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Utilization of Gynecologic Services in Women with Breast Cancer Receiving Hormonal Therapy

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Abstract

Background—The selective estrogen receptor modulator tamoxifen is now widely used for the treatment and prevention of breast cancer. Tamoxifen use has been associated with a variety of gynecologic problems. Despite the frequency with which hormonal therapy is used for the treatment of breast cancer, limited population-level data is available to describe the occurrence of gynecologic conditions and the use of surveillance testing in women who are receiving tamoxifen and aromatase inhibitors.

Objective—We performed a population-based analysis among women with breast cancer receiving hormonal therapy with tamoxifen, a drug commonly used in premenopausal and sometimes postmenopausal women, to determine the frequency of gynecologic abnormalities and use of diagnostic and surveillance testing. We compared these findings to women treated with aromatase inhibitors, agents commonly used in postmenopausal women.

Study Design—The MarketScan database was used to identify women diagnosed with breast cancer from 2009–2013 who underwent mastectomy or lumpectomy. Women receiving tamoxifen

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(<50 vs. ≥50 years) were compared to women ≥50 years of age treated with aromatase inhibitors. We examined the occurrence of gynecologic symptoms and diseases (vaginal bleeding, endometrial polyps, endometrial hyperplasia, and endometrial cancer) and gynecologic procedures and interventions (transvaginal ultrasound, endometrial biopsy, hysteroscopy/dilation and curettage, and hysterectomy). Time-dependent analyses were performed to examine symptoms and testing.

Results—A total of 75,170 women, including 15,735 (20.9%) <50 treated with tamoxifen, 13,827 (18.4%) women ≥50 treated with tamoxifen, and 45,608 (60.7%) women ≥50 years treated with aromatase inhibitors were identified. The cumulative incidence of any gynecologic symptom or pathologic diagnosis during the study period was 20.2%, 12.3%, and 3.5%, respectively ($P<0.001$) while the cumulative incidence of any gynecologic procedure or intervention during the study period was 34.2%, 20.9% and 9.0%, respectively ($P<0.0001$). Among women without symptoms or pathology, interventions were performed in 20.0%, 11.0%, and 6.8% respectively ($P<0.0001$).

Conclusion—Compared to women taking aromatase inhibitors, gynecologic symptoms, procedures and pathology are higher for both pre-and post menopausal women with breast cancer on tamoxifen. Increased efforts to curb use of gynecologic interventions in asymptomatic women are needed.

Introduction

The selective estrogen receptor modulator tamoxifen is now widely used for the treatment and prevention of breast cancer.^{1,2} While the drug has predominantly anti-estrogenic properties, it also has pro-estrogenic effects on uterine tissue. This stimulatory effect on the uterus can lead to endometrial proliferation as well as endometrial hyperplasia and cancer.^{3–6} In the National Surgical Adjuvant Breast and Bowel Project B-14 study, the risk of endometrial cancer among women treated with tamoxifen was 1.6 per 1000 patient years compared to 0.2 per 1000 patients years in women receiving placebo.³

Tamoxifen use has been associated with a variety of gynecologic problems. Women receiving tamoxifen are at increased risk for a number of benign gynecologic conditions including endometrial polyps, leiomyoma, endometriosis, and ovarian cysts.⁷ Despite the increased risk of these abnormalities, routine surveillance with transvaginal sonography and endometrial sampling has not been shown to be efficacious.^{8–11} As such, the American Congress of Obstetricians and Gynecologists recommends against routine surveillance in most asymptomatic women receiving tamoxifen.⁸

In addition to tamoxifen, hormonal therapy with aromatase inhibitors is also frequently utilized in postmenopausal women with breast cancer. Aromatase inhibitors inhibit the action of aromatase that converts androgens into estrogens. Despite the frequency with which hormonal therapy is used for the treatment of breast cancer, little is known about the occurrence of gynecologic conditions and the use of surveillance testing in women who are receiving tamoxifen and aromatase inhibitors. We performed a population-based analysis among women with breast cancer receiving tamoxifen and aromatase inhibitors to determine the frequency of gynecologic abnormalities and use of diagnostic and surveillance testing.

Women with breast cancer receiving tamoxifen were compared to subjects receiving aromatase inhibitors.

Methods

Data Source

The Truven Health MarketScan database was analyzed.¹² The database includes a sample of patients enrolled in the commercial health plans of approximately 100 payers. MarketScan captures claims on over 50 million covered lives, includes all inpatient and outpatient claims and use of prescription drugs.¹² The database collects detailed information on monthly enrollment and allows longitudinal data capture on patients. Data was de-identified and deemed exempt by the Columbia University Institutional Review Board.

