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# Influence of exogenous hormones on the recurrence and progression of cancer

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*In the last few years, hormone replacement therapy (HRT) has become widely used everywhere in the world. Apart from favourable effects of HRT, such as a significant decrease in the psycho-physical menopause-related difficulties, lower mortality due to cardiovascular diseases and lower incidence of osteoporosis, some questions related to possible association between the use of this therapy and the rise, recurrence and progression of cancer have not been resolved yet. According to the majority of studies published so far, HRT is not associated with an increased risk of the onset, recurrence and progression of cancer. Moreover, some findings even indicate the possibility that HRT might exert a protective effect against the rise, recurrence and progression of cancer.*

*Key words:* estrogen replacement therapy; neoplasms, breast-neoplasms; menopause

## Introduction

In the 60's, the use of hormone replacement therapy was found to have increased considerably. However, in the 70's, this treatment again became less popular, when it was established that the use of exogenous estrogens was associated with 3-4 times higher risk of endometrial carcinoma. Later on it was found that no such risk was present when exogenous estrogens were combined with progestagens. In view of these new findings, the use of HRT is such a combined form underwent another increase in the 80's. Copious (also controversial) information provided by recent studies pointed out that possible correlation between HRT and the onset and progression of cancer should be studied in detail. Therefore, to our knowledge, the first international seminar dedicated to this pressing issue was organized in 1995 in Budapest.[1]

Our report deals with the effectiveness of HRT and the findings on its presumed influence on the recurrence and progression of cancer. The critical review has been completed with a preliminary report of our own findings, as well as with the latest recommendations related to the use of exogenous sex hormones.

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## The influence of HRT on the recurrence and dissemination of cancer

In women treated for cancer, HRT in menopause is associated with two hormone-dependent entities which are important in oncology, i.e. the influence of pregnancy on the recurrence and progression of cancer, and the influence of oral contraceptives on cancer occurrence. In both instances, the concentrations of sex hormones in the blood of affected women exceed normal values (average cut-off values). It had long been believed that both situations entailed a particular danger: thus, pregnancy in women treated for cancer could accelerate an onset of recurrence and progression while oral contraceptive use were associated with a greater probability of cancer occurrence, particularly that of the breast. However, many studies published so far have discarded these hypotheses.[2]

Despite the scarce data, the influence of HRT has been most extensively studied in patients treated for breast cancer. It is an indisputable fact that breast cancer is the most frequent cancer in females. Apart from that, it is also well known that early psycho-physical symptoms of menopause, such as depression, phobias and psychic instability, which all may lead to severe disharmony in the patient's family and surroundings, as well as blushing and night sweating, are frequently more apparent in breast cancer patients than in those with other types of cancer.[3] It is believed that the more severe menopausal changes seen in patients who have undergone surgery for breast cancer could be attributable to the loss of this psychologically important and typically female external organ. We presume that these patients had more frequendy psyhyatrical treatment than others.

Considering the fact that elsewhere also HRT was indicated only in patients with severe climacteric problems, mostly owing to the suspected risk for cancer progress. The scientific evidence collected so far is relatively scarce. None of the retrospective studies published has been able to associate an increased risk of cancer recurrence or progression with the use of HRT.[4] Moreover, in the most recent report by Eden et al. published in 1996, it has been suggested that HRT might even exert a protective effect in this respect.[5]

Some epidemiological data indicate that despite

– the risk associated with a greater number of menstrual cycles and the related events,

– laboratory evidence on the influence of estrogens on the accelerated growth of mammary cells, and

– clinical effectiveness of tamoxifen (a selective estrogen antagonist) in patients with metastatic breast cancer,

The following facts should not be ignored:

– not all postmenopausal breast cancer patients have a better prognosis than premenopausal ones,

– after completed chemotherapy, the prognosis of premenopausal breast cancer patients with regular menstrual cycles is not worse than that of those without restored ovarian function;

– after two months of tamoxifen therapy, premenopausal patients present with elevated serum estradiol levels;

– among premenopausal breast cancer patients OC users do not survive worse than non-users of oral contraceptives.

It has been established that some stromal, fatty and carcinoma cells of the breast have the potential of synthesising estrogens locally from androgens, a pre-stage of estrogens. We presume that the level of local estrogens in the breast is independent of serum estrogens. The very local values of estrogens seem to be most relevant for the onset and metastasizing of breast cancer. It is also believed that tamoxifen reduces the levels of estrogens in the breast and metastatically changed cells, mainly through the competitive binding to estrogen receptors. Tamoxifen reduces cell proliferation. Given in low doses, it exerts a cytotostatic effect (increased G1 phase of the cell cycle resulting in a prolongation of cell division phase) while in high doses it is cytotoxic (arrest of G1 phase and cessation of cell division). We presume that the antiproliferative effect of Tamoxifen is also expressed through growth factors or C protein kinase inhibition.[2] Besides being estrogen antagonist, Tamoxifen is also estrogen agonist prevailingly active in the liver, bones and endometrium. While Tamoxifen reduces the risk of the onset of thromboembolic conditions and osteoporosis, it does not alleviate menopausal vasomotoric disorders. Moreover, it has been found that in 15-20 % of cases Tamoxifen might even worsen these symptoms. The results of some studies have shown that a long-term use of Tamoxifen may increase by 3-5 times the risk of endometrial carcinoma.[4]

