Effects of tamoxifen on the human female genital tract: review of the literature

M. Varras[1], *M.D., Ph.D., Consultant*; **D. Polyzos**[1], *M.D., Registrar*; **Ch. Akrivis**[2], *M.D., Ph.D., Consultant*

[1]*Obstetrics and Gynaecology, "G. Gennimatas", General State Hospital of Athens, Second District National Health System of Athens*
[2]*Obstetrics and Gynaecology, "G. Chatzikosta" General State Hospital of Ioannina, Ioannina, District National Health System of Epirus (Greece)*

Summary

Tamoxifen is a non-steroidal triphenylethylene derivate, with clear antioestrogenic effects on the breast, that is orally administrated for the treatment of breast cancer and its prevention in a high-risk population. This article analyzes the effects of tamoxifen on the adult human female genital tract and considers its carcinogenicity in the gynaecological reproductive organs. It has been found that tamoxifen causes oestrogenic changes of the vaginal and cervical squammous epithelium and increases the incidence of cervical and endometrial polyps. The action of tamoxifen on the human endometrium in postmenopausal women is connected with simple oestrogenic effects including hyperplasia, while in others with endometrial cystic atrophy. In cases where tamoxifen induces endometrial polyps and hyperplasia, the extensive fibrosis accounts for difficulties in obtaining endometrial biopsy or resecting the polyps. In premenopausal patients tamoxifen disrupts the menstrual cycles and causes ovarian cysts, while in postmenopausal patients it induces ovarian cystic tumors and endometriomas. Also, postmenopausal patients treated with tamoxifen may develop endometriosis, adenomyosis and leiomyomata. In addition, randomized trials have shown a link between tamoxifen use in breast cancer patients and the development of endometrial carcinomas. Moreover, of note is the fact that the association of tamoxifen therapy with uterine mesenchymal neoplasms is higher than expected. In conclusion, the most worrying gynaecological side-effect of tamoxifen is the well-known increased risk of endometrial carcinomas. Women with breast cancer treated with tamoxifen should undergo annual gynaecological examination, but endometrial sampling should be obtained only in the event of endometrial bleeding.

Key words: Tamoxifen; Uterine carcinoma; Uterine polyp; Endometrial hyperplasia; Uterine sarcoma; Ovarian cyst.

Introduction

Tamoxifen is a non-steroidal triphenylethylene derivative, which like most antihormones has antagonistic and agonistic oestrogenic effects, depending on the target tissue [1]. It has clear antagonistic oestrogenic effects on breast tissue and is widely used for the management of patients with oestrogen receptor-positive, node-negative carcinoma of the breast [2]. Multiple clinical trials have shown tamoxifen to improve recurrence-free interval and overall survival in both premenopausal and postmenopausal women with advanced or recurrent breast cancer [3-5]. Moreover, tamoxifen has been advocated as a long-term adjuvant therapy in node-positive breast cancer patients [6]. In addition, it has been shown that a combination of tamoxifen and chemotherapy reduces the risk of recurrences of breast cancer in the ipsilateral breast and development of cancer in the contralateral breast [7]. Finally, breast cancer prophylaxis in high-risk healthy women, is another possible use for this agent [8].

In regards to the side-effects of tamoxifen, the majority of its acute side-effects, include hot flashes, vaginal discharge, oedema, nausea, vomiting, visual disturbances and depression and only 4% of the patients will discontinue the drug because of the adverse effects [9, 10]. Moreover, tamoxifen has oestrogenic effects on the endometrium acting as an oestrogenic agonist. Several reports suggest that breast cancer patients receiving tamoxifen treatment have a higher rate of cervical and endometrial polyps, endometrial hyperplasia and adenocarcinomas. In addition, there is evidence that tamoxifen may induce uterine body tumors, such as stromal sarcomas, leiomyosarcomas and malignant mixed epithelial-nonepithelial tumors.

In this study, we reviewed the international literature regarding the effects of tamoxifen on the human female genital tract, regarding patients with breast cancer, and considered its role in the case of carcinogenesis .

Tamoxifen and its mechanism of action

Tamoxifen can be a complete oestrogen antagonist, a partial oestrogen agonist or/and a complete oestrogen agonist, depending on the gene and the tissue that is being studied [11]. Regarding the action of tamoxifen in the case of positive oestrogen receptors of malignant breast cells, a proposed mechanism is the following: Tamoxifen binds to the oestrogen receptor (like oestrogen) within the hormone-binding domain (HBD) with high chemical affinity. The result of this binding is the creation of dimmers of activated oestrogen receptors. These dimmers bind to the oestrogen response elements (EREs) of the genome of breast cells. However, in contrast with the oestrogen, tamoxifen does not induce the structural changes to oestrogen receptors in order to activate the region that mediates the transcription (oestrogen-

Revised manuscript accepted for publication November 7, 2002

inducible transcriptional activating function, AF-2). Therefore in the breast, tamoxifen acts as an oestrogen antagonist because it binds the oesrogen receptors and blocks oestrogens to exert their mitogen action. Yet, sometimes it is possible that the action of tamoxifen in the breast becomes agonistic for oestrogens because of alterations of the oestrogen receptors, such as mutations, or because of non-feasible binding of tamoxifen to the breast cells. For these reasons, the observed resistance of some patients to tamoxifen may be explained, besides the fact that their malignant breast cells contain oestrogen receptors [11, 12]. Jordan *et al.*, showed that a remarkable percentage of women with malignant breast cells negative for oesrogen receptors demonstrated clinical response to tamoxifen [13]. This mechanism of action of tamoxifen could be explained by its activity upon the function of protein kinase C, by the reduction of the plasma levels of insulin-like growth factor I, and by the production of transforming growth factor-β from the stromal cells [13].

Regarding the action of tamoxifen in the endometrium a proposed mechanism follows: Tamoxifen binds to the oestrogen receptor in the oestrogen-binding domain (HBD), which is located in the functional domain E of the oestrogen receptor and it forms dimmers of activated oestrogen receptors (receptor dimerization). These dimmers bind to the specialized oestrogen response elements (EREs) of the DNA in the endometrial cells. This binding allows the activation of the function of the region AF-1 of the oestrogen receptor, which mediates activation of the transcription (oestrogen-independent transcriptional activating function, AF-1) (Figure 1). The mitogen function of tamoxifen in the endometrium is perhaps explained by the activation of proto-oncogenes which is exclusively made by the function of the region AF-1. In contrast, in the breast as mentioned above, the expression of proto-oncogenes depends on the activation of the function of the region AF-2, which is only activated by oestrogens (oestrogen-inducible transcriptional activating function, AF-2). The over-expression of proto-oncogenes caused by the tamoxifen may be responsible for carcinogenesis in the endometrium [11, 12]. Varras *et al.*, suggested an accessional mechanism of the cancerous action of tamoxifen in the endometrium by the induction of mutation in codon 12 of the K-*ras* oncogene [14].

Effects of tamoxifen on the vagina

Vaginal dryness

Several studies have reported oestrogenic changes of the vaginal epithelium in postmenopausal patients during long-term tamoxifen use [15-17]. Mortimer *et al.*, studied the sexual function in breast cancer patients treated with tamoxifen [18]. They found an increase in maturation index in vaginal epithelium in 69% of postmenopausal patients. However, the presence of an oestrogen effect on the vaginal epithelium coincided with negative effects on sexuality as manifested by vaginal dryness and dyspareunia [18]. These contradictory effects of tamoxifen on the maturation index on the one hand and vaginal function on the other hand could not be explained by the authors [15]. Although prospective data about the effect of tamoxifen on the vaginal epithelium in premenopausal breast cancer patients are lacking, vaginal dryness and painful intercourse during tamoxifen administration have been reported as well [15, 19]. Treatment of vaginal dryness by vaginal administrated oestiol (E_3) causes measurable serum levels of E_3 in postmenopausal women. However, this treatment is not recommended for patients with breast cancer because of the association of oestrogen and breast cancer [15, 20]. An alternative approach in these patients with non-hormonal polycarbophil-based vaginal moisturizers can significantly reduce vaginal dryness [15, 21].

