

Surveillance for Endometrial Cancer in Women Receiving Tamoxifen

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Recent studies showing a protective effect of tamoxifen in women at high risk for breast cancer have expanded the indications of the drug. While acting as an estrogen antagonist in the breast, tamoxifen can have estrogenic effects on the endometrium; consensus opinion is that tamoxifen increases the risk for endometrial cancer. Because an increasing number of women are taking tamoxifen, a strategy for gynecologic surveillance is needed. Studies examining the relation between risk for endometrial cancer and tamoxifen use have conflicting results. However, because of an overall interpretation that tamoxifen use slightly increases risk for endometrial cancer, some researchers advocate routine ultrasonography and endometrial biopsy for screening asymptomatic women receiving tamoxifen.

This paper reviews the literature on endometrial cancer in women taking tamoxifen and the usefulness of various screening methods in this setting. Risk factors and screening criteria for endometrial cancer in the general population are discussed, and a strategy for surveillance of women taking tamoxifen is proposed. Patients should be screened for signs or symptoms of endometrial abnormality before taking tamoxifen. This evaluation, which should include a careful history, pelvic examination, and Papanicolaou smear, should be repeated annually while the patient is receiving tamoxifen. Although transvaginal ultrasonography is not recommended for routine screening, it is indicated if an adequate pelvic examination cannot be performed or if additional risk factors are present. The likelihood of abnormality is greater for patients who have abnormal bleeding, discharge, abnormal glandular cells on Papanicolaou smear, or an endometrial measurement on ultrasonography of more than 8 mm; these findings should prompt an aggressive evaluation of the endometrium.

Since the early 1980s, tamoxifen has become the standard adjuvant therapy for patients with breast cancer, reducing the risk for a second case of contralateral primary breast cancer by 30% to 50% (1, 2). The current recommended regimen for adjuvant tamoxifen therapy is 20 mg/d for 5 years. Results from the Breast Cancer Prevention Trial (3) have led to the recent approval of tamoxifen as a chemopreventive agent in women at high risk for developing breast cancer. Tamoxifen is structurally related to diethylstilbestrol and clomiphene citrate. While acting as an estrogen antagonist in the breast, it has estrogen agonist activity in other tissues, increasing thickness of the vaginal epithelium, reducing serum cholesterol levels, and preserving bone density in postmenopausal women (4–11). Laboratory studies have demonstrated estrogen-like effects on steroid hormone receptors in the endometrium (12) and growth-promoting effects on endometrial carcinoma cells (13). During the past decade, several reports (14–20) have cited an increased incidence of endometrial abnormality, ranging from polyps to cancer, in women receiving tamoxifen. Although tamoxifen has been implicated in the development of endometrial cancer, many epidemiologic and genetic risk factors that predispose women to breast cancer can also increase the overall risk for developing gynecologic cancer (21, 22). Many recommendations have been made regarding routine screening of these women for endometrial cancer, including the 1996 American College of Obstetricians and Gynecologists (ACOG) committee opinion, which left evaluation to the discretion of the individual practitioner (23). Because indications for tamoxifen use are broadening, a strategy for gynecologic surveillance is needed.

Methods

Studies that evaluated the relation between risk for endometrial cancer and tamoxifen use were identified by searching MEDLINE with the keywords *tamoxifen* and *endometrial carcinoma* for English-language articles published between 1966 and 1998. The resulting bibliographies were re-

Ann Intern Med. 1999;131:127-135.

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Table 1. Risk Factors Associated with Endometrial Cancer

Study (Reference)	Risk Factor	Estimated Relative Risk
—	Obesity	
—	>21–50 lb overweight	3
Wynder et al. (25)	>50 lb overweight	9
Grady et al. (29)	Exogenous unopposed estrogen therapy*	2.3
MacMahon (26)	Late menopause (after 52 years of age)	2.4
Brinton et al. (28)	Nulliparity†	2.8
Coulam et al. (30)	Chronic anovulation	3.1
Vasen et al. (31)	Familial cancer syndrome	6.7
McMahon (26) and Meredith et al. (32)	Pelvic radiation	8.0

* From meta-analysis data of overall risk for endometrial cancer in women who used estrogen compared with women who had never used estrogen. Risk seems to increase with longer exposure.

