International Journal of Gynecology & Obstetrics 64 (1999) 59–63

International Journal of GYNECOLOGY & OBSTETRICS

Article

Estrogen replacement therapy in breast cancer survivors

F. Guidozzi

Department of Obstetrics and Gynaecology, Johannesburg Hospital, University of the Witwatersrand Medical School, Johannesburg, South Africa

Received 10 June 1998; received in revised form 16 October 1998; accepted 16 October 1998

Abstract

Objective: To determine whether estrogen replacement therapy (ERT) adversely affected outcome of breast cancer survivors. *Method*: A prospective descriptive study of all breast cancer survivors who requested ERT because of intractable menopausal symptoms. All patients presented voluntarily as gynecological outpatients and were all given oral continuous opposed ERT: 20 premarin and medroxyprogesterone and four tibolone. *Results*: Twenty-four patients who had previously been treated for breast cancer 8–91 months prior to their initiating ERT have been observed for 24–44 months. There were 15 patients with stage 1, eight with stage 2 and one with stage 4 breast cancer. The mean age of the patients at commencement of ERT was 48 years (range 42–61). Two patients had a biopsy of a suspicious breast nodule: both of which were benign. There have not been any recurrences to date. *Conclusion*: Breast cancer survivors did not have their outcome adversely affected by ERT during an observation period of 24–44 months. © 1999 International Federation of Gynecology and Obstetrics

Keywords: Estrogen therapy; Breast cancer survivors

1. Introduction

Breast cancer survivors have for a long time been denied the beneficial effects of estrogen replacement therapy because of the belief that estrogen would activate or accelerate the growth of occult breast cancer or facilitate breast carcinogenesis. Even at present the standard care provided by oncologists, surgeons and the majority of gynecologists is to strongly discourage prescription of estrogen replacement to the breast cancer survivor. Although there are theoretical justifications for this position, the limited number of studies emphasizing this factor offer little support for such dogma. Be it due to the fear of litigation, the lack of guidelines provided by national professional societies or the lack of prospective studies, breast cancer survivors are continuously being denied estrogen which will relieve symptoms that make their lives more tolerable.

0020-7292/99/$ - see front matter
PII: S0020-7292(98)00222-7

With the advent of mammography and improvement in treatment strategies of breast cancer, there are at present more breast cancer survivors than ever before who, as informed consumers, are increasingly enquiring about and or are requesting estrogen replacement therapy.

Not only may the debilitating menopausal symptoms be due to a natural menopause, but they may well be precipitated by the adjuvant chemotherapy or the oral ingestion of tamoxifen in the premenopausal women. Hot flushes, mood swings, emotional disorders, sleep disturbances, dyspareunia and atrophic vaginitis with its attendant urinary tract infections are only a few of the very often debilitating symptoms. Estrogens will alleviate these symptoms, have significantly beneficial effects on the cardiovascular, cerebrovascular systems and osteoporosis, and improve memory, concentration and may well have beneficial effects by decreasing the incidence of Alzheimer's disease [1,2]. A nested case-control study from the Leisure World retirement community in southern California and cohort studies from Baltimore and New York suggest that postmenopausal estrogen therapy reduces the risk of Alzheimer's disease by about one third to one half, although no significant risk reduction is reported from a Seattle case-control study. Some studies have noted a dose–response relationship, in which greater estrogen exposures are associated with greater risk reductions [3]. No randomized controlled trials of estrogen for the primary prevention of Alzheimer's disease has been reported.

Although some of these effects may be more insidious in the long-term, they decrease potentially fatal consequences of estrogen deficiency. In fact, at present, death from a non-neoplastic condition is common among node-negative breast cancer survivors of which cardiovascular disease is the most common cause [4]. Therefore by denying breast cancer survivors the benefits of estrogen replacement, not only are we diminishing their quality of life, we may well be reducing their overall survival by increasing the risk of cardiovascular disease and osteoporotic fractures.

In the face of mounting pressure to obtain some information for this growing population of breast cancer survivors, a retrospective study was undertaken to determine whether estrogen replacement therapy adversely affected the outcome of breast cancer survivors.

