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Special Paper

A Realistic Clinical Perspective of Tamoxifen and Endometrial Carcinogenesis

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Tamoxifen has been the endocrine treatment of choice for all stages of breast cancer for nearly a decade. Millions of women are currently receiving tamoxifen worldwide, while large-scale randomised trials have been launched aiming to investigate the drug's merit as a preventive agent. However, there are now concerns about tamoxifen's potential carcinogenicity. The goal of this review is to address these concerns, re-evaluate the available data from laboratory biological models and those from clinical reports and put the whole issue into perspective. Our focus is the association between tamoxifen and the increased frequency of endometrial tumours, while key issues, such as the role of duration of tamoxifen therapy, are also addressed. Finally, we discuss the various monitoring strategies for early detection of endometrial lesions and pertinent problems most likely to be encountered by clinicians taking care of patients who are receiving tamoxifen.

Key words: tamoxifen, endometrial cancer, breast cancer, anti-oestrogens, carcinogenicity
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INTRODUCTION

TAMOXIFEN IS the endocrine therapy of choice for women with breast cancer. The worldwide overview of adjuvant systemic therapy demonstrated tamoxifen's beneficial effects in increasing disease-free and overall survival in oestrogen receptor (ER) positive patients and provided indirect evidence that long-term (>2 years) is better than short-term (≤2 years) therapy [1].

Tamoxifen is a non-steroidal anti-oestrogen that blocks the growth promoting effects of oestrogens in breast tissue, mainly through competitive inhibition of the ER mechanism [2]. This action interrupts a number of autocrine and paracrine growth factor pathways that are critically involved in cell proliferation (reviewed in [3]). Although tamoxifen is clearly an inhibitor of breast cancer growth, its effects throughout the human body vary and could be best characterised as mixed oestrogenic and anti-oestrogenic properties. It is the oestrogenic properties that account for preservation of bone mineral density in postmenopausal women [4, 5], decrease of low-density lipoprotein (LDL) cholesterol [6], increase of sex-hormone binding globulin (SHBG) [7] and reduction of fatal myocardial infarctions [8].

All the oestrogenic effects of tamoxifen are desirable and could lead to lower morbidity and mortality following the menopause. However, an unopposed fully oestrogenic stimulus could have serious consequences in the uterus. Therefore, it must be asked: what is the evidence that tamoxifen is an oestrogen in the uterus? Long-term tamoxifen treatment results in a variety of asymptomatic benign endometrial changes [9] and women using this drug have an increased detection of endometrial cancer [10]. The increasing number of reports about the gynaecological effects of tamoxifen has produced some concern in the clinical community [11, 12], especially in view of the ongoing trials that are testing the worth of tamoxifen as a preventive agent for breast cancer [13–15].

The opponents of tamoxifen therapy have focused their criticisms on the reported association between tamoxifen treatment and an increased incidence of endometrial cancer. Indeed, since Killackey's first report of three cases of endometrial cancer in tamoxifen-treated breast cancer patients [16], numerous similar cases have appeared in the literature. Recently, we surveyed the world literature and found a total of 250 endometrial carcinomas in breast cancer patients with

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history of tamoxifen exposure [17]. However, these cases must be placed in perspective—there are 7 million woman years of experience with tamoxifen. The current process of data collection to examine an association with endometrial cancer must be evaluated, based on what is known about the association between endometrial cancer and breast cancer. A number of issues need to be addressed to form a clear opinion about the risks to the patient taking tamoxifen. The first is the basis for the concern and the validity of the clinical database. Typically, there are only a few cases of endometrial cancer in each report, most of which are either case-reports or come from small uncontrolled trials. Patients have often taken tamoxifen for a variable duration and at different doses. The authors evaluate their database at different times so a comparison between studies is often difficult. Although the case-reports are insufficient to form a conclusion about a cause-and-effect relationship about tamoxifen and endometrial cancer, a small percentage of cases come from double-blind randomised trials and we will discuss the findings of these trials in detail.

It is the goal of our review to re-examine the association between tamoxifen and endometrial cancer and formulate a strategy for patient monitoring based on our evaluation of the risk–benefit ratios. First, we will consider the issue of tamoxifen-induced carcinogenesis in the laboratory and then address the association between tamoxifen and endometrial cancer.

TAMOXIFEN AND CARCINOGENESIS

Carcinogenesis is a multistage process that involves initiation (genotoxicity), promotion (epigenetic effects) and proliferation of a tumour. In the case of tamoxifen, the target tissues of interest are the liver and the uterus. Conventional methods (Ames assay and the human lymphocyte chromosome test) used to screen chemicals for potential carcinogenicity have proved negative for tamoxifen [18]. However, 10 years ago, Yager and associates were the first to provide evidence that tamoxifen might be carcinogenic in rats by demonstrating that it promoted the formation of liver lesions that were initiated by known liver carcinogens [19]. During the past 4 years, several groups have reported the initiation and promotion of liver tumours in various strains of rats by the oral administration of large doses of tamoxifen [20–27]. Tamoxifen's carcinogenicity in this model is clearly dose-related and there seems to be a threshold level of approximately 3 mg/kg/day [21]. Interestingly, the various strains of rats demonstrate different levels of susceptibility to tamoxifen's carcinogenic activities [23]. The reason for this is a differential activation of tamoxifen and its metabolites to form DNA adducts in rat liver [24–26]. In contrast, female mice [24] and female hamsters [28] appear to be less susceptible to DNA adduct formation upon tamoxifen administration. The metabolism of tamoxifen in the mouse is different from that in the rat [29], and it is important to point out that tamoxifen does not produce liver tumours in mice [30]. In humans, DNA adducts have been reported *in vitro* in cell lines [24, 31] and in liver microsomal preparation systems [32], but this may not be relevant to the clinical use of tamoxifen. Although much clinical work needs to be done, the first report of *in vivo* DNA adduct formation in tamoxifen-treated women showed no difference when compared to women not treated with tamoxifen [33].

The laboratory findings would be of concern if tamoxifen was a new drug, and the tests will certainly be relevant for the evaluation of new anti-oestrogens. In the case of tamoxifen, however, the clinical experience can be used to evaluate the extent of liver carcinogenesis. The question must be asked: are the toxicology studies in rats relevant to clinical usage? Liver tumorigenicity in the laboratory is dependent on dose, duration of treatment and species [34]. Most importantly, the daily doses of tamoxifen used in the rat experiments (5–35 mg/kg/day) are 15–120 times the dose (285 μg/kg/day) administered to humans (based on a daily administration of 20 mg to a 70 kg postmenopausal woman). Another major point is that administration of tamoxifen starts at 6 weeks of age (postpuberty) in the rat and continues for the rest of the animal's life [34]. Although testing a drug's carcinogenicity employs administration of toxic doses, this pattern bears no resemblance to the dosing schedule for women who usually receive tamoxifen for up to 5 years, around 6–8% of a woman's lifetime. Drug administration is usually after the age of 50. The animal dosage regimen is equivalent to a 14 year old woman taking 40 tablets (20 times the recommended dose) daily until the age of 40.

The incidence of hepatocellular carcinoma is extremely low in the West [35], so any dramatic increase in incidence would be observed with ease. To date, the Stockholm trial has reported two cases of hepatocellular carcinoma in tamoxifen-treated women [36] and the most recent update of the trial showed no significant difference in the incidence of liver cancer between tamoxifen-treated patients and controls [37]. Similarly, an epidemiological study showed no increase in the incidence of hepatocellular carcinoma in the U.S. since tamoxifen was introduced in 1977 [38]. By contrast, oral contraceptives cause a 10-fold increase in the risk of hepatocellular carcinoma [39].

