A total of 18 studies have been published concerning the possible relationship of tamoxifen to endometrial cancer.

Introduction

There is consensus that tamoxifen is effective in preventing both metastatic disease and contralateral breast cancer. Because of its effectiveness in breast cancer treatment, the drug is now the subject of clinical trials for breast cancer prevention in healthy women at high risk for developing the disease. However, there has been considerable controversy over the possibility that tamoxifen either causes or stimulates endometrial cancer, and this has discouraged enrollment in the prevention trial.

The controversy began with a series of case reports of women diagnosed with endometrial cancer after tamoxifen treatment. Since those initial case reports, a variety of epidemiologic studies have been reported, although the findings of those studies have been far from unanimous.

It is the purpose of this paper to critically examine the epidemiologic evidence that has accumulated to date. In particular, the issues of confounding variables and bias will be explored to attempt to reconcile the differing results of the various studies.

In performing this critical analysis, I have chosen to use only studies reporting original data, and have omitted from the review most case reports, review articles, and position papers concerning tamoxifen.

The Common Epidemiology of Breast and Endometrial Cancers

Breast and endometrial cancers share many risk factors. Risk is age related and increases with early menarche, late menopause, nulliparity, obesity, and estrogen replacement therapy (ERT), although the magnitude of the risk varies for each disease. Because of their common risk factors (mostly estrogen-related), it is not surprising that the two diseases occur more frequently in the same individual than would be expected by chance.

The risk factors common to both diseases can all be viewed as potential confounding variables in any study of the relationship between breast cancer and endometrial cancer. A confounding variable is a factor related to both the independent and the outcome variable. Avoiding bias, and recognizing and controlling potentially confounding variables are issues in every epidemiologic study of the possible role of tamoxifen and endometrial cancer following breast cancer.

The epidemiologic approach to the question of possible carcinogenic effects of tamoxifen involves a choice of either cohort or case-control studies. The most obvious cohorts of tamoxifen-exposed women are the participants in the many clinical trials of the drug.

In designing a cohort study, the epidemiologist must define not only the exposed cohort but the reference cohort against which to compare the exposed group. Naturally, women in the trials who were randomized to not receive the drug are a likely comparison group, although there may be some advantage (eg, availability, sample size) to using other cohorts or populations (such as U.S. SEER data) for comparison.

It must be remembered, however, that even without tamoxifen treatment, breast cancer patients will be expected to have a higher incidence of endometrial cancer than will women without breast cancer, thus artificially inflating relative risk estimates based on the experience of non-breast cancer patients.

Surveillance Bias

If the comparison group or reference population is not under the same surveillance as women in the clinical trial, there will also be an opportunity for surveillance bias. Because tamoxifen-treated women are under closer medical watch than the general population, any second disease (eg, endometrial cancer) is more likely to be detected. This bias will be especially important if the second disease is characterized by long duration, low mortality, and infrequent symptoms.
of endometrial carcinoma. A high proportion of endometrial carcinoma may be diagnosed only after an occult phase that has been estimated to average four to six years.[9] Because of shared risk factors, and also because of surveillance bias, one can predict that any standardized incidence ratio of a tamoxifen-treated clinical trial cohort will be elevated if a non-trial population is the comparison group.

**Ascertaint Bias**

If the comparison group is another arm of a randomized clinical trial, then surveillance bias should not be operative. However, tamoxifen is known to induce several gynecologic symptoms. The nonmalignant gynecologic complications are well described in a review by Assikis and Jordan.[10] A woman undergoing tamoxifen treatment is about three times as likely to see a gynecologist because of symptoms such as hot flashes or bleeding due to endometrial proliferation.[11-13] The frequency of gynecologic conditions leads to an increase in doctor visits, which creates an ascertainment bias. Ascertainment bias will also be present, as will surveillance bias, in any comparison between a tamoxifen-exposed cohort and the general population. This bias has been recently discussed.[14]

Because of surveillance and ascertainment biases, clinical trial cohorts are not ideal groups for the study of any tamoxifen-endometrial cancer relationship unless the non-tamoxifen group undergoes the same degree of gynecologic investigation as the tamoxifen group. To date, this has not been the case. Because they were never designed to ascertain risk of endometrial cancer, the clinical trials were not planned with the same degree of gynecologic surveillance for all trial arms. Neither was there appropriate documentation of possible confounding variables, especially estrogen replacement therapy (ERT), pre- or post-tamoxifen treatment.

