

Does tamoxifen use increase the risk of endometrial cancer in premenopausal patients?

In a large, nationwide retrospective longitudinal cohort study that examined the occurrence of endometrial cancer and other uterine pathology in patients using tamoxifen for treatment of invasive breast cancer compared with breast cancer patients not receiving tamoxifen, the authors found **a 3.77-fold increased risk of endometrial cancer in premenopausal patients using tamoxifen. These data conflict** with multiple previously published randomized controlled trials that demonstrated an increased risk of endometrial cancer in the postmenopausal population (but not in premenopausal patients). The experts suggest that **a study design issue in the recent study may explain these disparate findings.**

Ryu KJ, Kim MS, Lee JY, et al. Risk of endometrial polyps, hyperplasia, carcinoma, and uterine cancer after tamoxifen treatment in premenopausal women with breast cancer. *JAMA Netw Open*. 2022;5:e2243951.

EXPERT COMMENTARY

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Tamoxifen is a selective estrogen receptor modulator (SERM) approved by the US Food and Drug Administration (FDA) for both adjuvant treatment of invasive or metastatic breast cancer with

hormone receptor (HR)-positive tumors (duration, 5 to 10 years) and for reduction of future breast cancers in certain high-risk individuals (duration, 5 years). It is also occasionally used for non-FDA approved indications, such as cyclic mastodynia.

Because breast cancer is among the most frequently diagnosed cancers in the United States (297,790 new cases expected in 2023) and approximately 80% are HR-positive tumors that will require hormonal adjuvant therapy,¹ physicians and other gynecologic clinicians should have a working understanding of tamoxifen, including the risks and benefits associated with its use. Among the recognized serious adverse effects of tamoxifen is the increased risk of endometrial cancer in menopausal patients. This adverse effect creates a potential conundrum for clinicians who may be managing patients with tamoxifen to treat or prevent

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breast cancer, while also increasing the risk of another cancer. Prior prospective studies of tamoxifen have demonstrated a statistically and clinically significant increased risk of endometrial cancer in menopausal patients but not in premenopausal patients.

A recent study challenged those previous findings, suggesting that the risk of endometrial cancer is similar in both premenopausal and postmenopausal patients taking tamoxifen for treatment of breast cancer.²

Details of the study

The study by Ryu and colleagues used data from the Korean National Health Insurance Service, which covers 97% of the Korean population.² The authors selected patients being treated for invasive breast cancer from January 1, 2003, through December 31, 2018, who were between the ages of 20 and 50 years when the breast cancer diagnosis was first made. Patients with a diagnostic code entered into their electronic health record that was consistent with menopausal status were excluded, along with any patients with a current or prior history of aromatase inhibitor use (for which one must be naturally, medically, or surgically menopausal to use). Based on these exclusions, the study cohort was then assumed to be premenopausal.

The study group included patients diagnosed with invasive breast cancer who were treated with adjuvant hormonal therapy with tamoxifen (n = 34,637), and the control group included patients with invasive breast cancer who were not treated with adjuvant hormonal therapy (n = 43,683). The primary study end point was the finding of endometrial or uterine pathology, including endometrial polyps, endometrial hyperplasia, endometrial cancer, and other uterine malignant neoplasms not originating in the endometrium (for example, uterine sarcomas).

Because this was a retrospective cohort study that included all eligible patients, the 2 groups were not matched. The treatment group was statistically older, had a higher body mass index (BMI) and a larger waist circumference, were more likely to be

hypertensive, and included more patients with diabetes than the control group—all known risk factors for endometrial cancer. However, after adjusting for these 4 factors, an increased risk of endometrial cancer remained in the tamoxifen group compared with the control group (hazard ratio [HR], 3.77; 95% confidence interval [CI], 3.04–4.66). In addition, tamoxifen use was independently associated with an increased risk of endometrial polyps (HR, 3.90; 95% CI, 3.65–4.16), endometrial hyperplasia (HR, 5.56; 95% CI, 5.06–6.12), and other uterine cancers (HR, 2.27; 95% CI, 1.54–3.33). In a subgroup analysis, the risk for endometrial cancer was not higher in patients treated for more than 5 years of tamoxifen compared with those treated for 5 years or less.

Study strengths and limitations

A major strength of this study was the large number of study participants (n = 34,637 tamoxifen; n = 43,683 control), the long duration of follow-up (up to 15 years), and use of a single source of data with coverage of nearly the entire population of Korea. While the 2 study populations (tamoxifen vs no tamoxifen) were initially unbalanced in terms of endometrial cancer risk (age, BMI, concurrent diagnoses of hypertension and diabetes), the authors corrected for this with a multivariate analysis.

Furthermore, while the likely homogeneity of the study population may not make the results generalizable, the authors noted that Korean patients have a higher tendency toward early-onset breast cancer. This observation could make this cohort better suited for a study on premenopausal effects of tamoxifen.

Limitations. These data are provocative as they conflict with level 1 evidence based on multiple well-designed, double-blind, placebo-controlled randomized trials in which tamoxifen use for 5 years did not demonstrate a statistically increased risk of endometrial cancer in patients younger than age 50.³⁻⁵ Because of the importance of the question and the implications for many premenopausal women being treated

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with tamoxifen, we carefully evaluated the study methodology to better understand this discrepancy.