Surprisingly, rat liver carcinogenesis with tamoxifen has been linked with the increased incidence of endometrial tumours detected in patients receiving tamoxifen. This is despite the fact that no adducts have been reported from human uterine samples [40] and animal model systems have not described the induction of endometrial cancer by tamoxifen. The only laboratory evidence for an association between tamoxifen and endometrial cancer risk is the increase in the growth rate of transplanted human endometrial cancer that occurs in athymic animals treated with tamoxifen [41, 42]. There is one report of *de novo* development of an endometrial cancer in a woman who was prospectively followed up while on tamoxifen therapy [43]. Hysteroscopy and endometrial biopsy initially showed no detectable uterine lesions, but after 36 months of tamoxifen treatment, a G3 endometrial cancer was diagnosed. Although the case is of interest, undetectable malignant cells could have been present at the time of baseline assessment.

In contrast to the issue of tamoxifen and the cause of endometrial cancer, a case can be made for the development of uterine polyps during tamoxifen treatment. Endometrial polyps constitute a rather uncommon pathology that has been linked to an increased incidence of endometrial cancer. A number of reports [9, 44–46] have shown an unusually high prevalence of these lesions in tamoxifen-treated women, while in some cases, neoplastic growth seems to occur within the polyps. A possible explanation would be that tamoxifen favours the development of malignancy within the polyp. The fact that such polyp cancers arise on a background of endometrial glandulocystic atrophy suggests a different mechanism than

the one encountered with conventional oestrogens. It could be that endometrial polypogenesis forms an essential, intermediate stage between simple hyperplasia and carcinoma [44]. Nevertheless, the factors regulating an individual's susceptibility to localised endometrial changes are poorly understood. Tamoxifen is clearly not the only important factor involved, as the majority of women on tamoxifen have an atrophic endometrium. Perhaps there is a genetic predisposition towards endometrial polyps or similar lesions.

With this in mind, we will briefly consider the problems of retrospective data analysis in uncontrolled studies that were not designed to answer the question of an association between tamoxifen and the detection of endometrial cancer.

CONFOUNDING VARIABLES IN CLINICAL TRIALS

Undoubtedly double-blind randomised trials constitute the most reliable way to prospectively determine whether a causal relationship between tamoxifen and endometrial cancer exists. A number of biases may still be present and thus limit the validity of the results. It is not uncommon for trials to include choice of proof bias, resulting from lack of randomisation with respect to other known risk factors for endometrial cancer such as history of oestrogen replacement therapy (ERT), obesity, diabetes mellitus, early menarche and late menopause. Tamoxifen-treated patients are more likely to present with uterine bleeding which will lead to further diagnostic evaluations (active detection bias). With all the publicity regarding the gynaecological complications seen with tamoxifen exposure, treated patients are more likely to be examined by a gynaecologist (selection bias) and thus lead to an early diagnosis of occult endometrial disease. It is known that women harbour undetected endometrial cancer. A 5-fold greater number of 'silent' endometrial cancers were discovered in a series of 50,000 autopsies when these results were compared to the reported rate for the same geographical area during the same time period [47].

Case–control studies from tumour registries have documented that breast cancer patients have an increased relative risk (RR) for endometrial cancer. This was shown to be 1.4 in the Connecticut Tumour Registry [48], 1.33 in the Finnish Tumour Registry [49] and 1.72 in Sweden [50]. In the latter case, the RR was shown to be age-dependent and rose to 2.4 for a woman over the age of 70. A prospective trial with hundreds of breast cancer patients revealed a 6-fold increase of secondary endometrial tumours [51].

Clearly, age differences in populations being examined is a confounding variable. Elderly women have a higher propensity of high-grade, advanced-stage endometrial cancer [52]. It would, therefore, seem prudent to evaluate clinical reports very carefully before formulating a precise conclusion about the extent and grade of endometrial malignancies associated with tamoxifen.

CLINICAL TRIALS

Although most of the reported endometrial cancer cases come from case-reports or retrospective case–control studies, some double-blind randomised trials have documented an increased frequency of endometrial carcinoma in tamoxifen-treated patients. Some of these trials were designed in a way to address the issue of secondary malignancies prospectively, but they all suffer from the biases mentioned in the previous section.

The first report of a higher frequency of endometrial cancer in patients receiving tamoxifen came from Sweden. In the Stockholm trial, 1846 postmenopausal breast cancer patients were randomised to receive postoperatively either 40 mg/day of tamoxifen for 2 years or placebo [36]. Treated patients who were disease-free at the 2-year end point were re-randomised to receive an additional 3 years of tamoxifen or placebo. Although tamoxifen conferred a substantial benefit in controlling contralateral breast cancer, there was an increase in the detection of endometrial malignancies which was reported to be proportional to the duration of therapy. The authors concluded that "... the cumulative frequency of endometrial cancers was significantly greater in patients who continued on tamoxifen (for a total of 5 years) than in those who stopped their treatment at 2 years...". They presented these findings in graphical form (Figure 1), where there is a clear difference between the curve representing patients randomised to 5 years of tamoxifen and the curve representing 2 years of therapy. The patients randomised to 2 years of tamoxifen had a cumulative frequency of endometrial cancer no different than controls. However, no details about the individual patient characteristics were presented. In 1993, the Stockholm trial group published an update of their findings [53]. Seventeen endometrial cancers were diagnosed in the tamoxifen-treated group and five in the control group. Interestingly, if these data are plotted as the duration of tamoxifen versus the detection of endometrial cancer, then the majority (13/17) of patients only received 2 years of tamoxifen or less (Figure 2). In the most recent update of the Stockholm trial, a total of 23 endometrial cancers were reported for the tamoxifen-treated group and 4 cases for the control group [37]. It is mentioned that one of these 23 patients was assigned to the treatment group but refused to take the medication so the actual RR would be 4.4 for tamoxifen users versus never users. When depicted graphically, the cumulative incidence of endometrial cancer in tamoxifen-treated patients produced a curve that rises rapidly after 12 years of follow-up. Based on these findings, the authors concluded that the endometrial malignancies "several years after cessation of treatment may suggest that tamoxifen also initiated some of the observed endometrial malignancies" [37]. The graph was unfortunately not accompanied by spec-

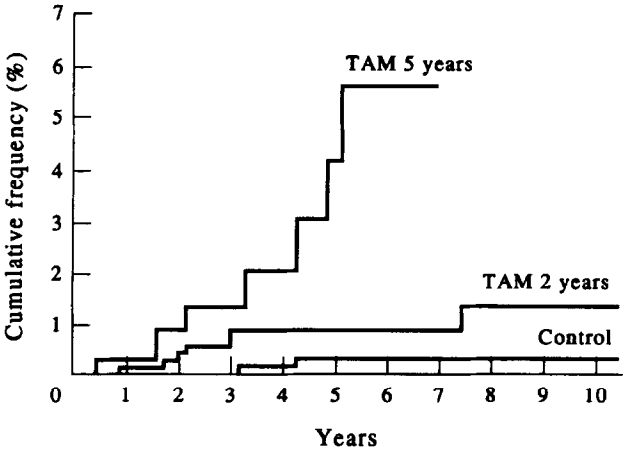

Figure 1. Cumulative frequency of uterine cancer by allocated treatment in the Stockholm trial. TAM, tamoxifen. Reproduced by permission from Fornander T, Rutqvist LE, Cedermark B, *et al.*, Adjuvant tamoxifen in early breast cancer: occurrence of new primary cancers. *Lancet* 1989, 1, 117–120.

