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

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Key words: VAGINAL ESTROGEN, BREAST CANCER

ABSTRACT

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.

INTRODUCTION

Breast cancer is a significant women's health problem and a leading cause of morbidity and mortality. With the majority of women being postmenopausal at diagnosis, together with an increasing incidence and improved survival, there are an increasing number of breast cancer survivors experiencing both the short- and long-term consequences of estrogen deficiency. The occurrence and management of menopausal symptoms in women with breast cancer are thus becoming increasing problems. The role of estrogen as a promoter of breast cancer is well recognized, and this has resulted in these women being denied hormones for fear of stimulating a recurrent or

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new tumor. However, some menopausal women with breast cancer will experience significant symptoms, and for these women the main issue is symptom control. For some of these women the only bothersome menopausal symptoms are those attributable to postmenopausal vaginal atrophy. These symptoms can cause considerable discomfort. Estrogen replacement therapy is the mainstay of treatment of vaginal atrophy. Symptoms may not be controlled by alternative nonhormonal means. To deny these women estrogen therapy would potentially also deny them a reasonable quality of life.

Urogenital tissue is estrogen-sensitive and atrophies after the menopause. Pelvic tissues undergo epithelial thinning, reduced vascularity, decreased muscle bulk, loss of collagen, loss of adipose tissue and loss of water-retaining ability[1]. The atrophic changes that result from chronic estrogen deprivation lead to reduced sexual activity, bladder problems and a general decrease in quality of life, and can cause more severe problems in the elderly if left untreated.

Symptoms resulting from vaginal atrophy include vaginal irritation, dryness and pruritus, lack of lubrication, dyspareunia, discharge and postcoital bleeding. Vaginal dryness is generally the first symptom noticed[1], whereas dyspareunia is reportedly the most significantly increased symptom[2]. With hypoestrogenism the vagina shortens and narrows, and the vaginal walls become thinner, less elastic, pale in color and smoother as rugation decreases. Reduced secretions are produced in the atrophic vagina, and the onset of lubrication with sexual arousal slows. The vagina becomes progressively friable, with petechiae, ulcerations and bleeding occurring with minimal trauma[1,3]. Glycogen production diminishes, resulting in an increase in vaginal pH and a change in vaginal flora with a reduction in lactobacilli and consequent loss of inhibition of contaminating flora[1]. The change in vaginal flora increases the susceptibility of women to urinary tract and vaginal infections[4].

The lower vagina and urethra both originate from the urogenital sinus embryologically, and thus experience similar hormonal effects and atrophic changes with the menopause. Estrogen receptors have been identified in the lower urinary tract[5]. Thus, lower urinary tract atrophy secondary to hypoestrogenism is a theoretical contributing factor in the development of urinary symptoms such as urinary frequency, dysuria, urgency, urge and stress incontinence and urinary tract infections. In support of this, recurrent urinary tract infections are shown to increase with age, with rates rising from 4% in 61-year-olds to 12% in 81-year-olds[6]. Molander and colleagues[7] showed a rate of 23% in 90-year-olds. Overall, 10–15% of women over 60 years have recurrent urinary tract infections[4]. Urinary incontinence is the menopausal patient's most important urinary symptom[6], with 15–30% of women over 60 years experiencing it. Stenberg and associates[6] found that urinary incontinence, both stress and urge, was experienced by 33% of 61-year-olds and 37% of 81-year-olds.

The prevalence of symptoms related to urogenital aging is estimated at 40–50% in the general postmenopausal population[3,6]. There are fewer data on the prevalence of symptoms in survivors of breast cancer. In a survey by Couzi and colleagues of 190 postmenopausal survivors of early-stage breast cancer, it was found that vaginal dryness was experienced by 48%, dyspareunia by 26% and difficulty with bladder control by 36% of subjects[8]. A survey by Ganz and co-workers showed that breast cancer survivors reported higher rates of hot flushes, vaginal dryness and urinary symptoms than similar, healthy postmenopausal women[9,10]. There are no data available as to the proportion of postmenopausal women with breast cancer whose only bothersome menopausal symptoms are related to urogenital atrophy.

The vaginal dryness that occurs in breast cancer survivors is due to the loss of endogenous estrogen, as occurs through the induction of a premature menopause in younger women with chemotherapy, and tissue aging itself[9,11]. The prohibition of estrogen in women with breast cancer may also increase the prevalence and severity of symptoms of urogenital atrophy. Tamoxifen is being used increasingly in the management of breast cancer and has both estrogenic and antiestrogenic effects. As an agonist to α estrogen receptors, tamoxifen is capable of estrogenization of the vulva and vagina[12,13], which should aid in the prevention and treatment of symptoms due to postmenopausal vaginal atrophy. However, tamoxifen therapy has been associated with both vaginal dryness and discharge[9], although recent data did not demonstrate excess vaginal dryness in women taking tamoxifen compared with placebo[14].

