treated patients compared to 5–15, 0–10 and 2–5%, respectively among non-treated women. A comparable case–control study was conducted among healthy women taking part in a breast cancer prevention trial. After 2 years [7], a proliferative endometrium was observed in 15% of tamoxifen patients, endometrial polyps in 8% and atypical hyperplasia in 16%. Placebo-treated women presented with 8, 2 and 0% of these lesions, respectively.

As breast cancer patients receiving tamoxifen most frequently have oestrogen receptor positive tumours, they are not totally comparable to patients with receptor negative tumours. In this sense, prospective cohort studies monitoring the uterine evolution during tamoxifen treatment are of great interest. Gal [8] followed 11 patients by Novak biopsies during 4–12 months and reported three endometrial hyperplasias. Achiron [9] observed that, among 45 patients with a normal endovaginal ultrasound, the endometrium of 25 remained atrophic after 12–36 months of tamoxifen. However, the mucosa of 12 became abnormally thick and 8 developed a polyp.

In our department, the uterine cavity of 57 postmenopausal breast cancer patients was regularly checked by means of hysteroscopy and endometrial biopsy before and during tamoxifen-treatment (12–144 months, mean 54). Endometrial atrophy was observed in 33.3%, glandulocystic atrophy in 26.3%, polyp in 35.5%, hyperplasia in 3.5% and carcinoma in 5.3%. Moreover, a polyp did appear in the cavity of 35.5%.

In conclusion, endometrial lesions are very frequent among asymptomatic breast cancer patients treated with tamoxifen. These women should be regularly evaluated for evidence of any intra-uterine anomaly. Moreover, it seems that endometrial polyps which are rare among untreated controls, are an important endometrial feature in these patients on tamoxifen. These polyps are often multiple and can be unusually large, occurring on a background of endometrial hyperplasia. These lesions should be resected and followed because of a possible pathogenetic relation between polypoid endometrial hyperplasia and malignancy.

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European Journal of Cancer, Vol. 34, Suppl. 4, pp. S19–S21, 1998

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

PII: S0959-8049(98)00092-6

II.3 Tamoxifen and Uterine Fibroids

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Tamoxifen, an anti-estrogen widely used for breast cancer treatment, has variable agonistic effects on the uterus (mostly concerning endometrium but also myometrium). 14 cases of growing uterine fibroleiomyomas during tamoxifen treatment which required hysterectomy are described. No myometrial malignancy was observed. © **1998 Elsevier Science Ltd. All rights reserved.**

TAMOXIFEN—A non-steroidal triphenylethyl compound derivative from diethylstilboestrol—has clinically dual anti-oestrogenic and oestrogenic actions. Because of these paradoxical agonist properties for oestrogen-sensitive tissues, some detrimental side-effects may occur on the internal genital tract in (postmenopausal) women taking tamoxifen. Various uterine pathologies have been reported: endometrial hyperplasia and polyps, endometrial carcinoma, adenomyosis, growth of leiomyoma.

In our institution surgical exploration with total hysterectomy was performed in 14 patients receiving tamoxifen who demonstrated rapid or progressive overgrowth of uterine

Table 1. Tamoxifen and growing uterine leiomyomas. Series of the Centre Jean Perrin (14 cases)

Patient			Tamoxifen			Fibroleiomyoma			
Case (*n*)	Age	Menopausal status	Daily dose (mg)	Exposure duration (months)	Total dose (g)	Submucous	Intramural	Subserous	Maximum diameter (cm)
1	67	15	30	84	75.6	+	–	–	5
2	65	11	30	12	10.8	+	+	+	5
3	70	20	20	3	1.8	–	–	+	12
4	72	29	20	6	3.6	–	–	+	6
5	60	2	20	18	10.8	+	+	+	6
6	47	3	20	45	27	+	–	+	10
7	46	1	20	12	7.2	–	+	+	9
8	48	1	20	8	4.8	+	+	+	9
9	49		20	12	7.2	–	–	+	10
10	67	18	20	36	21.6	–	+	+	8
11	58	2	20	12	7.2	+	+	+	8
12	46	4	20	52	31.2	–	+	+	5
13	42	2	20	24	14.4	–	+	–	6.5
14	48	–	20	120	72	+	+	+	5

leiomyoma. The purpose of this clinicopathological study was to summarise the conditions of long-term tamoxifen use in women having uterine fibroids.