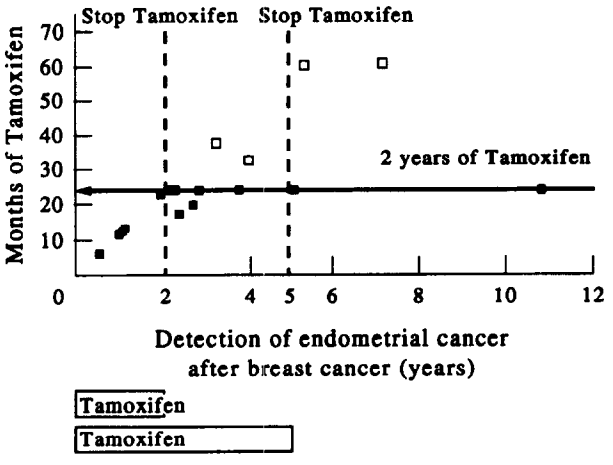

Figure 2. The occurrence of endometrial cancer in the Stockholm trial [53]. Patients were treated with tamoxifen for up to 2 years and then randomised to either an additional 3 years of tamoxifen or placebo.

ific data concerning the actual number of patients included in each treatment group that would be consistent with their previous publications [36]. In the initial report [36], there were only 38 women in the tamoxifen-treated group at 10 years follow-up; it would be fair to assume that patient deaths did occur so that the current update at 15 years follow-up may include far less than 30 women [37]. Conclusions based on this unstable area of an incidence curve are notoriously unreliable. Clearly, additional secure data are necessary to provide proof for any causal link between tamoxifen and endometrial cancer. Furthermore, there is the possibility of a detection bias with women being screened and stopping tamoxifen at the 2-year point because of changes in endometrial histology. All of the publicity surrounding this controversy has naturally created great caution in pathologists. The unique histology for patients treated with tamoxifen might cause alarm and a bias in diagnosing malignancy.

Perhaps, the best designed study to investigate the association of endometrial cancer and tamoxifen is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 trial [54]. In this study, 2843 oestrogen receptor positive, node negative breast cancer patients were randomised to either 20 mg of tamoxifen for 5 years or placebo. Tamoxifen-treated women that were disease-free at the 5-year endpoint were re-randomised to another 5 years of tamoxifen. The average follow-up period was 8 years. In addition, a group of 1220 women were registered to receive tamoxifen for 5 years, after which, disease-free patients were randomised for an additional 5 years of tamoxifen or placebo. 15 patients in the first group and 8 in the second developed endometrial cancer. One of the patients in the randomised tamoxifen group refused to take tamoxifen, while 2 placebo patients were on tamoxifen when the endometrial tumours were diagnosed. Most of these tumours were well-differentiated (17/22) and confined to the uterus (20/23). With regard to the Stockholm trial conclusion that long-term tamoxifen leads to more endometrial cancers, the data from the NSABP trial do not seem to support this notion. Of the 24 endometrial cancer cases diagnosed in this study, 5 had received 1 year or less of tamoxifen therapy, 6 had received between 1 and 3 years, 9 patients were treated for 3–5 years and finally 4 patients were treated for longer than 5 years. These data show a rather constant rate of endometrial cancer over time on the drug.

The overall annual hazard rate of endometrial cancer in the NSABP trial was 1.2/1000 for the tamoxifen group and the cumulative frequency at 5 years follow-up was 6.3/1000 leading to RR 7.5 (95% confidence interval (CI) 1.7–32.7). This relative risk appears alarming but, as the authors point out, the incidence of endometrial cancer in the placebo group was unusually low. Based on the SEER* data, the RR would be 2.2 instead of 7.5 [54]. A similar RR (2.3) would also result if the authors employed the endometrial cancer incidence reported for the placebo group in the NSABP B-06 trial [54].

In addition to concerns with long-term tamoxifen therapy, there are also concerns about very short-term tamoxifen treatment. We have recently addressed the issue in the literature [55]. A Danish study that compared postoperative radiotherapy (RT) treatment versus RT plus 30 mg tamoxifen (TMX) daily for 48 weeks reported a standardised incidence ratio for endometrial cancer of 1.9 (95% CI 0.8–3.9) for tamoxifen-treated patients [56] and a cumulative incidence of 1.00% versus 0.30% for the RT alone group ($P < 0.11$) after a follow-up of 10 years [57]. No decrease in the incidence of contralateral breast cancer was reported, probably because the duration of tamoxifen therapy (48 weeks) was much too short to be effective. The authors presented their findings graphically (Figure 3) in their initial report [56], where RT+TMX patients had an apparently increased incidence of endometrial cancer when compared to RT alone. Interestingly, in their follow-up publication [57], they also included in their graph the findings from a third group of patients (low-risk) that received no postoperative treatment. It is apparent from Figure 4 that the incidence of endometrial cancer in the non-treated low-risk group is very close to that of the RT+TMX group. Indeed, if one compares the incidence in the RT+TMX group (8.1/1000) to the non-treated control group (6/1000) the RR = 1.35. Although these data are stat-

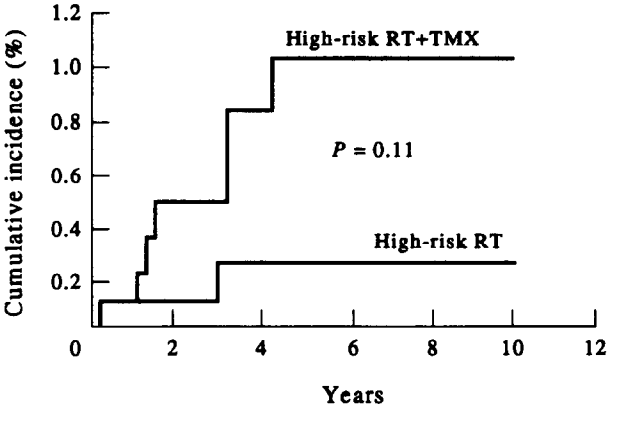

Figure 3. Cumulative incidence of adenocarcinoma of the uterine corpus among breast cancer patients at high risk of recurrence, treated adjuvantly with postoperative radiotherapy (high-risk RT) or radiotherapy and tamoxifen (high-risk RT+TMX) [56].

*SEER is an acronym for the Surveillance, Epidemiology and End Results programme. SEER is a set of geographically defined, population-based central tumour registries in the United States, operated by local non-profit organisations under contract to the National Cancer Institute (NCI). Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

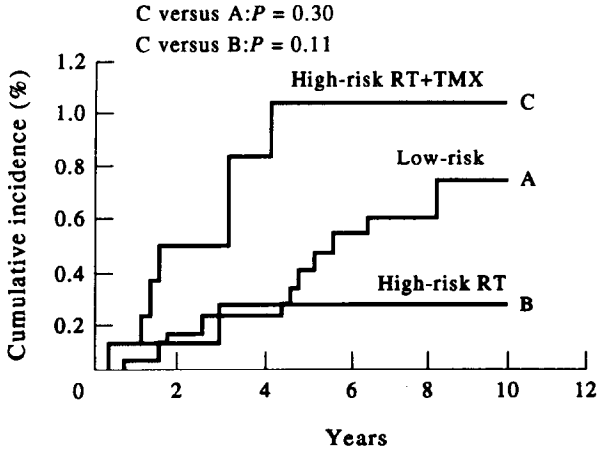

Figure 4. Cumulative frequency of endometrial cancer subsequent to breast cancer. A, low-risk group; B, high-risk RT group; C, high-risk RT+TMX group. Reproduced by permission from the Scandinavian University Press from Andersson M, Storm HH, Mouridsen HT. Carcinogenic effect of adjuvant tamoxifen treatment and radiotherapy for breast cancer. *Acta Oncologica* 1992, 31, 2, 259–263.

istically not significant and contain very few events the report created concern and uncertainty for the clinicians and patients.

Up to now, we have discussed clinical trials that have provided an association between tamoxifen therapy and endometrial cancer occurrence. There are, however, trials that have showed no increase in the frequency of endometrial malignancies when patients were treated with tamoxifen. The Scottish trial that administered 20 mg of tamoxifen daily, for 5 years or until relapse, reported no difference in the frequency of endometrial tumours [58]. The Christie Hospital trial in which patients were randomised to receive 20 mg daily for 1 year detected one tumour in each group after a follow-up period of 13 years [59]. We have collated the data from all major clinical trials concerning the incidence of endometrial carcinoma in tamoxifen-treated women (Table 1). In our analysis, we have excluded pathologies other than endometrial carcinoma, such as sarcomas and mixed Müllerian tumours. The overall conclusion of clinical trials is that there is a 2-fold increase in endometrial carcinoma risk in tamoxifen-treated patients (0.79% versus 0.37%).