Patients and Procedures

We identified women age 18–95 years with breast cancer (ICD-9 174.x) diagnosed from 2009–2013 who underwent mastectomy or lumpectomy within 3 months of diagnosis. Patients with a diagnosis of a secondary malignant neoplasm of breast (ICD-9 198.2, 198.81) in the 3 months prior or 3 months after the surgical procedures were excluded. Patients were classified as receiving either tamoxifen or an aromatase inhibitor (anastrozole, letrozole or exemestane) if they had any of the outpatient pharmaceutical claims with the corresponding generic or brand name drugs within 18 months of the surgical procedures. Patients who had only one drug claim were excluded. Given the challenges of distinguishing prevalent cases of breast cancer that previously may have received hormonal therapy, we did not include an untreated control group.

We defined the follow-up period as the time from the first claim for tamoxifen or an aromatase inhibitor to 6 months after the last claim. If a patient had a gap of >3 months in which the drug was stopped, any claims after the gap were excluded. Patients who received both tamoxifen and aromatase inhibitors in the follow-up period were excluded. The primary group of interest was women ≥ 50 years of age who received tamoxifen. These patients were compared to women <50 years of age who received tamoxifen and to women ≥ 50 years of age treated with aromatase inhibitors (since aromatase inhibitors are only used in postmenopausal women).

Outcomes

The primary outcomes included gynecologic symptoms or diagnoses and gynecologic procedures. The following gynecologic diagnoses were examined: vaginal bleeding, endometrial polyp, atypical endometrial hyperplasia, other endometrial hyperplasia, and endometrial cancer (Supplemental Table). Gynecologic procedures and interventions included transvaginal ultrasound, endometrial biopsy, hysteroscopy/dilation and curettage, and hysterectomy. Two composite measures were developed and included: any gynecologic diagnosis, encompassing any of the above symptoms and pathologic entities, and any gynecologic intervention, which included patients who had any of the above described tests.

Follow-up time was calculated as the number of months from the first claim for tamoxifen or an aromatase inhibitor until 6 months after the last claim. For each gynecologic diagnosis and intervention, we recorded time-to-the-first occurrence, and censored the patient at the end of the follow-up period if she had none of the occurrences.

Clinical and demographic characteristics included age (<40, 40–49, 50–59, 60–69 and 70 years), year of surgery (2009–2013), and region (Northeast, North central, South, West, unknown). Comorbidity was measured using the Charlson comorbidity score and classified as 0, 1, or 2.^{13,14}

Statistical Analysis

The associations between the clinical and demographic characteristics and treatment with tamoxifen or aromatase inhibitors were examined using χ^2 tests. Follow-up time was compared using ANOVA. The gynecologic diagnoses and interventions were reported as number and percentage in 0–6, 7–12, 13–24, and 24–36 months after receiving tamoxifen or aromatase inhibitors. Log-rank tests were used to compare the Kaplan-Meier estimates of cumulative incidence curves of the occurrence of gynecologic diagnoses and interventions. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, North Carolina). All statistical tests were two-sided. A P-value of <0.05 was considered statistically significant.

Results

A total of 75,170 women including 13,827 (18.4%) women 50 years of age treated with tamoxifen, 15,735 (20.9%) <50 years of age who received tamoxifen and 45,608 (60.7%) women 50 years treated with aromatase inhibitors were identified (Table 1, Figure 1). Anastrozole was the most common aromatase inhibitor utilized followed by letrozole. Women who received tamoxifen were younger and had fewer comorbidities than those treated with aromatase inhibitors ($P<0.0001$).

The cumulative incidence of any gynecologic symptom or pathologic diagnosis during the study period was 20.2% in women <50 and 12.3% in women 50 treated with tamoxifen, and 3.5% for those women 50 years of age who received aromatase inhibitors ($P<0.0001$) (Table 2, Figure 2). Vaginal bleeding was the most common symptom in all 3 cohorts. Endometrial cancers were diagnosed in 0.2% of women <50 treated with tamoxifen, 0.5% of those 50 treated with tamoxifen and 0.8% of those treated with aromatase inhibitors ($P<0.0001$), while atypical endometrial hyperplasia was found in 0.2%, 0.2%, and 0.03%, respectively ($P<0.0001$). Similarly, endometrial polyps were more common with tamoxifen, occurring in 4.0%, 3.7% and 0.6% of the women, respectively ($P<0.0001$).

For all three cohorts, vaginal bleeding was most commonly noted in the initial 6-month period after initiation of hormonal therapy and was less frequently diagnosed in later periods. In contrast, the occurrence of atypical endometrial hyperplasia and endometrial cancer was relatively constant throughout the study periods (Table 2).

The cumulative incidence of any gynecologic procedure or intervention during the study period was 34.2% in women <50 years of age who received tamoxifen, 20.9% in women 50 years of age treated with tamoxifen and 9.0% in those 50 years of age treated with aromatase inhibitors ($P<0.0001$) (Table 3, Figure 2). The most common intervention was transvaginal ultrasound, which was performed in 30.5%, 18.9%, and 8.3% of the groups, respectively. Endometrial biopsy (10.4% vs. 7.2% vs. 1.0%), hysteroscopy/dilation and curettage (5.3% vs. 4.6% vs. 0.7%) and hysterectomy (5.5% vs. 2.8% vs. 0.9%) were all more frequently undertaken in those treated with tamoxifen, particularly in women <50 years of age, compared to those treated with aromatase inhibitors ($P<0.0001$ for all). For all three cohorts, the use of diagnostic tests and procedures was greatest immediately after initiation of the drugs and then declined over time.