Since many postmenopausal women would have received ERT prior to their breast cancer diagnosis and some may have received ERT afterward, it is probably the most potent confounding variable of all, and it has been reported to increase endometrial cancer risk by as much as ninefold[8,15-17] or more with prolonged duration of use.

**Case-Control Studies**

As an alternative to following a cohort, one may use a case-control study, either population-based or within a cohort (the nested case-control study). Although cases of endometrial cancer are readily selected from any population, one must be aware of possible bias. If case selection is influenced in any way by ascertainment due to tamoxifen treatment, the study will be biased, since the exposure variable influences identification of cases.

Even if a group of endometrial cancer patients is selected without knowledge of previous exposure to tamoxifen, ascertainment bias may be present but unrecognized. Tamoxifen-induced gynecologic symptoms may have triggered the investigation that led to the diagnosis of endometrial cancer. Since the gynecologic symptoms from tamoxifen do not differ from common symptoms due to other or unknown causes, there is no easy way to identify the proportion of cases that may have been ascertained because of the tamoxifen-induced symptoms. Presumably, controls are selected from a population without an equally high probability of gynecologic investigation. As a result, there is considerable chance that any case-control study of this nature will suffer from a bias, of unknown magnitude, that will elevate relative risk estimates.

It is also possible that because of tamoxifen-associated symptoms, some women may have been prescribed estrogen therapy, adding yet another possible confounder to the situation. Although previous breast cancer is generally considered a contraindication for ERT, I know of several gynecologists who have chosen to ignore this contraindication and who continue to prescribe oral estrogens for estrogen-deficiency symptoms. Thus, it can be expected that the case-control study, like the cohort study, will be somewhat biased unless extreme care is taken in selection of cases and controls. Specific case-control studies will be examined in detail later in this article.

Similarly, since it is an important epidemiologic principle that cases should be selected without regard for exposure, any case-control study originating with a series of endometrial cancer cases appearing after tamoxifen treatment will be biased, no matter how subsequent controls are identified. For that reason, a series of tamoxifen-exposed endometrial cancer patients should not be converted into a case-control "study" by selecting a group of controls to complement exposed cases already collected. The conversion of a set of cases known to be tamoxifen-exposed into a case-control study indicates that the investigator is testing the hypothesis on the data which generated it, a clear violation of statistical principles.

Problems of ascertainment of appropriate cases carry over to the selection of controls, since this group should resemble the cases in as many ways as possible, except for tamoxifen exposure. In both cohort and case-control studies, the biases discussed above all tend to increase the apparent
relative risk of endometrial cancer due to tamoxifen. These biases could thus create either a spurious elevation of the relative risk or conceal any protective effect that would have been reflected as reduction in relative risk. Surveillance and ascertainment biases can be overcome only by using populations in which the comparison group (for cohort studies) or control group (for case-control studies) has a frequency and intensity of gynecologic examinations that equal the tamoxifen-treated cohort or the cases in a case-control study.

A further problem for any epidemiologic study is the issue of latency. One must be careful to define latency, since to some it may mean time from exposure to tumor initiation, and to others the time to clinical appearance. For the epidemiologist, the latter definition is the usual, but it does allow for several phases of the tumor, including tumor initiation, promotion, and, finally, sufficient growth to create symptoms. Although the latency period for induction of endometrial cancer is unknown, experience with other cancers and other substances suggests that as many as five years or more may be needed for cancer to develop and be detected.

It is still possible, however, that tamoxifen could either promote tumor growth or cause symptoms (eg, bleeding) from a pre-existing tumor, thus shortening latency. This issue will be addressed with reference to specific studies.

Although tamoxifen has undergone many clinical trials, none of its published studies give mortality rates for endometrial cancer, and few trials report on incidence of endometrial or other non-breast cancers. This leads one to suspect publication bias, wherein investigators in trials with an excess of endometrial cancer publish, while those without do not.