† For nulliparous women compared with women who have given birth to at least one child. Risk seems to decrease with increasing parity.

viewed. Articles that compared the risk for endometrial cancer in tamoxifen-treated patients and untreated patients were selected. Studies that examined the use of various screening methods in this sample were also identified by searching MEDLINE (using the keywords *endometrial cancer*, *pathology*, *tamoxifen*, *ultrasound*, *sonohysterography*, *endometrial biopsy*, and *hysteroscopy*) and by reviewing abstracts to identify those in which screening methods were directly compared or were tested in patients who subsequently had a pathologic evaluation of the endometrium. Case reports and small case series were not included.

Epidemiology of Endometrial Cancer

Endometrial cancer is the most common gynecologic cancer in the United States; it is diagnosed in approximately 36 000 women each year (24). An estimated 1% to 3% of postmenopausal women will receive a diagnosis of endometrial cancer before 75 years of age, and the average age at diagnosis is estimated to be 61 years. Endometrial cancer occurs more frequently in white women, who have a lifetime risk of 2.4% (compared with 1.3% in black women). The risk factors for endometrial cancer that have been consistently found in epidemiologic studies are related to increased estrogen exposure and include nulliparity, late onset of menopause, unopposed estrogen hormone therapy, obesity, estrogen-producing ovarian neoplasms, and a history of anovulation, often caused by polycystic ovary disease (25–32) (Table 1). Women who have a family history of hereditary nonpolyposis colorectal cancer or have received pelvic radiation are also at higher risk for endometrial cancer (31, 32). Despite its prevalence, endometrial cancer results in approximately 50% fewer deaths in the United States than

ovarian cancer does because most women present with abnormal bleeding when the disease is in the early stages.

Screening for Ovarian and Endometrial Cancer

Yearly screening with the Papanicolaou smear has dramatically reduced the incidence of cervical cancer in the United States. Endometrial and ovarian cancer can be detected by pelvic examination and Papanicolaou smear, but these screening tests are not reliable methods for detecting early disease. In most women, endometrial cancer is detected by endometrial biopsy performed because of abnormal bleeding; however, an abnormal finding on Papanicolaou smear can occasionally be the first indication of endometrial disease in asymptomatic women. A Papanicolaou smear-based diagnosis of atypical glandular cells of undetermined significance can indicate an endometrial lesion and should prompt evaluation with endometrial biopsy and colposcopy (33). The finding of benign endometrial cells on Papanicolaou smears of postmenopausal women who are not receiving hormone replacement therapy is associated with endometrial hyperplasia or cancer in 13% of cases (34) and also warrants follow-up with endometrial biopsy.

Additional screening tests for ovarian epithelial adenocarcinoma and endometrial adenocarcinoma, the two types of gynecologic cancer most frequently associated with breast cancer, are not currently recommended for the general population (35). Serum CA-125 testing and pelvic ultrasonography have been offered to women at risk for ovarian cancer, but no effective screening test is available (36). Transvaginal ultrasonography allows evaluation of the endometrial cavity and measurement of the thickness of the endometrial lining. An endometrial thickness of 5 mm or less in a postmenopausal woman is a strong negative predictor for cancer (37). Endometrial biopsy is recommended 1) for women with abnormal bleeding; 2) during evaluation of Papanicolaou smear findings of endometrial cells in postmenopausal women and atypical glandular cells of undetermined significance; and 3) for screening women with high-risk syndromes, such as hereditary nonpolyposis colon cancer (38, 39). However, other risk factors for endometrial cancer can indicate endometrial sampling in the absence of bleeding.

