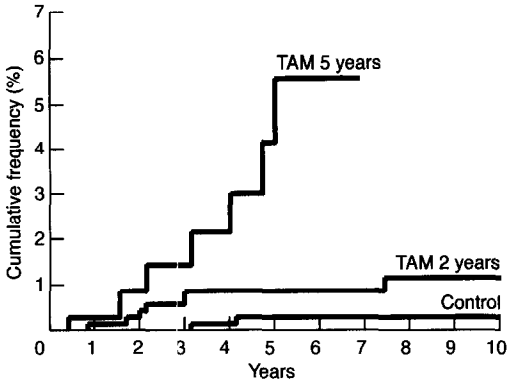

Figure 1. Cumulative frequency of uterine cancer by allocated treatment in the Stockholm Trial. Tam, tamoxifen reproduced by permission from Fornander T, Rutqvist LE, Cedemark B, *et al.* Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancer. *Lancet* 1989, i, 117–120.

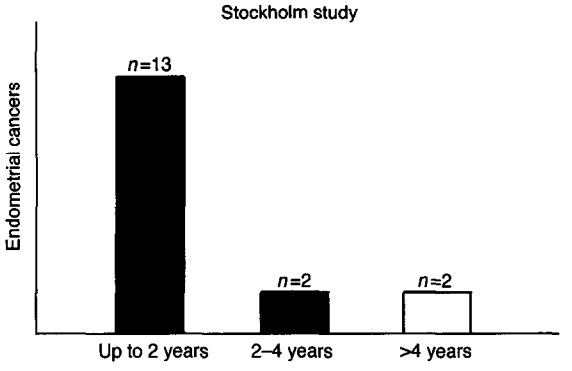

Figure 2. Incidence of endometrial cancer from Fernando T, Hellstrom AC, Moberger B. *J Natl Cancer Inst* 1993, 85, 1850–1955.

following the report by Fornander and colleagues [3] on the histopathology of the endometrial tumours in the Stockholm Trial, we noted that patients receiving tamoxifen usually developed endometrial cancer in less than 2 years (12/16) [4] (Figure 2). We therefore concluded that occult disease was being detected. Indeed the idea is based on the known fact that postmenopausal women harbour five times more endometrial cancers than are presented clinically [5]. Clearly, if this is the case all studies that include monitoring of tamoxifen-treated patients will naturally become biased because those patients will be screened who are concerned or have a vaginal discharge (a known side-effect of tamoxifen).

In summary, the initial paper [1] that called for screening of patients taking tamoxifen has resulted in a detection bias based on overscreening. The epidemiology data base is flawed because of the selective screening of women. However, the idea that tamoxifen is detecting occult disease rather than causing cancer still holds true. Most endometrial cancers are detected within 5 years rather than the 10 year minimum required for carcinogenesis through initiation and promotion.

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IV.8 Tamoxifen to Treat Endometrial Cancer

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THE EPITHELIAL and stromal transformations induced by tamoxifen in cultures of normal and neoplastic endometrium show its oestrogenic, antagonistic and agonistic action, inhibiting on one side the proliferation of the endometrial adenocarcinoma, on the other side causing polypoid endometrial hypertrophy in some breast cancer patients under long-term tamoxifen treatment.

Adjuvant therapy in early endometrial cancer and hormonal treatment of advanced or recurrent adenocarcinoma by means of tamoxifen or of a combination of tamoxifen and high-dose medroxyprogesterone acetate will be discussed.

The histological response, *in vivo*, of primary endometrial adenocarcinoma to short-term tamoxifen treatment is characterised by rapid transformation of pseudostratified carcinomatous

glands to monolayered structures consisting of high cylindrical and even atrophic cells, with a low mitotic index, with frequently observed atrophy and necrosis. At histochemical observation, tamoxifen induces glycogen accumulation in more than half of the adenocarcinomas; it seldom induces mucopolysaccharide accumulation.

