Abstract
Aims—To determine the type of endometrial abnormalities associated with prolonged tamoxifen treatment and to investigate the correlation between tamoxifen dose and any abnormalities detected.

Methods—Endometria from 19 prospectively collected breast cancer patients treated with tamoxifen were ascribed a pathological diagnosis and the findings compared with those in a control group matched for age and presentation. The abnormalities were related to cumulative tamoxifen dose.

Results—The two asymptomatic treated patients had generalised simple endometrial hyperplasia at necropsy. No endometrial abnormalities were seen at necropsy in the two control cases. Of the 17 patients treated with tamoxifen who underwent surgery for gynaecological symptoms, 11 had hyperplastic endometrial polyps characterised by epithelial metaplasias and patchy periglandular condensation of stroma. Two women had primary endometrial malignancies with myometrial invasion, and three women, one of whom had previously presented with a benign polyp, had an endometrial polyp-cancer on a background of hyperplasia. Endometrial malignancies were confined to women who had taken more than 35 g of tamoxifen. The control group included no endometrial polyp-cancers, only one patient with an endometrial polyp, four women with endometrial hyperplasia and four with primary endometrial malignancy.

Conclusions—These findings support a link between prolonged tamoxifen treatment and endometrial malignancy and identify a subgroup of patients—that is, those who have taken more than 35 g of tamoxifen, who may be at increased risk of endometrial cancer. The spectrum of pathological findings in patients treated with tamoxifen suggests that the drug promotes endometrial growth and that endometrial polyps may be an important intermediate step in endometrial carcinogenesis.

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Tamoxifen is a non-steroidal triphenylethylene derivative with predominant anti-oestrogen activity. It has long been in widespread use in the management of established breast carcinoma. Perceived as safe, effective, and with negligible side effects, it has recently been advocated as of potential value in breast cancer prevention and its efficacy as a preventive agent is currently being evaluated in asymptomatic women deemed to be at increased risk of breast cancer.

Although an oestrogen antagonist in the breast, tamoxifen is structurally closely related to the synthetic oestrogen diethylstilbestrol and is known to have oestrogen agonist activity in the vaginal epithelium and endometrium of postmenopausal women. In keeping with such an effect, recent studies have reported an increased incidence of endometrial carcinoma, polyps, and hyperplasia in women treated with tamoxifen. However, existing publications on the pathology of endometrium in women treated with the drug are few and far between, and the association between tamoxifen dose and endometrial disease has not been studied. This study investigates the relation between tamoxifen dose and the endometrial abnormalities detected in a group of breast cancer patients who received prolonged tamoxifen treatment.

![Figure 2: A benign endometrial polyp in a 54 year old woman treated with tamoxifen who underwent hysterec tomy for postmenopausal bleeding.](image)