Methodological concerns

In the study by Ryu and colleagues, we found the definition of *premenopausal* to be problematic. Ultimately, if patients did not have a diagnosis of menopause in the problem summary list, they were assumed to be premenopausal if they were between the ages of 20 and 50 and not taking an aromatase inhibitor. However, important considerations in this population include the cancer stage and treatment regimens that can and do directly impact menopausal status.

Data demonstrate that early-onset breast cancer tends to be associated with more biologically aggressive characteristics that frequently require adjuvant or neoadjuvant chemotherapy.^{6,7} This chemotherapy regimen is comprised most commonly of Adriamycin (doxorubicin), paclitaxel, and cyclophosphamide. Cyclophosphamide is an alkylating agent that is a known gonadotoxin, and it often renders patients either temporarily or permanently menopausal due to chemotherapy-induced ovarian failure. Prior studies have demonstrated that for patients in their 40s, approximately 90% of those treated with cyclophosphamide-containing chemotherapy for breast cancer will experience chemotherapy-induced amenorrhea (CIA).⁸ Although some patients in their 40s with CIA will resume ovarian function, the majority will not.^{8,9}

Due to the lack of reliability in diagnosing CIA, blood levels of estradiol and follicle stimulating hormone are often necessary for confirmation and, even so, may be only temporary. One prospective analysis of 4 randomized neoadjuvant/adjuvant breast cancer trials used this approach and demonstrated that 85.1% of the study cohort experienced chemotherapy-induced ovarian failure at the end of their treatment, with some fluctuating back to premenopausal hormonal levels at 6 and 12 months.¹⁰

Furthermore, in the study by Ryu and colleagues, there is no description or confirmation of menstrual patterns in the study group to support the diagnosis of ongoing premenopausal status. Data on CIA and loss of ovarian function, therefore, are critical to the accurate categorization of patients as premenopausal or menopausal in this study. The study also relied on consistent and accurate recording of appropriate medical codes to capture a patient’s menopausal status, which is unclear for this particular population and health system.

In evaluating prior research, multiple studies demonstrated no increased risk of endometrial cancer in premenopausal women taking tamoxifen for breast cancer prevention (TABLE).^{3,5} These breast cancer prevention trials have several major advantages in assessing tamoxifen-associated endometrial cancer risk for premenopausal patients compared with the current study:

- Both studies were prospective double-blind, placebo-controlled randomized clinical

TABLE Risk of endometrial cancer in patients taking 5 years of tamoxifen vs placebo according to prospective RCTs^{3,5}

Trial	Premenopausal (< age 50)			Postmenopausal (≥ age 50)		
	RR (95% CI) vs placebo	Incidence/1,000 over 5 years		RR (95% CI) vs placebo	Incidence/1,000 over 5 years	
		Tamoxifen	Placebo		Tamoxifen	Placebo
NSABP-P1 ³	1.21 (0.41–3.6)	1.32	1.09	4.01 (1.7–10.9)	3.05	0.76
IBIS meta-analysis ⁵	1.19 (0.53–2.65)	0.15	0.08	3.32 (1.95–5.67)	5.6	1.5

Abbreviations: CI, confidence interval; IBIS, International Breast Cancer Intervention Study; NSABP-P1, National Surgical Adjuvant Breast and Bowel Project P-1 Study; RCTs, randomized controlled trials; RR, risk ratio/relative risk.

WHAT THIS EVIDENCE MEANS FOR PRACTICE

While the data from the study by Ryu and colleagues are provocative, the findings that premenopausal women are at an increased risk of endometrial cancer do not agree with those of well-designed previous trials. Our concerns about categorization bias (that is, women in the treatment group may have been menopausal for some or all the time they were taking tamoxifen but were not formally diagnosed) make the conclusion that endometrial cancer risk is increased in truly premenopausal women somewhat specious. In a Committee Opinion (last endorsed in 2020), the American College of Obstetricians and Gynecologists (ACOG) stated the

following: “Postmenopausal women taking tamoxifen should be closely monitored for symptoms of endometrial hyperplasia or cancer. Premenopausal women treated with tamoxifen have no known increased risk of uterine cancer and as such require no additional monitoring beyond routine gynecologic care.”¹² Based on multiple previously published studies with solid level 1 evidence and the challenges with the current study design, we continue to agree with this ACOG statement.

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breast cancer prevention trials with carefully designed and measured outcomes.

- Since these were breast cancer prevention trials, administration of gonadotoxic chemotherapy was not a concern. As a result, miscategorizing patients with chemotherapy-induced menopause as premenopausal would not be expected, and premature menopause would not be expected at a higher rate than the general population.
 - Careful histories were required prior to study entry and throughout the study, including data on menopausal status and menstrual and uterine bleeding histories.¹¹
- In these prevention trials, the effect of tamoxifen on uterine pathology demonstrated

repeatable evidence that there was a statistically significant increased risk of endometrial cancer in postmenopausal women, but there was no similar increased risk of endometrial cancer in premenopausal women (TABLE).^{3,5} Interestingly, the magnitude of the endometrial cancer risk found in the premenopausal patients in the study by Ryu and colleagues (RR, 3.77) is comparable to that of the menopausal group in the prevention trials, raising concern that many or most of the patients in the treatment group assumed to be premenopausal may have indeed been “menopausal” for some or all the time they were taking tamoxifen due to the possible aforementioned reasons. ●

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