**Clinical Trial Cohorts**

**The National Surgical Adjuvant Breast and Bowel Project B-14**

This project (also known as NSABP B-14), described in several publications, involves 2,843 breast cancer patients randomly assigned to either tamoxifen (20 mg/day) or placebo from January 1982 to January 1988.[11,13] An additional 1,220 women registered to receive the drug without randomization. Trial patients were followed an average of eight years and registered patients an average of five years. The end date for the follow-up has not been published.

For endometrial cancer, the authors report an average annual incidence rate of 1.7/1000 in the tamoxifen group, compared to a rate of zero for the placebo group. The lack of any cases in the placebo group prevents any computation of relative risk, and throws into question the usefulness of this reference group. Recognizing this, the authors compared the tamoxifen group against two other populations— the NSABP B-06 placebo group and SEER data, which cover about 10 percent of the US population.

On the basis of those comparisons, the relative risk for tamoxifen-treated women is 2.3 (NSABP B-06) or 2.2 (SEER). In considering the SEER comparison, it should be remembered that breast cancer itself confers a relative risk for endometrial cancer of 1.7 over a 20-year period, with most of the excess incidence in the first five years after breast cancer diagnosis.[7] Thus, there is little, if any, increase in endometrial cancer incidence over that expected.

The original relative risk of 7.5 reported in this study was based upon 15 cases of endometrial cancer, compared to the original placebo group. Of the 15, however, two were sarcomas, and one other was found not to be carcinoma on pathology review. Of the 12 true endometrial cancers, one never received the drug and five others had fewer than three years of latency. Results for the registered group were similar to those for the clinical trial.

Within the randomized trial, there were five deaths attributed to endometrial cancer among the tamoxifen group with no such deaths in the placebo group. The authors give a detailed account of the errors in pathology in some cases, and of the total lack of tamoxifen exposure in one of the five.

There is no statistical analysis of mortality from endometrial cancer.

As with the other trials, this study was not designed to examine the relationship of tamoxifen to endometrial cancer. The authors point out that the tamoxifen group had more gynecologic attention than the placebo group, creating both ascertainment and surveillance biases. Although there is evidence from the cancer cases that some placebo women took the drug and some tamoxifen women never received the drug, the extent of this break in randomization is not known for the great majority of participants.

There is incomplete information concerning use of exogenous estrogens before, during, and after tamoxifen treatment. To control for the effect of age, it appears that the randomization was stratified only on the basis of above and below age 50 at time of entry into the trial. This may be too crude a stratification for a disease as age-dependent as endometrial carcinoma.
In summary, the alternative relative risk of about two, as reported by Fisher et al, is of a magnitude that can be explained by increased gynecologic surveillance which increased the probability of diagnosis, as well the effect of confounding by other variables such as age, and especially by ERT, for which the authors had incomplete data.

Because the higher reported relative risk of 7.5 is based upon an intention-to-treat analysis, and has the other problems discussed above, that estimate should probably be disregarded.

**The Stockholm Study**

The Stockholm study results were originally presented in three papers by Fornander et al.

Postmenopausal, postsurgical patients were randomized to either two years of 40 mg daily tamoxifen or no tamoxifen. From November 1976 to September 1986, 931 patients were allocated to the tamoxifen group and 915 to the control group. The patients also received either radiotherapy or adjuvant CMF chemotherapy comprised of cyclophosphamide, methotrexate, and 5-fluorouracil.

In the 1989 report of follow-up through May 1987, the authors reported a risk ratio of 6.4 for uterine cancers in the tamoxifen-treated group, based on 13 cases in the treated group, and two cases in the control group.

In their 1991 report of this trial, with slightly shorter follow-up (to January 1987), the authors report similar results for endometrial cancer (with minor discrepancies) and the important finding that tamoxifen-treated patients had a relative risk of 3.2 for admission to hospital for benign gynecologic disease other than prolapse or bleeding. This finding indicates that gynecologic symptoms were much more common in the tamoxifen group, leading to a greater likelihood of diagnosis of any previously silent endometrial cancer.

In 1993, the authors reported on a follow-up through 1990. The number of endometrial cancer cases with tamoxifen treatment was now 17, compared to five among those not receiving tamoxifen.

