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Title Abbrev:	Climacteric
Citation:	1998 Jun;1(2):137-42
Article:	A cohort study of hormone replacement therapy give
Author:	Dew J; Eden J; Beller E; Magarey C; Schwartz P; Crea P; Wren
NLM Unique ID:	9810959 Verify: PubMed
PubMed UI:	11907916
ISSN:	1369-7137 (Print)
Publisher:	Parthenon Pub., New York :
Copyright:	Copyright Compliance Guidelines
Authorization:	barb
Need By:	N/A
Maximum Cost:	**$15.00**
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A cohort study of hormone replacement therapy given to women previously treated for breast cancer

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Key words: ESTROGEN,PROGESTIN,HORMONEREPLACEMENTTHERAPY,BREASTCANCER

ABSTRACT

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.

INTRODUCTION

Women who have had breast cancer are usually denied hormone replacement therapy (HRT) for fear of stimulating growth of their cancer or inducing a new breast cancer. However, for some women, menopausal symptoms may be so severe that to ignore them would be to deny these women a reasonable quality of life. Also, as screening mammography is detecting an increased number of early-stage breast cancers, many women may survive their tumor only to die years later of a cardiovascular event or a hip fracture which may have been prevented by the use of HRT.

Estrogens, progestins and androgens have all been implicated in the pathophysiology of breast cancer[1], but it is estrogen that is most strongly implicated. HRT encompasses a wide variety of combinations of sex steroids; however, currently, the three most popular regimens are either unopposed estrogen, estrogen and sequential progestin, or continuous combined therapy where both the

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ORIGINAL ARTICLE

Received 26–8–97
Revised 21–10–97
Accepted 12–11–97

estrogen and progestin are taken daily without a break. From various biological studies, it seems likely that each of these regimens will affect the breast differently and therefore be associated with differing risks of developing breast cancer[1–5]. We have previously published data on 90 women with a personal history of breast cancer treated with continuous combined HRT, using an estrogen with a moderate dose of progestin (medroxyprogesterone acetate (MPA) 50 mg or norethisterone 5 mg[2]. When compared with matched controls, the HRT users had a relative risk (RR) of recurrence of 0.40 (95% CI 0.17–0.93)[2]. In this present study, most subjects were deliberately given a moderate dose of progestin for three reasons. First, a moderate-to-high dose of progestin is an effective treatment for breast cancer[6]. Second, moderate doses of progestins have been shown significantly to reduce hot flushes when compared with a placebo, with an efficacy rate of around 66%[7–9]. Third, there is increasing biological evidence that continuous progestin offers significant advantages to the breast over sequential therapy[3–5]. It has been the practice of the Menopause Unit at the Royal Hospital for Women, Randwick, Sydney to offer women with a history of breast cancer, having significant hot flushes, a trial of progestin only (most commonly MPA 50 mg) for 1 month. If there was no relief from their symptoms after 4 weeks, then an estrogen was added to the regimen. We would now like to report follow-up of 167 women who had taken estrogen for menopausal symptoms after treatment for breast cancer. This group includes 90 subjects previously reported[2] but includes a larger group with longer follow-up.

METHODS

Study patients

The study group was comprised of 1472 women with breast cancer treated by surgeons and gynecologists a three teaching hospitals in south eastern Sydney (The Royal Hospital for Women, St. Vincent's Hospital and St. George Hospital). There were no deliberate exclusions. Medical records were abstracted for all 1472 subjects. If the follow-up from records was incomplete, then the subject's general practitioner or the subject herself was contacted. For study purposes, follow-up was defined as incomplete if the last contact date with the subject was prior to January 1, 1995. In 60 cases (4%), follow-up data were not available. A total of 167 subjects (11.3%) had used an oral or transdermal estrogen for severe menopausal symptoms after their treatment for breast cancer. Table 1 summarizes the demographics of the total database as well as the subgroup of estrogen users.

Amongst the estrogen users, the median time interval from diagnosis to starting therapy was 3 years (range 0–26 years), with a median time on therapy of 1.6 years (range 0.25–22 years). The HRT users took a median of 0.625 mg conjugated equine estrogen (CEE) equivalents daily (0.625 mg = 1.25 estrone sulfate = 2 mg estradiol valerate = 50 μg estradiol patch). The range of dosage was 0.3–2.5 mg CEE equivalents daily.

