

Review

Breast cancer and climacteric complaints: Weighing up risks of hormone therapy against quality of life

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Abstract

Women with severe menopausal symptoms can, at their request, be treated effectively with hormone therapy. Good information about the advantages and disadvantages of hormone therapy should precede this decision.

For women with breast cancer or an inherited increased risk of breast cancer and severe, often therapy-related climacteric symptoms, a high degree of reticence is appropriate in relation to hormone therapy.

If the quality of life is seriously affected in these often-young women with these iatrogenic climacteric complaints, then careful consideration must be given to the various treatment modalities.

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1. Introduction

One needs to be reluctant in prescribing hormone therapy in breast cancer survivors suffering from severe climacteric complaints. Alternatives, such as phyto-

estrogens, SSRI's and clonidine, should always be discussed first when treating women, who have had breast cancer or who have an inherited increased risk of breast cancer.

In The Netherlands the annual number of breast cancer patients is 12,000. Genetic factors are supposed to account for 5–10% of breast cancer so about 1000 patients have an inherited breast cancer. From these patients only a minority are postmenopausal as compared with incident breast cancer who are mainly postmenopausal. Assuming that about 50% of breast cancer patients have severe climacteric

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complaints about 5000 patients may want to be treated with hormone therapy.

Hormone therapy for menopausal symptoms has proven to be effective, but it also has risks [1]. A possible increased risk of breast cancer has led to discussions that are often confusing for both doctor and patient. Despite a large number of published studies it is not possible to give evidence-based advice to early postmenopausal women, given that for this group there have been no properly randomized studies [2]. Consequently reticence is appropriate when giving hormones to healthy women with menopausal symptoms. In 2005 the Dutch Association of Obstetrics and Gynecology drew up the clinical guideline “Hormone therapy of symptoms in the climacteric and post menopause”. This guideline states that “low dosage hormone therapy is the first-choice therapy for healthy postmenopausal women with menopausal symptoms that interfere with the quality of life, provided the treatment lasts less than 5 years” [3].

In this article we discuss a number of treatment modalities for women with severe climacteric symptoms, who have had breast cancer or who have an inherited increased risk of breast cancer.

2. Estrogen and breast cancer risk

Reproductive and hormonal factors appear to be important risk factors for breast cancer (see Table 1). It appears from prospective studies that postmenopausal women with relatively high endogenous serum concentrations of estrogens have a significantly increased risk of getting breast cancer, in comparison to postmenopausal women with relatively low serum concentrations [4]. The

Table 1
Risk factors for breast cancer

| Indicator | Low risk group | High risk group | Relative risk |
|------------------------------|----------------|-----------------|---------------|
| Gender | Man | Woman | 150 |
| Age | 30–34 years | 70–74 years | 17 |
| Family anamnesis | No | Yes | 2.6 |
| Age of menarche | >14 years | <12 years | 1.5 |
| Age of first delivery | <20 years | >30 years | 1.9–3.5 |
| Breast feeding | >16 months | 0 months | 1.37 |
| Oral contraception | Never used | Ever used | 1.07–1.2 |
| Parity | >5 | 0 | 1.4 |
| Bone density | Low | High | 2.7–3.5 |
| Age of ovariectomy | <35 years | – | 3.0 |
| Age of natural menopause | <45 years | >55 years | 2.0 |
| BMI postmenopause | <22.9 | >30.7 | 1.6 |
| Serum oestradiol | Low | High | 1.8–5.0 |
| Mammographic density | 0% | >75% | 6.0 |
| ET: only oestrogen | Never used | Current use | 1.0–1.4 |
| EPT: oestrogen + progestagen | Never used | Current use | 1.2–1.7 |
| Alcohol | Never used | Current use | 1.38 |
| Smoking | Never used | Current use | 1.5 |

Modified according to Clemons and Goss [18].

relation between high estrogen levels and an increased risk for breast cancer is demonstrable 5 years before the diagnosis is made. These results indicate a causal link between exposure to circulating estrogens and the development of cancer. Three-quarters of all mammary carcinomas are estrogen-receptor (ER) positive and endogenous estrogens play an important role in the growth regulation of these ER-positive tumours [5].

An increased exposure to both endogenous and exogenous sex hormones appears to be expressed in the mammogram. High mammographic density of the breast tissue without the use of hormone therapy is associated with a four to six times increased relative risk for breast cancer compared with low density [6]. Increases in mammographic density are also seen with the use of hormone therapy and make early detection of tumours more difficult. The effect of combined hormone therapy on mammographic density is greater than estrogen monotherapy. Two to 3 weeks after stopping hormone therapy, the mammographic density reduces to the level prior to treatment. Tibolone (Livial[®]) gives little or no increase in mammographic density [7].