Pathology review of the 17, however, found one patient with a mixed mesodermal tumor, not endometrial cancer. The findings translate to a relative risk of about three. However, of the 16 endometrial cancers among the tamoxifen-treated group, five were diagnosed in the first two years and 10 within the first three years.

In the series of Fornander reports, a nonsignificant increase in cancer mortality was reported, with at least three deaths attributed to endometrial cancer in the tamoxifen group. The data presented are inadequate for a proper examination of the effect of tamoxifen on mortality.

Although the Fornander et al results are widely interpreted that tamoxifen increases endometrial cancer incidence with a relative risk of about six, closer examination of the published data does not support this conclusion. Rather, the magnitude of risk is about three, similar to the risk of hospital admission for benign gynecologic conditions after tamoxifen treatment. Furthermore, most of the endometrial tumors occurred within the first few years, with insufficient latency to attribute carcinogenesis to tamoxifen. The data suggest one or more of four alternatives:

1. Tamoxifen treatment increases the likelihood of diagnosis of pre-existing endometrial cancer by greater diagnostic activity (ascertainment bias);
2. Tamoxifen increases the likelihood of uterine bleeding from pre-existing endometrial cancers;
3. Tamoxifen greatly accelerates tumor initiation;
4. Tamoxifen greatly accelerates tumor growth.

There are several caveats to any interpretation of the Fornander et al reports. The clinical trial was never designed to examine the endometrial cancer issue. The authors present no data concerning the major potential confounder of ERT. It is clear that some of the group assigned to tamoxifen never began treatment. Although the authors are certain of the tamoxifen/nontamoxifen status of patients diagnosed with endometrial cancer, there is no report of any validation of the treatment status of the other women in the trial. Thus, the denominators of the tamoxifen exposed and unexposed are in doubt. Finally, there is the issue of reporting. It may be that endometrial cancer in tamoxifen-treated women is more likely to be reported (to a registry or to trial investigators) than cancer in cases without such treatment.

A subsequent report of this study by Rutqvist, as part of a meta-analysis, will be discussed later in this article.

**The Danish Trial**

The Danish trial had three treatment arms; after primary surgery, low-risk patients (n = 1,828) were given no further therapy, while the high-risk group was randomized to either radiotherapy alone (n = 846) or radiotherapy with tamoxifen (n = 864). Maximum follow-up was 12 years.
Among the low-risk group, 11 women developed endometrial cancer, for a Standardized Incidence Ratio (SIR) of 1.1. The radiotherapy only group had two cases, for an SIR of 0.6, while the tamoxifen group had seven cases with an SIR of 1.9. None of the SIRs was statistically significant when compared either to the Danish population or to each other.

The average latency for the low-risk group was 4.3 years after surgery, and for the radiotherapy plus tamoxifen group, only 2.3 years. This disparity in the time since surgery indicates that ascertainment bias may well have been operating. Among the tamoxifen-treated, all endometrial cancers occurred within the first five years, with six of the seven occurring in the first four years.

The Danish trial had problems with small numbers and lack of information concerning confounding variables. The tamoxifen group was also slightly older. Because the groups were compared to the Danish population for calculation of SIRs, both surveillance and ascertainment biases are probable. Despite indicating a risk ratio of 3.3 (NS), the most recent data from this study offer little or no support for a relationship between tamoxifen and endometrial cancer.

**The South Swedish Study**
Problems with this study were described even before the results were published.[23,24] After radical mastectomy, 719 postmenopausal breast cancer patients were randomized into three treatment arms: radiotherapy alone, radiotherapy plus tamoxifen, or tamoxifen alone. There were two, four, and five cases of endometrial cancer, respectively. Although the authors present no statistical analysis, they comment that the incidence of endometrial cancer in the three groups did not differ to a statistically significant degree.