**Clinical presentation and pathological findings in women treated with tamoxifen compared with untreated controls**

<table>
<thead>
<tr>
<th>Case No</th>
<th>Symptoms</th>
<th>Age</th>
<th>Endometrial pathology</th>
<th>Control pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PMB</td>
<td>54</td>
<td>Benign polyp (3 cm); background simple endometrial hyperplasia</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>2</td>
<td>PMB</td>
<td>52</td>
<td>Benign polyp (3-3 cm); background cystic atrophy</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>3</td>
<td>PMB</td>
<td>54</td>
<td>Benign polyp (6 cm); focus of secondary carcinoma within polyp and background simple endometrial hyperplasia</td>
<td>Endometrial polyp</td>
</tr>
<tr>
<td>4</td>
<td>Menorrhagia</td>
<td>54</td>
<td>Two benign polyps (5 cm and 1-3 cm); background cystic atrophy</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>5*</td>
<td>PMB</td>
<td>74</td>
<td>Benign polyp (4 cm); no background endometrium</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>6</td>
<td>PMB</td>
<td>59</td>
<td>Benign polyp (2-3 cm); no background endometrium</td>
<td>Endometrial abnormality</td>
</tr>
<tr>
<td>7</td>
<td>PMB</td>
<td>52</td>
<td>Benign polyp (1-5 cm); no background endometrium</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>8†</td>
<td>Clear discharge</td>
<td>59</td>
<td>Benign polyp (5 cm) and background simple endometrial hyperplasia</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>9†</td>
<td>PMB</td>
<td>67</td>
<td>Benign polyp (6 cm), three previous polyps, and background simple endometrial hyperplasia</td>
<td>Endometrial hyperplasia (polyplasmoma)</td>
</tr>
<tr>
<td>10</td>
<td>PMB</td>
<td>58</td>
<td>Two benign polyps (6 cm and 3 cm), and background simple endometrial hyperplasia</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>11</td>
<td>PMB</td>
<td>81</td>
<td>Three benign polyps (16 cm, 4 cm and 4 cm) and background simple hyperplasia</td>
<td>Malignant mixed Müllerian tumour</td>
</tr>
<tr>
<td>12</td>
<td>Menorrhagia</td>
<td>47</td>
<td>Progestogen changes only†</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>13</td>
<td>Menorrhagia</td>
<td>49</td>
<td>Progestogen changes only†</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>14</td>
<td>Necropsy</td>
<td>85</td>
<td>Simple endometrial hyperplasia</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>15</td>
<td>Necropsy</td>
<td>91</td>
<td>Simple endometrial hyperplasia</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>16</td>
<td>PMB</td>
<td>58</td>
<td>Adenocarcinoma with focal sarcomatous differentiation and extensive myometrial infiltration</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>17</td>
<td>Menorrhagia</td>
<td>49</td>
<td>Invasive well differentiated adenocarcinoma with extensive myometrial invasion</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>18</td>
<td>PMB</td>
<td>70</td>
<td>Background simple endometrial hyperplasia, multiple hyperplastic polyps with varying degrees of cytological atypia, and a polypoid superficial carcinoma</td>
<td>No endometrial abnormality</td>
</tr>
<tr>
<td>19†</td>
<td>PMB</td>
<td>62</td>
<td>Background simple endometrial hyperplasia and multiple benign polyps with foci of superficial carcinoma</td>
<td>Endometrial carcinoma</td>
</tr>
<tr>
<td>20*</td>
<td>Necropsy</td>
<td>76</td>
<td>Background hyperplasia with focal atypia and benign polyp with microscopic focus of adenocarcinoma</td>
<td></td>
</tr>
</tbody>
</table>

*Same patient
†External cases
§ Recent progestogen therapy
Methods
The study population comprised 19 breast cancer patients treated with tamoxifen. The data were collected prospectively between 1987 and 1992. It includes two necropsies, 14 women who underwent surgery at the University Hospital of Wales for tamoxifen-associated gynaecological symptoms, and three patients treated at other hospitals in the area.

The two necropsy patients, aged 85 and 92, had died of myocardial infarction and lobar pneumonia, respectively. Neither was known to have had any gynaecological symptoms and there was no history in either woman of any other hormone treatment.

The symptomatic patients ranged in age from 47 to 81 years (mean 58·5 years) and presented with prolonged irregular perimenopausal bleeding (n = 4), post menopausal bleeding (n = 12), or vaginal discharge (n = 1). Treatment consisted of either polypectomy (n = 5) or hysterectomy (n = 12). Three patients had received progestogens for menorrhagia but none had received any other form of endocrine treatment.

The specimens were fixed in 10% buffered formalin and routinely processed. Every specimen was ascribed a pathological diagnosis following examination of the haematoxylin and eosin stained sections and before tamoxifen dose was known. Information about daily tamoxifen dose and duration of treatment was obtained from the case notes. The cumulative dose of tamoxifen was calculated from the daily dose of the drug and the duration of treatment, taking into account recorded alterations in daily dose and assuming that there are 30 days per calendar month.

A control group, matched as closely as possible to the study group for age at presentation, was selected for comparison. The mean age of the control patients was 60·8 years while the mean age of the test group was 61·8 years.

Two postmenopausal breast cancer patients who had received no tamoxifen or any other endocrine treatment, had had no gynaecological symptoms, and who had died over the study period were selected as controls for the two asymptomatic test cases.

The symptomatic group of study patients was compared with a control group of age-matched women presenting with identical symptoms over the last two years of the study. None of the patients in this control group had breast cancer and none had received tamoxifen, hormone replacement therapy, or any other endocrine treatment which might have affected endometrial morphology.

Results
The results are summarised in the table. One test patient (case 5) features twice, having had a benign endometrial polyp after 16 months of tamoxifen treatment and a superficial endometrial carcinoma in a second endome-
trial polyp, discovered at necropsy, after a further 30 months of tamoxifen treatment.

CONTROL GROUP
No endometrial abnormalities were detected at necropsy in the two uteri from the breast cancer patients who had not received tamoxifen. Of the remaining 17 control patients, four had endometrial hyperplasia, three had primary endometrial carcinoma, one had a malignant mixed Müllerian tumour, one had an endometrial polyp, and eight had no clinically relevant endometrial abnormalities.