Vaginal candidiasis

Recurrent vaginal candidiasis has been reported in postmenopausal women taking tamoxifen [15]. This condition is rare in eldery women because it occurs only in glucogen-rich, vaginal epithelium and it is known that the middle and superficial zone of the multilayered vaginal squammous non-keratinizing epithelium contain glycogen only when stimulated by oestrogen [15].

Effects of tamoxifen on the cervix

Oestrogen-like effects on cervical squamous epithelium

Long-term treatment with tamoxifen has been associated with oestrogen-like effects on cervical epithelium [15-17]. The effect of tamoxifen on squamous epithelium does not seem to be dose or time dependent [23]. Lahti *et al.*, reported that high maturation occurs in at least 60% of cases of postmenopausal women receiving tamoxifen and that the changes become apparent as early as four weeks after initiation of treatment [24]. Also, it has been reported that complete squamous maturation is not achieved in most patients [22, 23, 25]. These findings confirm the partial oestrogenic-agonist effect of tamoxifen on cervical epithelium. This incomplete maturation suggests that the mechanism of action of tamoxifen might be different from that of oestrogen stimulation [23].

Polyps

Cervical polyps are defined as localized, pendunculated or sessile outgrowths of the endocervical mucosa. The surface is lined by a cervical columnar epithelium, which contains similarly lined glands. Several histological types of polyps are recognized: (a) "Fibrous polyp", (b) "vascular polyp", (c) "mixed polyp" and (d) "decidual polyp". "Fibrous polyp" is composed almost entirely by fibrous connective tissue with few glands, while in "vascular polyp", a large number of blood vessels form the major component. "Mixed polyps" arise from the region of the isthmus and contain both endocervical and endometrial

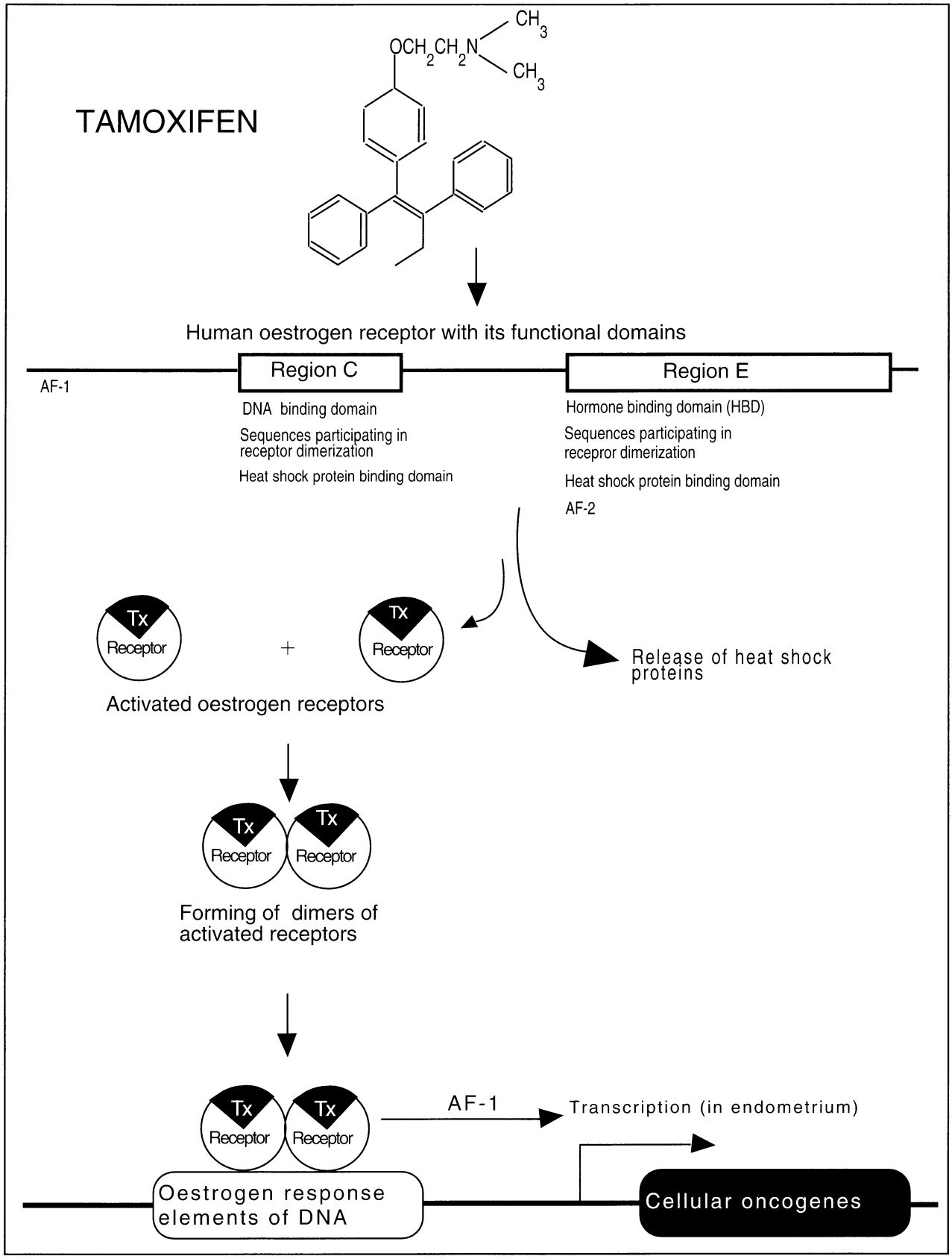


Figure 1. — The proposed mechanism of action of tamoxifen in the endometrium; (Tx: tamoxifen).

glands. Finally, "decidual polyps" occur during pregnancy and the stroma undergo decidual changes. Carcinoma in cervical polyps (either glandular or squammous type) is very rare (less than 0.3%) [26]. The association of tamoxifen with cervical polyps has been demonstrated by several studies. Lahti *et al.* (1993), found that endocervical polyps were twice as common in the tamoxifen group than in the control group [27].

Effects of tamoxifen on the endometrium

Atrophy

The action of tamoxifen on the human endometrium in some postmenopausal women is connected with a simple oestrogenic effect, which includes a proliferative or hyperplastic endometrium, while in others with an endometrial atrophy [1, 28]. "Endometrial cystic glandular atrophy" is diagnosed histologically when multiple cystic spaces lined by atrophic endometrium are present within a dense fibrous stroma [29]. Touraine *et al.* [1], in a retrospective hysteroscopic study in 40 postmenopausal patients treated by tamoxifen as an adjuvant therapy for breast cancer, found in all the patients the same pattern of endometrial atrophy: a smooth, white and brilliant endometrium associated in most cases with multiple scattered protuberances. In the cases where the endometrial biopsy was possible (24/40) the luminal epithelium was very thin and unistratified, while the glands were dilated, cystic and with flattened epithelium. Mitoses were rare. Contrasting with the epithelial atrophy, the stroma was always dense, rich in collagen and with large oedematous areas. Globally, it is known as "endometrial cystic glandular atrophy" [1]. Touraine *et al.,* in order to explain the simulataneous presence of an atrophic mucosa, dilated cystic glands and a dense oedematous stroma, suggested a dissociated antioestrogenic and weak oestrogenic effect of tamoxifen on various components of the endometrium [1]. The increase in the size of the glands might be due to a weak oestrogenic stimulation of tamoxifen on glandular epithelium secretion resulting in the increase of fluid inside the glands. In contrast, the presence of a thin and atrophic epithelium has to do with the lack of stimulatory effects of tamoxifen on growth of the epithelium. Finally, the thick and oedematous stroma may be due to an oestrogenic effect of tamoxifen [1].