2. Materials and methods

Twenty-four patients with a history of breast cancer presented for estrogen replacement therapy (ERT) because of overwhelming menopausal symptoms. Hot flushes were the predominant symptom in the vast majority of patients, followed by mood swings, insomnia and depression. All women included in the study were given oral continuous opposed ERT for a minimum of 2 years. Twenty were given 0.625 mg Premarin and 5 mg Provera (medroxyprogesterone) daily whilst four were given Livifem (tibolone) daily.

At the time of presentation 17 were naturally menopausal (mean age 56 years, range 48–61 years), 2 patients had a previous hysterectomy and bilateral salpingo-oophorectomy, whilst premature ovarian failure had occurred in five patients who had received adjuvant chemotherapy (mean age 43, range 41–45 years). All patients had undergone some form of surgery. The breast cancer treatment is shown in Table 1. Six patients had received adjuvant Tamoxifen, but all had completed their course at the initial presentation for ERT. During the observation period, the patients were seen three times a year by the author, were sent for annual mammograms and were taught to self-examine their breasts (on a weekly basis). They also continued to see their breast surgeon annually. Three patients had pre-

Table 1
Breast cancer treatment

Surgery	
Segmental mastectomy	4
Unilateral mastectomy	18
Bilateral mastectomy	2
Postsurgery	
Radiotherapy	7
Chemotherapy	6
Radio- and chemotherapy	3

Table 2
Characteristics and outcome of breast cancer survivors

No of patients:		24
Stage 1:		15
2:		8
4:		1
Age:		48 years (42–61)
ERT initiation:		34 months (8–91)
ERT duration:		32 months (24–44)
Observation period:		24–44 months
Overall follow-up:		68 months (32–134)
Nodal status:	Negative	6
	Positive	8
	Unknown	10
ER status:	Positive	2
	Negative	2
Recurrences:		0/24

sented with a history of subsequent breast reconstructive surgery.

3. Results

Three patients had a first degree relative with breast cancer, five a second degree relative whilst two had a first and second degree relative. Three patients had been on ERT at the time of the original diagnosis. Six patients were on antihypertensives, nine on antidepressants and 12 on sleeping tablets. The mean age of the patients was 48 years (range 42–61). The patients had commenced their ERT at a mean of 34 months (range 8–91) since the diagnosis of their breast cancer. The mean duration of the ERT has been 32 months (range 24–44) with an overall observation period of 68 months (28–134) since their original diagnosis. Two patients who had reconstructive surgery had a biopsy of suspicious nodules: both of which showed benign disease. Nodal and receptor status was only known in 14 and four patients, respectively. The patient characteristics and outcome are shown in Table 2.

4. Discussion

Despite a wealth of data, the controversy surrounding the potential impact of ERT on the development of breast cancer persists. In almost 50 studies, including three meta-analyses, the relative risk estimates for developing breast cancer with ERT ingestion hover at approximately 1.3, with almost as many studies indicating non-significantly decreased risks of breast cancer from estrogen use as those indicating a non-significantly increased risk [5,6]. Of those studies observing significantly increased risk, all have been in different subgroups of estrogen users or due to an increase in a subgroup. No study has observed any significantly increased risk of breast cancer in their total patient population of estrogen users. In addition there appears to be evidence indicating that all women who develop breast cancer while receiving ERT, have a more favorable prognosis with respect to tumour grade and to final clinical outcome [6–8].

Several recently published editorials and commentaries have challenged the dogma that ERT is to be avoided in breast cancer survivors and all have emphasized the need for an open mind [9–14]. Nevertheless in the absence of data from prospective studies that definitely supports this management strategy, attending medical staff continue to show reluctance to prescribe ERT to breast cancer survivors.

There is a paucity of literature pertaining to Tibolone usage in breast cancer survivors and outcome. Two patients in this study were given Tibolone because their poor libido was the most significant issue, whilst the other two were given it because of their poor response to our conventional therapy. There is some data to suggest that Tibolone may have some antimitotic effects on breast carcinogenesis [15,16]. Tibolone is a progesterone-like synthetic steroid that is structurally-related to 19-nortestosterone derivatives, such as norethynodrel and norethisterone. It has weak estrogenic, progestogenic and androgenic properties, which are tissue-specific, and also has

been shown to be effective in the treatment of hot flushes, sweating and headaches. Tibolone prevents bone loss, does not adversely effect liver function or carbohydrate metabolism, appears to have a positive effect on the cardiovascular profile primarily by lowering HDL, triglycerides and lipoprotein (a), and is associated with relatively low rates of vaginal bleeding and does not induce endometrial proliferation [16].

