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Estrogen Replacement Therapy in Breast Cancer Survivors: A Matched-Controlled Series
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Menopausal Hormone Therapy (HT) in Patients With Breast Cancer
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Hormone replacement therapy after breast cancer: 10 year follow up of the Stockholm randomized trial
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European J of Cancer Volume 49, Issue 1, Jan 2013, pp 52-59

Abstracts

Hormone replacement therapy in previously treated breast cancer patients

Alan G. Wile, Richard W. Opfell, David A. Margileth
Short communication, volume 165, issue 3, p. 372-375, March 01, 1993

We report our experience with 25 women previously treated for breast cancer who subsequently received hormone replacement therapy (HRT) for the relief of menopausal symptoms and the prevention of postmenopausal cardiovascular disease and osteoporosis. Two patients had in situ disease, 13 had stage I disease, 7 had stage II disease, 1 had stage III disease, and 2 had invasive cancer of undetermined stage.
Seventeen patients (group I) began HRT less than 24 months after primary breast cancer therapy, and 8 patients (group II) began HRT more than 24 months after breast cancer therapy.
The HRT-free interval for group I patients averaged 7.9 months and for group II patients averaged 64.5 months.
The average period of observation while receiving HRT for the entire group was 35.2 months (range: 24 to 82 months).
Three of 25 patients have had a recurrence, all in group I. One patient developed local recurrence after breast conservation treatment, and her condition was salvaged by further wide excision.
Two patients developed recurrence after mastectomy, and one patient ultimately died of systemic disease.
The overall survival rate for the entire group was 96%. Overall survival of high-risk group I patients, with a mean follow-up of 30.4 months, was 94%.
We recognize that this report of HRT in a small group of patients does not have the power to demonstrate an adverse effect of HRT on breast cancer.
However, the lack of an obvious adverse effect of HRT in this group of breast cancer patients and the known beneficial effect of HRT on postmenopausal cardiovascular disease and osteoporosis warrant formal prospective trials of HRT in such patients.

Hormone Replacement Therapy for Breast Cancer Survivors. A Pilot Study

P J DiSaia, E A Grosen, F Odicino, B Cowan, S Pecorelli, A G Wile, W T Creasman
Cancer 1995 Nov 15; 76(10 Suppl):2075-8

Abstract
Background: Traditionally, breast cancer survivors were not considered as candidates for hormone replacement therapy (HRT) because of the possibility that an occult metastatic site of disease might be activated, thus negatively influencing the outcome for the patient.
Methods: A retrospective review of 77 breast cancer survivors who have taken HRT was conducted.
Results: Seven recurrences were reported among the 77 patients studied in-depth, with correlations to stage, age, and node and receptor status. There have been no recurrences among the 33 additional patients who were placed on the study after the completion of this analysis.

Conclusions: No significant adverse outcome was detected in this group of breast cancer survivors receiving HRT. Given the established benefits of HRT, a reappraisal of this subject is necessary, and a prospective randomized trial is essential.

Hormone Replacement Therapy in Breast Cancer Survivors: A Cohort Study

P J DiSaia, E A Grosen, T Kurosaki, M Gildea, B Cowan, H Anton-Culver
1996 May;174(5):1494-8.

Abstract
Objective: Our purpose was to measure any adverse effect (if one exists) of hormone replacement therapy administered to breast cancer survivors.
Study design: Forty-one patients from a group of 77 patients who received hormone replacement therapy after therapy for breast cancer were matched with 82 comparison patients not receiving hormone replacement therapy. Both groups were taken from the same population on the basis of cancer registry of the Cancer Surveillance Program of Orange County and were compared with regard to survival results.
Results: An analysis of survival time and disease-free time revealed no statistically significant difference between the two groups.
Conclusions: No obvious adverse effect of hormone replacement therapy could be shown in this pilot study. A case is made for a prospective randomized trial.

Breast Cancer Survival and Hormone Replacement Therapy: A Cohort Analysis

P J DiSaia 1 , W R Brewster, A Ziogas, H Anton-Culver
2000 Dec;23(6):541-5.

Abstract
Controversy exists regarding the safety of hormone replacement therapy (HRT) after a diagnosis of breast cancer. The objective of this study is to perform a matched cohort analysis to evaluate the impact of HRT on mortality in breast cancer survivors. Patients with breast cancer who received HRT after diagnosis of breast cancer were identified.
Control subjects were identified from the regional cancer registry. Matching criteria included age at diagnosis, stage of breast cancer, and year of diagnosis. Controls were selected only if they were alive at the time of initiation of HRT of the matched case. Only subjects not included in a previously reported matched analysis were selected.
One hundred twenty-five cases were matched with 362 controls. Ninety-eight percent (123/125) of the cases received systemic estrogen; 90/125 (72%) also received a progestational agent. The median interval between diagnosis of breast cancer and initiation of HRT was 46 months (range 0-401 months). The median duration of HRT was 22 months (range 1-357 months). The risk of death was lower among the HRT survivors; odds ratio 0.28 (95% confidence interval 0.11-0.71). This analysis does not suggest that HRT after the treatment of breast cancer is associated with an adverse outcome.