**The Rutqvist et al Re-Analysis**
In their 1995 re-analysis of three previous studies, Rutqvist et al combined results from the Stockholm, South Swedish, and Danish studies.[20] The study received editorial criticism on statistical grounds, especially concerning the possible relationship of tamoxifen to risk of colorectal cancer.[25]

**Table 1** displays the numbers published for the Stockholm trial, at various times. The size of this trial has been consistently increasing, because of the continued acquisition of patients until 1990. Rutqvist et al, however, give no data concerning the latency of the endometrial cancers, nor do they discuss pathologic findings. There is no explanation as to why the total number of endometrial cancers in the controls appears to have fallen over time. One of the differences with the previous Fornander et al analyses may be because Rutqvist et al have now used an intention-to-treat analysis, which is a dubious technique when second primary cancers are the concern.

In using the data from the Danish trial, Rutqvist et al omitted any consideration of the 1,828 patients who received no treatment at all.[21,22] As discussed above, the radiation therapy-only group had a low endometrial cancer incidence (SIR = 0.6) while the untreated group had an SIR of 1.1. By selecting the lower incidence group as their referent population for calculation of relative risks, Rutqvist et al artificially inflated the relative risk calculation for tamoxifen.

The third study included by Rutqvist et al, the South Swedish Breast Cancer Study, has many well-documented problems of patient compliance and morbidity and mortality reporting. [23,24] For these reasons, it is probably preferable not to include this study in any attempted meta-analysis. In summary, Rutqvist et al attempted a meta-analysis of three different studies, using numbers that do not match previous publications. Each study has, in and of itself, various methodological difficulties. Finally, there are severe statistical problems as outlined by Simon.[25]

**The International Breast Cancer Study**
This study followed 320 postmenopausal patients, 167 of whom received a combination of tamoxifen with prednisone, while the remaining 153 were only observed.[26] The study reported a mean observation period of 96 months. None of the patients (treated or untreated) had an endometrial cancer appear during the observation period.

**The Edmonton-Toronto Study**
In 1991, a group of Canadian investigators published an abstract describing the results of a tamoxifen trial.[27] Of 1,874 women treated with tamoxifen, there were two sarcomas and one endometrial carcinoma of the uterus. In the 8,201 patients without tamoxifen treatment, there were 26 adenocarcinomas and two sarcomas. This gives a relative risk of 0.47 (CI = 0.14-1.54) for endometrial cancer.

**The Christie Hospital Clinical Trial**
Ribiero and Swindell reported on 10 years of follow-up of a clinical trial in which premenopausal postsurgical patients received either radiation or tamoxifen while postmenopausal patients received either tamoxifen or no further treatment.[28] Patients were randomized after stratification by menopausal status, with 481 receiving tamoxifen and 480 receiving no tamoxifen.
After 10 years of follow-up, each of the two groups had one case of endometrial cancer. The small numbers of endometrial cancers limit the power of this study, but the data fail to support any association between tamoxifen and endometrial cancer.

**The Scottish Trial**

Stewart reported a set of four trials involving 1,312 patients, of whom 747 received tamoxifen, about half as short-term therapy and half as long-term adjuvant treatment.[29] Each group recorded one new case of endometrial cancer. Although it is not clear as to how rates were calculated, the author reported no increase in endometrial cancer incidence.

A follow-up to the Scottish trials was published as an abstract indicating an increased risk of uterine (site not otherwise specified) cancer after 10 years of tamoxifen therapy.[30] This information is difficult to interpret because of the paucity of data supplied within the abstract. There is no information concerning either the pathology of the tumors or the ERT status of the women.

**The Breast Cancer Adjuvant Chemo-Hormone Therapy Cooperative Group (GROCTA) Trial**

This trial followed 504 patients, age 35 to 60 years, randomized into three groups: tamoxifen, chemotherapy, or tamoxifen plus chemotherapy.[31,32] The patients were followed for a median period exceeding 60 months. Only one woman in the combination therapy group developed endometrial cancer. Gynecologic symptoms, however, were significantly more frequent in tamoxifen-treated women.

**The Eastern Cooperative Oncology Group (ECOG) Study**

This publication consists of 168 postmenopausal women given either tamoxifen or placebo, followed for a median of 10 years.[33] There were 83 in the placebo group and 85 in the tamoxifen group. One endometrial cancer occurred in each group.