STUDY GROUP
The two asymptomatic necropsy patients who had been treated with tamoxifen both had an enlarged uterus with generalised thickening of the endometrium within which numerous cysts of varying size were identifiable macroscopically (fig 1). Microscopic examination showed simple endometrial hyperplasia with cystic dilatation of endometrial glands and a fibrotic endometrial stroma. No evidence of atypical hyperplasia or malignancy was seen.

A range of endometrial findings was seen in the symptomatic patients treated with tamoxifen. Endometria from two of the three women treated with progestogen showed stromal decidualisation with no other major pathological findings; both these women had received very low doses of tamoxifen. The remaining 15 symptomatic women treated with tamoxifen had pathological abnormalities of the endometrium which fell into two main categories: benign endometrial polyps occurring on a background of endometrial hyperplasia; and primary endometrial malignancies.

Eleven patients had benign endometrial polyps (fig 2) which ranged in size from 1.5 cm to 16 cm (mean 5 cm). Four women had multiple polyps either synchronously or metachronously. The polyps occurred on a background of simple endometrial hyperplasia in six of eight instances where background endometrium was available for assessment. Microscopically, the polyps were characterised by patchy periglandular condensation of stroma (fig 3A), proliferative activity in epithelial and stromal cells (fig 3B), and an admixture of epithelial metaplasias including squamoid (fig 4A), papillary oxyphil cell (fig 4B), apocrine (fig 4C), and mucinous (fig 4D) metaplasias. Periglandular stromal condensation, proliferative activity, and epithelial metaplasias coexisted in 12 of 15 benign endometrial polyps in this group of patients. The remaining three benign endometrial polyps, all from a patient treated with progestogen (case 11) lacked proliferative activity but did show periglandular stromal condensation and epithelial metaplasias. In contrast, a consecutive series of 40 endometrial polyps of the usual type revealed no instances in which these three microscopic features coexisted in the same polyp.

Altogether there were five endometrial malignancies associated with tamoxifen. One of these was an adenocarcinoma of the

Figure 4 The range of epithelial metaplasias seen in tamoxifen-associated benign endometrial polyps included (B) papillary oxyphil cell metaplasia, (C) apocrine metaplasia and (D) mucinous metaplasia (haematoxylin and eosin).
Pathology of endometrium treated with tamoxifen

endometrium with sarcomatous areas (carci-
mosarcoma) and another a well differentiated
endometrial carcinoma; in both, the tumour
showed extensive myometrial infiltration. In
three additional cases a superficial endome-
trial carcinoma (fig 5) confined to the
endometrium occurred within an endometrial
polyp. The background endometrium in these
uteri with superficial endometrial carcinoma
showed cystic hyperplasia with benign polyps
(fig 5). The background benign polyps in
these cases were characterised by hyperplasia
with varying degrees of cytological atypia as
well as focal periglandular stromal condensa-
tion and epithelial metaplasia.

Figure 6 summarises the correlation
between endometrial pathology, tamoxifen
dose, and duration of treatment. The patient
(case 5), who initially presented with post-
menopausal bleeding from an endometrial
polyp and who subsequently was found to
have an endometrial polyp-cancer at
necropsy, features twice in this figure. Primary
endometrial malignancy occurred in patients
treated either with 20 mg or 40 mg tamoxifen
daily. However, the tumours in the former
group developed after a longer period of treat-
ment than those occurring in patients treated
with the higher daily dose. All five primary
endometrial malignancies occurred in women
who had taken a cumulative tamoxifen dose of
more than 35 g. Of the remaining six women
who had received tamoxifen in excess of this
threshold dose, four had benign endometrial
polyps and two had generalised endometrial
hyperplasia.

Discussion

This study has revealed a spectrum of prolif-
erative abnormalities among women treated
with tamoxifen, comprising generalised sim-
ple endometrial hyperplasia in the two asym-
ptomatic patients and hyperplasia with polyps,
polyp-cancers, or primary invasive malignan-
cies in the symptomatic patients. The control
group of women showed a much lower inci-
dence of endometrial polyps, no endometrial
polyp-cancers, and a higher incidence of “no
endometrial abnormality”.