Another research method to investigate the association between tamoxifen and the endometrium is to search retrospectively for the prevalence of endometrial tumours in patients with a history of tamoxifen exposure.

Table 1. Reports of endometrial carcinomas (EC) in major clinical randomised trials. Histological types other than carcinomas have been excluded

Study	[Ref.]		Tamoxifen treated Total	Tamoxifen treated EC	Controls Total	Controls EC
Toronto	[72]		198	0	202	1
NATO	[73]		564	0	567	0
Danish	[56, 57]		864	7	1828	11
Scottish	[58]		661	1	651	3
Christie	[59]		282	1	306	1
ECOG-1178	[74]		85	1	83	1
Stockholm	[36, 37, 53]		1372	21	1357	5
NSABP B-14	[54]	Randomised	1419	15	1424	2
		Registered	1220	7		
			6665	53	6418	24
				0.79%		0.37%

CASE–CONTROL STUDIES

In 1993, Magriples and colleagues [60] reported the results of a survey of the Yale/New Haven Tumor Registry for the decade 1980–1990. They found 53 cases with a history of breast cancer who subsequently developed endometrial cancer. 15 of these patients had taken 40 mg tamoxifen daily for an average duration of 4.2 years. The authors reported that 67% of the tamoxifen-treated patients had poorly differentiated endometrial tumours. In addition, 33% of these patients reportedly died of endometrial cancer. Typically, endometrial tumours in patients with a history of oestrogen exposure are of low stage and grade and since the growth promoting effects of tamoxifen are attributed to its oestrogenic properties it is thought that they should behave accordingly. These findings contradicted this widely held belief and raised additional concerns in respect to tamoxifen's evaluation as a preventive agent. A closer look at the Yale study however, reveals a number of interesting points. First, five out of the 15 tumours occurred in patients who had received tamoxifen for 1 year or less and 3 out of the 5 deaths were in this subgroup. In these cases, the interval between initiating tamoxifen therapy and the diagnosis of an endometrial tumour was too short to ascribe causal properties to tamoxifen; it would rather seem more probable that a pre-existing undiagnosed endometrial tumour was further stimulated to produce symptoms. A second point of interest is the grading system used in this report. In their classification, high grade tumours include grade 3 endometrioid carcinomas in addition to all papillary-serous, clear-cell carcinomas and mixed Müllerian tumours, regardless of grade. This contrasts with the standard grading classification that is based on the histological grade and not the histological type. In Table 2 we compare the Yale findings with those of our review as well as the SEER data [61]. Clearly, the preponderance of poor grade tumours of the Yale study is not the general rule of clinical experience. In Figure 5, the cumulative number of endometrial carcinomas classified by grade is shown.

A case–control study from The Netherlands searched through the population-based Netherlands Cancer Registry

Table 2. Stage and grade for endometrial carcinomas in tamoxifen-treated patients in the Yale report [60] are compared with our review of all published data up to the end of 1995 and the SEER data [61]. Uterine tumours other than carcinomas have been excluded

	Yale		Review		SEER
Stage					
I	7/9	78%	184/234	79%	74%
II–IV	2/9	22%	50/234	21%	26%
Grade					
Good (grade 1,2)	5/13	38%	185/225	82%	79%
Poor (grade 3)	8/13	62%	40/225	18%	21%

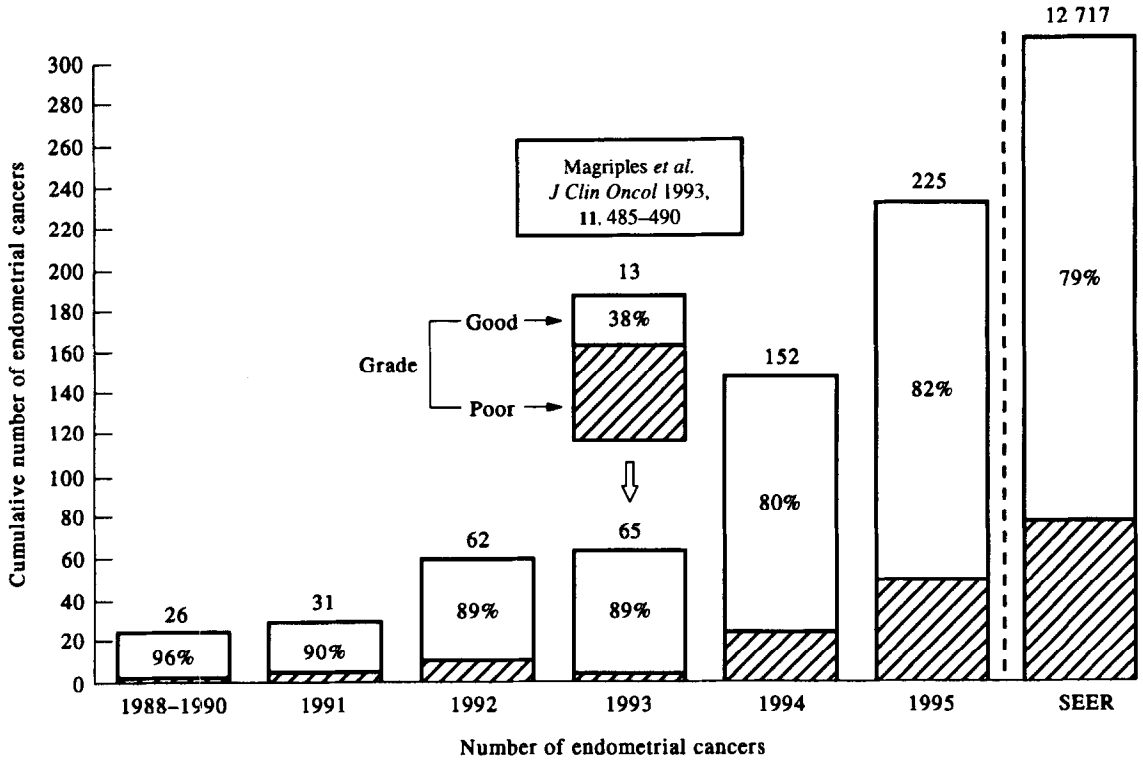

Figure 5. The cumulative number of endometrial carcinomas is depicted with regard to grade: good (grade 1, 2) (open bars) or poor (grade 3) (hatched bars). Data regarding the grade were available for 225 out of 349 cases (excluding the Yale study data [60]). In contrast to the Yale data, our review demonstrates that the majority of endometrial carcinomas were of good grade, similar to the SEER data [61]. Histological types other than carcinomas were not included.

and identified 98 patients with an initial diagnosis of breast cancer and a subsequent endometrial cancer and matched them with 285 controls [62]. The authors estimated the risk of developing an endometrial malignancy to be 1.3 for tamoxifen users versus non-users. More interestingly, they noticed a significant ($P < 0.049$) trend of increasing risk with duration of tamoxifen use. The RR was 2.3 if tamoxifen was taken for more than 2 years and rose to 3.0 for a duration of 5 years or more. Although the cases in this study were matched with controls in respect to age, year of breast cancer diagnosis and survival with intact uterus, they were not matched for other major risk factors especially oestrogen replacement therapy (ERT). A second point of controversy is the fact that the eligibility criterion called for a minimum of 3 months interval between the two cancer diagnoses. However, this interval might be too short to correlate tamoxifen with stimulation of the endometrium.

A study similar to the one performed in Yale/New Haven was undertaken in Memorial Sloan-Kettering Hospital in New York [63]. The authors identified 77 breast cancer patients who were later diagnosed with a uterine corpus malignancy. 27 of them had received 20 mg of tamoxifen daily as part of their therapy for an average follow-up of 4.5 years. A comparison between treated and non-treated women, revealed no difference in the distribution of stage, grade or adverse histological types.

