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IV.1 Tamoxifen, a Human Carcinogen or the Share of Common Risk Factors?

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Breast and endometrial cancers share common risk factors and therefore a slight excess risk of endometrial cancer is expected among breast cancer patients. Yet, this does not explain the risk of endometrial cancer linked to tamoxifen use. When background risk is adequately controlled, an effect of tamoxifen is still seen, increasing with duration of use and further supported by experimental evidence of carcinogenicity. © **1998 Elsevier Science Ltd. All rights reserved.**

DO BREAST and endometrial cancers share aetiologic factors? Yes. Does that explain the increased risk of endometrial cancer seen in tamoxifen users? No. Both of the above questions are perfectly valid and both have to be assessed as carefully as possible. Epidemiology is one of the powerful tools which may give us means of evaluating the role of hormones and/or antihormones in cancers such as the breast and the endometrium.

Breast cancer is hormono-related and has been closely linked to the reproductive life of women and more recently to genetics. Risk of cancer of the breast is increased in women who had early menarche, none or late bearing children and late menopause. Exogenous hormone use, such as long-term use of oral contraceptives prior to a first pregnancy, or long-term use of hormone replacement therapy have also been associated with a slight increase of breast cancer. It is generally thought that other effects which are currently being investigated such as diet and environmental exposures, when they do play a role, do it through an hormonal pathway, the condition necessary for development of the disease being an hormonal imbalance with a relative hyperoestrogeny.

A number of risk factors for cancer of the endometrium are similar to the ones identified for breast cancer. The parallel is particularly striking in postmenopausal women, where obesity and exposure to exogenous hormones play a role. It has also been shown in studies conducted in population-based cancer registries, that the co-occurrence of both breast and endometrial cancers in women is not rare, yet infrequent. Therefore, one expects women who had breast cancer to have an increased risk of endometrial cancer of the order of 1.3 compared to women without breast cancer.

It is now recognised that tamoxifen, as used for the treatment of breast cancer, is linked to an increased risk of endometrial cancer. This effect has been both demonstrated in randomised controlled trials as well as in specifically designed epidemiological studies [1]. The most convincing evidence and the reason why we are able to allude to the carcinogenicity of tamoxifen for the endometrium is that, in all studies having identified a risk, the women with breast cancer were not compared to women not having had breast cancer, but to other women also having had breast cancer. Therefore, the baseline risk was higher than in the general population for both groups of breast cancer patients, be they treated with tamoxifen or not. The excess risk found in several randomised controlled trials [2, 6], in a cohort study [7] as well as in all [8–14] but one [15] case–control study, is in favour of an aetiologic role of tamoxifen and not a mere reflection of a higher background risk.

Also in favour of an aetiologic link between tamoxifen and endometrial cancer is the influence of duration of treatment [9, 11] as well as physiopathological considerations of menopausal status [10] or age [12]. Finally, supporting evidence also comes from the demonstration of carcinogenicity in animal studies [1, 16].

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IV.2 Does Risk of Endometrial Cancer Increase with Longer Duration of Tamoxifen Use?

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The effects of tamoxifen duration and dosage on the risk of endometrial cancer have not yet been examined extensively. In the six studies that examined the effect of duration of treatment, a significantly positive trend was found in four, a non-significant positive trend in one and a non-significant negative trend in one. © **1998 Elsevier Science Ltd. All rights reserved.**

OVER THE past decade conclusive evidence has emerged that tamoxifen treatment is associated with moderately increased risk of endometrial cancer [1]. Table 1 gives an overview of the most important studies examining the risk of endometrial cancer in relation to tamoxifen use [2–9]. There are four reports on randomised controlled trials, four case–control studies and one cohort study. In these studies, the risk of endometrial cancer among tamoxifen-treated women is 2- to 7-fold increased as compared to the risk in non-users. A more precise estimate of the risk is not yet available. The large variation in risks presented in Table 1 is likely to be partly related to the instability of the estimates, due to the relatively small numbers of endometrial cancers included in individual studies. This variation may also reflect, however, differences in the daily dosage and duration of tamoxifen between the various patient populations.

The effects of tamoxifen duration and dosage on the risk of endometrial cancer have not been examined extensively. In most clinical trials, it is not possible to study these effects since duration and dosage vary little among the patients included in individual studies [3–5]. A comparison of the trial reports (Table 1) suggests that dosage is not a major risk factor; roughly similar risk increases of endometrial cancer have been observed after daily tamoxifen dosages of 20 and 40 mg [2, 5, 7]. In a combined analysis of three Scandinavian trials, the relative risk of endometrial cancer in tamoxifen-

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