3. Family history

A strong positive family history for breast cancer and/or carriers of a BRCA1 or BRCA2 gene mutation is an important risk factor for breast cancer (and for ovarian cancer). The risk of breast cancer for these women can be reduced to approximately half by means of a prophylactic bilateral salpingo-ovariectomy (pBSO) carried out premenopausally. The risk of ovarian carcinoma is reduced even more through this intervention. This laparoscopic operation is relatively simple, but results in severe estrogen-deficiency phenomena. A detailed simulation study made a reasonable case for hormone therapy for this group of women after pBSO having no unfavorable effect on survival, provided the use of hormone therapy did not last more than 5 years or until the age of 50 [8]. Recent research reported that in women after pBSO, hormone therapy does not have an unfavorable effect on the breast cancer risk in a relatively short postoperative follow-up of 3.6 years [9]. Despite the reassuring results reported above, doctors in general will be very reticent about prescribing oral estrogen–progestogen medications. The possibilities of non-hormonal alternatives and of local use of estrogens (estriol vaginally) and progestogens (progestogen-containing intra-uterine system) must be explored first. In addition the use of tibolone should be considered, given the favorable clinical profile [7].

4. Breast cancer

The treatment of breast cancer is highly effective, but the cost is high in terms of the occurrence of severe side effects. A considerable proportion of breast cancer patients report

severe climacteric symptoms and other complaints ascribed to estrogen deficiency. These complaints are often a direct consequence of the adjuvant treatment with the aid of tamoxifen or aromatase inhibitors, chemotherapy or suppression or ablation of the ovarian function [10]. There is naturally a great reluctance with regard to the use of estrogen-containing substitution. Yet there are women whose private life is so seriously affected by the side effects of long-term adjuvant therapy (lasting years) that they repeatedly request some form or other of medical help.

From research it seems that 20–40% of well-informed women with a history of breast cancer do wish hormone therapy for menopausal symptoms [11,12]. The data concerning the positive and negative effects of hormone therapy on breast cancer patients are limited. A meta-analysis of 11 observational studies found no increased risk of recurrent breast cancer when hormone therapy was used [13]. The patients in these studies were apparently very carefully selected. It is quite possible that the risk of a recurrence of breast cancer (or a primary tumor in the other breast) is increased with the use of hormone therapy in women with a history of breast cancer. Prospective randomized studies should provide an answer to this. However the HABITS study – a prospective, controlled non-blinded study – in women after the diagnosis of breast cancer was terminated prematurely in 2004, because women with hormone therapy had an unacceptably high risk (relative risk 3.29; 95% confidence interval 1.48–7.35) of a recurrence [14]. The Stockholm study demonstrated no increased risk, but was also terminated [15].

The Liberate study is the only randomized, placebo-controlled, double-blind study still running. Worldwide, 3148 women with a history of breast cancer are being given tibolone or placebo for menopausal symptoms [16]. The principal goal of the LIBERATE study is to demonstrate that tibolone does not increase the risk of breast cancer, but does eliminate the severe symptoms, however long term data are not yet available. Tibolone add-back during adjuvant tamoxifen use in a pilot appeared to be quite acceptable and effective in reducing menopausal symptoms [17].

5. Medical advice

Given the severity of their menopausal symptoms, some breast cancer patients expect medical advice after a thorough, repeated consultation. Because of the lack of reliable studies, it is difficult to give evidence-based advice [10]. A non-hormonal alternative for hormone therapy often gives too little alleviation. It is important to give lifestyle advice in any case. Also complementary methods from the field of alternative medicine can be discussed.

We have produced a preferential order of treatment modalities for severe menopausal symptoms that affect the quality of life [10]. This applies to healthy women with a BRCA-mutation after pBSO before the age of 46 and for

breast cancer patients after or during adjuvant treatment. The first choice is to give lifestyle advice about weight, alcohol, smoking, exercise and diet. The second choice concerns non-hormonal alternatives such as phyto-estrogens, clonidine and SSRI's. The third and final option is hormone therapy of maximally 5 years (After hysterectomy: estrogen or tibolone. For women with a uterus: an estrogen with a progestogen containing IUS, tibolone or a combination of estrogen with progestogen). The proviso for treatment involving hormone therapy is that the increased risk of breast cancer is outweighed by the quality of life. The woman makes that choice herself after informed consent.

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