More recently, Cook and coworkers [64] reported their findings from a nested case–control study involving the cancer registry of western Washington. Of 12598 breast cancer patient records, 42 had a secondary diagnosis of endometrial cancer. After matching cases with control subjects, they identified a total of only 9 cases that also had a history of tamoxifen therapy. The RR for endometrial cancer in tamoxifen-treated women was estimated to be 0.6 (95% CI 0.2–1.9). In addition, a non-significant trend of decreasing risk over larger cumulative dose (>7.5 g) of tamoxifen was reported. These findings are provocative as they contrast with the study from The Netherlands [62], but the power of the U.S. study is limited by the very low number of cases. The detection of endometrial cancer in patients receiving tamoxifen is a very rare occurrence.

In contrast, a case–control study concerning 1017 breast cancer patients treated at Wilford Hall Medical Center identified 108 women who had received tamoxifen [65]. The odds ratio for developing endometrial cancer was calculated to be 15.2 (95% CI 2.8–84.4) for tamoxifen users. However, the authors point out that the patients who received tamoxifen were more likely to have had risk factors associated with endometrial cancer such as hypertension and diabetes mellitus.

Overall, we have illustrated that the clinical trial data and the epidemiology data have gone some way in pointing to an association but not a causal relationship between tamoxifen and endometrial cancer. The issue is still an important research question for tamoxifen and any new anti-oestrogen being used as an adjuvant therapy or which may be used as a preventive agent. As a result of the clinical uncertainty, we will describe the overall database and we will consider the clinical consequences of these data for patient evaluation.

THE EXTENT OF THE ASSOCIATION BETWEEN TAMOXIFEN AND ENDOMETRIAL CANCER

We have updated our review of the world's literature up to the end of 1995 and now found a total of 349 endometrial

Table 3. Endometrial carcinomas, mixed Müllerian tumours (MMT) and sarcomas observed during tamoxifen treatment for breast cancer as reported in the literature from 1984 to 1995

Endometrial carcinomas	349
Mixed Müllerian tumours	18
Sarcomas	9
Patients	
Postmenopausal	200
Premenopausal	2
Duration of tamoxifen therapy	
≤2 years	91
>2 years	108

carcinomas (Table 3). The vast majority of the cases involve postmenopausal women who were given variable doses of tamoxifen for different periods of time. Although specific data with regard to dose or duration of therapy are not available for all cases, we have calculated the average mean duration of tamoxifen therapy to be 40.7 months. The prevailing dose was 20 mg of tamoxifen daily and there is no obvious relationship between high-dose tamoxifen treatment and endometrial cancer. In addition, a number of non-carcinomatous uterine tumours such as mixed Müllerian tumours (MMT) and sarcomas have been reported to occur during tamoxifen therapy and we have chosen to list them separately in the table. The annual number of endometrial carcinomas in tamoxifen-treated patients, as they are presented in the literature, is illustrated in Figure 6. We have specifically pointed out key publications that prompted clinicians to investigate endometrial-related effects in tamoxifen-treated women.

FURTHER UNANSWERED QUESTIONS

The process of unravelling the complex issue of cause of carcinogenesis in humans requires multiple studies from differing points of view. We have illustrated in our arguments how the scientific literature is inconsistent and retrospective data collection can be unintentionally misleading. In the case of an association between tamoxifen and endometrial cancer, it is difficult to be certain about the answer because biases naturally slip into the clinical database once an issue becomes a public concern. In the case of tamoxifen, the concern has occurred for more than half a decade and it is obvious that women with symptoms from tamoxifen have been screened more frequently than those not taking tamoxifen. This is good medical practice but it may become bad epidemiology. Simple analytical tools that are used to determine a carcinogenic risk from an industrial source, for example, cannot be used in the case of endometrial cancer. Excessive selective screening can alter the result of an already present occult disease.

There is no doubt that large doses of tamoxifen cause liver tumours in selected inbred strains of rats. It is fair to say that society must develop protective measures to prevent novel drugs from causing harm during the treatment of human disease. However, the view that these tests are equivalent to "canaries to protect miners from gas" may be too simplistic. The human is genetically robust compared to the rat that is inbred for susceptibility to toxic hazards. In the case of tamoxifen, if the same animal tests had been reported in 1973, this would have inadvertently caused the premature death of tens of thousands of women with breast cancer. The tests of today would have prevented the development of tamoxifen in the early 1970s and a whole treatment modality would have been denied to the physician [66]. Clearly, government agencies need to take a close look at the appropriateness of animal test results in a retrospective public debate about successful treatment modalities.

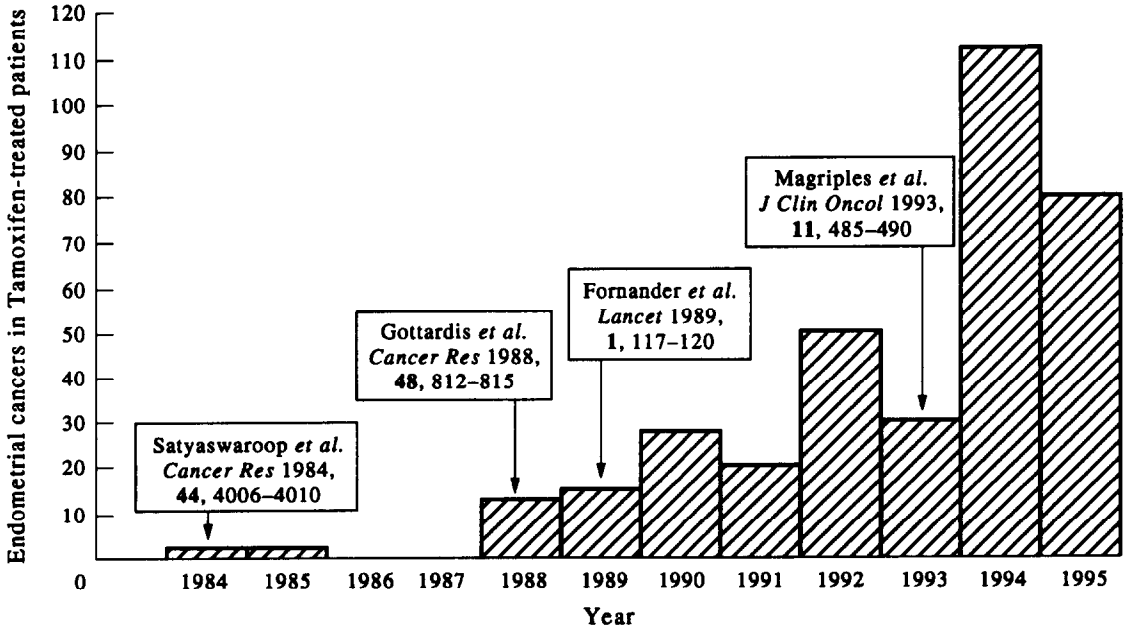

Figure 6. The annual number of endometrial carcinomas in tamoxifen-treated breast cancer patients reported in the literature for the time period 1984–1995. Key publications that attracted clinicians' attention are highlighted. Satyaswaroop and associates [41] and Gottardis and associates [42] provided the first biological model of tamoxifen-stimulated endometrial growth that prompted clinical trials to address the issue.

Although a modest increase in the detection of endometrial cancer in patients exposed to tamoxifen occurs, several questions remain to be answered: (1) If the scientific research community requires the production of DNA adducts for a causal relationship in uterine carcinogenesis [33, 40], further study in the human is clearly required. Preliminary studies have proved to be negative [33], but certain women with the correct local P_{450} profile for metabolic activation of tamoxifen to a carcinogen may be susceptible to endometrial cancer. Perhaps these women could be identified. (2) The original animal studies with implanted human endometrial carcinomas demonstrated that tamoxifen could support the growth of pre-existing disease [41, 42]. These results do not support a causation model. However, tamoxifen appears to produce an atrophic effect on epithelial cells in the majority of women. How does tamoxifen act as an anti-oestrogen in the majority and as an apparent oestrogen in the minority? One explanation could be that oestrogen initiates the promotional process for the initiated cells long before tamoxifen is taken, but that tamoxifen can provoke the clonal selection of quiescent malignant cells many years later. (3) Although the hypothesis described in (2) could be a laboratory project, epidemiology could answer the question partly by considering whether women who are diagnosed with endometrial cancer in their early 60s during tamoxifen therapy took oestrogen replacement therapy (ERT) in their 50s. Alternatively, as a prospective research experiment, postmenopausal breast cancer patients, who are naturally more oestrogenic than others, could be evaluated for their long-term uterine responsiveness to tamoxifen.