Between 1983 and 1997, 14 hysterectomies were performed for tamoxifen-induced growth of uterine leiomyomas. Mean age was 57 years at time of surgery (42–72). 12 women were postmenopausal. Tamoxifen was prescribed at the dose of 20 mg daily or 30 mg daily. The uterine fibroids were asymptomatic at the start of tamoxifen. Pelvic examination was considered as normal in 2 patients. Silent and stable uterine fibroids were present in 3, the state of genital tract was unknown in 8. Symptomatology occurring during tamoxifen exposure was vaginal bleeding and/or pelvic pain.

The leiomyomas were resected by hysterectomy: abdominal hysterectomy in 10 cases, laparoscopically assisted vaginal hysterectomy in 4 cases. From the surgical specimen reports, the location, number and size of leiomyomas were recorded. Paraffin sections were prepared from the surgically removed leiomyomas and stained with haematoxylin and eosin. The sections were evaluated microscopically for primary malignancy (especially sarcoma) or secondary malignancy (metastatic from the breast).

Hormonal receptor contents—oestrogen receptors (ER) and progesterone receptors (PR) have been determined by radio-immunological assay on eight leiomyomas.

Mean duration of tamoxifen use before surgery was 29 months (3–120). Mean cumulative tamoxifen dose was 21 g (1.8–75.6 g).

All kinds of anatomical locations of uterine leiomyomas were represented: submucosal myomas, intramural myomas, subserosal myomas. Myomas in all locations were observed in four instances (pts 5, 8, 11, 14). The smallest leiomyoma was 5 cm in largest diameter; the largest (subserosal) leiomyoma was 12 cm.

No malignancy was found on microscopic examination. The mitotic activity of the benign smooth muscle tumours did not appear excessive. The features of leiomyosarcoma was never observed and the leiomyomas were never involved by malignant cells from the breast. Coexisting endometrial proliferative disorders such as endometrial polyp, glandulocystic hyperplasia, but no endometrial carcinoma have been observed. Myxoid pattern of the myoma was seen in 7 cases.

High levels of PR were constantly found in those leiomyomas (in each case > 300, mean value≠702 fmol per mg of cytosolic proteins).

It remains an obvious and undisputed fact that the development of uterine leiomyomata is dependent on oestrogen. In postmenopausal patients in whom leiomyoma are expected to decrease in size after withdrawal of ovarian oestrogen production, growth of the leiomyomata may be attributable to increase in either systemic or local oestradiol concentration. Furthermore, various paracrine and/or autocrine growth factors such as insulin-like growth factor-1 may also induce uterine enlargement acting synergistically with oestrogen.

Currently there are few available data regarding the short- and long-term effects of tamoxifen on the hormonal receptor status in leiomyoma. Immunohistochemical studies for steroid receptors were obtained in the fibroid tumours in 8 of our cases. That growing leiomyoma exhibited strong positive progesterone receptors is consistent with an oestrogenic effect of tamoxifen. It is suggested that tamoxifen was bound to the receptor sites of the leiomyoma providing stimulation and consequently enlargement.

It has been put forward that this increase may be related to growth enhancement of fibroid tumours already present at the time of initiation of the hormone therapy. We did not find any malignancy.

In the literature there is a paucity of data on malignant transformation of uterine fibroids induced by tamoxifen

Table 2. Oestrogen receptors (ER) and progesterone receptors (PR) in leiomyomas growing during tamoxifen treatment. Radio-immunological assay (fmol/mg of cytosolic proteins)

Case (*n*)	ER	PR
7	106	578
8	42	458
9	103	502
10	38	364
11	42	433
12	86	739
13	87	584
14	78	1970
Mean value	72	703

therapy: 5 cases have been published. Existing evidence associating tamoxifen treatment with uterine leiomyosarcoma may be regarded as unsubstantiated and anecdotal.