Table 4 displays the use of diagnostic testing and interventions in women without a documented gynecologic symptom or pathologic diagnosis. Overall, interventions were performed in 20.0% of women <50 years of age on tamoxifen, 11.0% in women 50 years of age on tamoxifen and in 6.8% of those 50 years receiving aromatase inhibitors ($P<0.0001$) (Table 4, Figure 2). Among women <50 years treated with tamoxifen without symptoms or pathology, the cumulative use of transvaginal ultrasound was 18.6%, while endometrial biopsy was performed in 1.3%, hysteroscopy and curettage in 0.4%, and hysterectomy in 2.4%.

Comment

We noted that gynecologic testing and procedures are commonly performed in women receiving adjuvant hormonal therapy for breast cancer. Gynecologic pathology was more common in women receiving tamoxifen compared to aromatase inhibitors and more common in younger compared to older women receiving tamoxifen. Additionally, tamoxifen treated women were more likely to undergo diagnostic testing and evaluation. However, even among women receiving tamoxifen without underlying gynecologic pathology or symptomatology, we noted the use of diagnostic testing and interventions in a subset of women.

The risk of uterine cancer is an adverse consequence of tamoxifen therapy.^{2–4,15–20} A meta-analysis that included over 50,000 patients reported a relative risk of 2.7 for the development of endometrial cancer in tamoxifen treated women compared to controls.¹⁹ In addition to endometrial cancer, tamoxifen has also been associated with an increased risk of uterine sarcomas.⁴ A review of NSABP trials using tamoxifen reported an incidence of uterine sarcomas of 0.17 per 1000 women-years in those with an intact uterus. This appears higher than the general population-based risk for uterine sarcomas.⁴

While the risk of uterine cancer is the most recognized gynecologic effect of tamoxifen, tamoxifen users are also at increased risk for a number of other abnormalities of the genital tract. Data from the NSABP Breast Cancer Prevention Trial (BCPT) Protocol P-1 reported an increased risk of leiomyomas, ovarian cysts, endometrial polyps, endometriosis and endometritis among women randomized to tamoxifen compared to placebo.⁷ Within this cohort, over one-third of tamoxifen users reported vaginal bleeding that they described as

bothersome.⁷ Vaginal bleeding or endometrial pathology was found in 18% of tamoxifen users <50 years of age and in 9% of those ≥50 years in our cohort. Not surprisingly, given the aromatase inhibitors decrease the production of estrogen, gynecologic pathology was uncommon among aromatase inhibitor users.²¹

There is limited data describing the performance of gynecologic testing and procedures in women receiving tamoxifen. Within the NSABP BCPT P-1 cohort, the annual rate of curettage was 32 per 1000 women while hysteroscopy was performed in 6 per 1000, hysterectomy in 24 per 1000 and oophorectomy in 16 per 1000 women. The rates of all of the interventions were markedly higher in women who received tamoxifen compared to placebo and increased in premenopausal vs. postmenopausal women.⁷ We noted a higher cumulative rate of many of these procedures within 36 months of initiation of tamoxifen and also identified that transvaginal sonography and endometrial biopsy were frequently utilized. Similarly, testing was markedly higher in younger compared to older women. Notably, even in the subset of women without gynecologic symptoms or a documented pathologic diagnosis, use of testing was seen in some women.

Although women treated with tamoxifen are at elevated risk for gynecologic pathology, screening has largely proven to be ineffective. Tamoxifen can induce hypertrophy of the endometrial stroma limiting the utility of sonographic evaluation of endometrial thickness for neoplasia.^{8,11,22} Like ultrasound, screening endometrial biopsy has also not been shown to be effective for endometrial cancer screening.^{8–11} Recent data has shown that postmenopausal women with endometrial polyps prior to initiation of tamoxifen therapy are at increased risk for endometrial hyperplasia and recurrent polyps and these women are now considered to represent a high-risk group.^{8,23–25} Based on these data, the American College of Obstetricians and Gynecologists specifically recommends against endometrial surveillance in women not considered high risk, noting that such surveillance can lead to unnecessary and costly downstream testing.⁸ Despite these recommendations, we noted that surveillance testing was utilized in some pre- and postmenopausal women on tamoxifen. Given clear recommendations that such testing may lead to unnecessary interventions in women, promoting evidence based gynecologic care for tamoxifen users may not only reduce cost, but also improve patient safety.

