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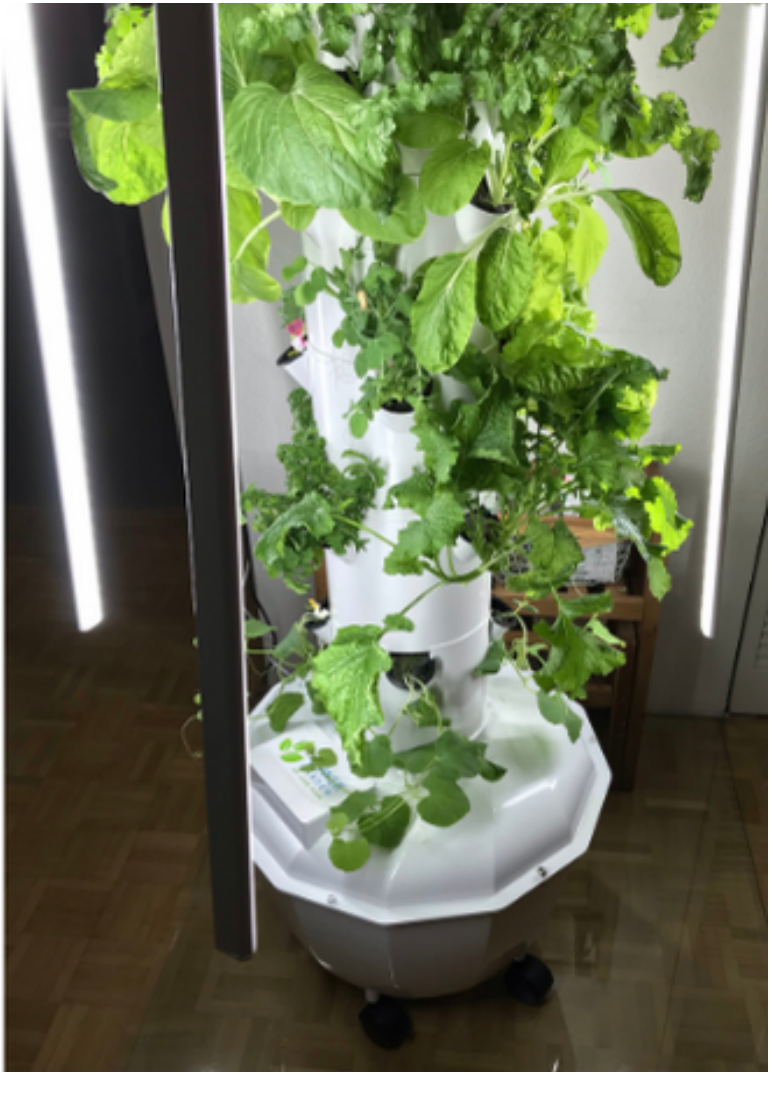

H. J. Senn, R. Richter

HORMONE REPLACEMENT THERAPY AND BREAST TISSUE: THE ONCOLOGIST'S POINT OF VIEW

Summary

The contribution deals with the ambivalence of breast cancer patients and of physicians, especially oncologists with HRT in relation to the risk of subsequent breast cancer development. Unfortunately, there are many opinions and retrospective data about this issue, but still no results of (ongoing) prospective studies. In this context, any biologic „escape" with compounds, not exerting stimulatory effects on the mammary gland such as for example tibolone is welcomed. However, the clinical data with tibolone in experimental and especially clinical breast cancer are too scanty to justify its present inclusion in adjuvant (postoperative) or even chemopreventive studies.

THE PROBLEM OF AMBIVALENCE WITH HRT AND BREAST CANCER DEVELOPMENT

Breast cancer is the most common cancer in women in developed countries, affecting every 10–12th female in the Western world, and there is a distinct increase of incidence towards the North in Europe as well as in the Americas. Switzerland is among the countries with the highest breast cancer incidence worldwide, but according to the EUROCARE study, chances to survive the manifest disease with optimal treatment are also highest among European countries. Breast cancer incidence and hence mortality are also rapidly growing in Asia [1].

Estrogens are known to stimulate the mammary glands and also the growth of mammary tumours and this growth stimulating effect can be blocked experimentally and clinically by antiestrogens such as tamoxifen. This effect is now well documented in metastatic disease as well as in the adjuvant (curative) treatment situation in early operable breast cancer [2]. A possible relationship between hormone replacement therapy (HRT) and breast cancer development is a major reason for "modern" women not to consider or to discontinue HRT, despite their uncontested beneficial effect in the prevention of osteoporosis and cardiovascular disease. As a matter of fact, most if not all drug informations, accompanying estrogenic compounds so have been listing a history of breast cancer among the contraindications for their use, leading to hundreds of engaged discussions with intelligent and health-oriented patients, suffering from major symptoms of hormonal deprivation after the (successful) treatment of their breast cancer.