From a clinical viewpoint, the best results are obtained using 40 mg tamoxifen orally daily; the more differentiated the tumour is, the longer the duration of response to tamoxifen therapy. Metastatic lesions respond irrespective of their site, maximum response being in vaginal metastases. Moreover, the possibility of using tamoxifen either as an alternative for progestogens or as a synergist opens interesting perspectives. The oestro-antagonistic action of tamoxifen is predominant on well-differentiated, oestrogen receptors (ER)- and progesterone receptors (PR)-positive cancers, while the oestro-agonistic action is manifest in poorly differentiated ER- and PR-negative neoplasias. For that reason, tamoxifen can be administered alone in the treatment of well-differentiated hormone-dependent endometrial adenocarcinomas; optional addition of low-dose (LD)-medroxyprogesterone acetate can relieve some troublesome side-effects such as hot flushes. In the management of moderately or poorly differentiated cancers, hormonal manipulation by means of the combined, successive administration of tamoxifen and high-dose (HD)-medroxyprogesterone acetate is recommended. In the long term, hormone therapy, particularly in cases of relapse, cyclical tamoxifen and gestogen therapy are indicated.

Adjuvant hormonal therapy in early endometrial adenocarcinoma by means of tamoxifen limits the local recurrence rate to 1.6% compared to 3.7% in the control group and achieves a better prognosis in terms of disease-free survival and overall survival.

Administration of tamoxifen at a dosage ranging from 20, 30 to 40 mg a day, in first-line treatment of advanced or recurrent endometrial adenocarcinoma induces an objective response rate of respectively 20, 30 and 53%. Currently, tamoxifen may have a useful role in recurrent endometrial cancer, because of its low toxicity and lack of side-effects; however, the response rates are low. This is an intensively frustrating situation because tamoxifen clearly has the ability to produce dramatic and long-lasting remissions.

Tamoxifen induces a highly significant increase in PR that is apparently functional, as judged by an increase in the progestin-sensitive enzyme, oestradioldehydrogenase and the histological evidence of a characteristic secretory response following medroxyprogesterone administration and that is consistent with oestrogenic activity of tamoxifen in endometrial carcinoma. This agonistic activity, as well as the antagonistic one, is not cell specific, but has some gene selectivity. In this respect the combination of tamoxifen and progestogens in a concomitant or cyclical therapy seems an attractive approach in first-line or especially in second-line hormonal therapy of those patients who failed to respond to, or had responded initially to, hormonal monotherapy. Combined administration of tamoxifen and progestogens may produce better results in terms of duration of response and survival than a single drug treatment schedule.

In that way, first-line combined hormonal therapy can completely cure early endometrial adenocarcinoma and permit a successful pregnancy later on. Adjuvant combined hormonal therapy of early endometrial cancer by means of tamoxifen and medroxyprogesterone caproate during more than 3 years, achieves a 19% increase in 5 year survival rate. In 20 patients with advanced or recurrent, poorly differentiated endometrial adenocarcinoma combined sequential treatment by means of tamoxifen and medroxyprogesterone induced 1 complete remission and 10 stabilisations.

Second-line tamoxifen therapy of advanced or recurrent endometrial carcinoma after initial treatment by means of progestogens is especially successful (complete remission rate of 64%) in patients previously responding to medroxyprogesterone with, however, a shorter duration of the remission.

However, tamoxifen cannot be recommended routinely as an effective secondary treatment for patients with progestin refractory, advanced endometrial cancer.

Second-line combination therapy by means of tamoxifen and medroxyprogesterone in patients with advanced endometrial carcinoma relapsed after responding to medroxyprogesterone alone induces a 62.5% objective response rate, and relapsed after responding to tamoxifen alone, 60.8%. On the contrary, in patients not responding to previous medroxyprogesterone or tamoxifen therapy, the combined regimen achieves an objective remission rate of 47.6%, respectively 61.9%.

In conclusion, although monotherapy by means of tamoxifen seems, based on fundamental and clinical data, efficient in the cure of endometrial adenocarcinoma, a combination with high-dose medroxyprogesterone acetate is better indicated in some cases.

By analogy, prevention of tamoxifen-induced endometrial cancer by administration of local progestogens should be evaluated.