Estrogen has a known mitogenic effect on breast cells, and is thought to be contraindicated in women with breast cancer for fear of stimulating disease progression. As a result, breast cancer survivors presenting with symptoms of vaginal

atrophy are often offered vaginal moisturizers and lubricants. Many, but not all, of these women will obtain relief from their vaginal dryness and dyspareunia. They will not obtain relief from their lower urinary tract symptoms[15–17].

Because ethics committees have been reluctant to permit a prospective double-blind randomized trial of hormonal therapy, a cohort study, to determine the effects of hormones given to women previously treated for breast cancer, was performed. In the present study, those women whose only significant menopausal symptom was vaginal dryness and who had not responded to alternative therapies were offered a low-dose topical vaginal estrogen cream or tablet. These were women who subjectively presented with bothersome symptoms related to vaginal atrophy not responsive to vaginal moisturizers and lubricants who were willing to use topical vaginal estrogen therapy. Because of its limited systemic absorption this application is thought to have little effect on breast cell activity[18–20].

Although estrogen is said to be contraindicated in patients successfully treated for breast cancer, currently there are no firm data to substantiate this rationale, nor are there randomized controlled trials to support the use of hormone replacement therapy (HRT) after breast cancer. Our group previously reported results from the same cohort of 167 women with a personal history of breast cancer treated with combined continuous oral estrogen and progestogen. The uncorrected hazard ratio for estrogen–progestogen users was 0.67 (95% confidence interval (CI) 0.38–1.16, $p = 0.15$) and the corrected hazard ratio was 0.99 (95% CI 0.40–2.47, $p = 0.99$). A further 106 subjects used a progestogen alone as a treatment for menopausal flushes and not as a treatment for their breast cancer. The uncorrected hazard ratio for progestogen-only users was 0.85 (95% CI 0.44–1.65, $p = 0.64$) and the corrected hazard ratio was 0.93 (95% CI 0.40–2.18, $p = 0.87$)[21]. A number of other small cohort and case–control studies have used HRT in women previously treated for breast cancer without adverse effect[22–29]. None of these studies has shown an increased risk of recurrence.

Findings in the group of women who elected to use topical vaginal estrogen therapy in the management of their symptoms related to vaginal atrophy are discussed in the present article.

MATERIALS AND METHODS

The study group comprised 1472 women with histologically confirmed breast cancer, treated by three surgeons and two gynecologists at three teaching hospitals in south-eastern Sydney, Australia: The Royal Hospital for Women, St Vincent's Hospital and St George Hospital. All women with breast cancer treated by these doctors were included in the study. There were no deliberate patient exclusions. Medical records were abstracted for all 1472 subjects. Where possible, the subject, her general practitioner and any other breast surgeon, medical oncologist or radiation oncologist involved in her care was contacted for follow-up and to complete the patient's data. In 60 cases (4.1%), complete follow-up data were not available.

In total, 342 subjects (23.2%) used a form of hormonal therapy in the management of their menopausal symptoms. In 69 of these subjects (4.7%) their only bothersome menopausal problems were vaginal symptoms. In these women, low-dose topical vaginal estrogen cream or tablets were used. These patients were compared with the rest of the database.

The demographics of the subgroup of vaginal estrogen users were compared with those of the remaining database. Demographic results are expressed as means with ranges or as percentages. The p values were calculated using the t test for means and the χ^2 test for proportions (%), with a p value of 0.05 as the significance level.

A cohort study of hormone therapy after breast cancer was performed. The subgroup of topical vaginal hormone users was compared with all other subjects in the database. A Cox regression analysis was performed using sex hormone usage as a time-dependent covariate. Disease-free interval was the outcome measured. Results are expressed as a hazard ratio with 95% confidence interval. The hazard rate is defined as the probability of disease recurrence or of a subject dying from breast cancer over the study period[30]. This analysis corrected for both time from diagnosis to starting hormonal therapy and time while actually using hormonal therapy. A second analysis was performed adjusting for factors known to affect breast cancer prognosis. This second Cox regression analysis adjusted for tumor size, number of axillary nodes involved, age at diagnosis, age at menarche and parity.