Risk for Endometrial Cancer as a Result of Tamoxifen Use

The reported relative risk for endometrial cancer associated with tamoxifen use ranges from 0.6 to

Table 2. Randomized, Controlled Trials of Tamoxifen and Relative Risk for Endometrial Cancer*

Study (Reference)	Patients	Tamoxifen Dose	Duration of Use	Relative Risk (95% CI)
	<i>n</i>	<i>mg</i>		
Fornander et al. [Stockholm Trial] (40)	1846	40	2–5 y	6.4 (1.4–28)
Andersson et al. [Danish Breast Cancer Trial] (41)	1710	30	48 wk	1.9 (0.8–3.9)
Ryden et al. [South Sweden Breast Cancer Trial] (43)†	719	30	1 y	NS
Curtis et al. [National Surgical Adjuvant Breast and Bowel Project B-14] (48)	284	20	5 y	7.5 (1.7–32)
Boccardo et al. [Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group] (50)‡	504	30	5 y	NS
Ribeiro et al. [Christie Hospital] (51)	961	20	1 y	NS
Scottish Trial (52)	747	20	5 y	NS
Powles et al. [Royal Marsden Hospital] (54)	2012	20	10 y	NS
Nolvadex Adjuvant Trial (55)	1285	20	2 y	NS

* NS = not significant.

† Included 239 patients randomly assigned to receive tamoxifen or radiation therapy to chest wall.

‡ Included 171 patients randomly assigned to receive tamoxifen or chemotherapy.

15.2. The Stockholm Trial (40) found a relative risk of 6.4 for endometrial cancer among 1846 women randomly assigned to receive tamoxifen, 30 to 40 mg/d, or placebo. Although two other large Scandinavian trials, the Danish Breast Cancer Trial and the South Sweden Breast Cancer Trial, did not show statistically significant increased risk (41–43), a meta-analysis (44) that combined these three studies and included data from 4914 women found a relative risk of 4.1 (95% CI, 1.9 to 8.9). These trials were not originally designed to evaluate risk for endometrial cancer and therefore did not control for other patient characteristics, such as use of hormone therapy, hysterectomy, or obesity. In addition, patients receiving tamoxifen have more frequent gynecologic symptoms, which leads to increased surveillance (45). Resulting concerns over selection and ascertainment bias have fueled debate over the degree of risk actually attributable to tamoxifen in these studies (46). The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14, which randomly assigned 2843 patients to receive tamoxifen, 20 mg/d, or placebo for 5 years, found that tamoxifen therapy was associated with a relative risk of 7.5 (CI, 1.7 to 32.7) for developing endometrial cancer (47). However, the placebo group in this trial had an unusually low incidence of endometrial cancer. When population data from the Surveillance, Epidemiology, and End Results (SEER) database of 87 323 patients with breast cancer was substituted as the comparison group, a relative risk of 2.2 was found. In the only available large cohort study (48), which also used the SEER database, patients receiving tamoxifen had an increased incidence of endometrial cancer; the ratio of observed incidence to expected incidence was 2.06 (CI, 1.59 to 2.55), compared with a slightly increased incidence in the no-treatment group (relative risk, 1.23 [CI, 1.11 to 1.36]). Several other randomized trials and case-control studies have not found a significant increased risk among patients receiving tamoxifen

(49–61), but these studies have been criticized for lack of statistical power, inadequate follow-up time, and short duration of tamoxifen use in the women studied (Tables 2 and 3).

Despite the problems of bias in the published studies, the overall data and the biological plausibility of an effect have led to a general consensus that tamoxifen confers an increased risk (perhaps two- to threefold) for endometrial cancer among postmenopausal women.

Endometrial Surveillance in Women Who Use Tamoxifen

Endometrial Sampling

In a prospective cohort study of 2586 healthy, asymptomatic postmenopausal women (62), screening for endometrial cancer by biopsy was not found to be cost-effective because it detected only 1.7 cases of cancer per 1000 person-years. If a relative risk of 4.0 with tamoxifen use is assumed, approximately 6.8 cases of detected cancer per 1000 person-years would be expected. The yield from such a strategy would therefore be low. In addition, although outpatient biopsy is usually a simple and straightforward procedure, the presence of cervical stenosis can preclude outpatient sampling and require dilatation and curettage under anesthesia. In one study (63), 76 of 209 women with abnormal ultrasonography findings (31%) could not undergo outpatient endometrial sampling because of stenosis and would have required dilatation and curettage. Recent studies have found that endometrial abnormalities occurring in the setting of tamoxifen use seem to be more heterogeneous than is usual, with focal hyperplastic lesions coexisting in a background of atrophy (64). Therefore, the false-negative rate of sampling by biopsy may be higher in these patients, leading some researchers to argue for hysteroscopic

cally directed biopsy for all patients receiving tamoxifen who require sampling (65). However, other researchers are concerned that the discomfort of annual or semiannual endometrial sampling could compromise compliance with tamoxifen therapy or deter women from having regular gynecologic examinations.

