Since 1985 we have witnessed an overall reduction in breast cancer mortality in the U.K. which in large part must be attributed to the widespread adoption of adjuvant tamoxifen, but it is essential not to be complacent and it is likely that we are close to recognising the limitations of this useful and relatively non-toxic agent [20, 21].

The theme of this international conference is tamoxifen and the uterus. It would be irresponsible of us all if by exaggerating the risk of endometrial cancer, which in any case might be an artefactual adverse side-effect, we frightened women into refusing or abandoning their treatment. Indirectly this could lead to thousands of unnecessary deaths world-wide in any one year.

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European Journal of Cancer, Vol. 34, Suppl. 4, pp. S8–S9, 1998

Printed in Great Britain
0959-8049/98$—see front matter

PII: S0959-8049(98)00085-9

I.2 From the Breast to the Uterus. The Past and the Present

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Discussing whether or not tamoxifen is truly responsible for endometrial side-effects can only be done if we also consider some historical events. Long before the introduction of tamoxifen, women with breast cancer were known to be at risk for endometrial cancer. Non-steroidal hormones to treat breast cancer and active detection bias added up to this increased risk. Presently, history seems to repeat

itself following the introduction of tamoxifen. Putting the whole historical issue into perspective, experimental models showing tamoxifen to be inhibitory in breast cancer tissue and stimulatory in endometrial cancer tissue led to well-designed clinical trials confirming tamoxifen's stimulatory effect upon the endometrium.

SUSPECTING A drug of producing an adverse reaction may follow the observation of a few events. Proving an association between the event and the drug may be very difficult. The situation with tamoxifen for breast cancer and increased endometrial pathology is even more complex, considering the following historical observations. In 1931, Taylor [1] was the first to report the coincidence of breast and uterine cancer. There is a 2-fold relative risk of endometrial cancer relative to breast cancer in women 60 years of age or over. This relationship is not unexpected in view of the common aetiological risk factors. Like breast cancer, the incidence of endometrial cancer is greatest in nulliparous women, those with an early menarche and late menopause, all physiological phenomena that result in longer exposure to oestrogen of ovarian origin. Breast and endometrial cancer share other risk factors such as obesity and the use of oestrogen replacement therapy (ERT) and hormone replacement therapy (HRT). The development of endometrial and breast cancer in obese women is believed to be mediated by endogenous oestrogens through the conversion of androstenedione to oestrone by aromatase in adipose tissue. Elevated levels of plasma oestrogens have been reported both in women with breast cancer and in women with endometrial cancer.

Well before tamoxifen was developed, Hoover found that the excess risk of uterine cancer in breast cancer patients was increased due to modalities to treat breast cancer [2]. Given the time period under study (1935–1971) and excluding those patients treated by irradiation of pelvic organs, increased risk was associated with the use of non-steroidal oestrogens such as diethylstilbestrol. At that time, non-steroidal oestrogens for postmenopausal breast cancer were linked with uterine cancers in the same way as conjugated oestrogens for menopausal symptoms and sequential oral contraceptives. However, based on the results of asymptomatic endometrial cancers in a series of autopsy studies and based on an increased awareness, Horwitz concluded that, detection-bias can lead to endometrial cancer risk odds that are raised by four to five times their true value [3]. The association between breast cancer and endometrial pathology is further complexed by the fact that breast cancer patients with an upper body fat distribution (android obesity), an important risk factor for endometrial cancer, have an increased number of oestrogen receptors (ER) [4]. Women with ER+ breast cancer, those selected for hormonal therapy, may therefore be biased towards more endometrial lesions even without taking hormones. Following the introduction of tamoxifen, another non-steroidal hormone, in the early 1970s and this time called 'anti-oestrogen', Ferrazzi reported in 1977 that tamoxifen is an oestrogen-agonist to the vaginal mucosa leading to an increase in karyo-picnotic index in 55% of postmenopausal breast cancer patients on tamoxifen [5]. These results in postmenopausal breast cancer patients were confirmed in the early 1980s by others also showing an increased cellularity in endometrial cells with an increase in nuclear size following tamoxifen treatment. At that time, in the mid 1980s, there was laboratory evidence for such an association between tamoxifen and endometrial cancer risk depending on ambient hormone levels showing an increase in growth rate of transplanted human endometrial cancer that occurs in athymic animals treated with tamoxifen. Endocervical and endometrial polyps, atypical endometrial cytology, adenomyosis, simple endometrial hyperplasia, atypical hyperplasia, four cases of endometrial adenocarcinoma and submucous fibroids were reported in the mid 1980s. Where some suggested that tamoxifen may interact with other breast cancer treatments to increase the risk of endometrial cancer, such as pelvic irradiation and chemotherapy, our case–control study and the increased incidence of endometrial cancers in one randomised clinical trial in the late eighties prompted others to address the issue (reviewed in ref. [6]).

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