Hyperplasia

Endometrial hyperplasia is an increase in endometrial volume characterized by a morphologically abnormal proliferative-type endometrium [29]. Hyperplasia with cytological atypia is classified as "atypical hyperplasia", while hyperplasias without cytological atypia are subdivided into "simple" and complex" forms [30]. In up to 23% of patients with "atypical hyperplasia", the hyperplasia progresses to carcinoma, whereas in only 2% of patients with hyperplasia without atypia, the hyperplasia progresses to carcinoma [29, 31]. In healthy postmenopausal women with low oestrogen levels the endometrium is thin and atrophic. Endometrial proliferation and hyperplasia have been frequently reported during tamoxifen treatment in postmenopausal patients [32]. The incidence of endometrial hyperplasia in postmenopausal patients with breast cancer treated with tamoxifen is 1.3% to 20%, as compared with the 0% to 10% incidence in postmenopausal patients with breast cancer who are not receiving tamoxifen and the general (symptomatic and asymptomatic) female population [9, 27-29, 31, 33-38]. On macroscopic examination, tamoxifen-stimulated endometrial hyperplasia is characterized by the diffusion of endometrial thickening, with a cut Swiss-cheese-like surface owing to the presence of multiple endometrial cysts of varying size [39, 40]. Microscopic examination confirms that there is a diffused endometrial thickening with cystically dilated glands which are clearly of endometrial origin. Some endometrial glands show glandular budding and other architectural abnormalities. The endometrial stoma is characteristically fibrotic with collagen bundles separating stromal cells [40]. This feature of tamoxifen-stimulated endometrium may be responsible for the difficulty in obtaining endometrial biopsy material from treated women with documented ultrasonographic and hysteroscopic abnormalities [40]. In the study by Cohen *et al.,* endometrial biopsy was attempted in 77 tamoxifen-treated postmenopausal breast cancer patients, but adequate endometrial tissue was obtained in only 23 cases (29%), even though 76 women had an ultrasonographically thickened endometrium [41]. Finally, it seems that the hyperplastic effects of tamoxifen on endometrial tissue could not be prevented by addition of a progestational agent [42, 43].

Polyps

On gross examination, endometrial polyps are pedunculated, smooth spheroidal, or cylindrical structures. They may be single or multiple and occur at all ages, with a peak incidence at about the age of 50. Microscopically, they contain a mixture of three components: 1) a stroma of dense fibrous tissue, 2) thick-walled vascular channels, and 3) endometrial glands [28, 29, 44]. Polyps generally are of one or two types. The first type consists of functional endometrium with proliferative activity that parallels the hormonal cycle of the adjacent nonpolypoid endometrium. The second and more common type consists of hyperplastic endometrium, often cystic, which responds to estrogenic stimulation but lacks a response to progesterone. The finding of hyperplastic endometrial glands within a polyp, suggests the presence of endogenous or exogenous oestrogenic activity [28]. Several studies have analyzed the endometrial histology of patients receiving tamoxifen and there seems to be a 12% incidence of endometrial polyps in such patients [32]. When breast cancer patients not receiving tamoxifen are studied, the incidence of endometrial polyps is roughly 4% [32]. In the study of McGonigle *et al.* (1996), the

high incidence of endometrial polyps in tamoxifen treated patients was found in postmenopausal patients, but this increase was not statistically significant among the premenopauasal patients [45]. These polyps are often multiple and usually much larger than sporadic polyps (mean diameter, 5 cm) [28, 29, 39, 40, 46]. Ismail *et al.*, suggests that the tamoxifen-associated polyps tend to develop on a background of endometrial hyperplasia [39]. Moreover, the incidence of endometrial cancer occurring in benign endometrial polyps is approximately 0.5% (47), this prevalence is higher in tamoxifen-associated endometrial polyps [40].

On microscopic examination, the tamoxifen-associated endometrial polyps are characterized by a combination of proliferative activity (cystic glandular dilation), aberrant epithelial differentiation (metaplasia), and a relatively hypocellular stroma with a patchy periglandular stromal consideration [28, 29, 39, 44]. They may also undergo ulceration and infarction and the consequent irregular friable appearance may resemble malignancy. In addition, extensive stromal reaction (ie, fibrosis) may account for difficulties in resecting tamoxifen-related polyps at hysteroscopy [29].

Hysteroscopic picture of pseudopolypoid glandulocystic "tamoxifen mucosa"

In the case of pseudopolypoid glandulocystic endometrium in postmenopausal patients treated with tamoxifen, hysteroscopy shows smooth, white, hypervascularized and atrophic endometrial layer, with scattered protuberances that represent glandulocystic atrophia (cystic atrophy). This "tamoxifen mucosa" with its protuberances differs macroscopically from the atrophic mucosa seen in postmenopausal women who are not receiving tamoxifen and the mucosa in these cases is characterized as pale, thin and without protuberances [29, 48].

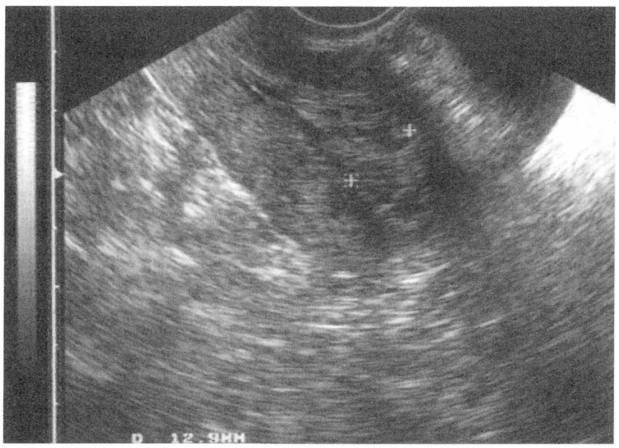
Cancer

The risk of developing endometrial cancer before the age of 85 is 1.1% [49]. Women with carcinoma of the breast have a higher risk than expected incidence of developing subsequent uterine carcinoma. This risk is estimated to be 1.72 times the risk of developing endometrial cancer [50]. This age-dependent cancer is approximately 1.0 time in women under the age of 50 and to 2.4 times in women, 70 years and older [50]. The reason that tamoxifen has oestrogen-like effects on the endometrium, might represent an endometrial carcinoma risk [51]. Killackey *et al.*, for the first time suggested a possible link between tamoxifen use in breast cancer patients and the development of endometrial carcinoma [52]. Subsequently, several case reports indicated an association between tamoxifen treatment and endometrial carcinoma. The first randomized study demonstrating an increased risk of endometrial cancer during adjuvant tamoxifen treatment was published in 1989 by Fornander *et al.* [53]. This study (the Stockholm trial) involved 931 patients treated with tamoxifen 40 mg daily for two to five years with a median follow-up of 4.5 years and 915 controls. The authors found a 6.4-fold increased endometrial cancer risk in the tamoxifen group compared with controls [53]. The relation between tamoxifen and endometrial cancer has been established with lower doses (20 mg daily) [7, 36, 54-56]. An overview of all the randomized tamoxifen trials in 1998, showed that the incidence of endometrial cancer was approximately doubled in trials of tamoxifen lasting one to two years and approximately quadrupled in trials of a five-year duration [57].

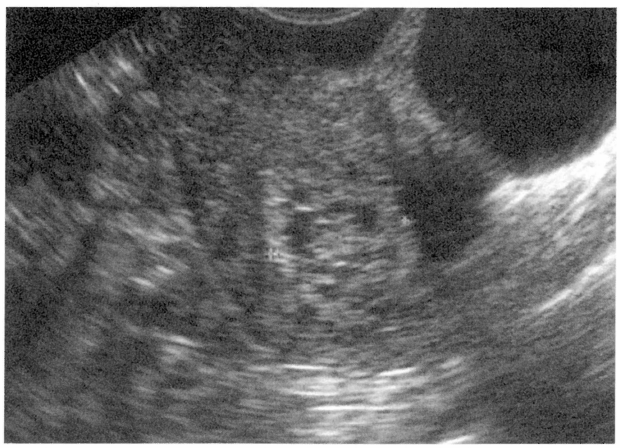
Although endometrial carcinomas that develop in the presence of unopposed exogenous oestrogen are predominantly early stage, low-grade, minimally invasive lesions having a favorable prognosis [58], there is some uncertainty about the pathological features of tamoxifen associated with endometrial adenocarcinomas [40]. Van Leeuwen *et al.*, showed an excess of well-differentiated tumors in tamoxifen users (52%) compared with non-users (32%) [56]. In contrast, Magliples *et al.* (1993), showed that tamoxifen-related endometrial cancers were more aggressive than endometrial cancers in the general population [59]. Also, Silva *et al.*, found that the serous type of endometrial carcinoma, which has a particularly poor prognosis, was the commonest subtype of endometrial carcinoma among tamoxifen-treated breast cancer patients (n=15), while endometrioid carcinoma was the commonest subtype among those not treated with tamoxifen (n=57) [60]. Finally Barakat *et al.*, demonstrated no significant difference in stage, grade or histologic subtype in breast cancer patients who subsequently develop corpus cancer [9].

