [PubMed - in process]

progestin = "Provera" (medroxyprogesterone)

NOT progesterone

Am J Surg. 2008 Oct;196(4):505-11. FULL-TEXT ARTICLE Links

Improved breast cancer survival among hormone replacement therapy users is durable after 5 years of additional follow-up.

Christante D, **Pommier S**, **Garreau J**, **Muller P**, **LaFleur B**, **Pommier R**.

Division of Surgical Oncology, Department of Surgery, Portland, OR, USA.

BACKGROUND: We previously reported that breast cancer patients who used hormone replacement therapy (HRT) had significantly lower stage tumors and higher survival than never-users. We present an update with longer follow-up, HRT use data, and in vitro research. METHODS: Our database of 292 postmenopausal breast cancer patients was updated to include HRT type, duration, and disease status. In vitro effects of estrogen (E) and/or medroxyprogesterone (MPA) on breast cancer cell growth were measured. RESULTS: Tumor prognostic factors were better and survival rates higher for both E and combination HRT users of any duration. Use greater than 10 years correlated with node-negative disease, mammographically detected tumors, and 100% survival. E supported minimal proliferation; MPA induced cell death; E+MPA results were similar to E alone. CONCLUSIONS: HRT users, regardless of type or duration of HRT use, continued to have higher survival rates. In vitro results supported the clinical finding that outcomes for users of E and E+MPA were similar.

HRT after Breast Cancer

Against HRT

Harefuah. 2004 Oct;143(10):753-6, 764. Links

[Hormone replacement therapy in breast cancer survivors: the Israeli Society for Clinical Oncology and Radiotherapy policy letter]

[Article in Hebrew]

Siegelmann-Danieli N, **Ron I**, **Kaufman B**, **Uzieli B**, **Karminsky N**, **Inbar M**; **Israeli Society for Clinical Oncology and Radiotherapy**.

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The Israeli Society for Clinical Oncology and Radiotherapy appointed experts in breast cancer therapy to assess the Society's policy regarding hormone replacement therapy (HRT) in breast cancer survivors with menopausal symptoms. The first policy letter was published in November 2002, and referred to available literature at that time which included retrospective data alone. The professional literature suggested no increased risk in breast cancer recurrence or cancer specific mortality, and no effect on overall survival with the use of HRT for a limited period (up to 3 years). This data served as the rationale for international prospective studies. Former committee recommendations and precautions are detailed in the original publication. In February 2004, the interim analysis of a prospective trial, the HABIT (Hormonal replacement therapy after breast cancer--is it safe?) was published. In that trial, breast cancer survivors with menopausal symptoms were randomized to HRT (estrogens with or without progestins) or no therapy for 2 years. A total of 434 women were recruited from centers in Scandinavia who participated with the International Breast Cancer and the European Organization for Research and Treatment groups. Analysis was restricted to 345 women with at least one follow up report; median follow-up period was 2.1 years. The relative risk for breast cancer event was 3.5 (95% C.I. 1.5-8.1) in HRT users as compared with the non-HRT group and the HABIT trial was terminated. Study limitations are discussed. Thereby, at this time HRT can no longer be considered safe in breast cancer survivors. Physicians treating breast cancer survivors for severe menopausal symptoms should present study results and alternative non-hormonal treatment options to allow patients optimized consented treatment decisions.

Harefuah. 2002 Nov;141(11):994-6, 1008. Links

[Hormone replacement therapy in breast cancer survivors: the Israeli Society for Clinical Oncology and Radiotherapy policy letter]

[Article in Hebrew]

Siegelmann-Danieli N, **Ron I**, **Kaufman B**, **Uzieli B**, **Karminsky N**, **Inbar M**; **Israeli Society for Clinical Oncology and Radiotherapy**.

Assaf Harofeh Medical Center, Zerifin.