Estrogen Replacement Therapy After Breast Cancer: A 12-Year Follow-Up

George N. Peters, MD, Tomasina Fodera, MD, Jennifer Sabol, MD, Stephen Jones, MD, and David Euhus, MD

Annals of Surgical Oncology, 8(10):828 - 832, 2001

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.

Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality

E S O'Meara, M A Rossing, J R Daling, J G Elmore, W E Barlow, N S Weiss

2001 May 16;93(10):754-62.

Abstract
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 then 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.

Hormone Replacement Therapy and Beyond. The Clinical Challenge of Menopausal Symptoms in Breast Cancer Survivors

Joanne E Mortimer
Geriatrics 2002 Sep;57(9):25-31.

Abstract
Early diagnosis and refinements in anti-cancer regimens have significantly reduced the mortality rate from breast cancer. In fact, breast cancer survivors represent the largest group of cancer survivors In the United States. Most breast cancer cases are diagnosed after menopause and those women diagnosed before menopause become menopausal as a result of chemotherapy. Thus a significant number of breast cancer survivors must also contend with symptoms and consequences of menopause, particularly hot flashes, night sweats, mood disorders, and bone loss. The available data suggest a possible role for hormone therapy (estrogen alone, or, combination estrogen/progestin) in the management of menopausal symptoms in select breast cancer survivors. Well-designed controlled trials are needed in this population. In the meantime, some nonhormone therapies may be options for management of hot flashes, vaginal dryness, and osteoporosis.

Cancer Recurrence and Mortality in Women Using Hormone Replacement Therapy: Meta-Analysis

Linda N Meurer, Sarah LenÃ¡
Meta-Analysis J Fam Pract 2002 Dec;51(12(:1056-62

Abstract

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.

Hormone Replacement Therapy in Breast Cancer Patients and Survivors

Giuseppe Del Priore 1 , Mehrangiz Hatami
Curr Women's Health Rep 2003 Apr;3(2):165-9.

Abstract
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.

Estrogen Replacement Therapy in Breast Cancer Survivors: A Matched-Controlled Series

David A Decker, Jane E Pettinga, Nancy VanderVelde, Raywin R Huang, Larry Kestin, John H Burdakin
Menopause Jul-Aug 2003;10(4):277-85.

Abstract
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.

Menopausal Hormone Therapy (HT) in Patients wWith Breast Cancer

Pelin Batur, Carol E Blixen, Halle C F Moore, Holly L Thacker, Meng Xu
Maturitas 2006 Jan 20;53(2):123-32.

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

ineffective. Future trials should focus on better ways to identify breast cancer survivors who may safely benefit from HT versus those who have a substantial risk of reoccurrence with HT use
Conclusion: We observed lower risks of recurrence and mortality in women who used HRT after breast cancer diagnosis then 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.

Hormone replacement therapy after breast cancer: 10-year follow-up of the Stockholm randomised trial

FahlÃ©n M[1], Fornander T, Johansson H, Johansson U, Rutqvist LE, Wilking N, von Schoultz E.
European J of Cancer Volume 49, Issue 1, Jan 2013, pp 52-59

Abstract
Background
The management of hormonal deficiency symptoms in breast cancer survivors is an unsolved problem. While hormone replacement therapy (HRT) may increase the risk of breast cancer in healthy women, its effects on recurrence is unclear. Observational studies have suggested decreased recurrence rates from HRT. The few clinical trials in this field have all been closed preterm.
Methods
The Stockholm trial was started in 1997 and designed to minimize the dose of progestogen in the HRT arm. Disease-free women with a history of breast cancer were randomized to HRT (*n* = 188) or no HRT (*n* = 190). The trial was stopped in 2003 when another Swedish study (HABITS, the Hormonal Replacement After Breast Cancer Is it Safe?) reported increased recurrence. However the Stockholm material showed no excess risk after 4 years of follow-up. A long term follow-up has now been performed.
Findings
After 10.8 years of follow-up, there was no difference in new breast cancer events: 60 in the HRT group versus 48 among controls (hazard ratio (HR) = 1.3; 95% confidence interval (CI) = 0.9 - 1.9). Among women on HRT, 11 had local recurrence and 12 distant metastases versus 15 and 12 for the controls. There were 14 contra-lateral breast cancers in the HRT group and four in the control group (HR = 3.6; 95% CI = 1.2 - 10.9; *p* = 0.013). No differences in mortality or new primary malignancies were found.
Interpretation
The number of new events did not differ significantly between groups, in contrast to previous reports. The increased recurrence in HABITS has been attributed to higher progestogen exposure. As both trials were prematurely closed, data do not allow firm conclusions. Both studies found no increased mortality from breast cancer or other causes from HRT. Current guidelines typically consider HRT contraindicated in breast cancer survivors. Findings suggest that, in some women symptom relief may outweigh the potential risks of HRT.