Screening the endometrium

The endometrium can be screened by transvaginal ultrasonography, hysterosonography, cervical dilation and curretage and hysteroscopy combined with directed biopsies. Transvaginal sonography is an effective and practical screening method to detect pathologic changes in the endometrium [27]. Generally, the endometrium in postmenopausal patients is considered abnormal if it is more than 5 mm thick and in that case further investigations should be carried out [32]. Women undergoing tamoxifen treatment have a thicker endometrium as compared with that in control subjects (9-13 mm versus 4.0-5.4 mm) [29]. The most common endometrial transvaginal ultrasonographic pattern seen in women treated with tamoxifen is a thickened endometrium with cystic spaces [29]. The presence of large dilated cystic glands, as well as oedematous stroma, in breast cancer patients treated with tamoxifen might account for the thickened appearance of the mucosa on ultrasound examination [1]. Also, the classic Swiss-cheese appearance of endometrial polyps in tamoxifen treated patients is well known [61]. Figures 2 and 3 demonstrate via transvaginal ultrasonography the classic Swiss-cheese appearance of an endometrial polyp in a 59-year-old patient with breast cancer treated with tamoxifen for four years. Figure 4 shows the



ig. 2



ig. 3

Figures 2 & 3. — Tranvaginal ultrasonographic image of the classic Swiss-cheese appearance of an endometrial polyp in a 59-year-old patient with breast cancer treated with tamoxifen for four years (Figure 2: transverse image, Figure 3: longitudinal image).

hysteroscopic view of the polyp in the same patient before its removal. Pathologic examination disclosed fragments of a fibro-adenomatous benign endometrial polyp with decidual reaction. The remainder of the endometrium showed decidual reaction with fibrotic stroma and foci of haemorrhage. However, in women treated with tamoxifen, the sonographic diagnosis is erroneous. Much of the increased endometrial thickness seen in the tamoxifen treated patients is submucosal and "cystic glandular atrophy" which may be revealed at biopsy [32]. Love *et al.*, found that transvaginal ultrasonography is a poor screening tool because of its high false-positive rate (46%) [8]. Lathi *et al.*, found that a cutoff of more than 5 mm would detect only 51.2% of abnormal endometrial pathologies in such patients [27], while Kedar *et al.*, found that the positive predictive value of an endometrial thickness of more than 8 mm was 100% for the detection of an abnormal pathology [35]. Oedema and hyperplasia of the myometrium during tamoxifen treatment could contribute to the thickened endometrium and thus to the false sonographic appearance of endometrial hyperplasia [48].

In cases where transvaginal sonohysterography is non-diagnostic or is suggestive of an abnormality, hysterosonography can provide additional information. Hysterosonography can define endoluminal lesions that are pedunculated or sessile and can determine better whether an abnormality is endometrial or subendometrial. Tepper *et al.*, in a prospective study found that patients receiving tamoxifen had an endometrial thickness of more than 8 mm at transvaginal ultrasonography. Whereas, hysterosonography had high sensitivity (100%) and high positive predictive value (95.5%). On the other hand, dilation and curettage (D & C) is not suitable for clarifying transvaginal sonography findings in postmenopausal women, because polyps are often missed and the endometrial sampling is often insufficient to confirm atrophy [27]. Therefore, hysterosonography or hysteroscopy will be required if there is endometrial thickening because in tamoxifen-treated patients the only value of the transvaginal sonography is only a normal finding [48]. Outpatient hysteroscopy combined with directed biopsies remains an uncomfortable and relatively invasive technique that requires specialized equipment, making it an inappropriate screening tool [8]. Moreover, it is difficult to perform biopsy on tamoxifen-treated endometrium even in the presence of apparent hysteroscopic abnormalities [8]. Many authors have suggested that endometrial screening in asymptomatic women treated with tamoxifen does not seem to be useful. In contrast, endometrial sampling is important if vaginal bleeding occurs in postmenopausal tamoxifen-treated patients because this symptom cannot be assumed to be caused by endometrial atrophy [28]. The opinion article of the American College of Obstetricians and Gynaecologists in 1996 [62] set the following recommendations for women with breast cancer treated with tamoxifen:

(i). Women with breast cancer should undergo annual gynaecological examinations, including pap smear and bimanual and rectovaginal examinations.

(ii). Any abnormal bleeding, including blood discharge, spotting or any other gynaecological symptom, should be evaluated thoroughly. Any bleeding or spotting should be investigated by means of biopsy.

Figure 4. — Hysteroscopic image of the same patient, showing an endometrial hypervascularized polyp (arrow).

(iii). Practitioners should be alert to the increased incidence of endometrial malignancy. Screening procedures or diagnostic tests should be performed at the discretion of the individual gynaecologist.

(iv). If atypical hyperplasia develops, use of tamoxifen should be discontinued and dilation and curettage or other appropriate management should be instituted within an appropriate interval.

(v). If tamoxifen therapy must be continued, hysterectomy should be considered in women with atypical endometrial hyperplasia.

(vi). Tamoxifen treatment may be reinstituted after hysterectomy for endometrial carcinoma, in consultation with the physician responsible for the woman's breast care.

Effects of tamoxifen on the uterine body

Uterine fibroids

Several studies have explained an increase in myometrial volume, and growth of uterine myomas in postmenopausal patients following the administration of tamoxifen [35, 36, 63-65]. It is of interest that in almost all the cases the pathology report on the surgical specimens did not show any evidence of malignancy [63, 66]. In addition, the leiomyomas observed in women treated with tamoxifen do not differ histologically from those found in untreated women [29].

Adenomyosis

Adenomyosis is a common non-neoplastic condition in which endometrial glands and stroma are found within the myometrium [67]. In postmenopausal patients taking tamoxifen, adenomyosis has been reported [15]. In postmenopausal, tamoxifen-treated patients, oestrogen receptors and progesterone receptors have been described in adenomyosis in a similar concentration as in premenopausal non-tamoxifen users [68]. However, it is not clear, if the apparent increase in the incidence of adenomyosis in women treated with tamoxifen, is a true phenomenon or simply represents a spectrum of tamoxifen-associated cysts ("adenomyosis-like changes") [29, 69]. Indeed, it is known that endometrial cystic atrophy is diagnosed histologically when multiple cystic spaces lined by atrophic endometrium are present within a dense fibrous stroma [29]. In the cases of patients treated with tamoxifen, the exact location of the cysts is controversial. Some investigators report that the cysts extend to the endometrial-myometrial junction but clearly reside within the endometrium, while others have placed cysts in the proximal portion of the myometrium ("adenomyosis-like changes") [29].

Cancer

Uterine sarcomas account for 3-5% of all uterine malignancies [70, 71]. The overall annual incidence is approximately 17 per million [72]. Unlike uterine epithelial tumors, which carry a relatively good prognosis, uterine sarcomas are characterized by a high rate of local recurrences and a high rate of recurrent metastases [72]. Uterine sarcomas have been classified into three main histologic subgroups, in order of decreasing incidence: malignant mixed epithelial-nonepithelial tumors, leiomyosarcomas and endometrial stromal sarcomas [72]. Variants of malignant mixed epithelial-nonepithelial tumors are the malignant mixed müllerian tumors (or carcinosarcoma), the adenosarcomas and the adenofibromas [73]. The mesenchymal component of the malignant mixed epithelial-nonepithelial tumors may be homologous or heterologous. The homologous component is composed of tissue with differentiation normally found in the uterus, while the heterogenous component is composed of other elements foreign to the uterus (rhabdo, lip, chondro or osteo- differentiations) [73, 74]. Malignant mixed müllerian tumors (carcinosarcomas) are composed of a mixture of malignant epithelial and stromal components [75]. Müllerian uterine adenosarcomas are biphasic and possess a malignant stroma, which may exhibit heterologous differentiation, coupled with a benign glandular element [76]. The most common of the uterine mesenchymal tumors are the malignant mixed müllerian tumors (carcinosarcomas), representing less than 1.5% of malignant tumors of the uterus [71]. These neoplasms are commonly bulky and polypoid, filling the endometrial cavity, and which invade the myometrium early in their course, representing an advanced stage at the time of the diagnosis. Uterine tumors arising after pelvic irradiation show that a disproportionate number represent malignant mixed müllerian tumors [71, 75]. Müllerian adenosarcomas are rare tumors, and compose only 8% of all uterine sarcomas [70], which are considered to have a low malignant potential even in rare instances in which heterologous elements are present [77]. The usual site of origin is the endometrium; however, cases have been reported arising in the myometrium, cervix, ovary and peritoneum [76]. In the largest published series of müllerian uterine adenosarcomas, the most common finding was tissue protruding from the external cervical os [70]. The morphological distinction between adenofibroma and adenosarcoma of the uterus may sometimes be difficult. Zaloudek and Norris, [78] found four key criteria that can be used to distinguish between adenofibromas and adenosarcomas: (1) The degree of mitotic activity. Adenofibromas have fewer than four mitotic figures per 10 HPF in the most active areas, while adenosarcoma has four or more. (2) A marked degree of atypia of mesenchymal cells. (3) A histological malignant heterologous element. (4) Myometrial invasion. The second, third and fourth criteria are unique to adenosarcoma, but because they are not present in every tumor, they are less applicable than the assessment of mitotic activity [78]. Malignant transformation in fibroids is a rare event and it occurs in less than 0.4% [66, 79, 80]. Endometrial sarcomas represent 26% of uterine sarcomas [81] and are composed of cells identical to or closely resembling those of endometrial stroma [82]. They are subdivided into low and high grade neo-