Ultrasonography

Ultrasonography has been used to triage women receiving tamoxifen; an endometrial biopsy is recommended when the lining is thickened. Several studies have examined the use of ultrasonography followed by endometrial sampling to identify women who have abnormal endometrial characteristics and are receiving tamoxifen (Table 4). Kedar and colleagues (66) performed ultrasonography after a median treatment time of 24 months (range, 0 to 75 months) on 111 asymptomatic postmenopausal women at risk for breast cancer who were randomly assigned to receive tamoxifen, 20 mg/d, or placebo. Among women receiving tamoxifen, the thickness of the endometrial lining was greater than 5 mm (mean, 9.1 mm) in 49%; the mean thickness for women receiving placebo was 4.8 mm. The incidence of premalignant or malignant change was 16%; 10 women had atypical hyperplasia, and no women had cancer. The authors concluded that an endometrial thickness greater than 8 mm on ultrasonography had a 100% positive predictive value for endometrial disease.

In contrast, a study of 72 asymptomatic, postmenopausal patients with breast cancer who received tamoxifen, 20 to 30 mg/d, for 21 months (67) reported an endometrial thickness greater than 5 mm in 71 of 72 patients on vaginal ultrasonography; endometrial sampling, however, showed insufficient or normal tissue in 67 patients (92%). Three patients had benign polyps, 1 patient had proliferative endometrium without atypia, and 1 patient had endometrial cancer. In another study (63), annual ul-

trasonography screening of 737 postmenopausal patients with breast cancer receiving tamoxifen, 20 mg/d, for a median duration of 50 months showed an endometrial thickness greater than 6 mm in 209 patients (28%). In the 108 patients from whom samples were subsequently obtained, 1 case of hyperplasia and 1 case of cancer were found. The rate of cancer (1 of 737 patients) was no different from that expected in the general population. The poor correlation between lining measurements by ultrasonography and endometrial abnormality in asymptomatic women who used tamoxifen has been found in other studies and is probably a result of tamoxifen-induced subepithelial stromal hypertrophy (68–72). A duration-dependent increase in the stromal component was found after histologic study of the stromal–epithelial endometrium ratio in women receiving tamoxifen (73). Despite the apparently thickened endometrium on ultrasonography, most women receiving tamoxifen demonstrate an atrophic endometrium on biopsy. Measurements of the endometrial lining in women receiving tamoxifen have increased variability; however, endometrial cancer is usually associated with a measurement greater than 10 mm. In our review of studies that used ultrasonography to detect tamoxifen-associated endometrial cancer, we noted no cases in which cancer was found in a patient with an endometrial lining measurement of 8 mm or less.

The ability of ultrasonography and endometrial sampling to identify lesions among symptomatic patients is much greater, particularly among postmenopausal women. Cheng and coworkers (74) found that 67% of postmenopausal women receiving tamoxifen who reported abnormal bleeding (22 of 33 women) had a pathologic finding, including 6 women (19%) with premalignant or malignant lesions. It is therefore recommended that abnormal bleeding in such patients be promptly and aggressively evaluated. Office endometrial biopsy is usually the first step; however, if biopsy findings are nega-

Table 3. Case–Control and Cohort Studies of Tamoxifen Use and Endometrial Cancer*