Table 1 Study group demographics. Values are expressed as mean (range) or *n* (%)

	All other subjects	*Vaginal estrogen users*	*p Value*
n	1403	69	
Age at diagnosis (years)	55.6 (21–96)	53.8 (22–83)	0.3
Age at menarche (years)	13 (9–19)	12.8 (10–15)	0.2
Age at menopause (years)	48.3 (29–66)	47.5 (36–56)	0.4
Gravidity (*n*)	2.7 (0–13)	2.6 (0–8)	0.9
Parity (*n*)	2.1 (0–9)	2.2 (0–5)	0.7
Total mastectomy	772 (55%)	43 (62%)	0.3
Partial mastectomy, glands and radiotherapy	631 (45%)	26 (38%)	—
Distal metastases at diagnosis	31 (2.2%)	0 (0%)	0.3
Gland-negative disease	828 (59%)	33 (48%)	0.1
Maximum tumor diameter (cm)	2.3 (0.1–26)	2.0 (0.1–9)	0.8
Axillary glands involved (*n*)	2.0 (0–50)	1.8 (0–25)	0.4
ER-positive	208/340 (61%)	12/33 (36%)	0.2
PR-positive	128/232 (55%)	1/8 (13%)	0.03
Tamoxifen usage	701 (47%)	33 (48%)	0.7

ER, estrogen receptor; PR, progesterone receptor

RESULTS

The demographics of the subgroup of vaginal estrogen users were compared with those of all other subjects on the database (Table 1). When vaginal estrogen users were compared with all other subjects there was no significant difference between the two groups except that the vaginal estrogen users were less likely to be progesterone receptor-positive ($p = 0.03$). In the present study, patients were not excluded if they had an estrogen receptor-positive tumor. Information on receptor status was available on 23% of the total database. It was not policy to deny women taking tamoxifen, who were experiencing severe symptoms of vaginal atrophy, from also using topical vaginal estrogen therapy. The decision whether to treat with tamoxifen was made by the treating surgeons. Tamoxifen therapy was used in 48% of women using vaginal estrogens, of whom 48% were given it as primary therapy for early-stage breast disease and 38% as treatment for recurrent breast cancer. In the total database 47% used tamoxifen, in 42% as primary treatment of early-stage breast cancer and in 28% as treatment for secondary breast cancer. Tamoxifen therapy was continued along with their hormonal therapy.

Sixty-nine subjects (4.7%) elected to use topical vaginal estrogen therapy for the relief of their symptoms of vaginal atrophy after their treatment for breast cancer. Among the estrogen users, the median time interval from diagnosis to starting estrogen therapy was 5.25 (range 0–20) years. The median time on therapy was 1.0 (range 0.1–5) year. The median follow-up was 5.5 years, the range being 0.5–29 years.

Low-dose vaginal estrogens used were estriol creams and pessaries (Ovestin®; Organon, Lane Cove, Australia) in 36 (52%) and estradiol 25-μg tablets (Vagifem®; Novo Nordisk, North Rocks, Australia) in 33 (48%).

There were four deaths (6%) among the vaginal 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.

There were six tumor recurrences (9%) among the vaginal estrogen users and 330 (22.4%) in the entire database. The median disease-free interval was 4.5 (range 0.5–29) years. A Cox regression analysis was performed. 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% CI 0.11–0.80, $p = 0.02$). The analysis was repeated, adjusting for the known prognostic variables of tumor size, axillary node status, age at diagnosis, age at menarche and parity. The corrected hazard ratio was 0.57 (95% CI 0.20–1.58, $p = 0.28$). This suggests that topical estrogen usage was not associated with an increased risk of recurrence of breast cancer. There was no evidence from this study to indicate any difference in the risk of recurrence of breast cancer for women

using topical vaginal estrogen therapy compared with those who used no hormonal therapy.

DISCUSSION

This study was unable to demonstrate an increase in the risk of breast cancer recurrence for women who used a low-dose topical estrogen in the management of their symptoms of vaginal atrophy. The finding suggests that the use of topical vaginal estrogens appears to be a safe form of hormone therapy in women successfully treated for breast cancer who are experiencing distressing urogenital symptoms. Of interest is the short median duration of usage of 1 year. As this is an ongoing cohort study, some subjects had recently commenced therapy, thus contributing to the low median time on therapy. Likewise, they have not been advised to cease therapy. If therapy has been ceased it has been their own choice, either due to symptom improvement or possibly their concern regarding the effects of hormones on breast cancer.

We would postulate that, for women with breast cancer, because of its limited systemic absorption, low-dose vaginal estrogen cream and tablets are safe and effective methods of pharmacological therapy for those who require treatment of urogenital symptoms. Little or no systemic absorption occurs with estradiol vaginal tablets, and there is little or no evidence of endometrial proliferation occurring with the 25-μg dose[18,19]. Limited systemic absorption has been reported with the use of vaginal estriol cream or suppositories[20], while marked systemic absorption can occur with Premarin® (Baulkham Hills, Australia) cream[3]. Endometrial proliferation has not been reported with vaginal estriol preparations[19,20].

As systemic hormonal therapy is not generally accepted as first-line treatment of the menopause in women with breast cancer, alternative measures aimed at symptom control, improving quality of life issues related to estrogen deficiency and disease prevention should be fully explored initially.