plasms [81] and differ from müllerian uterine adenosarcomas in that they are usually monophasic mesenchymal neoplasms [78]. Malignant mixed müllerian tumors and endometrial sarcomas have been shown to be oestrogen and progesterone positive receptors, although not as frequently or at levels as high as those in endometrial adenocarcinomas [75, 83, 84]. In addition, malignant mixed müllerian tumors are thought to represent basically an epithelial neoplasm of the endometrium with sarcomatous dedifferentiation, sharing most of the risk factors and epidemiological characteristics of uterine adenocarcinomas [70, 85-88].

Tamoxifen has been associated with the occurrence of uterine sarcomas, and in the literature several cases after tamoxifen therapy have been reported. Most of these sarcomas were malignant mixed müllerian tumors, while few cases of müllerian adenosarcomas of the uterus, as well as endometrial stromal sarcomas have also been reported [15, 40]. However, it is not clear yet whether tamoxifen treatment is associated with atypical changes in leiomyomas [63]. Sabatini *et al.*, published a case of uterine leiomyoma with neoplasmatic degeneration in a postmenopausal woman treated with tamoxifen [66]. Further cases must be documented in order to clarify whether tamoxifen is associated with the development of uterine leiomyosarcomas. Regarding the development of uterine carcinosarcomas in tamoxifen treated women, Fotiou *et al.*, [85] analyzed ten well-documented reported cases from the international literature, plus two of their own cases. The age of the patients varied from 43 to 90 years (mean = 72.6 years) and only one patient was premenopausal. The duration of treatment was over a six-year period in ten out of 12 cases and only two patients were under a six-year treatment (3 years and 16 months, respectively). In ten out of 12 cases for which information on the dosage was given, a daily dose of 20 mg was prescribed. In five cases a striking common feature was a large polypoid mass filling the uterine cavity, which protruded into the vagina. In four cases in the literature for whom the histological characteristics were mentioned [67, 75, 89, 90], as well as in the two cases reported by Fotiou *et al.*, [85] an heterologous type of carcinosarcoma was present. Regarding the outcome, eight out of ten patients were reported as having died of disease and the other two as suffering from advancement of the disease. These findings suggest: (a) The age distribution is quite similar to the one reported for endometrial adenocarcinoma patients. (b) More than five-years of continuous treatment is usually required for the formation of this neoplasm. (c) These usually lethal tumors did not exist before the commencement of tamoxifen treatment. (d) Not only the duration of tamoxifen treatment, but also the daily dose administrated may be relevant in tumor formation. Finally, Evans *et al.*, pointed out that the histological characteristics of carcinosarcomas in women treated and not treated with tamoxifen were quite similar [89]. In addition to the above study, McCluggage *et al.*, [91] studied 19 postmenopausal patients with breast cancer who received 20 mg of tamoxifen daily, finally showing evidence of uterine carcinosarcoma. The age of diagnosis of carcinosarcoma ranged from 47 to 91 years (mean 71 years) and the duration of treatment ranged from 1 to 15 years (mean 7.1 years). Ten tumors were Stage I, one Stage II, seven Stage III and one Stage IV. Ten of the carcinosarcomas were homologous, and nine contained heterologous elements. The overall prognosis was extremely poor even with low-stage disease. Fifteen patients died within 35 months of the diagnosis of carcinosarcoma (mean 12 months), two patients were alive with very short follow-up periods and two were lost to follow-up. This study supports an association between tamoxifen therapy and the development of uterine carcinosarcoma. In addition, since uterine carcinosarcomas are highly aggressive neoplasms, usually more than the original breast cancer, such an association is highly significant. Additionally, müllerian adenosarcomas of the uterus have also been reported to be related to tamoxifen. In a review of the literature by Arici *et al.*, 13 müllerian adenosarcomas cases following tamoxifen therapy were reported. In these ten out of 11 cases, women had received tamoxifen for a period of five months to four years, in one case for five years and in one case for eight years. The clinical and pathological features of these cases were similar to previously reported müllerian adenosarcoma cases except for their association with tamoxifen therapy [76, 92-97]. Considering the rarity of these tumors, it seems that the association of tamoxifen therapy with mesenchymal neoplasm is higher than expected.

Effects of tamoxifen on the ovaries

The effects of tamoxifen on the human ovaries were first described by Klopper and Hall in 1971. They showed that tamoxifen induced ovulation in anovulatory infertile women [98]. It seems that tamoxifen has a direct effect on the ovaries of premenopausal women, since the serum oestrogen rise is not accompanied by a rise of FSH and LH levels [15]. Tamoxifen has also been shown to disturb the menstrual cycles in premenopausal patients causing irregular cycles, oligomenorrhea and amenorrhea in almost half of the patients [15]. Mouritas *et al.*, suggested that even in premenopausal patients with amenorrhea caused by tamoxifen, contraceptive barriers or intrauterine devices are necessary because pregnancies have been described and tamoxifen might be teratogenetic, as it acts as an anti-oestrogen agent on the developing fetus [15]. The hyperoestrogonism of tamoxifen in premenopausal patients has been reported to cause ovarian cysts such as luteinised or follicular cysts, benign unilateral corpus luteum cysts or bilateral "simple" functional cysts [40]. In addition, in postmenopausal patients prolonged tamoxifen use has been shown to induce ovarian cystic tumors or endometrioid cysts [40]. Although torsion of a cystic ovary during treatment has been described [99], surgical intervention is rarely required and in functional asymptomatic monolocular cysts patients should be followed conservatively [15]. Varras *et al.*, [100] reported a case of a 40-year-old breast cancer

patient who presented to the gynaecologists with an ultrasound report indicating a right ovarian cyst with a maximum diameter of 5.5 mm. The patient had discontinued the combined chemotherapy cycles because of their adverse side-effects and was under oral tamoxifen treatment at a dose of 20 mg daily. The authors after consulting with the patient and obtaining written consent, performed a total abdominal hysterectomy with bilateral salpingo-oophorectomy for three main reasons: (a) Although the ultrasound scan and the preoperative Ca125 levels were suggestive of a benign ovarian cyst, the size of the ovarian cystic structure was larger than 5 cm, without any regression after two months of observation. Therefore, the possibility of ovarian malignancy had to be excluded. (b) The authors believed, that an oophorectomy could be beneficial for the primary disease of the patient. Bryant and Weir, [101] have found that women aged less than 50 years old with operable carcinoma of the breast and with positive axillary nodes benefited significantly from prophylactic oophorectomy, both in the relapse-free status at five years and in the survival and relapse-free status at ten years. In addition, Nomura *et al.*, [102] suggested that in premenopausal patients with oestrogen-positive breast cancer, therapy with oophorectomy and daily oral administration of 20 mg tamoxifen may be equivalent in prolonging relapse-free survival and overall survival to chemotherapy or to chemotherapy and tamoxifen therapy. (c) A hysterectomy enabled the patient to avoid the adverse side-effects of tamoxifen to the uterus. In that patient, the incidental findings of extramedullary hematopoiesis in the uterine isthmus were scientifically interesting, which subsequently heralded widespread infiltration of bone marrow by neoplasmatic cells [100].