The Israeli Society for Clinical Oncology and Radiotherapy requested that experts in breast cancer therapy assess the Society's policy regarding the use of hormone replacement therapy (HRT) in breast cancer survivors. The following recommendations are based on updated literature, which is limited since it summarizes only retrospective data. There is currently no evidence of an increased risk of breast cancer recurrence, death attributable to cancer, or overall mortality among breast cancer survivors who use HRT. We therefore recommend that there is no need to avoid HRT in women with menopausal symptoms who are interested in receiving such treatment, as long as ovarian ablation does not play a major role in their adjuvant therapy. Women should be informed about the limitations of available data. There are some concerns regarding the use of HRT in patients whose tumors developed while undergoing HRT and in such cases treatment should be reserved only for those with severe menopausal symptoms. For women with milder symptoms or those who are not interested in HRT, other treatment options should be outlined. The policy should be updated according to future publication of results from ongoing randomized prospective studies.

J Natl Cancer Inst. 2008 Apr 2;100(7):475-82. Epub 2008 Mar 25.

Links

Erratum in:
J Natl Cancer Inst. 2008 May 7;100(9):685. Maenpa, Johanna [corrected to Maenpaa, Johanna].
Comment in:
J Natl Cancer Inst. 2008 Apr 2;100(7):451-2.

Increased risk of recurrence after hormone replacement therapy in breast cancer survivors.

Holmberg L, **Iversen OE**, **Rudenstam CM**, **Hammar M**, **Kumpulainen E**, **Jaskiewicz J**, **Jassem J**, **Dobaczewska D**, **Fjosne HE**, **Peralta O**, **Arriagada R**, **Holmqvist M**, **Maenpaa J**; **HABITS Study Group**.
Collaborators (25)

Holmberg L, **Hammar M**, **Maenpaa J**, **Kumpulainen E**, **Iversen OE**, **Fjosne HE**, **Rudenstam CM**, **Jaskiewicz J**, **Jassem J**, **Dobaczewska D**, **Peralta O**, **Arriagada R**, **Straehle C**, **Holmqvist M**, **Lidin-Lindkvist A**, **Schaerlig-Strausak M**, **Zuniga M**, **Kvisgaard B**, **Andersson H**, **Nordenskjöld B**, **von Smitten K**, **Kvinnsland S**, **Soderqvist G**, **A'Hern R**, **Sacks N**.

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BACKGROUND: Hormone replacement therapy (HT) is known to increase the risk of breast cancer in healthy women, but its effect on breast cancer risk in breast cancer survivors is less clear. The randomized HABITS study, which compared HT for menopausal symptoms with best management without hormones among women with previously treated breast cancer, was stopped early due to suspicions of an increased risk of new breast cancer events following HT. We present results after extended follow-up. METHODS: HABITS was a randomized, non-placebo-controlled noninferiority trial that aimed to be at a power of 80% to detect a 36% increase in the hazard ratio (HR) for a new breast cancer event following HT. Cox models were used to estimate relative risks of a breast cancer event, the maximum likelihood method was used to calculate 95% confidence intervals (CIs), and chi(2) tests were used to assess statistical significance, with all P values based on two-sided tests. The absolute risk of a new breast cancer event was estimated with the cumulative incidence function. Most patients who received HT were prescribed continuous combined or sequential estradiol hemihydrate and norethisterone. RESULTS: Of the 447 women randomly assigned, 442 could be followed for a median of 4 years. Thirty-nine of the 221 women in the HT arm and 17 of the 221 women in the control arm experienced a new breast cancer event (HR = 2.4, 95% CI = 1.3 to

4.2). Cumulative incidences at 5 years were 22.2% in the HT arm and 8.0% in the control arm. By the end of follow-up, six women in the HT arm had died of breast cancer and six were alive with distant metastases. In the control arm, five women had died of breast cancer and four had metastatic breast cancer (P = .51, log-rank test). CONCLUSION: After extended follow-up, there was a clinically and statistically significant increased risk of a new breast cancer event in survivors who took HT.

HRT after Breast Cancer

Misc.

Oncology (Williston Park). 1999 Feb;13(2):245-8, 251-4, 257 passim. Links

Treatment of estrogen deficiency symptoms in women surviving breast cancer. Part 2: Hormone replacement therapy and breast cancer.