**The Royal Marsden Chemoprevention Trial**

Although this is a pilot study for a massive chemoprevention study, it does provide data for 2,012 women receiving tamoxifen from October 1986 to June 1993.[34] Mean follow-up was 35 months. Unfortunately, the authors do not give numbers for the incidence of endometrial carcinoma in the trial and predict that results will be available for determining that risk only after the year 2002. To date, however, they have seen no evidence that would deter them from continuing the trial and expanding it to a larger study. The study did find a higher incidence of fibroids with tamoxifen, but there was no significant increase in the hysterectomy rate.

**Clinical Studies**

**The Neven Prevalence Study**

Neven et al performed hysteroscopies on 14 patients taking tamoxifen and 42 controls.[35] Both cases and controls had abnormal postmenopausal bleeding. Three controls and one case were found to have endometrial cancer. Although numbers are small, the study demonstrates an identical prevalence of endometrial cancer in the two groups, and does not support the elevated risk reported in the Fornander and Fisher studies. However, the authors noted that the tamoxifen group had an increased incidence of endometrial polyps and hyperplasia, both conditions that could lead to bleeding and, hence, more investigation, had they been left to become symptomatic.

**The Cleveland Study**

Hubay et al have reported the results of a randomized controlled trial comparing tamoxifen plus chemotherapy to chemotherapy alone.[36] Of 311 women receiving tamoxifen and followed for eight years, only one case of nonfatal endometrial cancer was reported. No cases occurred in the chemotherapy group.

**The Athens Series**

In 1992, Potamianou et al published a five-year follow-up of 288 breast cancer patients treated with tamoxifen and 108 not treated with tamoxifen.[37] They reported no cases of endometrial cancer in either group. Although this is not a randomized clinical trial, and there is no information concerning why women were or were not given tamoxifen treatment, there appears to be no increase in risk from tamoxifen.

**The Lahti Cross-Sectional Study**

Lahti et al performed hysteroscopies on 103 asymptomatic breast cancer patients, 51 of whom had been treated with tamoxifen.[38] One of the tamoxifen patients had endometrial carcinoma, as compared to two not exposed to the drug. Like the study by Neven et al, this paper demonstrates that tamoxifen-treated women do not appear to have a higher rate of endometrial cancer when the controls are subjected to the same intensity of investigation, such as hysteroscopy. The tamoxifen group did have a statistically significant increase in the prevalence of endometrial polyps.
The Hardell Study
In a series of letters to the editor, Hardell described a collection of cases of endometrial cancer in women with a history of breast cancer.[39-41] After the first publication, he selected a number of controls to attempt to change the case series into a case-control study. Because the cases were first selected due to their tamoxifen exposure, the approach is invalid as a case-control study. Even so, exposure to tamoxifen alone (without pelvic irradiation) produced no significant elevation in the odds ratio (OR = 2.6, CI = 0.7-9.6).

Case-Control Studies

The Netherlands Case-Control Study
In 1994, vanLeeuwen et al published their case-control study of endometrial cancer following breast cancer.[42] Using registries, they identified 98 such patients. They then selected 385 controls, matched on the basis of age, year of breast cancer diagnosis, and survival time with an intact uterus. Using multivariate analysis, the authors reported a relative risk from tamoxifen treatment of 1.3 (CI = 0.7-2.4). Although there was no significant elevation in relative risk for any particular cumulative dose or duration of treatment, both duration and cumulative dose showed a significant trend (P = 0.049 and p = 0.046, respectively). For both duration and cumulative dose, the highest relative risk was 3.0 (based on three cases) and was not statistically significant. In both instances, the lower quartiles of tamoxifen exposure gave relative risks of less than unity. Clearly, this study is open to differing interpretations, and can be considered compatible with either no effect or a mild effect. Although the authors inserted several control variables, including ERT, the numbers are small for calculating dose-response relationships, especially in the absence of any significant relative risk for any single dose or duration, or ever/never treated. Although it is a case-control study based on registry cases, there is still a possibility of ascertainment bias because of the increased gynecologic symptoms and diagnostic testing among the tamoxifen-treated women. For that reason, minor elevations of relative risk are compatible with ascertainment bias.