Tamoxifen and endometriosis

Ectopic endometrial tissue outside the uterus is called endometriosis [15]. In postmenopausal patients taking tamoxifen, endometriosis has been reported [15, 103]. As endometriosis is an oestrogen-dependent disease and is rare in postmenopausal women, the findings of endometriosis in postmenopausal women treated with tamoxifen raises the possibility of a link between tamoxifen and endometriosis [15, 40]. However, it is not clear, whether tamoxifen causes *de novo* endometriosis, and whether it exacerbates pre-existing endometriosis [15].

Referrences

[1] Touraine Ph., Driguez P., Cartier I., Yaneva H., Kuttenn F., Mauvais-Jarvis I.: "Lack of induction of endometrial hyperplasia with tamoxifen". *Lancet,* 1995, *345,* 254.

[2] Jordan G.V.: "Long term adjuvant tamoxifen therapy for breast cancer". *Breast Cancer Res. Treat.,* 1990, *15,* 125.

[3] Buchanan R.B., Blamey R.W., Durrent K.R. *et al.*: "A randomized comparison of tamoxifen with surgical oophorectomy in premenopausal patients with advanced breast cancer". *J. Clin. Oncol.,* 1986, *4,* 1326.

[4] Cole M.P., Jones C.T.A., Todd I.D.H.: "A new antiestrogenic agent in late breast cancer: An early aproisal of ICI146,474". *Br. J. Cancer,* 1971, *25,* 270.

[5] American College of Obstetrician and Gynecologists: "Tamoxifen and endometrial cancer". ACOG Committee Opinion No 169. Washington, DC, American College of Obstetricians and Gynaecologists, 1996.

[6] Nolvadex Adjuvant Organization: "Controlled trial of tamoxifen as a single agent in the management of early breast cancer". *Br. J. Cancer,* 1988, *57,* 608.

[7] Fisher B., Constantino J.P., Redmond C.K., Fisher E.R., Widkerham D.L., Cronin W.M., and other NSABP contributors: "Endometrial cancer in tamoxifen-treated breast cancer patients: findings for the National Surgical Adjuvant Breast and Bowel Projects (NSABP) B-14". *J. Natl. Cancer Inst.,* 1994, *86,* 527.

[8] Love R.R.: "Tamoxifen prophylaxis in breast cancer". *Oncology* (Huntingt), 1992, *6,* 33.

[9] Barakat R., Wong G., Curtin J.P., Vlamis V., Hoskins W.J.: "Tamoxifen use in breast cancer patients who subsequent develop corpus cancer is not associated with a higher incidence of adverse histologic features". *Gynecol. Oncol.,* 1994, *55,* 164.

[10] Malfetano J.H.: "Tamoxifen-associated endometrial carcinoma in postmenopausal breast cancer patients". *Gynecol. Oncol.,* 1990, *39,* 82.

[11] Anderson E., Howell A.: "The molecular biology of endocrine responsiveness in breast cancer". In: "Molecular Biology for Oncologists". Yarnold J.R., Stratton M., McMillan T.J. (eds.), London, Chapman & Hall, 1996, 217.

[12] Varras M., Spandidos D.A.: "Molecular biology of gynaecological cancer". In: "Gynaecological Oncology" (in Greek). Pektasidis D., Demopoulos M.-A. (eds.). Athens: Medical Publications Paschalidis P., 2001, 68.

[13] Jordan V.C.: "Estrogen receptor-mediated direct and indirect antitumor effects of tamoxifen". *J. Natl. Cancer I.,* 1990, *82,* 1662.

[14] Varras M.N., Zachos G., Spandidos D.A.: "Endometrial carcinoma in a breast cancer patient treated with tamoxifen: Activation of K-ras proto-oncogene". *Oncol. Rep.,* 1997, *4,* 1045.

[15] Mourits J.E., De Vries G.E., Willemse P.H.B., Ten Hoor K.A., Hollema H., Van der Zee A.G.J.: "Tamoxifen treatment and gynecologic side effects: A review". *Obstet. Gynecol.,* 2001, *97,* 855.

[16] Ferrazzi E., Cartei G., Mattarazzo R., Fiorentino M.: "Estrogen-like action of tamoxifen on vaginal epithelium". *Br. Med. J.,* 1977, *1,* 1351.

[17] Boccardo F., Bruzzi P., Rubagotti A., Nicolo G., Rosso R.: "Estrogen-like action of tamoxifen on vaginal epithelium in breast cancer patients". *Oncology,* 1981, *30,* 281.

[18] Mortimer J.E., Boucher L., Baty J., Knapp D.L., Ryan E., Rowland J.: "Effect of tamoxifen on sexual functioning in patients with breast cancer". *J. Clin. Oncol.,* 1999, *17,* 1488.

[19] Ganz P.A., Coscarelli A., Fred C., Kahn B., Polinski M.L., Petersen L.: "Breast cancer survivors: Psychosocial concerns and quality of life". *Breast Cancer Res. Treat.,* 1996, *38,* 183.

[20] Mattson L.A., Cullberg G.: "Vaginal absorption of two estiol preparations. A comparative study in postmenopausal women". *Acta Obstet. Gynecol. Scand.,* 1983, *62,* 393.

[21] Bygdeman M., Swahn M.L.: "Replens versus dienoestrol cream in the symptomatic treatment of vaginal atrophy in postmenopausal women". *Maturitas,* 1996, *23,* 259.

[22] Gu M., Jacobsen J., Erroll M., Hoda S.A.: "Pap smears of patients on tamoxifen (lett.)". *Diag. Cytopathol.,* 1997, *16,* 96.

[23] Abadi M.A., Barakat R.R., Saigo P.E.: "Effects of tamoxifen on cervicovaginal smears from patients with breast cancer". *Acta Cytol.,* 2000, *44,* 141.

[24] Lahti E., Vuopala S., Kauppila A., Blanco G., Ruokonen A., Laatikainen T.: "Maturation of vaginal and endometrial epithelium in postmenopausal breast cancer patients receiving long-term tamoxifen". *Gynecol. Oncol.,* 1994, *55,* 410.

[25] Stern C.E., Tom P.M., Rios C.N.: "Cervicovaginal cytology in women treated with tamoxifen for breast carcinoma (abst.)". *Am. J. Clin. Pathol.,* 1998, *109,* 485.

[26] Coleman D.V., Evans D.M.D.: "Biopsy Pathology and Cytology of the Cervix". London: Chapman and Hall, 1988.

[27] Lahti E., Blanco G., Kauppila A., Apaja-Sarkkinen M., Taskinen P.J., Laatiakainen T.: "Endometrial changes in postmenopausal breast cancer patients receiving tamoxifen". *Obstet. Gynecol.,* 1993, *81,* 660.

[28] Corley D., Rowe J., Curtis M.T., Hogan W.M., Noumoff J.S., Livolsi V.A.: "Postmenopausal bleeding from unusual endometrial polyps in women on chronic tamoxifen therapy". *Obstet. Gynecol.,* 1992, *79,* 111.

