Published in final edited form as:

Am J Obstet Gynecol. 2011 December ; 205(6): 535.e1–535.e5. doi:10.1016/j.ajog.2011.06.067.

Gynecologic Conditions in Participants in the NSABP Study of Tamoxifen and Raloxifene

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The authors report no conflict of interest

This is original research. Related works have been presented/published in part as listed below. These previous works report on the original research on tamoxifen and the subsequent research on raloxifene, as well as their gynecological implications, and are available upon request:

Wickerham DL, Fisher B, Wolmark N, Bryant J, Costantino JP, Bernstein L, Runowicz CD. Association of tamoxifen and uterine sarcoma. *J Clin Oncol* 2002; 20(11):2758–60.

Chalas E, Costantino J, Wickerham DL, Runowicz CD. Author Reply to Letter to the Editor on: Benign gynecologic conditions among participants in the Breast Cancer Prevention Trial. *Am J Obstet Gynecol* 2005; 194(4):1205.

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Abstract

Objective—This study reports the gynecologic conditions in postmenopausal women (intact uterus upon enrollment) in the National Surgical Adjuvant Breast and Bowel Project (NSABP) Study of Tamoxifen and Raloxifene (STAR)/P-2 Trial.

Study Design—This study, with a median follow-up of 81 months, evaluated the incidence rates/risks of gynecologic conditions among women treated with tamoxifen and raloxifene.

Results—Compared to tamoxifen, women taking raloxifene had a lower incidence of uterine cancer (RR 0.55)/endometrial hyperplasia (RR 0.19), leiomyomas (RR 0.55), ovarian cysts (RR 0.60), endometrial polyps (RR 0.30) and had fewer procedures performed. Women on tamoxifen had more hot flashes ($P < .0001$), vaginal discharge ($P < .0001$), and vaginal bleeding ($P < .0001$).

Conclusions—Our results suggest that tamoxifen has more of an estrogenic effect on the gynecologic reproductive organs. These effects should be considered in counseling women on options for breast cancer prevention.

Keywords

Breast cancer prevention; gynecologic conditions; tamoxifen; raloxifene

Introduction

Breast cancer represents a major health hazard for women in the United States. Findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) (P-1) resulted in tamoxifen being approved by the US Food and Drug Administration for the prevention of breast cancer in high-risk women.¹ Studies evaluating raloxifene in postmenopausal women with osteoporosis demonstrated a reduction in invasive breast cancer in postmenopausal women. These studies concluded that the risk of estrogen receptor-positive invasive breast cancer was decreased by 72% and by 66% with 4 and 8 years respectively, of raloxifene treatment.^{2,3} The NSABP P-2 trial, known as the Study of Tamoxifen and Raloxifene (STAR), was launched to directly compare tamoxifen with raloxifene. The STAR/P-2 trial was a prospective, double-blind, randomized clinical trial of 19,747 healthy postmenopausal women at increased risk of breast cancer. The STAR/P-2 trial resulted in raloxifene's being approved by the FDA for the prevention of breast cancer in high-risk women.^{4,5}

This assessment was undertaken to report in detail on the gynecologic conditions occurring among postmenopausal women with an intact uterus upon enrollment in the STAR/P-2 trial.

Materials and Methods

This trial was approved by local human investigations committees or institutional review boards in accordance with assurances filed with and approved by the Department of Health and Human Services. Written informed consent was required for participation in this trial.

To be eligible for this trial, women had to be postmenopausal, at least 35 years of age, and have a 5-year predicted risk for breast cancer of at least 1.66%. Breast cancer risk was

determined using the Gail model, as modified and applied in the Breast Cancer Prevention Trial (BCPT/P-1).⁶ The details of the STAR/P-2 methodology are described in the initial report of the study.⁴ The participants were randomly assigned to receive either 20 mg/d of tamoxifen plus placebo (9,736), or 60 mg/d of raloxifene plus placebo (9,754) for 5 years. Because the formulations of tamoxifen and raloxifene tablets were dissimilar, it was necessary to use placebo tablets to maintain the double blinding of treatment assignment. The enrollment period began on June 1, 1999, and ended on November 4, 2004. This report is based on a cut-off date of March 31, 2009.