It is at first sight surprising to find prolifera-
tive endometrial abnormalities in women
treated with tamoxifen as the drug, used for
its oestrogen antagonist effects in breast carci-
noma, might be expected to exert similar
effects on the endometrium with consequent
inhibition of endometrial growth. However,
tamoxifen exerts a well documented oestro-
gen-like effect on cervico-vaginal squamous
epithelial differentiation in postmenopausal
women. Previous observations, which
suggested a similar oestrogen-like effect on
the postmenopausal endometrium, have been
supported by a recent study which found that
breast cancer patients treated with the drug
had a thicker endometrium than untreated
controls, on transvaginal sonography, and a
lower incidence of atrophic endometrium on
hysteroscopy. The occurrence, in the present
study, of proliferative endometrial abnor-
malities in all but two treated women (both of

Figure 5 (A) Multiple endometrial polyps in a 70 year old woman treated with tamoxifen who underwent hysterectomy for postmenopausal bleeding. (B) On microscopic examination, there was background endometrial hyperplasia and one polyp contained (C) a superficial endometrial carcinoma (haematoxylin and eosin).
ever, the patchy nature of this stromal change, the relative paucity of mitotic activity, and absence of cytological atypia and atypical mitoses in the tamoxifen-associated polyps was thought to militate against a diagnosis of Müllerian adenosarcoma.

The occurrence of three endometrial polycancers in this relatively small group of women treated with tamoxifen was unexpected as these lesions are otherwise extremely rare. Although no precise figures for incidence are available, only four polycancers were noted in a study of 1100 endometrial polyps.29 The high prevalence of these rare lesions in this study population can only be explained by a sustained stimulus which favours the development of malignancy in endometrial polyps; the only candidate for this role, in this group of patients, is tamoxifen.

The polyp-cancers in this group of women occurred on a background of endometrial hyperplasia and multiple polyps showing a variable degree of atypical hyperplasia of their epithelial elements. These observations suggest that endometrial polypogenesis may form an important, perhaps essential, intermediate stage between simple endometrial hyperplasia and endometrial malignancy. I suggest that in susceptible patients simple endometrial hyperplasia is followed by endometrial polyps, atypical endometrial hyperplasia, and carcinoma. This proposed sequence of events agrees with the reported risk of subsequent endometrial carcinoma of 0.4-1.1% for simple endometrial hyperplasia,21,22 3-5% for polyps,23 and 23% for atypical hyperplasia.22 The factors which influence an individual’s susceptibility to this sequence of events are poorly understood. However, tamoxifen is clearly not the only important factor involved as, of the three women who received the highest cumulative dose of the drug, two had simple hyperplasia, one had multiple polyps, and none had a malignancy. An inherited predisposition to endometrial polyps or carcinoma, or both, may also be a factor.

The cancers in the present study were confined to women who had received a total tamoxifen dose in excess of 35 g, irrespective of the daily dose of the drug. This observation suggests that the development of endometrial cancer in women treated with tamoxifen is related not to the daily dose of the drug but to the total dose taken, and that there is a threshold dose above which symptomatic patients have a high risk of an underlying endometrial carcinoma. The existence of this dose threshold, with the implication that women receiving the lower daily dose of the drug will develop endometrial carcinoma after a longer period of treatment, may explain the disparities in the reported incidence of endometrial carcinoma between the higher dose Stockholm trial10 and trials using the lower daily dose.24-26 If such a dose threshold is operative, an increase in the incidence of endometrial carcinoma among women receiving the lower daily dose would only become evident on follow up in excess of five years.

Figure 6 Tamoxifen dose and type of endometrial pathology. (A) Daily dose and duration of treatment; (B) cumulative dose of tamoxifen.
The ongoing breast cancer prevention trials using long term tamoxifen in asymptomatic women have imparted urgency to the study of the endometrial effects of this drug. The findings of this small study support a link between tamoxifen and endometrial cancer and indicate that gynaecological symptoms in women treated with tamoxifen warrant full investigation. They suggest a pathogenetic relation between polyoid endometrial hyperplasia and malignancy and identify a subgroup of patients (those who have taken more than 35 g of tamoxifen) who may be at increased risk of harbouring endometrial cancer. It is recommended that tamoxifen registers be established to facilitate adequate follow up of women receiving prolonged tamoxifen treatment and to determine the incidence of endometrial pathology associated with the use of this drug.

I thank Professor Sir Dillwyn Williams and Dr Robert Newcombe for helpful discussions. Drs John Dinnen (County Hospital, Hereford), Gareth Melville-Jones (Withybush General Hospital), and Windsor Fort (Royal Gwent Hospital) contributed the outside cases.

Pathology of endometrium treated with tamoxifen.

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