[29] Ascher S.M., Imaoka I., Lage J.M.: "Tamoxifen-induced uterine abnormalities: the role of imaging". *Radiology,* 2000, *214,* 29.
[30] Buckley C.H., Fox H.: "Endometrial hyperplasia and inta-endometrial adenocarcinoma. In: Biopsy pathology of the endometrium". Buckley C.H., Fox H. (eds.). London: Chapman and Hall, 1989, 149.
[31] Kurman R.J., Norris H.J.: "Endometrial hyperplasia and related cellular changes". In: Kurman R.J., ed. Blaustein's pathology of the female genital tract. New York, Springer-Verlag, 1994, 411.
[32] Wilking N., Isaksson E., von Schoultz E.: "Tamoxifen and secondary tumors. An update". *Drug Safety,* 1997, *16,* 104.
[33] Gal D., Kopel S., Bashevkin M., Lebowicz J., Lev R., Tancer L.: "Oncogenic potential on endometria of postmenopausal women with breast cancer: preliminary report". *Gynecol. Oncol.,* 1991, *42,* 120.
[34] Cheng W.F., Lin H.H., Torng P.L., Huang S.C.: "Comparison of endometrial changes among symptomatic tamoxifen-treated and nontreated premenopausal and postmenopausal breast cancer patients". *Gynecol. Oncol.,* 1997, *66,* 233.
[35] Kedar R.P., Bourne T.H., Powles T.J., Collins W.P., Ashley S.E., Cosgrove D.O. *et al.*: "Effects of tamoxifen on uterus and ovaries of postmenopausal women in a randomized breast cancer prevention trial". *Lancet,* 1994, *343,* 1318.
[36] Cohen I., Rosen D.J.D., Altaras M.M., Beyth Y., Shapira J., Yigael D.: "Tamoxifen treatment in premenopausal breast cancer patients may be associated with ovarian overstimulation, cystic formations and fibroid overgrowth". *Br. J. Cancer,* 1994, *63,* 620.
[37] Barlière M., Carles A., Galant C., Donnez J.: "Uterine side effects of tamoxifen: a need for systematic pretreatment screening". *Obstet. Gynecol.,* 1998, *91,* 40.
[38] Karlsson B., Granberg S., Wikland M. *et al.*: "Transvaginal ultrasonography of the endometrium in women with postmenopausal bleeding: a Nordic multicenter study". *Am. J. Obstet. Gynecol.,* 1995, *172,* 1488.
[39] Ismail S.M.: "Pathology of endometrium treated with tamoxifen". *J. Clin. Pathol.,* 1994, *47,* 827.
[40] Ismail S.M.: "Gynaecologic effects of tamoxifen". *J. Clin. Pathol.,* 1999, *52,* 83.
[41] Cohen I., Rosen D.J.D., Shapira J. *et al.*: "Endometrial changes in postmenopausal women treated with tamoxifen for breast cancer". *Br. J. Obstet. Gynecol.,* 1993, *100,* 567.
[42] De Muylder X., Neven P., De Sorner M., Yan Bell Y., De Muylder V., De Muylder E.: "Endometrial lesions in patients undergoing tamoxifen therapy". *Int. J. Gynecol. Obstet.,* 1991, *36,* 127.
[43] Malfetano J.H.: "Tamoxifen-associated endometrial carcinoma in postmenopausal breast cancer patients". *Gynecol. Oncol.,* 1990, *39,* 82.
[44] Schlesinger C., Seiryu K., Ascher S.M., Kendell M., Lage J.M., Silverberg S.G.: "Endometrial polyps: a comparison study of patients receiving tamoxifen with two control groups". *Int. J. Gynecol. Pathol.,* 1998, *17,* 302.
[45] McGonigle K.F., Lantry S.A., Odommaryon T.L. *et al.*: "Histopathological effects of tamoxifen on the uterine epithelium of breast cancer patients-analysis by menopausal status". *Cancer Lett.,* 1996, *101,* 59.
[46] Nuovo M.A., Nuovo G.J., McCaffrey R.M. *et al.*: "Endometrial polyps in postmenopausal patients receiving tamoxifen". *Int. J. Gynecol. Pathol.,* 1989, *8,* 125.
[47] Ramondetta L.M., Sherwood J.B., Dunton C.J., Palazzo J.P.: "Endometrial cancer in polyps associated with tamoxifen use". *Am. J. Obstet. Gynecol.,* 1999, *180,* 340.
[48] Neven P., Vergote I.: "Should tamoxifen users be screened for endometrial lesions?". *Lancet,* 1998, *351,* 155.
[49] Beral V.: "Prevention of cancers of the female genital tract". In: "The Biology of Gynaecological Cancer". Leake R., Gore M., Ward R.H. (eds.). London: RCOG Press, 1995, 217.
[50] Adami H.-O., Krusemo U.B., Bergkvist L., Persson I., Pettersson B.: "On the age-dependent association between cancer of the breast and the endometrium. A nationwide cohort study". *Br. J. Cancer,* 1987, *55,* 77.
[51] Stears V., Gelmann E.P.: "Does tamoxifen cause cancer in humans?". *J. Clin. Oncol.,* 1998, *16,* 779.
[52] Killackey M.A., Hakes T.B., Pierce V.K.: "Endometrial adenocarcinoma in breast cancer patients receiving antiestrogens". *Cancer Treat. Rep.,* 1985, *69,* 237.
[53] Fornander T., Rutqvist L.E., Wilking N.: "Effects of tamoxifen on the female genital tract". *Ann. N. Y. Acad. Sci.,* 1991, *622,* 469.
[54] Rutqvist L.E., Johansson H., Signomklao T., Johansson U., Fornander T., Wilking N.: "Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group". *J. Natl. Cancer Inst.,* 1995, *87,* 645.
[55] Sasco A.J., Chaplain G., Amoros E., Saez S.: "Endometrial cancer following breast cancer: effect of tamoxifen and castration by radiotherapy". *Epidemilogy,* 1996, *7,* 9.
[56] Van Leeuwen F.E., Benraadt J., Coebergh J.W.W. *et al.*: "Risk of endometrial carcer after tamoxifen treatment of breast cancer". *Lancet,* 1994, *343,* 448.
[57] Early Breast Cancer Triallist's Collaborative Group: "Tamoxifen for early breast cancer: an overview of the randomized trials". *Lancet,* 1998, *351,* 1451.
[58] Edwood J.M., Boyes D.A.: "Clinical and pathological features and survival of endometrial cancer patients in relation to prior use of estrogens". *Gynecol. Oncol.,* 1980, *10,* 173.
[59] Magliples U., Naftolin F., Schartz P.E., Carcangiu M.L.: "High-grade endometrial carcinoma in tamoxifen-treated breast cancer patients". *J. Clin. Oncol.,* 1993, *11,* 485.
[60] Silva E.G., Tornos C.S., Follen-Mitchell M.: "Malignant neoplasms of the uterine corpus in patients treated for breast carcinoma: the effects of tamoxifen". *Int. J. Gynecol. Pathol.,* 1994, *13,* 248.
[61] Timmerman D., Deprest J., Vergote I.: "Tamoxifen-induced endometrial polyp". *New Engl. J. Med.,* 1997, *336,* 1389.
[62] American College of Obstetricians and Gynecologist. Committee on Gynecologic Practice: tamoxifen and endometrial cancer, no. 169. Washington, DC, American College of Obstetricians and Gynecologists, 1996, 1.
[63] Dilts P.V., Hopkins M.P., Chang A.E., Cody R.L.: "Rapid growth of leiomyoma in patient receiving tamoxifen". *Am. J. Obstet. Gynecol.,* 1992, *166,* 167.
[64] Ugwumadu A.H.N., Harding K.: "Uterine leiomyosarcoma and endometrial proliferation in postmenopausal women treated with the anti-oestrogen tamoxifen". *Eur. J. Obstet. Gynecol.,* 1994, *54,* 153.
[65] Kang J., Baxi L., Heller D.: "Tamoxifen induced growth of leiomyomas. A case report". *J. Reprod. Med.,* 1996, *41,* 119.
[66] Sabatini R., Fazio F.D.I., Loizzi P.: "Uterine leiomyosarcoma in a postmenopausal woman treated with tamoxifen: case report". *Eur. J. Gynecol. Oncol.,* 1999, *20,* 327.
[67] McCluggage W.G., McManus D.T., Lioe T.F., Hill C.M.: "Uterine carcinosarcoma in association with tamoxifen therapy". *Br. J. Obstet. Gynecol.,* 1997, *104,* 748.
[68] Cohen I., Perel E., Tepper R., Flex D., Figer A., Shapira J., Altaras M.M., Fishman Bernheim J., Cordoba M., Yigel D., Beyth Y.: "Dose-dependent effect of tamoxifen on endometrial pathologies in postmenopausal breast cancer patients". *Breast Cancer Res. Treat.,* 1998, 1.
[69] Cohen I., Beth Y., Tepper R. *et al.*: "Adenomyosis in postmenopausal breast cancer patients treated with tamoxifen: a new entity?". *Gynecol. Oncol.,* 1995, *58,* 86.
[70] Clement P.B., Scully R.E.: "Tumors with mixed epithelial and mesenchymal elements. In: "Tumors and Tumor-Like Lesions of the Uterine Corpus and Cervix. Clement P.B., Young R.H. (eds.), New York: Churchill Livingstone, 1993, 329.
[71] Zaloudek C., Nourris H.J.: "Mesenchymal tumors of the uterus". In: Kurman R.J. (ed.) Blaustein's Pathology of the Female Genital Tract, Berlin, Heidelberg, New York: Springer, 1994, 487.
[72] Pautier P., Genestie C., Rey A., Morice Ph., Roche B., Lhommé C., Haie-Meder Ch., Duvillard P.: "Analysis of clinicopathologic prognostic factors for 157 uterine sarcomas and evaluation of a grading score validated for soft tissue sarcoma". *Cancer,* 2000, *88,* 1425.
[73] Treilleux I., Mignotte H., Clement-Chassagne C., Guastalla P., Bailly C.: "Tamoxifen and malignant epithelial-nonepithelial tumours of the endometrium : report of six cases and review of the literature". *Eur. J. Surg. Oncol.,* 1999, *25,* 477.
[74] Barwick K.W., LiVolsi V.A.: "Heterologous mixed müllerian tumor confined to an endometrial polyp". *Obstet. Gynecol.,* 1997, *53,* 512.
[75] Clarke M.R.: "Uterine malignant mixed mullerian tumor in a patient on long-term tamoxifen therapy for breast cancer". *Gynecol. Oncol.,* 1993, *51,* 411.