This small retrospective descriptive study in no way presumes to justify routine estrogen replacement therapy in breast cancer survivors. Obviously the main limitation of this study is its short duration of the follow-up of the patients after commencing hormone replacement therapy. As of yet there is no way of knowing whether the preliminary reassuring results are a mere statistical quirk, or whether they hide some long-term increase in the risk of recurrences. At least 5–10 years of follow-up will be required before data can definitively answer these concerns. Nevertheless this study does highlight the fact that there is convincing evidence that patient management must be individualized and that the dictatorial stance of 'pouring petrol onto the fire' by administering ERT to breast cancer survivors no longer holds ground. Patients require information pertaining to all the benefits and risks of ERT. In breast cancer survivors, the emphasis must be that a recurrence or second primary may occur as a natural evolution of the disease anyway. However, ERT will significantly improve quality of life without there being a plethora of literature to suggest it will adversely affect survival.

With the caveat that great caution should be applied to any comparisons, the results of the retrospective analysis of 270 breast cancer survivors who received ERT does not appear to deviate from the expected outcome data for recurrence [17]. Early data therefore does suggest that some breast cancer survivors can use HRT in the short-term without adverse effects.

While it may require a paradigm shift to change prescribing and management ideas, it is important that we as doctors keep in mind that quality of life is paramount. If the patient has been fully informed and we can improve quality of life without causing premature death, we will have gained a major advantage for women.

References

[1] Rozenberg S, Kroll M, Vandromme J. Decision factors influencing hormone replacement therapy. Br J Obstet Gynaecol 1996;103:92–98.

[2] Paganini-Hill A. Oestrogen replacement therapy and Alzheimer's disease. Br J Obstet Gynaecol 1996;103: 80–86.

[3] Henderson VW. The epidemiology of estrogen replacement therapy and Alzheimer's disease. Neurology 1997;48:S27–S35.

[4] Cobleigh MA, Berris RF, Bush T et al. Estrogen replacement therapy in breast cancer survivors. J Am Med Assoc 1994;272:540–546.

[5] Gambrell RD. Hormone replacement therapy and breast cancer risk. S Afr J Surg 1996;34:169–174.

[6] Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52 705 women with breast cancer and 108 411 women without breast cancer. Lancet; 350: pp.1047–1059. 1997

[7] Bergkvist L, Adami H-O, Persson I et al. Prognosis after breast cancer diagnosis in women exposed to estrogen and estrogen–progestogen replacement therapy. Am J Epidemiol 1989;130:221–227.

[8] Strikland DM, Gambrell RD, Jr, Butzin CA et al. The relationship between breast cancer survival and prior postmenopausal estrogen use. Obstet Gynecol 1992;80: 400–404.

[9] Creasman WT. Estrogen replacement therapy: Is previously treated cancer a contraindication? Obstet Gynecol 1991;77:309–312.

[10] Theriault RL, Vassilopoulou–Sellin R. A clinical dilemma: estrogen replacement therapy in postmenopausal women with a background of primary breast cancer. Am J Oncol 1991;2:709–717.

[11] Lobo RA. Hormone replacement therapy: oestrogen replacement after treatment for breast cancer? Lancet 1993;341:1313–1314.

[12] Marchant DJ. Estrogen-replacement therapy after breast cancer: risk vs. benefits. Cancer 1993;71:2169–2176.

[13] Spicer DV, Pike MC. Hormone replacement after breast cancer. Lancet 1993;342:183–184.

[14] DiSaia PJ. Hormone replacement therapy in patients with breast cancer. Cancer 1993;711:1490–1500.

[15] Gompel A, Kandouz M, Siromachkova M et al. The effect of tibolone on proliferation, differentiation and

apoptosis in normal breast cells. Gynecol Endocrinol 1997;11:77–79.

[16] Pasqualini JR, Chetrite G. Control of estrone sulfatase actively in human breast cancer cells: effect of tibolone and its metabolites. Gynecol Endocrinol 1997;11:69–75.

[17] Vassipoulou-Sellin R, Theriault R, Klein MJ. Estrogen replacement therapy in women with prior diagnosis and treatment for breast cancer. Gynecol Oncol 1997; 65:89–93.