Each of these research topics is valuable to further describe the actions of tamoxifen in the uterus. Additionally, it would be wise to require a systematic evaluation of any new anti-oestrogen with regard to uterine effects during long-term therapy. Nevertheless, the problem we have described is modest compared to the concern expressed by the patient.

Tamoxifen treatment is of established benefit to patients with breast cancer and it is now clear that the stage or grade of endometrial cancer associated with tamoxifen treatment is not unusual. Neverthless, physicians and patients must be aware that tamoxifen may lead to endometrial polyps and a low (2–3-fold) increase in endometrial cancer incidence. Although screening procedures have not been initiated for the general population because of the low incidence of the disease, there are suggestions that tamoxifen-treated patients warrant close scrutiny. There is general agreement that patients with abnormal vaginal bleeding should undergo prompt assessment with invasive diagnostic procedures. Hysteroscopy and dilatation and curettage (D&C) seem to confer the most reliable results.

In view of these guidelines, we will describe the current status of the effects of tamoxifen in the uterus to highlight the difficulties to be encountered with patient compliance and cost-effectiveness issues.

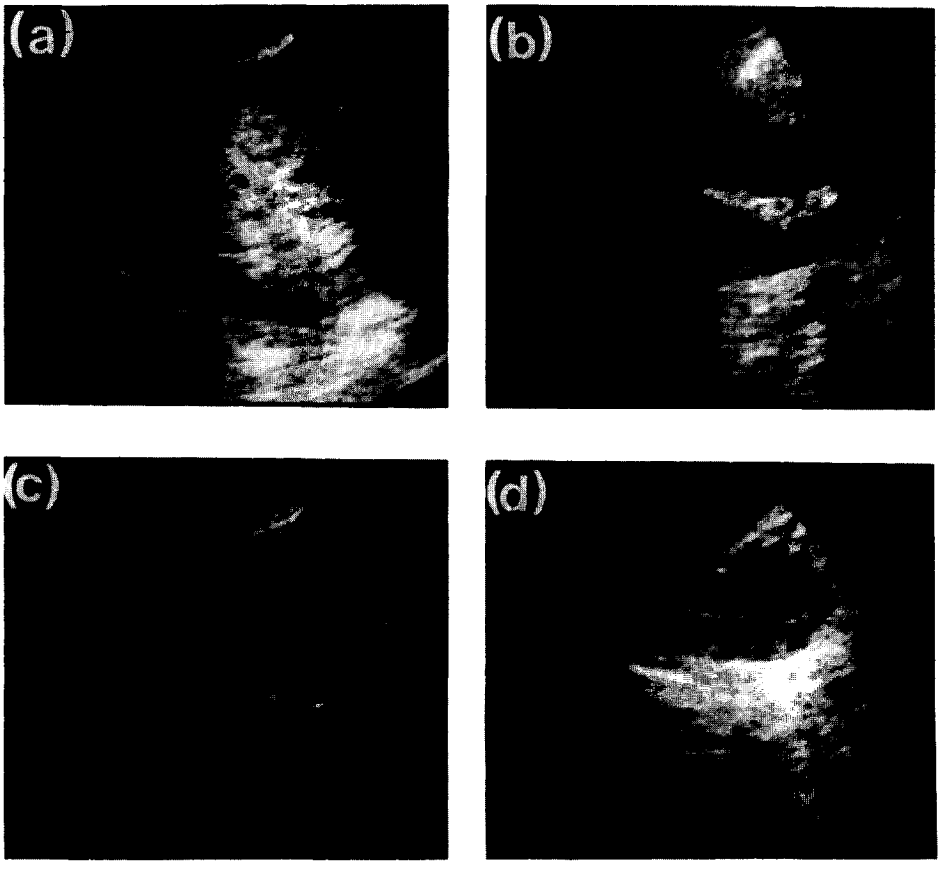

Figure 7. Tamoxifen and the endometrium. Images of transvaginal ultrasonography. (a) A 25 mm thickened endometrium with cystic appearance: endometrial polyp-cancer; (b) A 9 mm thickened endometrium: glandulocystic endometrial atrophy; (c) A rectilinear endometrium with a 5 mm thickening of the uterine fundus; (d) Saline infusion sonography: benign endometrial polyp (same patient as in (c)).

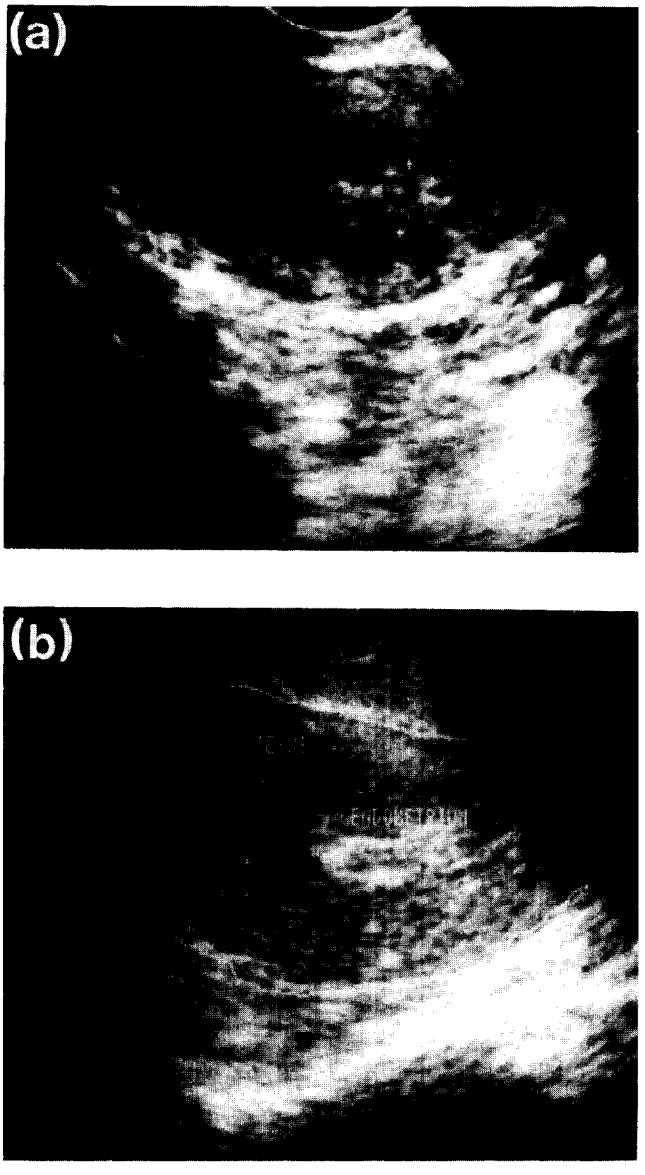

Figure 8. Tamoxifen and the endometrium. Images of transvaginal ultrasonography. (a) A 13 mm irregularly thickened endometrium: glandulocystic endometrial atrophy; (b) Saline infusion sonography: benign endometrial polyp (same patient as (a)).

MONITORING TECHNIQUES FOR ENDOMETRIAL LESIONS IN PATIENTS TREATED WITH TAMOXIFEN

One of the most controversial points regarding tamoxifen treatment is which monitoring strategies should be employed to ensure the earliest possible diagnosis of an endometrial lesion. As tamoxifen is now employed in trials investigating its merit as a preventive agent for breast cancer, gynaecologists are consulted more frequently for advice on the proper follow-up of these patients. Before discussing the proposed screening techniques, it is imperative that we put the whole issue into perspective.