While our study benefits from the inclusion of a large cohort of women, we recognize a number of important limitations. First, there may be misclassification of hormonal therapy in a small number of women and some women may switch classes. To limit this bias, we chose to utilize a relatively restrictive definition of hormonal therapy use and limited the cohort to only those women who were newly diagnosed with breast cancer and who underwent surgery. Second, there may be undercapture of diagnostic testing and gynecologic symptoms. While this is a concern with any study using administrative data, a priori we chose to include only diagnoses and procedures likely to generate a billing code. However, we acknowledge that there still may be undercapture of a small number of gynecologic diagnoses. Third, our comparison group consisted of women receiving aromatase inhibitors and not those who were untreated. We purposely chose aromatase inhibitor users as a comparator group to balance the underlying risk factor profile of women with breast cancer, and aromatase inhibitors are not known to increase risk for malignant or benign pathology.

Due to the fact that some conditions, such as endometrial cancer, were uncommon, our study may have been underpowered to detect small differences between groups. Lastly, using administrative data we are not able to explore more subjective patient and physician attitudes that may have influenced testing and follow-up.

These data demonstrate that the use of gynecologic surveillance testing is common among women with breast cancer receiving tamoxifen. Testing is utilized even in the absence of underlying pathology or symptomatology in some women. Given clear recommendations that such testing may lead to unnecessary interventions in women, promoting evidence based gynecologic care for tamoxifen users may not only reduce cost, but also improve patient safety.

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References

1. Fisher B, Costantino J, Redmond C, et al. A randomized clinical trial evaluating tamoxifen in the treatment of patients with node-negative breast cancer who have estrogen-receptor-positive tumors. *N Engl J Med*. 1989; 320:479–84. [PubMed: 2644532]
2. Davies C, Pan H, Godwin J, et al. Long-term effects of continuing adjuvant tamoxifen to 10 years versus stopping at 5 years after diagnosis of oestrogen receptor-positive breast cancer: ATLAS, a randomised trial. *Lancet*. 2013; 381:805–16. [PubMed: 23219286]
3. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst*. 1994; 86:527–37. [PubMed: 8133536]
4. Wickerham DL, Fisher B, Wolmark N, et al. Association of tamoxifen and uterine sarcoma. *J Clin Oncol*. 2002; 20:2758–60.
5. Bergman L, Beelen ML, Gallee MP, Hollema H, Benraadt J, van Leeuwen FE. Risk and prognosis of endometrial cancer after tamoxifen for breast cancer. Comprehensive Cancer Centres' ALERT Group. Assessment of Liver and Endometrial cancer Risk following Tamoxifen. *Lancet*. 2000; 356:881–7. [PubMed: 11036892]
6. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst*. 2005; 97:1652–62. [PubMed: 16288118]
7. Chalas E, Costantino JP, Wickerham DL, et al. Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. *Am J Obstet Gynecol*. 2005; 192:1230–7. discussion 7–9. [PubMed: 15846210]
8. Committee Opinion No. 601: Tamoxifen and uterine cancer. *Obstet Gynecol*. 2014; 123:1394–7. [PubMed: 24848920]
9. Bertelli G, Venturini M, Del Mastro L, et al. Tamoxifen and the endometrium: findings of pelvic ultrasound examination and endometrial biopsy in asymptomatic breast cancer patients. *Breast Cancer Res Treat*. 1998; 47:41–6. [PubMed: 9493974]
10. Fung MF, Reid A, Faught W, et al. Prospective longitudinal study of ultrasound screening for endometrial abnormalities in women with breast cancer receiving tamoxifen. *Gynecol Oncol*. 2003; 91:154–9. [PubMed: 14529676]
11. Love CD, Muir BB, Scrimgeour JB, Leonard RC, Dillon P, Dixon JM. Investigation of endometrial abnormalities in asymptomatic women treated with tamoxifen and an evaluation of the role of endometrial screening. *J Clin Oncol*. 1999; 17:2050–4. [PubMed: 10561257]