Study (Reference)	Patients Given Tamoxifen		Patients Not Given Tamoxifen		Dose	Duration of Tamoxifen Use	Relative Risk (95% CI)
	Total Patients	Patients with Endometrial Cancer	Total Patients	Patients with Endometrial Cancer			
	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)			
Curtis et al. (48)	14 358	73 (0.5)	72 965	384 (0.5)	NR	NR	–†
Katase et al. (49)	279	4 (1.4)	546	9 (1.6)	20–40	NR	1.001
Hardell (56)	12	4 (33)	82	11 (13)	40	NR	2.6 (0.7–9.6)
van Leeuwen et al. (57)	98	23 (23)	258	58 (22)	20–40	13–19	1.3 (0.7–2.4)
Cook et al. (58)	34	9 (26)	64	20 (31)	20	23	0.6 (0.2–1.9)
Cuenca et al. (59)	8	2 (25)	1947	402 (20)	20–40	28	0.5
Robinson et al. (60)	108	4 (4)	478	4 (0.8)	20	NR	15.2 (2.8–84.4)

* NR = not reported.

† Findings reported as ratios of observed to expected incidence for endometrial cancer. Among case patients, this ratio was 2.03 (CI, 1.59–2.53); among controls, this ratio was 1.23 (CI, 1.11–1.36).

Table 4. Studies Evaluating Ultrasonography as a Screening Method for Endometrial Abnormality

Study (Reference)	Patients	Tamoxifen Dose	Median Duration of Therapy	Patients with Abnormal Results on Ultrasonography	Patients with Premalignant or Malignant Conditions
	<i>n</i>	<i>mg</i>	<i>mo</i>		<i>n (%)</i>
Kedar et al. (66)					
Patients given tamoxifen	61	20	22	28 (46)	10 (16)
Patients not given tamoxifen	50	–	24	0	0
Cecchini et al. (63)					
Patients given tamoxifen	737	20	50	206 (28)	2 (2)
Cohen et al. (67)					
Patients given tamoxifen	72	20–30	21 (mean)	71 (99)	1 (<1)
Bertelli et al. (68)					
Patients given tamoxifen	89	20	15	48 (54)	0
Patients not given tamoxifen	34	–	15	4 (12)	1 (<1)
Hann et al. (69)					
Patients given tamoxifen	91	20	38.4 (mean)	51 (66)	5 (11)*

* Includes 2 patients with endometrial cancer and 3 patients with hyperplasias that were not otherwise specified. Both cases of cancer occurred in symptomatic women with postmenopausal bleeding.

tive, endometrial sampling under hysteroscopic guidance should be done before abnormality can be excluded.

Other Imaging Methods

Sonohysterography is useful in identifying endometrial polyps, which occur frequently in both premenopausal and postmenopausal patients receiving tamoxifen and are a common cause of abnormal bleeding (75–78). This technique, which involves the sterile instillation of saline into the endometrial cavity followed by ultrasonography, can better delineate endometrial thickness and contour. Several studies have demonstrated improved ability to accurately diagnose polyps using sonohysterography. Because endometrial polyps are a common cause of abnormal bleeding in the setting of tamoxifen use, sonohysterography is particularly helpful when transvaginal ultrasonography shows an apparently thickened endometrium; it can also provide useful information when surgical treatment is being planned. As another adjunct to ultrasonography, Doppler studies (79–81) have shown a correlation between tamoxifen use and lower pulsatility and resistance indexes; however, these values have not been predictive of significant abnormality. Another effective method of evaluating the endometrium is office hysteroscopy, which allows direct visualization of the cavity. Although it is comparable to transvaginal ultrasonography and sonohysterography in terms of sensitivity and specificity, hysteroscopy may not be as well accepted by patients (82, 83).

Pretreatment Evaluation

An additional strategy for surveillance of patients receiving tamoxifen was suggested by a recent study (84) in which patients were screened with transvag-

inal ultrasonography before beginning tamoxifen therapy. Forty-six of 264 asymptomatic postmenopausal patients with breast cancer (17%) were found on initial screening to have an abnormally thick endometrial lining (>4 mm); these patients had hysteroscopic examination and biopsy. Of the 46 patients, 34 had endometrial polyps, 7 had submucous myomas, 3 had simple hyperplasia, 1 had atypical hyperplasia, and 1 had endometrial cancer. The lesions were treated by surgical resection, and all patients received tamoxifen, 20 mg/d, for up to 3 years. Follow-up ultrasonography was performed annually. The authors found that 4 of 5 patients who subsequently developed premalignant or malignant lesions during this time had received a diagnosis of endometrial lesions before treatment.