[76] Bocklage T., Lee K, Belinson J.L.: "Uterine Mullerian adenosarcoma following adenomyoma in a woman on tamoxifen therapy". *Gynecol. Oncol.,* 1992, *44,* 104.
[77] Kerner H., Lichtig C.: "Müllerian adenocarcinoma presenting as cervical polyps: a report of a seven cases and review of the literature". *Obstet. Gynecol.,* 1993, *81,* 655.
[78] Zaloudek C.J., Norris H.J.: "Adenofibroma and adenosarcoma of the uterus". *Cancer,* 1981, *48,* 354.
[79] Ungwumadu A.H.N., Harding K.: "Uterine leiomyomata and endometrial proliferation in postmenopausal women treated with the anti-estrogens tamoxifen". *Eur. J. Obst. Gynecol. Reprod. Biol.*, 1994, *54,* 153.
[80] Kimyay Y., Cengiz C., Tolunay S.: "Endometrial polyps, cystic glandular hyperplasia and atypical leiomyoma associated with tamoxifen therapy". *Int. J. Gynecol. Obstet.,* 1994, *46,* 69.
[81] Tosi P., Sforza V., Santopietro R.: "Estrogen receptor content, immunohistochemically determined by monoclonal antibodies in endometrial stromal sarcoma". *Obstet. Gynecol.,* 1989, *73,* 75.
[82] Chang K.L., Crabtree G.S., Lim-Tan S.K., Kempson R.L., Hendrickson M.R.: "Primary uterine endometrial sromal neoplasms. A clinicopathologic study of 117 cases". *Am. J. Surg. Pathol.,* 1990, *14,* 415.
[83] Klein W., Maier T., Geyer H., Pfleiderer A.: "Estrogen and progesterone receptors in endometrial cancer and their prognostic relevance". *Gynecol. Oncol.,* 1990, *38,* 59.
[84] Sutton G.P., Stehman F.B., Michael H., Young P.C., Ehrlich C.E.: "Estrogen and progesterone receptors in uterine sarcomas". *Obstet. Gynecol.,* 1986, *68,* 709.
[85] Fotiou S., Hatjieleftheriou G., Kyrousis G., Kokka F., Apostolikas N.: "Long-term tamoxifen treatment: A possible aetiological factor in the development of uterine carcinosarcoma: Two case-reports and review of the literature". *Anticancer Res.,* 2000, *20,* 2015.
[86] Sreenan J.J., Hart W.R.: "Carcinosarcomas of the female genital tract". *Am. J. Surg. Pathol.,* 1995, *19,* 666.
[87] Chumas J.C., Mann W.J., Tseng L.: "Malignant mixed Mullerian tumor of the endometrium in a young woman with polycystic ovaries". *Cancer,* 1983, *52,* 1478.
[88] Press M.F., Scully R.E.: "Endometrial 'sarcomas' complicating ovarian thecoma polycystic ovarian disease and estrogen therapy". *Gynecol. Oncol.,* 1985, *21,* 135.
[89] Evans M.J., Langlois N.E.I., Kitchener H.C., Miller I.D.: "Is there an association between long-term tamoxifen treatment and the development of carcinosarcoma (malignant mixed Mullerian tumor) of the uterus?". *Int. J. Gynecol. Cancer,* 1995, *5,* 310.
[90] Altaras M.M., Aviram R., Cohen I. *et al.*: "Case report. Role of prolonged stimulation of tamoxifen therapy in the etiology of endometrial sarcomas". *Gynecol. Oncol.,* 1993, *49,* 255.
[91] McCluggage W.G., Abdulkader M., Price J.H., Kelehan P., Hamilton S., Beattie J., Al-Nafussi A.: "Uterine carcinosarcoma in patients receiving tamoxifen. A report of 19 cases". *Int. J. Gynecol. Cancer,* 2000, *10,* 280.
[92] Arici D.S., Aker H., Yildiz E., Tasyurt A.: "Mullerian adenosarcoma of the uterus associated with tamoxifen therapy". *Arch. Gynecol. Obstet.,* 2000, *264,* 105.
[93] Clement P.B., Oliva E., Young R.H.: "Mullerian adenosarcoma of the uterine corpus associated with tamoxifen therapy: a report of six cases and a review of tamoxifen-associated endometrial lesions". *Int. J. Gynecol. Pathol.,* 1996, *15,* 222.
[94] Czernobilsky B., Mercer B.L.: "Endometrial pathology". *Curr. Opin. Obstet. Gynecol.,* 1997, *9,* 52.
[95] Jagavkar R.S., Shakespeare T.P., Stevevs M.J.: "Endometrial adenosarcoma with adjuvant therapy for breast carcinoma". *Aust. Radiol.,* 1998, *42,* 157.
[96] Kennedy M.M., Baigre C.F., Manek S.: "Tamoxifen and the endometrium: review of 102 cases and comparison with HRT-related and non HRT related endometrial pathology". *Int. J. Gynecol. Pathol.,* 1999, *18,* 130.
[97] Ostör A.G., Rollason T.P.: "Mixed tumors of the uterus". In: Fox H. (ed.). Obstetrical and Gynaecological Pathology, New York: Churchill Livingstone, 1995, 587.
[98] Klopper A., Hall M.: "New synthetic agent for the induction of ovulation. Preliminary trial in women". *Br. J. Med.,* 1971, *2,* 152.
[99] Barbieri R.L., Ferracci A.L., Droesch J.N., Rochelson B.L.: "Ovarian torsion in a premenopausal woman treated for breast cancer". *Fertil. Steril.,* 1993, *59,* 459.
[100] Varras M., Stylianidou A., Akrivis Ch., Galanis P., Stefanaki S., Antoniou N.: "Extamedullary hematopoiesis in the uterine isthmus: A case report and review of the literature". *Eur. J. Gynecol. Oncol.,* 2002, *22,* 227.
[101] Bryant A.J.S., Weir J.A.: "Prophylactic oophorectomy in operable instances of carcinoma of the breast". *Surg. Gynecol. Obstet.,* 1981, *153,* 660.
[102] Nomura Y., Shirouzu M., Takayama T.: "Direct comparison of adjuvant endocrine therapy, chemotherapy and chemoendocrine therapy for operable breast cancer patients stratified by estrogen receptors and menopausal status". *Breast Cancer Res. Treat.,* 1998, *49,* 51.
[103] Hajjar L.R., Kim W., Nolan G.H., Turner S., Raju U.R.: "Intestinal and pelvic endometriosis presenting as a tumor and associated with tamoxifen therapy: Report of a case". *Obstet. Gynecol.,* 1993, *82* (suppl.), 642.

Address reprint requests to:
M. N. VARRAS, M.D., Ph.D.
Platonos 33
Politia (Kifisia)
14563 Athens (Greece)