[No authors listed]

There are several million breast cancer survivors worldwide. In the United States, 180,000 women were diagnosed with breast cancer in 1997, and approximately 97,000 of these women have an extremely low chance of suffering a recurrence of their cancer. With an average age at diagnosis of 60 years and a 25-year expected duration of survival, the current number of breast cancer survivors in the United States may approach 2.5 million women. Since breast cancer is now being detected at an earlier stage than previously and since adjuvant chemotherapy may cause ovarian failure, an increasing number of women are becoming postmenopausal at a younger age after breast cancer treatment. This conference was convened in September 1997 to consider how menopausal breast cancer survivors should be treated at the present time and what future studies are needed to develop improved therapeutic strategies. A total of 59 breast cancer experts and patient advocates participated. The proceedings of the conference will be published in six installments in successive issues of ONCOLOGY. The first part, published last month, defined the problem and explored its magnitude and ramifications for patient management. This second part focuses on the benefits and risks of hormone replacement therapy (HRT) in patients with breast cancer.

J Steroid Biochem Mol Biol. 2002 Dec;83(1-5):123-32. FULL-TEXT ARTICLE Links

The menopause, hormone replacement therapy and breast cancer.

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Concern exists that the reduction in breast cancer risk associated with the onset of the menopause will be negated with exposure to hormone replacement therapy (HRT). Evidence from large-scale randomised HRT trials support observational data that have shown a modest increase in breast cancer risk with long-term use (i.e. >15 years) of combined therapy, although this falls following HRT cessation suggesting a growth-promoting effect. Randomised evidence demonstrates that the efficacy of anti-estrogens, aromatase inhibitors and raloxifene in the treatment and chemoprevention of breast cancer are restricted to women with oestrogen receptor positive (ER +ve) disease; however, HRT has not been associated conclusively with a predominance of hormone sensitive breast cancer. Despite stimulating the breast cancer cell growth, HRT has not been shown to increase breast cancer recurrence or mortality when prescribed to breast cancer survivors experiencing oestrogen deficiency symptoms and randomised trials have been recommended and commenced. In conjunction with controlled breast cancer trials demonstrating a therapeutic benefit of high dose estrogens and interest in the use of additive oestrogen therapy in patients developing resistance to oestrogen deprivation, the dogma that HRT is an absolute contra-indication following diagnosis is challenged.

Lancet Oncol. 2005 Sep;6(9):687-95. THE LANCET Oncology FULL-TEXT ARTICLE Links

Management of menopausal symptoms in patients with breast cancer: an evidence-based approach.

Hickey M, **Saunders CM**, **Stuckey BG**.

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Increasing numbers of women have menopausal symptoms after treatment for breast cancer. These symptoms can result directly from cancer treatments (such as oophorectomy, ovarian suppression, chemotherapy-induced ovarian failure, and antioestrogens), as a spontaneous event, or after discontinuation of hormone-replacement therapy. The onset of menopausal symptoms after treatment for breast cancer can have a long-lasting effect on quality of life, body image, sexual function, and self esteem. Hormone-replacement therapy that contains oestrogen is the most effective treatment for menopausal symptoms in healthy women. However, evidence from one randomised controlled trial suggests that use of hormone replacement therapy after breast cancer raises the risk of recurrence and of new primary breast cancer. As the incidence of breast cancer increases and survival continues to improve, the number of women with menopausal symptoms will probably rise. Safe and effective non-hormonal treatments for severe menopausal symptoms after breast cancer are urgently needed. Few studies have addressed the management of menopausal symptoms after breast cancer, and the quality of studies is generally poor. Progestagens, and selective inhibitors of serotonin and norepinephrine reuptake seem to offer reasonable symptom palliation, but the long-term effectiveness and safety of these preparations is not known. We propose that the management of menopausal symptoms in patients with a history of cancer requires a patient-centred, but multidisciplinary, approach.

Climacteric. 2008 Aug;11(4):322-8. informaworld Links

A survey among breast cancer survivors: treatment of the climacteric after breast cancer.

Antoine C, **Vandromme J**, **Fastrez M**, **Carly B**, **Liebens F**, **Rozenberg S**.