Upon enrollment in the NSABP STAR/P-2 trial, the study population consisted of 9,456 postmenopausal women with an intact uterus. As in the BCPT trial,^{1,7} women were monitored for symptoms of hot flashes, vaginal discharge, vaginal dryness, and abnormal vaginal bleeding, and the occurrence of numerous gynecologic conditions diagnosed during the study period were reported, including: endometrial adenocarcinomas, endometrial hyperplasia, leiomyomas, polyps, endometritis, endometriosis, and ovarian cysts. Surgical interventions, such as dilatation and curettage, hysteroscopy, laparoscopy, oophorectomy, and hysterectomy were similarly recorded in the study database.

The chi square test was used to compare the raloxifene and tamoxifen groups with regard to age, parity, history of oral contraceptive use, history of estrogen therapy, number of relatives with breast cancer, history of diabetes and hypertension, smoking status, and body mass index (BMI). The chi square test was also used to compare treatment groups by distribution by severity of self-reported symptoms. The analyses of the incidence of gynecologic conditions and surgical procedures mentioned above were performed to evaluate the differences between treatment groups. These analyses were based on the determination of risk ratios (RRs) of the incidence rates by treatment group (raloxifene compared with tamoxifen) and the 95% confidence intervals (CIs) on the RR. The incidence rates were calculated as the number of events divided by the person-years at risk. The 95% CIs were determined using the exact method assuming that the events followed a Poisson distribution, conditioning on the total number of events and person-years at risk.

Results were considered to be statistically significant if $P < 0.05$ or when the 95% CI for the RR did not include 1.00. The date file cut-off used for this analysis of March 31, 2009 was chosen to be consistent with that used for the update report of the main findings.⁵

Results

A total 4,739 women receiving tamoxifen and 4,717 women receiving raloxifene had an intact uterus upon entry (see CONSORT figure). The characteristics of the participants included in the current analysis are shown in Table 1. The groups were similar in baseline characteristics, including age, parity, BMI, history of oral contraceptive or estrogen use, family history of breast cancer, diabetes, hypertension, and smoking status. At a median follow-up of 81 months, significant differences existed in self-reported bothersome hot flashes ($P < 0.0001$), vaginal discharge ($P < 0.0001$) and vaginal bleeding ($P < 0.0001$) in patients receiving tamoxifen as compared with raloxifene (Table 2). Vaginal dryness was more common in patients receiving raloxifene ($P < 0.0001$).

The average annual rates of invasive uterine cancer, hyperplasia (with and without atypia), and hysterectomy during follow-up are shown in Table 3. The incidence of invasive cancer was 45% lower in the raloxifene group compared with the tamoxifen group (RR=0.55, 95% CI= 0.36–0.83). The risk of endometrial hyperplasia was almost 80% higher among women in the tamoxifen group as compared with those in the raloxifene group (RR=0.19; 95% CI = 0.12–0.29). Of those with hyperplasia, 82.5% had hyperplasia without atypia. The rate of hysterectomy for conditions other than invasive cancer in the tamoxifen group was more than twice that in the raloxifene group (RR=0.45; 95% CI=0.37–0.54), suggesting that the rates of invasive cancer and hyperplasia in the tamoxifen group would have been higher than actually observed if there were no differential in the rates of hysterectomy.

Women were also evaluated for other gynecologic conditions and surgical procedures (Table 4). Women taking raloxifene had a decreased incidence of leiomyomata (RR = 0.55; 95% CI = 0.49–0.62), ovarian cysts (RR = 0.60; CI = 0.49–0.74), polyps (RR = 0.30; 95% CI = 0.25–0.35), and endometriosis (RR = 0.32; 95% CI = 0.24–0.43). They were also less likely to undergo dilation and curettage (RR = 0.30; 95% CI = 0.26–0.35), hysteroscopy (RR = 0.29; 95% CI =0.24–0.35), and bilateral salpingo-oophorectomy or oophorectomy (RR = 0.50; 95% CI = 0.42–0.60).