A review of preliminary data from the British Pilot Breast Cancer Preventional Trial [67] revealed that, although endometrial abnormalities were more frequent in women receiving tamoxifen when compared to controls, the majority (61%) of the tamoxifen-treated women were diagnosed to have an atrophic endometrium after a median follow-up of 22 months. More recently, Gibson and associates [68] reviewed the medical records of breast cancer patients who underwent a D&C in the Memorial Sloan-Kettering Cancer Center during the period 1986–1993. Interestingly, the investigators found no difference in the incidence of endometrial pathological findings between tamoxifen users and non-users. It is evident, therefore, that although tamoxifen's association with uterine abnormalities has been the focus of negative publicity, most of the endometria in tamoxifen-treated women are atrophic, probably due to tamoxifen's anti-oestrogenic properties. Given that up to 39% of postmenopausal women receiving tamoxifen have some sort of endometrial abnormality [67], it is surprising that the relative risk of endometrial cancer is only 2–3/1000 women annually. It is safe to assume, therefore, that endometrial hyperplastic lesions, traditionally held as premalignant, rarely evolve into invasive cancers in tamoxifen-treated women.

No group of women taking tamoxifen has been clearly identified as being at greater risk, although the accumulated dose may be important [62, 71], and neither is there an established method of selecting a subgroup of asymptomatic women to undergo diagnostic procedures to exclude a neoplastic endometrial process. As to what techniques should be employed to screen symptomatic women, transvaginal sonography (TVS), dilatation and curettage (D&C) and hysteroscopy have been advocated as the most applicable.

TVS allows imaging of all uterine layers (fibroids) and of the ovaries (cysts). A finding of a thin rectilinear endometrium (<5 mm) will, in most cases, differentiate clinically important endometrial lesions from small polyps or foci of atypical hyperplasia that usually go undetected. Tamoxifen-induced endometrial changes result in a sonographically unique picture of an irregularly echogenic endometrium (Figures 7 and 8) that is attributed to cystic glandular dilatation, stromal oedema and oedema and hyperplasia of the adjacent myometrium. In support of this notion, a study that implemented DNA flow cytometry also provided evidence that tamoxifen's proliferative effect on the endometrium might be mediated through the stromal component [75]. Simple ultrasound may be very sensitive for endometrial pathology, but clearly its specificity deteriorates markedly in tamoxifen users. Another drawback of TVS is its inability to differentiate between benign and malignant lesions so that additional invasive procedures are required to reach a definitive diagnosis. To overcome these problems, some investigators have proposed the combination of ultrasound with colour Doppler flow measurement [67] while others have advocated contrast ultrasonography with intracavitary fluid instillation [69] (Figures 7d and 8b). Overall, TVS findings should be interpreted with caution in tamoxifen-treated women as the detection of a thickened endometrium may lead to overtreatment and mismanagement.

Hysteroscopy is a reliable diagnostic method as it allows direct visualisation of the uterine cavity, thus facilitating sampling of lesions such as hyperplasia, polyps (Figure 9a) and endometrial carcinoma (Figure 9b). At present, only a few gynaecologists are willing to use hysteroscopy as an outpatient procedure, although the hysteroscopes now available are safe and easy to handle, allowing atraumatic insertion. Routine hysteroscopy is superior to TVS in ruling out endometrial lesions in asymptomatic tamoxifen users. Typically, such patients demonstrate a white, smooth, yet hypervascularised

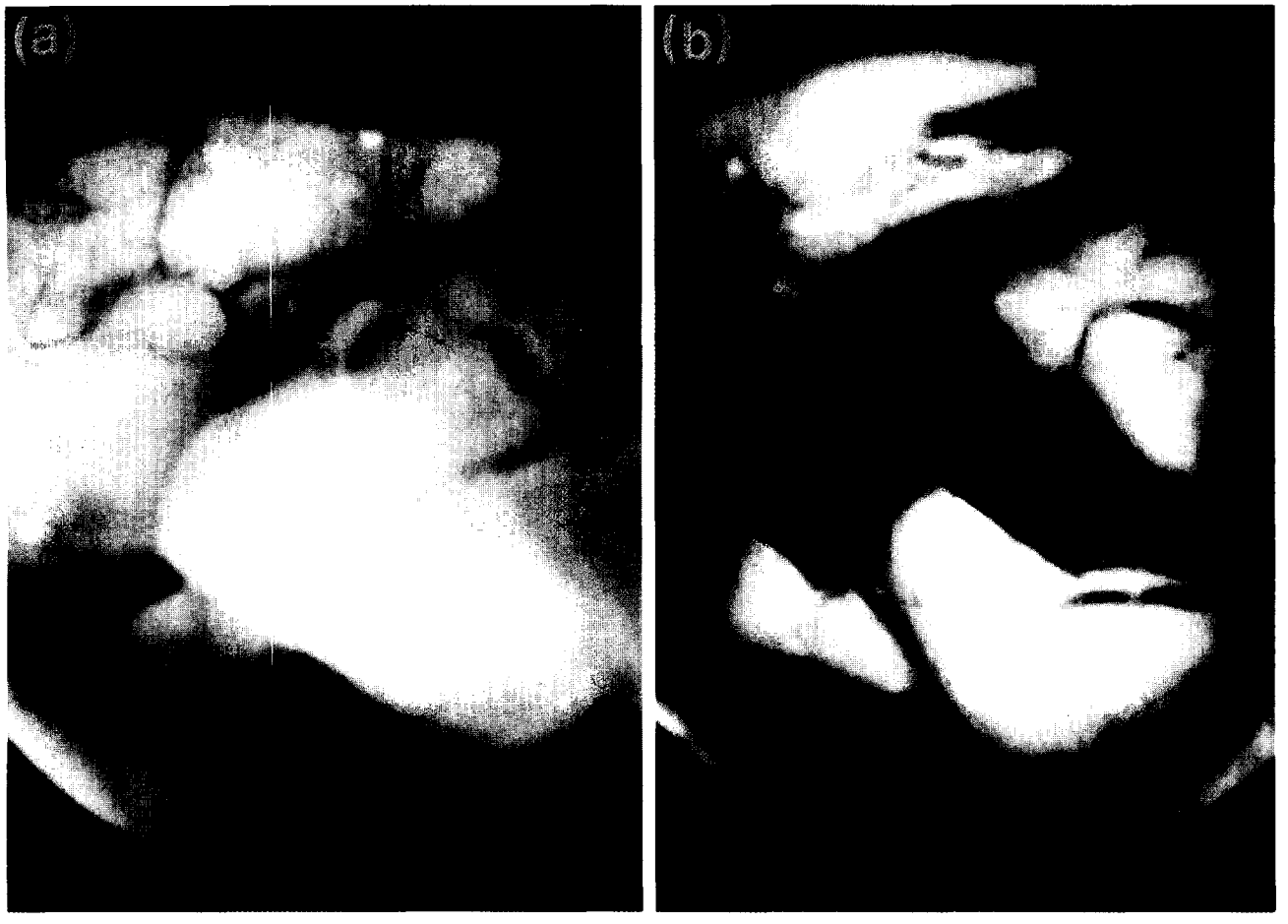

Figure 9. Tamoxifen and the endometrium. Hysteroscopic images. (a) Atrophic endometrium and benign polyp; (b) Endometrial polyps: well-differentiated endometrial adenocarcinoma.

endometrial surface with many scattered protuberances that represent subepithelial cystic dilated glands covered by a very thin layer of atrophic endometrium [70]. Similar changes are seen in the endocervical canal (Figure 10), occasionally also visible through direct speculum examination. Hysteroscopy's main problem is that, although specific for endometrial pathology, it requires treatment of all visible lesions to prevent any cancers occurring in polyps remaining untreated.