Department of Obstetrics and Gynecology, Free Universities of Brussels, Brussels, Belgium.

AIM: To evaluate the prevalence and type of menopausal treatments used by breast cancer survivors. To assess factors that impaired the quality of life of these patients. MATERIAL AND METHODS: A questionnaire assessing quality of life was sent to 325 breast cancer patients. A 66% valid response rate was obtained. Among these responses, 169 women were postmenopausal. The following results concern these patients only. RESULTS: Forty-five women were using some treatment to alleviate certain menopausal symptoms (26.6%). More than half of the patients used no therapy to alleviate menopausal symptoms, either because they had no symptoms (n = 43; 25.4%), they feared breast cancer recurrence (n = 24; 14.2%), they were advised not to use a treatment (n = 27; 16%), it had been shown to be inefficient (n = 5; 3%), or because of contraindication (n = 3; 1.8%). In this survey, 62.3% of postmenopausal women affected by breast cancer suffered from hot flushes (n = 94), of which half were severe (n = 46). Among women suffering from hot flushes, a third used various products to alleviate their symptoms (n = 30). Younger women suffered more often from vasomotor symptoms than did older women ($p < 0.000$). Current users of aromatase inhibitors suffered more from sexual disorders than did non-users ($p < 0.001$). They had more often an unsatisfactory sexual life ($p < 0.01$), more vaginal dryness ($p = 0.01$) and a decreased libido ($p < 0.02$) compared to non-users. CONCLUSION: More than 50% of postmenopausal women suffered from climacteric symptoms such as hot flushes, but few were taking a treatment to alleviate these symptoms.

Eur J Obstet Gynecol Reprod Biol. 2006 Feb 1;124(2):250-3. Epub 2005 Sep

6. FULL-TEXT ARTICLE Links

The thoughts of breast cancer survivors regarding the need for starting hormone replacement therapy.

Trinh XB, **Peeters F**, **Tjalma WA**.

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There is not only a need for scientific data regarding the risk of recurrence of breast cancer by starting hormone replacement therapy (HRT) but also regarding the patients' needs for HRT. OBJECTIVES: To examine the severity of climacteric complaints in breast cancer patients and to examine if they are willing to take HRT. METHODS: In November 2003, a questionnaire was sent to 469 breast cancer survivors. The survey examined on a scale base the severity of climacteric complaints and the patient's opinion on starting HRT. RESULTS: More than 76% of the patients complained that they experience or had experienced hot flushes or night sweating. More than half (53%) of this group found the inconvenience severe to extreme, affecting the patient's quality of life. A majority (80.5%) patients who had already taken HRT, found that it improved their quality of life substantially. When the results of observational studies were explained regarding HRT in breast cancer survivors, a majority said they would take or would consider taking HRT (57.9%). CONCLUSION: While physicians are more reserved in prescribing HRT in breast cancer survivors, a combination of severe symptomatic climacteric complaints and the willingness of the patient to be treated should at least result in a "consideration" of prescribing HRT.

Semin Oncol. 2006 Dec;33(6):696-707. ELSEVIER FULL-TEXT ARTICLE Links

Management of postmenopausal symptoms in breast cancer survivors.

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With the increasing numbers of breast cancers survivors, menopause, its symptoms, and its physical complications are becoming more prevalent problems in this patient population. Hormonal replacement, which has been the cornerstone therapy of menopausal related symptoms for decades, recently has been shown to increase breast cancer incidence as well as risk of recurrence and no longer should be recommended. Menopausal symptoms and complications such as hot flashes, vaginal dryness, dyspareunia, and osteoporosis leading to fractures have a negative impact on the quality of life of both breast cancer survivors and the general postmenopausal population. The purpose of this review is to discuss the evidence for the use of alternative therapies for menopausal symptoms, thus providing guidance and recommendations that should facilitate therapeutic decisions in the daily practice of medical oncologists and primary care physicians

Ann Oncol. 2001 Mar;12(3):301-10. Links

The role of hormone replacement therapy in women with a previous diagnosis of breast cancer and a review of possible alternatives.

Pritchard KI.