The Seattle Case-Control Study
In 1995, Cook et al published a population-based, nested case-control study from a cohort of women diagnosed with breast cancer between 1978 and 1990.[43] From the cohort, they were able to use 36 cases of endometrial cancer, that were then matched with 66 controls from the same cohort, based on the following criteria: year of breast cancer diagnosis, age, and stage of disease. Potential controls were disqualified if they had a previous hysterectomy. Through review of previous medical records, the study team also gathered data on several variables, such as ERT, family history, and other risk factors. The authors also went to considerable lengths for quality control, including verification of tamoxifen use. The relative risk for any tamoxifen use was 0.6 (CI = 0.3-1.9), and ranged from 0.2 (CI = 0.1-1.04) for women using tamoxifen for more than 12 months, to 1.6 (CI = 0.4-7.0) for less than one year of use. Clearly, there was no excess risk associated with tamoxifen use. The Cook study, like the vanLeeuwen study, has the potential for ascertainment bias, due to more frequent gynecologic exams among users of tamoxifen. Thus, even the relative risk of 0.6 may be biased upward, and it is possible that a significant protective effect of tamoxifen (against endometrial cancer) might exist and be hidden by the bias. Although the numbers are not large, the study has considerable power. Using a = 0.05, the study has an 80% power to detect a relative risk of 2.5 or greater. The authors point out that their follow-up (latency) for many of the women is not adequate to rule out a long-term effect. However, since the other studies that conclude that tamoxifen increases endometrial cancer risk are based upon the early-onset cases, the Cook study, with its careful consideration of the possible confounders (especially ERT), would seem to offset these earlier reports.

The Wilfred Hall Cohort
Although Robinson et al analyze and present this as a case-control study, the data collection is really more like a cohort study.[44] The authors assembled, from medical records, a cohort of 1,017 breast cancer patients diagnosed and treated between 1978 and 1989. The patients were not part of any formal clinical trial. Of the cohort, 586 patients were judged to have adequate records, a uterus in situ, and primary breast cancer. Of that group, 108 had received tamoxifen in varying doses, and 478 appeared to have had no tamoxifen. After an average of nine years of follow-up (range 5 to 16 years), four endometrial cancers had occurred in each group. The most appropriate analysis would have been to use incidence rates with person-years as a
Risk of Endometrial Cancer After Tamoxifen Treatment
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denominator. Instead, the authors treated the entire group as a large case-control study. Although the crude relative risk calculates out to 4.43 (CI = 1.12-17.42), the authors claim that by using a Mantel-Haenzel statistic, they find an odds ratio of 15.2 (CI = 2.8-84.4). This dramatic increase in the odds ratio by stratifying on the variables of hypertension and diabetes is remarkable. Also remarkable is the authors' decision not to stratify on age, since the tamoxifen patients were an average of five years older than the others. There is no information given as to latency (since breast cancer diagnosis) of the endometrial cancers, although mean duration of treatment was about 37 months. The study excluded from the analysis women who took tamoxifen for less than one year. This study is surprising in many respects. Although the authors gathered considerable data on several variables such as diabetes, hypertension, and family history, they make no mention of ERT prior to breast cancer. They have chosen to ignore the opportunity to perform a cohort analysis and instead have used a case-control approach. The results published (relative odds of 15.2) do not approximate the relative risk of 4.43 that can be calculated from their Table 3. Finally, this cohort is not a randomized clinical trial and we know nothing of the factors that influenced the clinicians' decision to treat or not to treat with tamoxifen. For all of the above reasons, this study should not be considered particularly useful in evaluating the tamoxifen-endometrial cancer relationship.

The Lyon Case-Control Study
Recently, Sasco et al published the results of a case-control study conducted in Lyon.[45] Earlier, some of the same authors had published a series of cases of breast cancer with subsequent endometrial cancer after tamoxifen therapy.[46] In the earlier paper, they mentioned that more definitive studies were now under way. If the original 20 cases described by Mignotte were included in the study reported in 1995, there is a likelihood of severe bias by using the cases with known tamoxifen exposure as a starting point. As the authors point out, the source of patients in the case-control study was a combination of a registry and data from participating hospitals in the region. There is no mention in the 1996 paper that the patients from the original case series were excluded.