Table 1 Demographics of the entire database of subjects with breast cancer with the estrogen users as a subgroup. Results are expressed as medians with ranges or as percentages

	All subjects (n = 1472)	*Estrogen users* (n = 167)	p
Age at diagnosis (years)	54 (21–96)	48.5 (24–77)	0.0001
Age at menarche (years)	13 (9–19)	13 (10–16)	NS
Age at menopause (years)	49 (29–66)	50 (29–57)	NS
Gravidity	2 (0–13)	3 (0–9)	NS
Parity	2 (0–9)	2 (0–6)	NS
Total mastectomy	713 (48%)	104 (62%)	0.0007
Partial mastectomy, glands, radiotherapy	759 (52%)	63 (38%)	
Distal metastases at diagnosis	256 (17%)	8 (5%)	0.00001
Gland-negative disease	661 (45%)	140 (84%)	0.00001
Maximum tumor diameter (cm)	2.6 (0.1–26)	1.5 (0.1–6)	0.0001
Number of axillary glands involved	0 (0–50)	0 (0–50)	0.0007
Estrogen receptor-positive	190/344 (55%)	39/62 (63%)	NS
Progesterone receptor-positive	113/233 (48%)	19/41 (46%)	NS
Tamoxifen usage	751 (51%)	34 (20%)	0.0001

NS, not significant

Table 2 Summary of the type of hormones taken by estrogen users

Hormone	*n*	%
Estrogen		
Conjugated equine estrogens	78	46.8
Estrone sulphate	68	40.7
Estradiol patches	13	7.8
Estradiol valerate	8	4.8
Total	167	
Progestin		
Medroxyprogesterone acetate	82	49.1
Norethisterone	64	38.3
Dydrogesterone	2	1.2
Levonorgestrel	4	2.4
Total	152	9.0

Table 2 contains the types of estrogen and progestin used by the HRT users. Amongst the HRT users, 152 (91%) also used a progestin, 148 continuously and four cyclically. The median dose of progestin used was 50 mg MPA equivalents (range 2.5–500 mg) daily. MPA 5 mg is equivalent to 0.5 mg of norethisterone.

A total of 106 other women were using a progestin alone as a treatment for menopausal flushes (and not as a treatment for breast cancer). Amongst the progestin-only users, the median time from diagnosis of breast cancer to starting therapy was 2 years (range 0–16 years), with a median time on therapy of 1 year (range 0.05–5.8 years). The median dose of progestin used expressed as MPA equivalents was 50 mg (10–100 mg) per day.

Of all subjects, 50% were using tamoxifen (Table 1) as adjuvant therapy. Amongst the estrogen users, 34 (20%) were using tamoxifen and this therapy was continued along with their hormonal therapy.

Statistical analysis

A Cox regression analysis was performed using sex hormone usage as a time-dependent covariate with a disease-free interval as the outcome. A second Cox regression analysis was performed adjusting for tumor size, axillary nodes, age at diagnosis, age at menarche and parity. Results are expressed as a hazard ration with 95% confidence intervals. The hazard rate is defined as the probability of a subject dying over the study period[10]. This analysis corrects both for time from diagnosis to starting HRT and for time whilst actually taking HRT.

Demographic results are expressed as medians (ranges). The p values in Table 1 were calculated using 2×2 tables and the Mann-Whitney U test.

Demographics

The descriptions of the entire group as well as the HRT subgroup are summarized in Table 1 and 2. It should be noted that the HRT users were more likely to have gland-negative disease, had smaller tumors, were younger at diagnosis and less likely to use tamoxifen than the average subject in our database.

RESULTS

Deaths

There were two deaths (1.2%) amongst the estrogen users and 169 (11.5%) in the entire database. Because a comparison of these two groups would be biased, no test of significance was applied, but evidence suggested that use of estrogen did not increase the risk of death.

Cox regression analysis

Hormone usage was entered as a time-dependent covariate with disease-free interval as the outcome. The analysis was repeated adjusting for tumor size, axillary node status, age at diagnosis, age at menarche and parity. The estrogen–progestin users had an uncorrected hazard ratio of 0.67 (95% confidence interval (CI) 0.38–1.16), with a corrected hazard ratio of 0.99 (95% CI 0.40–2.47). Subjects who used a progestin alone for menopausal symptoms had an uncorrected hazard ratio of 0.85 (95% CI 0.44–1.65) with a corrected hazard ratio of 0.93 (95% CI 0.40–2.18). This means that hormone usage was not associated with increased risk of recurrence of breast cancer.

A secondary Cox regression analysis was performed on the estrogen–progestin users, comparing high-dose progestin (≥ 10 mg MPA equivalents daily or more) and lower (< 10 mg MPA equivalents daily) or no progestin, as a time-dependent covariate with disease-free interval as the outcome. This analysis showed a non-significant difference in disease-free interval between the high-dose progestin and low- or no-dose progestin groups, with a hazard ratio of 1.24 (95% CI 0.49–3.10). The analysis was repeated adjusting for known prognostic variable and this time showed a non-significant difference in disease-free interval between the higher-dose progestin and the lower-

or no-dose progestin groups, with a hazard ratio of 1.96 (95% CI 0.53–7.34).

DISCUSSION

Estrogen has long been implicated as the main sex hormone involved in the pathogenesis and promotion of breast cancer. The case against estrogen is summarized in Table 3 and 4.