12. [Accessed June 21, 2015] Truven Health Analytics. MarketScan. at <http://truvenhealth.com/your-healthcare-focus/life-sciences/marketscan-databases-and-online-tools>
13. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992; 45:613–9. [PubMed: 1607900]
14. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987; 40:373–83. [PubMed: 3558716]
15. Chlebowski RT, Schottinger JE, Shi J, Chung J, Haque R. Aromatase inhibitors, tamoxifen, and endometrial cancer in breast cancer survivors. *Cancer*. 2015; 121:2147–55. [PubMed: 25757699]
16. Sismondi P, Biglia N, Volpi E, Giai M, de Grandis T. Tamoxifen and endometrial cancer. *Ann N Y Acad Sci*. 1994; 734:310–21. [PubMed: 7978932]
17. Altaras MM, Aviram R, Cohen I, Cordoba M, Yarkoni S, Beyth Y. Role of prolonged stimulation of tamoxifen therapy in the etiology of endometrial sarcomas. *Gynecol Oncol*. 1993; 49:255–8. [PubMed: 8504996]
18. van Leeuwen FE, Benraadt J, Coebergh JW, et al. Risk of endometrial cancer after tamoxifen treatment of breast cancer. *Lancet*. 1994; 343:448–52. [PubMed: 7905955]
19. Braithwaite RS, Chlebowski RT, Lau J, George S, Hess R, Col NF. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med*. 2003; 18:937–47. [PubMed: 14687281]
20. Runowicz CD, Costantino JP, Wickerham DL, et al. Gynecologic conditions in participants in the NSABP breast cancer prevention study of tamoxifen and raloxifene (STAR). *Am J Obstet Gynecol*. 2011; 205:535e1–5. [PubMed: 21872200]
21. Committee Opinion No. 663: Aromatase Inhibitors in Gynecologic Practice. *Obstet Gynecol*. 2016; 127:e170–4. [PubMed: 27214191]
22. Achiron R, Lipitz S, Sivan E, et al. Changes mimicking endometrial neoplasia in postmenopausal, tamoxifen-treated women with breast cancer: a transvaginal Doppler study. *Ultrasound Obstet Gynecol*. 1995; 6:116–20. [PubMed: 8535913]
23. Berliere M, Charles A, Galant C, Donnez J. Uterine side effects of tamoxifen: a need for systematic pretreatment screening. *Obstet Gynecol*. 1998; 91:40–4. [PubMed: 9464718]
24. Berliere M, Radikov G, Galant C, Piette P, Marbaix E, Donnez J. Identification of women at high risk of developing endometrial cancer on tamoxifen. *Eur J Cancer*. 2000; 36(Suppl 4):S35–6. [PubMed: 11056310]
25. Vosse M, Renard F, Coibion M, Neven P, Nogaret JM, Hertens D. Endometrial disorders in 406 breast cancer patients on tamoxifen: the case for less intensive monitoring. *Eur J Obstet Gynecol Reprod Biol*. 2002; 101:58–63. [PubMed: 11803101]

Figure 1.
Flowchart of cohort selection.

Figure 2A

Figure 2B

Figure 2C

Figure 2.

Figure 2A. Cumulative incidence of gynecologic symptoms in women receiving tamoxifen or aromatase inhibitors. 2B. Cumulative incidence of testing and interventions in women receiving tamoxifen or aromatase inhibitors. 2C. Cumulative incidence of testing and interventions in women without gynecologic pathology or symptoms for women receiving aromatase inhibitors or tamoxifen.

Table 1

Clinical and demographic characteristics of breast cancer patients who had postoperative tamoxifen or aromatase inhibitors

	Tamoxifen, < 50 years		Tamoxifen, 50 years		Aromatase inhibitors, 50 years		P-value
	N	(%)	N	%	N	%	
<i>All</i>	15,735	(20.9)	13,827	(18.4)	45,608	(60.7)	
<i>Age</i>							<0.001
< 30	232	(1.5)	3	3	3	3	
30–39	2,606	(16.6)	3	3	3	3	
40–49	12,897	(82.0)	3	3	3	3	
50–59	3	3	8,579	(62.0)	16,673	(36.6)	
60–69	3	3	3,226	(23.3)	17,688	(38.8)	
70	3	3	2,022	(14.6)	11,247	(24.7)	
<i>Year</i>							<0.001
2009	3,650	(23.2)	3,061	(22.1)	9,284	(20.4)	
2010	3,300	(21.0)	2,974	(21.5)	9,709	(21.3)	
2011	3,645	(23.2)	3,137	(22.7)	11,218	(24.6)	
2012	3,407	(21.7)	2,983	(21.6)	10,143	(22.2)	
2013	1,733	(11.0)	1,672	(12.1)	5,254	(11.5)	
<i>Region</i>							<0.001
Northeast	3,298	(21.0)	2,831	(20.5)	9,265	(20.3)	
North Central	3,599	(22.9)	3,584	(25.9)	11,639	(25.5)	
South	5,816	(37.0)	4,698	(34.0)	15,551	(34.1)	
West	2,754	(17.5)	2,530	(18.3)	8,600	(18.9)	
Unknown	268	(1.7)	184	(1.3)	553	(1.2)	
<i>Comorbidity (Charlson)</i>							<0.001
0	14,650	(93.1)	11,753	(85.0)	35,449	(77.7)	
1	979	(6.2)	1,638	(11.8)	7,516	(16.5)	
2	106	(0.7)	436	(3.2)	2,643	(5.8)	
<i>Aromatase inhibitors</i>							
Anastrozole	3	3	3	3	32,633	(71.6)	3
Letrozole	3	3	3	3	13,927	(30.5)	3

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	Tamoxifen, < 50 years		Tamoxifen, 50 years		Aromatase inhibitors, 50 years		P-value
	N	(%)	N	%	N	%	
Exemestane	3	3	3	3	5,733	(12.6)	3
Follow-up time, months (median, IQR)	13	(6–24)	14	(7–25)	15	(8–27)	<0.001