Comment

Although gynecologic conditions were not considered the primary end point of the NSABP STAR/P-2 study, interesting data have emerged from careful follow-up of these women during the study period. While there are some limitations to the generalization of the findings as almost all (93.5%) of the STAR/P-2 participants were white and the average Gail score (4.03%) was very high, the findings provide very important unbiased comparisons of the relative efficacy and toxicity of tamoxifen and raloxifene.

Our study findings support that tamoxifen has more of an estrogenic effect on the gynecologic reproductive tract organs than does raloxifene. These findings include an increase risk of: (1) invasive endometrial cancer, (2) endometrial hyperplasia both with and without atypia, and (3) leiomyomas, polyps, and endometriosis. Our findings also support that tamoxifen has more effect on the ovaries with an increase incidence of ovarian cysts. This may be reflective of the chemical structure of tamoxifen and its similarity to clomiphene.⁸ In addition to increasing the risk of gynecologic conditions, the differential effects of tamoxifen and raloxifene also resulted in more procedures performed in the tamoxifen group, including hysterectomy, salpingo-oophorectomy, oophorectomy, hysteroscopy, and laparoscopy. With the average annual rate of hysterectomy for reasons other than uterine cancer in the tamoxifen group (12.08 per 1000) being more than double than that found in the raloxifene group (5.41 per 1000), the increased risk of invasive uterine cancer associated with tamoxifen is likely higher than that which was actually observed.

Raloxifene and tamoxifen are good preventive choices for higher-risk postmenopausal women at risk for breast cancer, and there are differing gynecologic effects with each, respectively. These differing gynecologic effects should be considered when counseling women with an intact uterus on options for breast cancer prevention.

Acknowledgments

This study was supported by: Public Health Service grants U10-CA-37377, U10-CA-69974, U10-CA-12027, U10-CA-69651 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services; and by AstraZeneca Pharmaceuticals and Eli Lilly and Company

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Fig. 1.

CONSORT diagram: NSABP P-2

* Two women with bilateral mastectomy prior to entry and one woman with diagnosis of breast cancer prior to entry discovered after random assignment.

Table 1

Participant characteristics at time of random assignment for women with an intact uterus at entry in the NSABP STAR/P-2 trial

Participant Characteristic	Tamoxifen (n = 4739)		Raloxifene (n = 4717)		P
	No.	%	No.	%	
Age (years)					
49	237	5.0	233	4.9	0.99
50–59	2592	54.7	2584	54.8	
60–69	1516	32.0	1515	32.1	
70	394	8.3	385	8.2	
Mean (SD)	58.8 (6.8)		58.8 (6.8)		
Parity					
1	1252	26.4	1211	25.7	0.41
2	3487	73.6	3506	74.3	
History of oral contraceptive use					
No	1501	31.7	1540	32.6	0.31
Yes	3238	68.3	3177	67.4	
History of estrogen therapy					
No	1763	37.2	1823	38.6	0.15
Yes	2976	62.8	2894	61.4	
No. of relatives with breast cancer					
0	1489	31.4	1446	30.7	0.22
1	2399	50.6	2404	51.0	
2	710	15.0	752	15.9	
3 or more	141	3.0	115	2.4	
History of diabetes					
Yes	241	5.1	227	4.8	0.54
No	4498	94.9	4490	95.2	
History of hypertension					
Yes	1417	29.9	1383	29.3	0.54
No	3322	70.1	3334	70.7	
Smoking status					

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Participant Characteristic	Tamoxifen (n = 4739)		Raloxifene (n = 4717)		P
	No.	%	No.	%	
Never	2414	50.9	2448	51.9	0.29
Former	1860	39.2	1780	37.7	
Current	443	9.3	458	9.7	
Unknown	22	0.5	31	0.7	
BMI [*]					
<25.0	1619	34.2	1576	33.4	0.74
25.0 – 29.9	1638	34.6	1646	34.9	
30.0	1481	31.3	1494	31.7	
Mean (SD)	28.1(6.0)		28.2 (6.1)		

* BMI was unavailable for one person in the tamoxifen group and one person in the raloxifene group.