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Estrogen replacement therapy either with (HRT) or without (ERT) accompanying progesterone is routinely offered to well women at the time of menopause, in order to relieve vasomotor symptoms, (hot flashes), reduce urogenital atrophy and reduce the risks of cardiovascular disease, osteoporosis and perhaps colon cancer and Alzheimer's disease. It is generally felt however, that women with a previous diagnosis of breast cancer are not suitable candidates for such therapy since either estrogen or progesterone may be associated with an increased risk of cancer recurrence. There are however, a variety of approaches to menopausal therapy in such women. A careful history must first be taken in order to identify the symptoms or conditions of concern. Vasomotor symptoms can be reduced by the use of other medications such as the antidepressant venlafaxine (Effexor). Estring, a vaginal estrogen ring can be used to reduce genitourinary symptoms, with little systemic estrogen absorption. Osteoporosis can be prevented or treated with calcium supplements, exercise, improved diet, bisphosphonates and/or selective estrogen receptor modulators (SERMs) while cardiovascular risk can be reduced by diet and exercise, as well as the appropriate use of lipid lowering and antihypertensive medications.

Oncologist. 2001;6(4):353-62. Full Text Oncologist FREE Links

Hormone replacement in women with a history of breast cancer.

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Estrogen used alone (estrogen replacement therapy [ERT]) or with the addition of progesterone (hormone replacement therapy [HRT]) is known to be effective in reducing menopausal symptoms including hot flashes, vaginal dryness and urinary symptoms. It has been traditionally contraindicated, however, in women with a previous diagnosis of breast cancer because of fear that it may increase the risk of recurrence. There are considerable basic scientific data but little methodologically strong observational data and none from randomized studies concerning the use of ERT in women with a prior diagnosis of breast cancer. From our knowledge of the physiology of breast cancer, however, estrogen and/or progestational agents should be used with caution in women with a previous diagnosis of breast cancer. There are currently many alternatives to ERT/HRT in the prevention of menopausal symptoms such as vitamin E, clonidine and selective serotonin reuptake inhibitor antidepressants such as venlafaxine. There are also a variety of other approaches to the prevention of osteoporosis and cardiovascular disease including bisphosphonates, diet, and exercise; and diet, exercise, and statins, respectively. Other suggested beneficial effects of estrogen such as colon cancer prevention can be approached by the use of aspirin or the non-steroidals. Several trials of ERT/HRT used for 2 years versus no therapy in menopausal women with a previous diagnosis of breast cancer are ongoing in Europe and Britain, and should give us stronger data as to the role of HRT in this setting.

Drug Saf. 2005;28(12):1085-100. Links

Therapy for menopausal symptoms during and after treatment for breast cancer : safety considerations.

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Breast cancer is the most common newly diagnosed cancer in women. Life-time risk in the US is 1 in 8 (13.2%), in the UK it is 1 in 9 and in Australia it affects 1 in 11 women, of whom approximately 27% will be premenopausal at the time of their diagnosis. Many of these women will experience a sudden menopause as a result of chemotherapy, endocrine therapy or surgical interventions. For these women, the onset of menopausal symptoms is often sudden and severe. The management of such symptoms remains controversial. Women experiencing menopausal symptoms after breast cancer should be encouraged to avoid identifiable triggers for their symptoms and to consider lifestyle modification as a means of controlling those symptoms. When such measures fail, non-hormonal treatments may also be considered. These include clonidine, gabapentin and some antidepressants. Randomised trials have shown a significant difference in the symptom relief associated with various selective serotonin reuptake inhibitors and selective serotonin and noradrenaline (norepinephrine) reuptake inhibitors compared with placebo. Many women elect to use non-prescription complementary therapies to alleviate their menopausal symptoms. Systematic reviews of phytoestrogens have, however, failed to demonstrate significant relief of menopausal symptoms.More than 20 clinical trials have been conducted examining the relationship between postmenopausal hormone replacement therapy and breast cancer recurrence. The majority of these have been observational and have shown no increased risk of recurrence. However, the largest randomised trial that has thus far been conducted was recently halted because of a reported increase in the risk of recurrence amongst users of hormone replacement therapy. Tibolone, a selective tissue estrogen activity regulator, is a compound that exerts clinical effects both by receptor-mediated actions and tissue selective enzyme inhibition, and has been shown in preclinical studies to have different effects to estrogen on the breast. Although tibolone may prove safer than estrogen for long-term use in breast cancer survivors, the results of a large randomised trial are awaited to confirm this.The decision on how best to manage menopausal symptoms must thus be made on an individual basis and after thorough discussion and evaluation of the risks and benefits of each potential intervention.