Many of these women will obtain relief from their vaginal dryness and dyspareunia with vaginal moisturizers and lubricants[15–17], but will not obtain relief from their difficulty with bladder control. Non-hormonal treatment options for vaginal dryness are vaginal moisturizers such as Replens® (Winthrop, Lane Cove, Australia) or Sylik® (Geneva Marketing, Auckland, New Zealand). Replens is a polycarbophil moisturizing vaginal gel that binds to vaginal epithelial cells and maintains hydration, with a resultant improvement in vaginal fluid volume, moisture, elasticity and pH without a change in vaginal mucosal cytology[15]. In one study, when used three times a week, it proved to be as effective as dienoestrol cream for symptoms of vaginal atrophy in postmenopausal women[16]. When Replens was compared with a water-soluble placebo in women with breast cancer, both appeared substantially to ameliorate vaginal dryness ($p = 0.3$) and dyspareunia ($p = 0.05$)[17]. Water-based lubricants such as KY Jelly® (Johnson & Johnson, North Rocks, Australia), or vegetable oils, can provide temporary relief from vaginal dryness and dyspareunia[3]. Improvements in vulvovaginal complaints have been reported after the use of tamoxifen[1].

There is some evidence that life-style factors may also be important. Continued vaginal coitus may prevent the development of vaginal atrophy probably by maintaining epithelial blood flow and pH[31]. Cigarette smoking may adversely affect vaginal epithelium by increasing atrophic changes[3].

Ganz and colleagues recently performed a randomized controlled trial to test the efficacy of a comprehensive menopausal assessment intervention program in achieving relief of symptoms, and improving quality of life and sexual functioning in breast cancer survivors. The program involved symptom assessment, education, counselling and specific non-estrogen pharmacological and behavioral interventions for the symptoms of hot flushes, vaginal dryness, stress urinary incontinence and psychological problems. Patients receiving the intervention demonstrated a statistically significant improvement in menopausal symptoms ($p = 0.0004$) and sexual functioning ($p = 0.04$), but no significant change in quality of life ($p = 0.77$)[9].

In the only known report on vaginal estrogen cream application for the management of vaginal symptoms in women with breast cancer, Vassilopoulou-Sellin and colleagues[29] observed no tumor recurrences in a group of six women who were disease-free for a median of 49 months, who were treated with vaginal estrogens for a median of 47 months and followed for a median of 95 months from diagnosis. However, they did not comment on the type or dosage of estrogen cream used.

Several studies have now assessed use of the ultra-low-dose estradiol-releasing (7.5 μg/24 h over 3 months) vaginal ring in women with

symptoms attributable to postmenopausal vaginal atrophy. It has been shown to be efficacious, safe and significantly more acceptable than topical creams and pessaries as a method of delivering low-dose estrogen to urogenital tissue[32–34]. The main appeal to women is that they have complete control over its insertion and removal. It may also provide the added benefit of vaginal vault support. The ring has minimal effect on patient or partner comfort with intercourse[35]. However, a small number find it unsuitable because of a tendency for spontaneous expulsion with defecation, or they have problems with superficial erythema, but not ulceration, at the ring site[36]. There is limited systemic absorption, with plasma estradiol levels being within the normal postmenopausal range within 48 h of insertion[32]. Initial serum levels are measurable because of rapid absorption through a thin atrophic vaginal mucosa, but absorption is reduced once vaginal thickening has occurred[36]. In patients studied to date there was limited endometrial response only. For women with breast cancer, because of its limited systemic absorption, the ring is a safe and effective method of pharmacological therapy for those who require treatment of urogenital symptoms.

There is little evidence to support the use of topical estrogen therapy in the management of postmenopausal symptoms related to the lower urinary tract. Fantl and colleagues[37], in their meta-analysis of 166 articles, found that estrogen subjectively improves genuine stress incontinence in postmenopausal women ($p < 0.05$), and has no significant effect on the quantity of fluid lost but has a significant effect on the maximal urethral closure pressure ($p < 0.05$). Topical estriol cream has been shown to treat recurrent urinary tract infections successfully in postmenopausal women ($p < 0.001$)[4].

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 hormone therapy 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 symptoms are significantly more estrogen-deficient than women not having symptoms or having only mild symptoms[38].

In conclusion, these results related to the use of low-dose topical vaginal estrogen are encouraging, but emphasize the need for a randomized prospective clinical trial to confirm their safety. For the postmenopausal woman with breast cancer, symptoms related to urogenital atrophy, although not affecting longevity, may affect quality of life by causing extreme discomfort. Unlike hot flushes, which generally settle with time, urogenital symptoms continue throughout life and may even deteriorate. Hence, finding a therapy that is effective, safe and easy to use is important. Estrogen therapy, both local and systemic, has long been the mainstay of treatment for atrophic symptoms. Thus, it is important to establish whether it is safe to use in women with a history of breast cancer.

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