Table 2

Highest level of self-reported symptoms disclosed by participants with an intact uterus at entry in the NSABP STAR/P-2 trial

Symptoms/severity level	Tamoxifen (n = 4693)*		Raloxifene (n = 4669)*		P
	No.	%	No.	%	
Hot flashes bothersome					
No	670	14.3	774	16.6	<.0001
Slightly	692	14.7	912	19.5	
Moderately	1020	21.7	1031	22.1	
Quite a bit	1339	28.5	1215	26.0	
Extremely	972	20.7	737	15.8	
Vaginal discharge bothersome					
No	1765	37.6	2673	57.2	<.0001
Slightly	1276	27.2	1194	25.6	
Moderately	838	17.9	484	10.4	
Quite a bit	551	11.7	234	5.0	
Extremely	263	5.6	84	1.8	
Vaginal dryness bothersome					
No	1432	30.5	1315	28.2	<.0001
Slightly	924	19.7	893	19.1	
Moderately	915	19.5	822	17.6	
Quite a bit	802	17.1	924	19.8	
Extremely	620	13.2	715	15.3	
Vaginal bleeding bothersome					
No	3548	75.6	4042	86.6	<.0001
Slightly	666	14.2	443	9.5	
Moderately	233	5.0	100	2.1	
Quite a bit	153	3.3	53	1.1	
Extremely	93	2.0	31	0.7	

*Forty-six women in the tamoxifen group and 48 women in the raloxifene group opted not to complete follow-up quality-of-life questionnaires.

Table 3

Average annual rates of uterine disease in the NSABP STAR/P-2 trial

Type of Uterine Disease	Number of Events		Rate per 1000		Difference *	Risk Ratio (RR) [†]	RR 95% Confidence Interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene			
Invasive cancer	65	37	2.25	1.23	1.02	0.55	0.36 to 0.83
Hyperplasia	126	25	4.40	0.84	3.56	0.19	0.12 to 0.29
Without atypia	104	21	3.63	0.70	2.93	0.19	0.11 to 0.31
With atypia	22	4	0.77	0.13	0.64	0.17	0.04 to 0.51
Hysterectomy during follow-up [‡]	349	162	12.08	5.41	6.67	0.45	0.37 to 0.54

* Rate in the tamoxifen group minus rate in the raloxifene group.

[†] Risk ratio for women in the raloxifene group compared with women in the tamoxifen group.[‡] For conditions other than invasive cancer.

Table 4

Average annual rates of gynecological conditions and procedures by treatment group in the NSABP STAR P-2 trial

Condition or Procedure	Number of Events		Rate per 1000		Risk Ratio (RR) [†]	RR 95% Confidence Interval
	Tamoxifen	Raloxifene	Tamoxifen	Raloxifene		
Conditions						
Leiomyomas	757	443	28.40	15.56	0.55	0.49 to 0.62
Ovarian cysts	236	147	8.32	5.01	0.60	0.49 to 0.74
Polyps	575	185	21.06	6.28	0.30	0.25 to 0.35
Endometriosis	190	64	6.60	2.14	0.32	0.24 to 0.43
Procedures						
Curettage	673	218	24.30	7.32	0.30	0.26 to 0.35
Bilateral oophorectomy	371	192	12.80	6.46	0.50	0.42 to 0.60
Laparoscopy	14	4	0.46	0.13	0.28	0.07 to 0.90
Hysteroscopy	493	151	17.32	5.03	0.29	0.24 to 0.35

* Rate in the tamoxifen group minus rate in the raloxifene group.

[†] Risk ratio for women in the raloxifene group compared to women in the tamoxifen group.