Table 2

Gynecologic symptoms and pathology in breast cancer patients receiving postoperative tamoxifen or aromatase inhibitors

	0–6 months			7–12 months			13–24 months			24–36 months		
	N	%	P-value	N	%	P-value	N	%	P-value	N	%	P-value
Cumulative Incidence of Symptoms¹												
<i>Vaginal bleeding</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,173	(7.5)		1,934	(12.3)		2,667	(17.0)		2,902	(18.4)	
Tamoxifen, 50	522	(3.8)		896	(6.5)		1,257	(9.1)		1,384	(10.0)	
Aromatase inhibitors, 50 years	499	(1.1)		737	(1.6)		974	(2.1)		1,049	(2.3)	
<i>Endometrial polyp</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	162	(1.0)		329	(2.1)		525	(3.3)		621	(4.0)	
Tamoxifen, 50 years	144	(1.0)		276	(2.0)		441	(3.2)		513	(3.7)	
Aromatase inhibitors, 50 years	135	(0.3)		184	(0.4)		235	(0.5)		253	(0.6)	
<i>Other endometrial hyperplasia</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	119	(0.8)		233	(1.5)		357	(2.3)		416	(2.6)	
Tamoxifen, 50 years	93	(0.7)		193	(1.4)		302	(2.2)		340	(2.5)	
Aromatase inhibitors, 50 years	93	(0.2)		140	(0.3)		174	(0.4)		183	(0.4)	
<i>Atypical endometrial hyperplasia</i>			0.50			0.003			<0.001			<0.001
Tamoxifen, < 50 years	2	(0.01)		9	(0.1)		21	(0.1)		23	(0.2)	
Tamoxifen, 50 years	4	(0.03)		11	(0.1)		23	(0.2)		29	(0.2)	
Aromatase inhibitors, 50 years	7	(0.02)		9	(0.02)		11	(0.02)		12	(0.03)	
<i>Endometrial cancer</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	12	(0.1)		18	(0.1)		32	(0.2)		36	(0.2)	
Tamoxifen, 50 years	30	(0.2)		41	(0.3)		58	(0.4)		70	(0.5)	
Aromatase inhibitors, 50 years	253	(0.6)		304	(0.7)		351	(0.8)		369	(0.8)	
<i>Any gynecologic symptom</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,291	(8.2)		2,140	(13.6)		2,923	(18.6)		3,183	(20.2)	
Tamoxifen, 50 years	663	(4.8)		1,115	(8.1)		1,548	(11.2)		1,696	(12.3)	
Aromatase inhibitors, 50 years	859	(1.9)		1,184	(2.6)		1,498	(3.3)		1,599	(3.5)	
Incidence of Symptoms by Time Interval²												
<i>Vaginal bleeding</i>			<0.001			<0.001			<0.001			<0.001

	0–6 months			7–12 months			13–24 months			24–36 months		
	N	%	P-value	N	%	P-value	N	%	P-value	N	%	P-value
Tamoxifen, < 50 years	1,173	(7.5)		981	(6.2)		1,046	(6.7)		428	(2.7)	
Tamoxifen, 50 years	522	(3.8)		467	(3.4)		497	(3.6)		212	(1.5)	
Aromatase inhibitors, 50 years	499	(1.1)		282	(0.6)		291	(0.6)		108	(0.2)	
<i>Endometrial polyp</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	162	(1.0)		190	(1.2)		212	(1.4)		108	(0.7)	
Tamoxifen, 50 years	144	(1.0)		157	(1.1)		191	(1.4)		88	(0.6)	
Aromatase inhibitors, 50 years	135	(0.3)		56	(0.1)		62	(0.1)		25	(0.1)	
<i>Other endometrial hyperplasia</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	119	(0.8)		124	(0.8)		154	(1.0)		87	(0.6)	
Tamoxifen, 50 years	93	(0.7)		108	(0.8)		131	(1.0)		50	(0.4)	
Aromatase inhibitors, 50 years	93	(0.2)		60	(0.1)		40	(0.1)		15	(0.03)	
<i>Atypical endometrial hyperplasia</i>			0.50			0.001			<0.001			<0.001
Tamoxifen, < 50 years	2	(0.01)		7	(0.04)		13	(0.1)		2	(0.01)	
Tamoxifen, 50 years	4	(0.03)		7	(0.1)		12	(0.1)		6	(0.04)	
Aromatase inhibitors, 50 years	7	(0.02)		3	(0.01)		2	(0.00)		1	(0.00)	
<i>Endometrial cancer</i>			<0.001			<0.001			<0.001			0.002
Tamoxifen, < 50 years	12	(0.1)		10	(0.1)		18	(0.1)		5	(0.03)	
Tamoxifen, 50 years	30	(0.2)		23	(0.2)		28	(0.2)		16	(0.1)	
Aromatase inhibitors, 50 years	253	(0.6)		159	(0.4)		141	(0.3)		65	(0.1)	
<i>Any gynecologic symptom</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,291	(8.2)		1,118	(7.1)		1,165	(7.4)		499	(3.2)	
Tamoxifen, 50 years	663	(4.8)		595	(4.3)		634	(4.6)		265	(1.9)	
Aromatase inhibitors, 50 years	859	(1.9)		497	(1.1)		484	(1.1)		192	(0.4)	

¹ Cumulative incidence-occurrence of the outcome during the time period in the column or any previous time period.