Preventive medicine is costly and a screening programme of all women treated with tamoxifen would not be cost-effective. This notion is supported by (1) the huge discrepancy between the high rates of asymptomatic endometrial lesions and the quite low frequency of symptomatic endometrial cancers, and (2) the fact that although aggressive screening would most probably lead to early diagnosis, there is, to date, no evidence that this would confer a survival advantage. Endometrial cancer is a rather slowly progressing malignancy with high 5-year survival rates, in contrast to breast cancer relapse that results in a significant increase in morbidity and death. However, when there is only a small gain from tamoxifen treatment or the benefit/risk ratio is not clearly defined, as is the case with the volunteers participating in the chemoprevention trials, it is prudent that a policy of close surveillance is adopted. Ideally, women in the prevention trials should have a baseline assessment prior to initiation of tamoxifen administration and a regular follow-up on an annual basis, unless emerging symptoms require prompt intervention. Such a policy is in place in the United States for the NSABP prevention trial with tamoxifen. Today, if one chooses to screen the women in the prevention trials, the recommended screening tool for postmenopausal women is TVS, to select a subset of patients who may need further assessment with hysteroscopy or contrast sonography.

In the United States, the American College of Obstetricians and Gynecologists published its proposed guidelines in February 1996. These recommendations for women taking tamoxifen are as follows: (1) Women with breast cancer should have annual gynaecological examinations, including Pap tests and bimanual and rectovaginal examinations. (2) Any abnormal bleeding, including bloody discharge, spotting, or any other gynaecological symptoms, should be evaluated thoroughly. Any bleeding or spotting should be investigated by biopsy. (3) Practitioners should be alerted to the increased incidence of endometrial malignancy. Screening procedures or diagnostic tests should be performed at the discretion of the individual gynaecologist. (4) Women without breast cancer who are being treated with tamoxifen within a chemopreventive trial should be monitored closely for the development of endometrial hyperplasia or cancer. (5) If atypical hyperplasia develops, use of tamoxifen should be discontinued, and dilatation and curettage or other appropriate gynaecological management should be instituted within an appropriate interval. (6) If tamoxifen therapy must be continued, hysterectomy should be considered in women with atypical endometrial hyper-

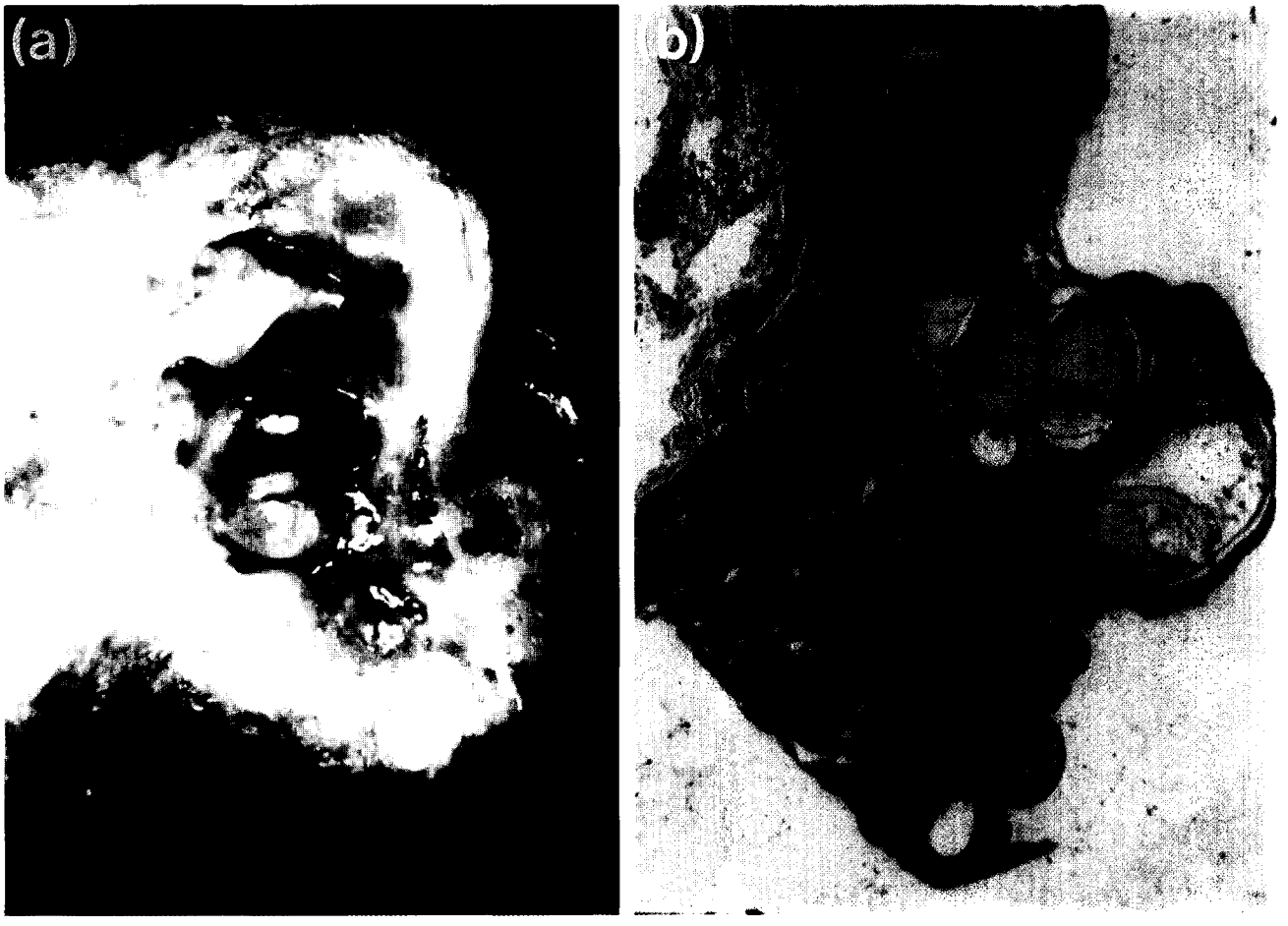

Figure 10. Tamoxifen and the endocervix. (a) Uterine specimen illustrating the endocervix: macroscopic view resembles an endocervical polyp; (b) Microscopic view: glandulocystic pseudopolypoid atrophy.

plasia. (7) Tamoxifen use may be reinstituted following hysterectomy for endometrial carcinoma in consultation with the physican responsible for the woman's breast care.

CONCLUSION

Tamoxifen has been the mainstay of adjuvant treatment for breast cancer for many years. Up to half a million women in the United States and, by extrapolation, several million women worldwide, are currently receiving tamoxifen. Its proven benefit in prolonging disease-free and overall survival has led to the concept of testing tamoxifen as a preventive agent for healthy women with a high risk of developing breast cancer. Since the benefits of such a treatment modality are as yet unknown, the clinical community and the patients themselves are posing appropriate questions concerning the safety of the drug. The focus of this criticism is targeted against the carcinogenic properties of tamoxifen in the liver of rat models, in conjunction with an association with increased frequency of endometrial cancer seen clinically. A review of what is known about tamoxifen, however, suggests that, in humans, there is no substantial evidence of liver carcinogenicity. As far as endometrial cancer is concerned, the mechanisms of tamoxifen's effect on the female genital tract remain poorly understood, but there is a definite low increase in the risk (2–3-fold) of developing endometrial cancer in patients treated with tamoxifen. However, the relationship between the length of therapy and the association with endometrial cancer may be a result of repeat patient sampling rather than carcinogenesis. Long-term therapy has a linear relationship with the frequency of endometrial cancers over time on the drug, while the rôle of daily dose remains controversial. More importantly, the modest increase in endometrial cancers arising in patients with a history of tamoxifen use have the same stage, grade, histology and outcome as those in the general population. Endometrial cancer is a rather slowly progressing malignancy and has a relatively favourable prognosis with high 5-year survival rates. In contrast, breast cancer relapse or metachronous contralateral breast cancer are the major causes of death in breast cancer patients. Tamoxifen's proven benefits in prolonging disease-free and overall survival far outweigh the risk of the additional toxicities.

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