PMID: 16329712 [PubMed - indexed for MEDLINE]

Cancer. 2002 Dec 15;95(12):2455-64.  Links

Relation of regimens of combined hormone replacement therapy to lobular, ductal, and other histologic types of breast carcinoma.

Daling JR, Malone KE, Doody DR, Voigt LF, Bernstein L, Coates RJ, Marchbanks PA, Norman SA, Weiss LK, Ursin G, Berlin JA, Burkman RT, Deapen D, Folger SG, McDonald JA, Simon MS, Strom BL, Wingo PA, Spirtas R.

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BACKGROUND: The incidence of invasive lobular carcinoma has been increasing among postmenopausal women in some parts of the United States. Part of this may be due to changes in classification over time. However, the use of combined (estrogen and progestin) hormone replacement therapy (CHRT) also has increased during the last decade and may account in part for the increase in invasive lobular breast carcinoma. METHODS: A large, multicenter case-control study of Caucasian and African-American women who were diagnosed at age < 65 years with their first invasive breast tumor from July 1, 1994 through April 30, 1998 was conducted. In-person interviews were conducted with 1749 postmenopausal patients, and their responses were compared with the responses of 1953 postmenopausal control women identified through random-digit dialing who met the study criteria of being postmenopausal at the time of diagnosis. Polytomous logistic regression was used to calculate the odds ratio (OR) as an estimate of the relative risk and to compute the 95% confidence interval (95%CI) associated with the use of various regimens of hormone replacement therapy (HRT) among women diagnosed with ductal breast carcinoma, lobular (or mixed lobular and ductal) breast carcinoma, and a grouping of other histologic types of breast carcinoma. RESULTS: Ever use of unopposed estrogen therapy (ERT) was not associated with an increase in the risk of any histologic type of breast carcinoma. The risk of invasive lobular breast carcinoma and the risk of breast carcinoma of the grouping of other histologies increased among women currently using CHRT (OR, 2.2; 95%CI, 1.4-3.3; and OR, 1.9; 95%CI, 1.0-3.4, respectively). The risk increase was greater for the mixed lobular-ductal type than for the pure lobular type of breast carcinoma, although the difference was not statistically significant. There was some indication that >or= 5 years of continuous CHRT (>or= 25 days per month of progestin) was associated with a higher risk of lobular breast carcinoma (OR, 2.5; 95% CI, 1.4-4.3) compared with sequential CHRT (< 25 days per month of progestin; OR, 1.5; 95%CI, 0.8-2.6). Current use of continuous CHRT was only moderately associated with risk of ductal breast carcinoma. CONCLUSIONS: Postmenopausal women who take CHRT appear to be at an increased risk of lobular breast carcinoma. Data from this study suggest that neither ERT use nor CHRT substantially increase the risk of ductal breast carcinoma among women age < 65 years.

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HRT after Breast Cancer
Mixed

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Hormone replacement therapy in breast cancer patients and survivors.

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Menopause is arguably the most important phase of a woman's social, physiologic, and personal life. Approximately 1.3 million women reach this age in the United States annually. In the past decade, numerous studies have correlated breast cancer and the use of ERT (estrogen replacement therapy) or HRT (hormone replacement therapy) in menopausal women. Whether this is an actual increase in the creation of new cancers or a result of a diagnostic or other bias has yet to be determined. Even more uncertainty surrounds the use of hormones once breast cancer is diagnosed. Previously, once a woman was diagnosed with an estrogen-dependent tumor, ERT and HRT were simply forbidden. As discussed herein, that is no longer the case.