This finding suggests that those patients most at risk from tamoxifen use were women with preexisting abnormalities (usually benign polyps). With a 24% overall prevalence of endometrial polyps in the general population, the risk for developing endometrial cancer within a benign polyp has been estimated at no more than 0.5% (85). However, one prospective study of 520 patients who had polyps removed but did not undergo hysterectomy found 17 cases of endometrial cancer during a median follow-up of 10 years; 2 cases were expected (86). It is not known whether polyps found in the setting of tamoxifen exposure, which are often large and display unusual histologic features, are more likely to undergo neoplastic change. In addition, it is not clear if any increased risk associated with polyps is caused by carcinoma in the polyp itself or if the presence of a polyp is an indication of a general proliferative tendency of the endometrium. Normal findings on pelvic examination and Papanicolaou smear and an absence of abnormal bleeding or discharge should be documented before tamoxifen therapy is begun. The benefit of additional pretreat-

ment screening with ultrasonography and endometrial biopsy in this high-risk population remains controversial. The ongoing, expanded Breast Cancer Prevention Study requires baseline endometrial evaluation for patients before treatment and should provide more data as to whether the presence of pretreatment abnormalities predicts risk.

Recommendations

We propose a strategy for surveillance of women taking tamoxifen (Figure). Pretreatment evaluation of patients should include a careful gynecologic history, pelvic examination, and Papanicolaou smear. Transvaginal ultrasonography to identify occult preexisting malignant abnormalities in the endometrium and potentially symptomatic benign lesions should be considered. The possibility that patients with preexisting endometrial abnormalities will be

predisposed to tamoxifen-induced premalignant and malignant changes awaits further study. Although routine monitoring with biopsy and ultrasonography of asymptomatic women receiving tamoxifen is not recommended, these tests should be considered in women with additional risk factors for endometrial disease. Transvaginal ultrasonography is useful for monitoring patients in whom pelvic examination is difficult because of obesity, cervical stenosis, vaginismus, or reluctance to be examined. Cervical stenosis prevents the vaginal egress of uterine bleeding, and an early diagnosis of endometrial cancer can be missed because of the absence of symptoms. Although an endometrial lining measurement of 5 mm or less in a postmenopausal patient not receiving tamoxifen is well supported, published studies on women who use tamoxifen have found that a measurement of 8 mm or less in a postmenopausal woman has a high negative predictive value for cancer. In all described cases of tamoxifen-associated