We still cannot provide a conclusive answer to the question about the role of hormone receptors in breast cancer patients. Also, the treatment of patients with metastatic breast cancer hides many unresolved questions. The fact is that an equally long 30 % remission of the disease can also be obtained by adding some estrogens and progesterones in postmenopausal patients with positive estrogen receptors.[1]

The least known, but – according to some reports – perhaps very important is the effect of progesterone on the breast.[6, 7] We suspect that the effect, which is believed to play a protective role in the rise of breast cancer, is very complex and dependent on several factors such as the type, dose and duration of progestagen use. While a short lasting progestagen use should exert a cell-proliferative effect, a long-lasting or continuous use should result in antiestrogen, antimitotic and antiproliferative effect.[4] Most investigations are centred particularly on this.

So, let us conclude our report on hormone replacement therapy in patients treated for breast cancer with the statement made by the Breast Cancer Committee of the East Oncology Group: There are many facts which speak in favor of the belief that estrogen therapy in breast cancer patients is safe. Therefore, the time has come for a change![1]

There are but few reports on the use of HRT in patients treated for other cancers, and therefore any critical conclusions in this respect would be premature. According to the scarce preliminary reports, HRT is not associated with an increased risk of cancer dissemination; moreover, some of the reports even indicate a protective effect of HRT, which is reflected in a lower rate of progression and better survival results.[1]

## HRT in patients treated for cancer at the Institute of Oncology in Ljubljana. Preliminary results.

In our patients treated for cancer, HRT was indicated only when menopausal problems were so severe that they were regarded as life threatening.

A revision of the data on patients treated for cancer at the Institute of Oncology, and receiving HRT was started in February 1996. Up to now, complete data have been collected for 25 patients. The average duration of HRT treatment was 38 months (4-120). In 22 cases both hormones, i.e. estrogens and progesterones, were used in accordance with the well known protective role of progestagens. In 21 patients, HRT (Cyclomenorrete, Trisequens, Trisequens f tablets) was applied in four week intervals, while the remaining patients received hormones (Gynodian depot injection and Dabroston tablets) in 6-8 week intervals or even less frequently. The uterus was surgically removed in 15 patients. Twenty-four patients were free of recurrence. Progression of the disease was established six months after HRT in one patient only; she had a highly malignant leiomyosarcoma of the uterus. With respect to the histologically verified highly malignant tumor, the progression was expected, and was therefore detected relatively early, when the patient was still asymptomatic. In this patients HRT was given in 6-8 week intervals. After the diagnosis of recurrence, the patient was reoperated, and has been without evidence of the disease 10 months since the primary therapy. She was further maintained on HRT because of severe menopausal problems.

Eight of 25 patients were treated for breast cancer. Two had metastases in the axillary lymph nodes, 5/7 had negative hormone receptors while in two patients these were positive: one patient had estrogen- and the other one progesterone receptors. All those 8 patients received estrogen & progesterone based HRT in the duration of 2 years on average. The mean delay from breast surgery to the start of HRT was 4 years, after a non-hormonal treatment had failed and the menopausal problems got progressingly worse.

Other patients who received HRT had been previously treated for cancer of the reproductive organs, Hodgkin's disease, NH lymphoma or carcinomas of the thyroid and rectum.

So far, none of the patients followed up for 4-120 months has presented with progression.

## Conclusion and recommendations

Recommendations for HRT in women at an increased risk of cancer, and in patients treated for cancer.

1) In women who are believed to be at a higher risk of cancer than the rest of normal female population, HRT is indicated only in the presence of menopausal problems, and not as prevention of thromboembolic conditions or osteoporosis.

2) In menopausal patients treated for cancer, HRT is indicated only in the case of severe menopausal problems.

3) In accordance with internationally accepted guidelines, HRT with estrogen alone is indicated in patients who have undergone hysterectomy or had their uterine mucosis destroyed by radical irradiation. In all others estrogen & progesterone based HRT should be used.

4) Prior to the administration of HRT, the patient should undergo a gynecological check, clinical breast examination and mammography. Regular follow up, including gynecological check and clinical examination of the breast, should be carried out every six months, while control mammographies should follow the routine set by the accepted guidelines for early detection of breast cancer.

5) In order to get a more comprehensive overview of the state of the art regarding HRT, further studies are also required in Slovenia, which would hopefully yield results that could prove useful at a national as well as international level.

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