The study is composed of 43 cases of endometrial cancer diagnosed at least one year after diagnosis of breast cancer, with 177 controls matched on age, region, year of breast cancer diagnosis, and survival from breast cancer. There is no mention of ERT.

The study reports an odds ratio of 1.4 (CI = 0.6-3.50) for ever-use of tamoxifen, with a dose of over 20 mg/day giving a slightly lower odds ratio than 20 mg or less. Castration, on the other hand, produced an odds ratio of 6.3 (CI = 1.5-26.1). A multivariate analysis increased the tamoxifen odds ratio to 2.8 (CI = 0.69-17.0) for five years or fewer and 4.4 (CI = 0.68-27.9) for more than five years. The multivariate analysis also reduced the castration odds ratio to 4.2 (CI = 0.57-30.8).

The mild and not statistically significant elevations of relative odds from tamoxifen treatment are compatible with both ascertainment bias (see earlier discussions) and/or bias due to an inclusion of the cases that prompted the study. There is also the possibility of more ERT in the tamoxifen-treated women, although this variable was not discussed. The study does not provide strong evidence for a causal link between tamoxifen and endometrial cancer.

Discussion
In assessing a potential causal relationship between tamoxifen and endometrial cancer, it is important to look at the epidemiologic strength of the reported association, its consistency, and whether the finding could be explained by some factor other than tamoxifen. Other criteria for causality include dose-response and biologic plausibility.

Table 1 indicates that the relative risks reported range from 0.47 (protective) to infinity. Most risks cluster near unity or under three, especially if appropriate controls are used. Epidemiologists would refer to this as a mild elevation in risk, at most. The studies by vanLeeuwen et al[42] and Cook et al[43] are probably the best-designed studies, since they were able to control for the potential confounding effect of ERT. These two studies, with overlapping confidence limits for odds ratio calculations, have compatible findings of no significant excess relative risk for persons ever treated with tamoxifen. The studies differ, however, in the question of dose-response, and there is no immediate explanation for the differences.

As a group, the Table 1 study results are inconsistent, with most trials not replicating the increased risks reported by Fornander and Fisher, and none of the case-control studies finding any significant increase in risk.

For this question, there is a high probability that most (including case-control) studies suffer from confounding and from bias of various sorts, as discussed above. The single greatest problem appears
to be the increased gynecologic surveillance of tamoxifen-treated women. This increase in surveillance (due to symptoms or concern over cancer) will almost certainly lead to a higher degree of endometrial cancer ascertainment among tamoxifen-treated women. Both of the large studies that report a significant increase in relative risk note that treatment and hospitalization for gynecologic symptoms were more frequent in the tamoxifen-treated group.[12,13]

In addition to the ascertainment and surveillance biases previously discussed, only two studies incorporated any variable concerning ERT, which may be more frequent in the tamoxifen-treated women because of the menopausal symptoms it induces.[42,43]

Because the clinical trials were never designed to answer the endometrial cancer question and because those trials all suffer from inadequate data concerning confounders (and even treatment compliance), they are of limited use in assessing the possible relationship.

The case-control studies have the advantage of being able to collect more data concerning ERT and other possible confounding variables. Because the vanLeeuwen and Cook studies can be interpreted as either contradictory or similar, they await confirmation, hopefully by studies with larger numbers.

Dose-response has been examined in only a few of the trials. The vanLeeuwen study found a significant trend with dose, but no statistically significant elevation in relative risk. The Cook study found lesser risk with higher dose.

The greatest lack of biologic credibility comes from the finding that many of the alleged tamoxifen-related cancers appeared within the first few years of starting therapy. Because of the probability that some or many of the endometrial tumors preceded the tamoxifen treatment, there are serious questions concerning the temporal association of the tumors with the drug. From the data, it is impossible to tell whether increased relative risks are due to the effect of increased surveillance, symptom-inspired investigation, promotion of bleeding in existing tumors, stimulation of a premalignant condition, or a combination of the above. It seems highly unlikely that the results to date reflect tumor initiation by tamoxifen.

Since the epidemiologic evidence fails to meet conventional criteria for association, the fairest conclusion is the Scottish verdict of "not proven" until further evidence is available. One would hope that future studies will be able to avoid or control for the severe confounding present in many of the studies reported thus far.

References:


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