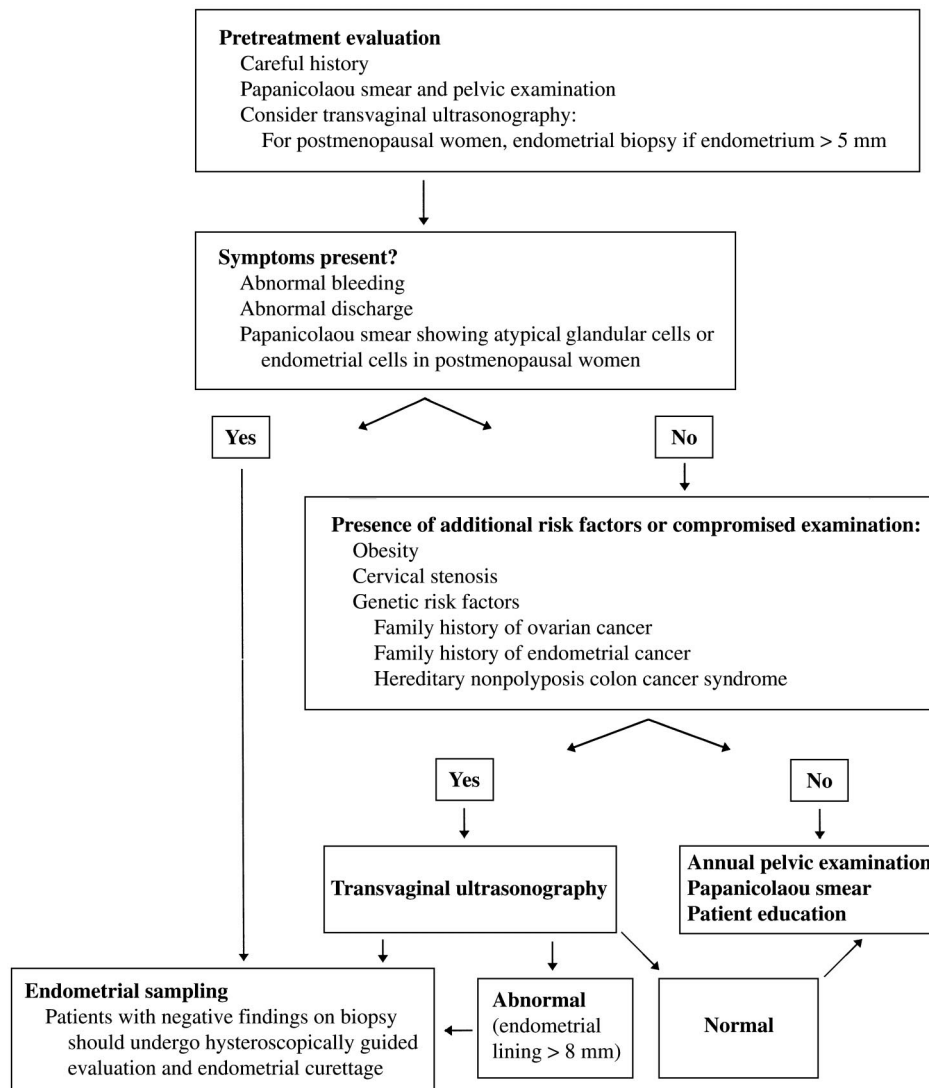


Figure. Suggested algorithm for surveillance of endometrial cancer in women receiving tamoxifen.

cancer for which ultrasonographic measurements were available, none were associated with an endometrial lining thickness of 8 mm or less.

Information from a gynecologic history and physical examination and a detailed family history can guide decisions about the intensity of gynecologic surveillance for individual patients. Annual endometrial biopsy is recommended for women with familial cancer syndromes, such as hereditary nonpolyposis colon cancer (38). Women with abnormal bleeding or vaginal discharge should have an endometrial biopsy. If the biopsy findings are negative, however, a more aggressive evaluation of the endometrium by hysteroscopy and endometrial curettage is needed in the presence of symptoms or abnormal findings on ultrasonography. A Papanicolaou smear-based diagnosis of atypical glandular cells of undetermined significance or the finding of benign endometrial cells on a Papanicolaou smear in postmenopausal women also indicate endometrial sampling.

The existing studies on the effect of tamoxifen on the endometrium have involved predominantly postmenopausal women because most of the women treated are in this group. Because of the new indication for tamoxifen as a chemopreventive agent, increasing numbers of premenopausal women will be exposed to the drug. It is unclear how these women will differ in terms of their risk for endometrial cancer. One study (87) found that premenopausal women who rapidly become amenorrheic while taking tamoxifen may be at particularly high risk for developing premalignant or malignant changes. However, insufficient evidence exists to justify increased surveillance on the basis of premenopausal status alone.

Conclusion

Despite concerns of selection and ascertainment bias in published studies, general consensus is that tamoxifen is associated with a two- to threefold increased risk for endometrial cancer and that this risk depends on both dose and duration of use. Patients with a personal or family history of breast cancer are at high risk for gynecologic cancer. Therefore, these women need to be educated about the early warning signs of endometrial cancer and questioned about these symptoms at the time of annual pelvic examination and Papanicolaou smear. Abnormal bleeding, vaginal discharge, or the finding of abnormal glandular cells on Papanicolaou smear should prompt a thorough evaluation of the endometrium. In the absence of symptoms, transvaginal ultrasonography or other methods should be used to screen for endometrial cancer on the basis of the ability to perform an adequate pelvic examination

and the presence of additional risk factors for endometrial cancer in individual patients.

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