In women thought to have uterine fibroids, tamoxifen is, nevertheless, given with cautious clinical and ultrasonographic follow-up. Because the enlargement of fibromyomas occurs sporadically, expectant management is allowed. Surgical exploration is carried out when symptoms are emerging and/or when the size of each individual fibroid equals or exceeds 5 cm, in order to rule out malignancy. The patient is eventually restarted on long-term use of tamoxifen until planned duration administration.

European Journal of Cancer, Vol. 34, Suppl. 4, pp. S21–S22, 1998

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

PII: S0959-8049(98)00093-8

II.4 Is Ovarian Cyst Formation Related to Tamoxifen Use?

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The non-steroidal anti-oestrogen tamoxifen has a number of gynaecological side-effects. Apart from an increased risk of endometrial carcinoma, recently ovarian cyst formation during tamoxifen has been observed. This induces the problem of whether or not intervention for these cysts is required. In a cross-sectional study of breast cancer patients receiving tamoxifen, patients only developed ovarian cysts if ovaries responded to tamoxifen, as shown by oestradiol production. Ovarian cysts were not likely to develop in women with amenorrhoea > 1 year or following high-dose chemotherapy. © **1998 Elsevier Science Ltd. All rights reserved.**

TAMOXIFEN IS a non-steroidal anti-oestrogen with gynaecological side-effects. Tamoxifen is extensively used as adjuvant treatment in breast cancer patients and in case of metastatic breast cancer. Over the last decade the concern about the side-effects of tamoxifen has focused on the occurrence of endometrial carcinoma with a 2.3–6.4-fold increased risk compared to non-users [1–3]. Only recently ovarian cyst formation during tamoxifen has been reported [4–6]. There are several situations known in gynaecological practice that can induce a higher incidence of cysts in the ovary such as treatment with certain oral contraceptives [7] and ovulation induction therapy. The major concern in case of cysts in the ovary is the fact that these cysts may be indicative for malignancy. This dilemma is even more pronounced in case of breast cancer patients as BRCA1- and BRCA2-carriers are at increased risk to develop ovarian cancer.

We reported earlier on a cross-sectional study that was performed in 75 breast cancer patients who used tamoxifen [8]. According to previous chemotherapy four groups were defined: 5 cycles standard-dose fluorouracil/epirubicin/cyclophosphamide (FEC) (group A, $n=25$), 4 cycles FEC plus one cycle high-dose cyclophosphamide, thiotepa and carboplatin chemotherapy (group B, $n=22$), miscellaneous chemotherapy (group C) and no chemotherapy (group D). The first two groups participated in a randomised adjuvant study in patients below 56 years of age with more than 3 tumour positive lymph nodes. The programme comprised transvaginal ultrasonography (TVU) and endocrine analysis (LH, FSH, oestradiol (E_2) and inhibin in serum). No patient had abdominal symptoms. Uni- or bilateral adnexal cysts were observed by TVU in 12 patients. Multiple regression analysis showed that cyst development was related to high E_2, younger age, and absence of high-dose chemotherapy. These parameters were, however, related to each other. No cysts occurred in patients with amenorrhoea > 1 year. All patients after high-dose chemotherapy had amenorrhoea, $E_2 <$ 0.10 nmol/l and did not develop ovarian cysts. In this study breast cancer patients receiving tamoxifen only developed ovarian cysts if ovaries responded to tamoxifen as indicated by E_2 production. Ovarian cysts were not likely to develop in women with amenorrhoea > 1 year or following high-dose chemotherapy.

There is increasing evidence that ovarian cysts occur at a higher rate during tamoxifen treatment. Further research is required to define whether medical or surgical intervention is indicated in patients with this type of cysts.

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