However, the case is not entirely convincing. Haddow and colleagues were the first to use synthetic estrogen to treat terminal cases of breast cancer. They indicated that, although synthetic estrogens could produce mammary tumors in certain strains of laboratory animals under specially defined experimental conditions, under different conditions the same estrogen could cause tumor regression[11]. In other words, the effect of a hormone depends on the pathophysiological setting. A given hormone may, in some circumstances, induce tumor growth but, in another setting, inhibit tumor progression. As a result, HRT and breast cancer risk should be considered in the context of the type and dosage of estrogen used, the progestin regimen, and whether or not aromatizable androgens were present. The impact of progestin is complex but there are data to support the hypothesis that cyclical progestins stimulate the breast, whereas continuous progestins, particularly if given in moderate or high dosage, reduce breast cancer risk[12]. Cell culture studies have shown that progestins reduce breast cell activity when estrogen is present in the culture medium, but may induce some transient proliferation in estrogen-free media[4,5]. In a series of elegant experiments, Clarke and Sutherland[4] and Musgrove and colleagues[5] have shown that, in those instances where progestin stimulation of breast cancer cell lines had occurred, increases in cell number had rarely even doubled, whereas estradiol or insulin typically increased cell numbers around sevenfold. Their cell cycle experiments showed that progestins initially induced an increase in cell numbers entering S phase, but, after 12 h of progestins, there was a reduction in cell cycle progression. After 24 h, the percentage of cells in S phase was lower than baseline and was maintained at 96 h[4]. They concluded that progestins transiently increase the rate of cells entering G1/S phase and that continued progestin therapy arrests these breast cancer cells in early G1 phase, maintaining quiescence. Progestins have been shown to inhibit aromatase activity, reduce intracellular estradiol levels, reduce the number of estrogen receptors, promote the production of estrone sulfate and inhibit the production of cathepsin-D, a mitogenic protein[4,5,13]. For this reason, the use of progestin in a continuous regimen offers an opportunity to control those factors which increase the rate of mitosis in breast cancer cells.

There is little doubt that estrogen can induce normal and some malignant cells to proliferate,

Table 3 The case against estrogen[1,2,16]

Estradiol stimulates the growth of some breast cancer cell lines in culture
Oophorectomy palliates some breast cancers and reduces the risk of recurrence
Breast cancer risk relates to age at menarche and age of menopause
Stopping HRT may cause some breast cancers to regress
Long-term estrogen usage may slightly increase the risk of breast cancer
Serum estradiol levels predict breast cancer risk

Table 4 Confounders for the 'estrogen hypothesis'[1,2]

Breast tissue estradiol levels are 20 times that of serum (before and after the menopause)
Breast tissue and serum levels of estradiol are unrelated
Fat around a breast cancer produces more estradiol than other fat sites within the same breast
Locally produced catecholestrogens bind reversibly to estrogen receptors and permanently activate them
Oophorectomy, stilbestrol and tamoxifen are all equally effective treatments for advanced breast cancer (and work best when estrogen receptors are present)
Pregnancy has little or no effect on the risk of breast cancer recurrence
The ovary does not make estrogen alone but also makes large amounts of androgen (the precursor for estrogen) as well as cyclical progestins

but there is considerable doubt that serum levels of estradiol are the main determinant of breast cell concentrations of estrogen. Toniolo and colleagues have provided some evidence that serum levels of estradiol predict breast cancer risk[14]. Furthermore, they showed that the percentage of estradiol bound to sex hormone binding globulin was negatively correlated with breast cancer risk, suggesting a protective effect. However, Bulbrook and colleagues[15] concluded that there was no relationship between serum (total or free), urinary or salivary estrogens and breast cancer risk. Breast epithelium and fat contain levels of estradiol more than 20 times that of serum[15] and this may be due to local aromatization within the breast fat cells. The increased fat content of the breast with advancing age may, in part, explain the maintenance of this high tissue to serum estradiol gradient after the menopause. Therefore, it would seem likely that local regulation of estrogen metabolism may be more relevant to breast cancer growth than serum levels of estradiol.

Confounding is always an important issue when considering cohort studies, and in this study we attempted to correct for known confounding factors. However, one obvious difference between the HRT users and the rest of the database is that the treatment group presented because of significant menopausal symptoms. There are data to suggest that women who have severe persistent hot flushes are significantly more estrogen-deficient than women not having symptoms or only having mild symptoms[16].

We would postulate that continuous combined HRT confers significant advantages over the older cyclic regimens. For example, these continuous regimens often result in amenorrhea. However, the impact of the moderate progestin dosage on heart risk has not been addressed in this study. If continuous estrogen–progestin does reduce breast cancer risk, then future studies may focus on balancing the 'breast vs. heart risk'. Breast cancer is common but, for some patients, menopausal symptoms are so severe that they would choose HRT to improve their quality of life despite any theoretical risks associated with estrogen. A large percentage of patients will have a significant reduction in the frequency of their hot flushes when using a moderate dose of progestin alone, while vaginal dryness may be treated with nonhormonal vaginal moisturizers or poorly absorbed topical estrogens.

These results, using combined estrogen and progestin, are encouraging, but need to be confirmed in a randomized prospective clinical trial. If these results are confirmed, then dose-finding studies should be conducted to establish the amount of continuous progestin required to inhibit breast cell activity. It is also possible that HRT regimens could be designed to reduce the risk of breast cancer.

Conflict of interest Nil.

Source of funding Nil.

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