² Incidence by time interval-occurrence of the outcome during the specific time period in the column.

Gynecologic interventions in breast cancer patients receiving postoperative tamoxifen or aromatase inhibitors

Table 3

	0–6 months			7–12 months			13–24 months			24–36 months		
	N	%	P-value	N	%	P-value	N	%	P-value	N	%	P-value
Cumulative Incidence of Interventions¹												
<i>Transvaginal ultrasound</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	2,383	(15.1)		3,650	(23.2)		4,534	(28.8)		4,798	(30.5)	
Tamoxifen, 50 years	1,225	(8.9)		1,918	(13.9)		2,458	(17.8)		2,607	(18.9)	
Aromatase inhibitors, 50 years	1,785	(3.9)		2,760	(6.1)		3,564	(7.8)		3,789	(8.3)	
<i>Endometrial biopsy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	486	(3.1)		953	(6.1)		1,461	(9.3)		1,633	(10.4)	
Tamoxifen, 50 years	321	(2.3)		597	(4.3)		885	(6.4)		991	(7.2)	
Aromatase inhibitors, 50 years	195	(0.4)		310	(0.7)		426	(0.9)		458	(1.0)	
<i>Hysteroscopy/D and C</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	244	(1.6)		466	(3.0)		713	(4.5)		828	(5.3)	
Tamoxifen, 50 years	156	(1.1)		334	(2.4)		550	(4.0)		633	(4.6)	
Aromatase inhibitors, 50 years	151	(0.3)		225	(0.5)		288	(0.6)		311	(0.7)	
<i>Hysterectomy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	282	(1.8)		497	(3.2)		764	(4.9)		862	(5.5)	
Tamoxifen, 50 years	117	(0.9)		219	(1.6)		345	(2.5)		389	(2.8)	
Aromatase inhibitors, 50 years	193	(0.4)		286	(0.6)		370	(0.8)		399	(0.9)	
<i>Any gynecologic intervention</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	2,722	(17.3)		4,125	(26.2)		5,106	(32.5)		5,386	(34.2)	
Tamoxifen, 50 years	1,380	(10.0)		2,123	(15.4)		2,725	(19.7)		2,886	(20.9)	
Aromatase inhibitors, 50 years	2,005	(4.4)		3,029	(6.6)		3,868	(8.5)		4,106	(9.0)	
Incidence of Interventions by Time Interval²												
<i>Transvaginal ultrasound</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	2,383	(15.1)		1,819	(11.6)		1,753	(11.1)		726	(4.6)	
Tamoxifen, 50 years	1,225	(8.9)		912	(6.6)		915	(6.6)		340	(2.5)	
Aromatase inhibitors, 50 years	1,785	(3.9)		1,148	(2.5)		1,186	(2.6)		484	(1.1)	
<i>Endometrial biopsy</i>			<0.001			<0.001			<0.001			<0.001

	0–6 months			7–12 months			13–24 months			24–36 months		
	N	%	P-value	N	%	P-value	N	%	P-value	N	%	P-value
Tamoxifen, < 50 years	486	(3.1)		492	(3.1)		592	(3.8)		241	(1.5)	
Tamoxifen, 50 years	321	(2.3)		287	(2.1)		346	(2.5)		143	(1.0)	
Aromatase inhibitors, 50 years	195	(0.4)		117	(0.3)		129	(0.3)		33	(0.1)	
<i>Hysterectomy/D and C</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	244	(1.6)		227	(1.4)		267	(1.7)		132	(0.8)	
Tamoxifen, 50 years	156	(1.1)		184	(1.3)		228	(1.7)		103	(0.7)	
Aromatase inhibitors, 50 years	151	(0.3)		77	(0.2)		65	(0.1)		25	(0.1)	
<i>Hysterectomy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	282	(1.8)		215	(1.4)		268	(1.7)		98	(0.6)	
Tamoxifen, 50 years	117	(0.9)		102	(0.7)		126	(0.9)		44	(0.3)	
Aromatase inhibitors, 50 years	193	(0.4)		93	(0.2)		84	(0.2)		30	(0.1)	
<i>Any gynecologic intervention</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	2,722	(17.3)		2,107	(13.4)		2,010	(12.8)		837	(5.3)	
Tamoxifen, 50 years	1,380	(10.0)		1,070	(7.7)		1,070	(7.7)		412	(3.0)	
Aromatase inhibitors, 50 years	2,005	(4.4)		1,255	(2.8)		1,274	(2.8)		514	(1.1)	

¹ Cumulative incidence-occurrence of the outcome during the time period in the column or any previous time period.