The best evidence on HRT with estrogens and its consequences come from a meta-analysis of epidemiological studies on this subject [3]. Its results demonstrated a 2–3 % increased risk of developing breast cancer for each subsequent year of use of estrogen regimens, with a 35 % increased risk of diagnosis in women who use HRT for 5 years or more. According to newer data, the combination of estrogen and gestagen compounds in HRT, possibly reducing subjective toxicity, does rather seem to stimulate breast cancer development instead of reducing it, as previously expected [4].

In this situation, there remains growing uncertainty among females about what to do and what to avoid in HRT, especially among women from kindreds with familial breast cancer and genetically increased personal breast cancer risk. Unfortunately, all our information policies towards the patients are greatly biased and depend on retrospective data at best, since a convincing prospective study, documenting either clear-cut benefit or innocence of HRT, regarding breast cancer stimulation is still missing in 2001. Some trials are now studying this question in a prospective, randomised manner:

1. The HABITs-trial, inaugurated by Scandinavian breast cancer study groups and supported by the IBCSG (International Breast Cancer Study Group), in operation only since roughly 3 years and its patient accrual is unfortunately highly deficient, since all of these trials come years too late to be attractive to females and their doctor's involved. Other new placebo-controlled long-term trials are:
2. The Women's Health Initiative trial, which will include 27,000 American women who will either receive HRT or else placebo treatment [5], and
3. The WISDOM-trial in 36,000 women, an international, placebo-controlled study of women taking estrogen, or estrogen + progesterone for 10 years with a further 10-years follow-up [5].

EFFECTS OF TIBOLONE ON BREAST CANCER RISK

In this ambivalent situation regarding HRT, any biologic and epidemiologic "escape" is welcomed. Tibolone, a synthetic compound with androgenic, estrogenic and gestagenic action is an interesting choice in this regard. There are so far no definitive studies that have directly examined the correlations between tibolone and breast cancer [6].

Even though circulating estrogens are low in postmenopausal patients, mammary cells have the potential of synthesise estrogens locally by chemical conversion of other steroids to estradiol. In human breast cancer concentration of estrogens are the same in the pre- as well as in

the postmenopausal women [6]. This conversion is achieved by high concentrations of various enzymes in breast tissue. Tibolone and its metabolites are potent inhibitors of some of these pathways. The conversion of estrone sulphate into estradiol in human breast cancer cell lines is inhibited in over 95 % at low concentrations of tibolone [7]. Tibolone has also the capacity of inhibiting chemically induced mammary tumours in rats. However, the clinical data with tibolone are very scanty: in one single trial in women with advanced breast cancer, failing tamoxifen, a modest treatment effect was seen in one out of 14 patients [8].

A 2-year prospective follow-up study of mammographic changes in women taking tibolone showed moderate decrease of breast density in 2 out 25 women, while there is usually increase in mammographic breast density in 11–27 % while on HRT with estrogenic compounds [9].

In summary, there is a great theoretical as well as practical need to know more about the interactions of HRT and breast cancer, especially in the light of new interesting compounds such as tibolone and their influence on normal as well as stimulated breast tissue and hormone dependent breast cancer cells in general. Testing of the effect of tibolone on the primary (chemo-)prevention of breast cancer has to await the results of adequate trials about its effect in manifest breast cancer and especially its efficacy and safety profile in trials of tertiary prevention, which is adjuvant postoperative therapy – or prevention of relapse and metastatic disease after primary, "curative" treatment. This, unfortunately, is yet a long way to proceed.

Prof. Dr. med. Hans-Jörg Senn

Born 1934 in Grueningen/Zurich, Switzerland. Medical study 1953 to 1959 in Zurich and Vienna, Graduation 1960 in Zurich. From 1961 to 1966 advanced studies as intern and assistant medical director in Switzerland and the USA, 1967–68 studies in oncology at Roswell Park Memorial Cancer Research Institute in Buffalo/USA, 1968–1972 head oncologist at the Medical University Policlinic Basel, 1973–1997 head physician of the Medical Clinic C (Oncology/Haematology/Gastroenterology) and founder and head of the tumour center at the Kantonsspital St. Gallen. From 1998 to date founder and head of the new center for tumour diagnosis and prevention in St. Gallen.

From 1987 to 1994 Hans Jörg Senn was president of the Swiss Institute for Applied Cancer Research (Bern).

Correspondence to:
Prof. Dr. med. Hans-Jörg Senn, MD
Zentrum für Tumordiagnostik und Prävention
Rorschacher Strasse 150
CH-9006 St. Gallen/Switzerland
E-mail: hjsenn@sg.zetup.ch

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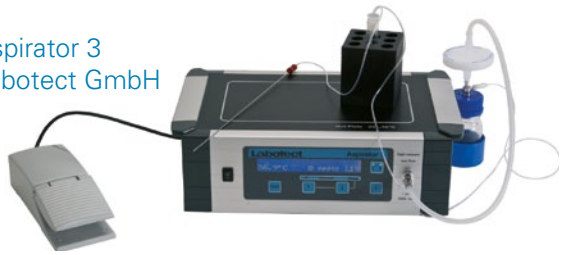

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