² Incidence by time interval-occurrence of the outcome during the specific time period in the column.

Gynecologic interventions in breast cancer patients receiving postoperative tamoxifen or aromatase inhibitors and not having gynecologic symptoms or pathology

Table 4

	0–6 months			7–12 months			13–24 months			24–36 months		
	N	%	P-value	N	%	P-value	N	%	P-value	N	%	P-value
Cumulative Incidence of Interventions¹												
<i>Transvaginal ultrasound</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,268	(10.2)		1,856	(14.9)		2,211	(17.7)		2,328	(18.6)	
Tamoxifen, 50 years	644	(5.3)		961	(8.0)		1,189	(9.8)		1,241	(10.3)	
Aromatase inhibitors, 50 years	1,313	(3.0)		2,052	(4.7)		2,652	(6.0)		2,826	(6.4)	
<i>Endometrial biopsy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	42	(0.3)		96	(0.8)		143	(1.1)		166	(1.3)	
Tamoxifen, 50 years	44	(0.4)		77	(0.6)		116	(1.0)		132	(1.1)	
Aromatase inhibitors, 50 years	35	(0.1)		50	(0.1)		65	(0.2)		69	(0.2)	
<i>Hysterectomy/D and C</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	19	(0.2)		29	(0.2)		39	(0.3)		45	(0.4)	
Tamoxifen, 50 years	14	(0.1)		24	(0.2)		33	(0.3)		37	(0.3)	
Aromatase inhibitors, 50 years	13	(0.03)		21	(0.1)		23	(0.1)		24	(0.1)	
<i>Hysterectomy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	147	(1.2)		217	(1.7)		289	(2.3)		304	(2.4)	
Tamoxifen, 50 years	53	(0.4)		82	(0.7)		110	(0.9)		114	(0.9)	
Aromatase inhibitors, 50 years	123	(0.3)		178	(0.4)		223	(0.5)		237	(0.5)	
<i>Any gynecologic intervention</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,368	(11.0)		1,984	(15.9)		2,367	(19.0)		2,495	(20.0)	
Tamoxifen, 50 years	693	(5.7)		1,023	(8.5)		1,272	(10.5)		1,327	(11.0)	
Aromatase inhibitors, 50 years	1,412	(3.2)		2,183	(5.0)		2,802	(6.4)		2,982	(6.8)	
Incidence of Interventions by Time Interval²												
<i>Transvaginal ultrasound</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,268	(10.2)		819	(6.6)		668	(5.4)		251	(2.0)	
Tamoxifen, 50 years	644	(5.3)		410	(3.4)		361	(3.0)		110	(0.9)	
Aromatase inhibitors, 50 years	1,313	(3.0)		853	(1.9)		875	(2.0)		353	(0.8)	

	0–6 months			7–12 months			13–24 months			24–36 months		
	N	%	P-value	N	%	P-value	N	%	P-value	N	%	P-value
<i>Endometrial biopsy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	42	(0.3)		54	(0.4)		48	(0.4)		24	(0.2)	
Tamoxifen, 50 years	44	(0.4)		34	(0.3)		40	(0.3)		19	(0.2)	
Aromatase inhibitors, 50 years	35	(0.1)		15	(0.03)		17	(0.04)		4	(0.01)	
<i>Hysterectomy/D and C</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	19	(0.2)		10	(0.1)		10	(0.1)		6	(0.1)	
Tamoxifen, 50 years	14	(0.1)		10	(0.1)		9	(0.1)		4	(0.03)	
Aromatase inhibitors, 50 years	13	(0.03)		8	(0.02)		2	(0.00)		1	(0.00)	
<i>Hysterectomy</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	147	(1.2)		70	(0.6)		72	(0.6)		15	(0.1)	
Tamoxifen, 50 years	53	(0.4)		29	(0.2)		28	(0.2)		4	(0.03)	
Aromatase inhibitors, 50 years	123	(0.3)		55	(0.1)		45	(0.1)		14	(0.03)	
<i>Any gynecologic intervention</i>			<0.001			<0.001			<0.001			<0.001
Tamoxifen, < 50 years	1,368	(11.0)		875	(7.0)		718	(5.8)		264	(2.1)	
Tamoxifen, 50 years	693	(5.7)		435	(3.6)		394	(3.3)		121	(1.0)	
Aromatase inhibitors, 50 years	1,412	(3.2)		905	(2.1)		907	(2.1)		363	(0.8)	

¹ Cumulative incidence-occurrence of the outcome during the time period in the column or any previous time period.

² Incidence by time interval-occurrence of the outcome during the specific time period in the column.