



Hormone replacement therapy and breast density after surgical menopause

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Abstract

Background: Women who have undergone surgical menopause due to a Bilateral-Salpingo-Oophorectomy (BSO), often require Hormone Replacement Therapy (HRT) to mitigate menopausal symptoms. The use of HRT has been shown to increase breast density and the risk of breast cancer in women with natural menopause. The purpose of this study was to evaluate breast density in women with breast cancer who received HRT after surgical menopause.

Methods: Our Institutional database was queried for post-menopausal women with newly diagnosed breast cancer from 1/2010 to 1/2016.

Patients were categorized into the following groups: 1) natural menopause with no HRT 2) BSO with no HRT 3) BSO with prior HRT usage or 4) BSO and current use of HRT at the time of diagnosis.

Results: 1106 women were eligible for analysis. 976 (88%) had natural menopause with no HRT, 63 (6%) had a BSO with no HRT, 51 (5%) had a BSO with previous history of HRT, and 16 (1%) had a BSO and were using HRT at time of malignancy diagnosis. Though not statistically significant, women who had a prior BSO and were currently on HRT had more dense breasts (69% heterogeneously or extremely dense) than women who had natural menopause with no HRT (44% heterogeneously or extremely dense). However, women who had a prior BSO and were on HRT in the past had significantly less dense breasts ($p=0.007$) than women who underwent natural menopause without HRT usage (67% vs. 56%). There were no differences observed in the tumor characteristics between all groups.

Conclusion: In our study cohort, women with history of surgical menopause who were on HRT at the time of breast cancer diagnosis had a trend towards more dense breasts. Surprisingly, women who were prior users had less dense breasts than women who never used HRT. Despite the change observed in breast density, the tumor characteristics do not differ with HRT usage, suggesting that variability in breast density did not correlate with stage of disease at presentation.



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Introduction

Increased mammographic breast density has been widely viewed as a strong predictor for the development of breast cancer. A 2006 meta-analysis by McCormack et al. showed that women with the highest breast densities are at 4-6 times higher risk for developing breast cancer [1]. Further, it showed that breast density was a stronger risk predictor than either Wolfe grade or BIRADS classification for future development of malignancy [1]. Given that mammography is less sensitive in women with dense breasts, the study suggested that this estimate actually underestimates the positive predictive value of breast density on development of malignancy [1,2]. Interestingly, breast cancer risk increases with age and weight, even as breast density decreases [3,4]. The Pike model (1983) suggests an explanation for this apparent paradoxical relationship, attributing cancer incidence to cumulative breast tissue hormonal exposure [3,4]. Hormonal exposure was proposed as one of the contributing factors and remains the focus of most predictive models and questionnaires for female patients [3,4].

The effect of HRT on breast density and breast cancer has been the focus of a recent study. The Women's Health Initiative (WHI) Postmenopausal Hormone Therapy Trials examined the effect of hormone replacement on women's health [5-7]. In 2003, the WHI reported that combined HRT (estrogen plus progestin) increases risk of breast cancer and those women were diagnosed with larger tumors and at later stages [7-9]. An ancillary study by McTiernan et al. looked at breast density in postmenopausal patients assigned to combined HRT or placebo after 1 year [10]. The study showed that the mean mammographic density increased by 6.0% in the HRT group, whereas the placebo group had a .9% decrease [8]. Subsequently, the WHI Trials found that women with previous hysterectomies given estrogen alone therapy were not at increased risk of cancer at 7 years. They did, however, require more frequent mammography (secondary to increased number of abnormalities on mammogram) [10].

Though the use of HRT has been linked to increased mammographic abnormalities and breast cancer, it can provide relief from moderate to severe hot flashes and symptoms of vulvar and vaginal atrophy. These symptoms can be particularly severe in women who have undergone surgical menopause. A 2011 study by Finch et al showed that vasomotor symptoms and decline in sexual function were significantly more dramatic in women who underwent Bilateral-Salpingo-Oophorectomy (BSO) prior to menopause than in women who underwent natural menopause, and that these symptoms were at least partially mitigated by the use of HRT [10,11]. After BSO, women have an abrupt rather than gradual reduction in hormone production [10,11]. Although 4-6% of women in the US undergo surgical menopause, the effect of HRT on breast density this cohort has not been thoroughly examined. The purpose of our study was to investigate the relationship of mammographic breast density, clinical and tumor characteristics in women who had BSO and used HRT.

Methods

Study participants

The Breast Cancer Database (BCD) at our medical center is a longitudinal registry that was established in January 2010. All patients undergoing definitive breast cancer surgery at our institution are eligible to enroll in the BCD. The variables collected

include information on personal and family history, screening history, methods of diagnosis, stage at diagnosis, details of treatment and outcomes. All clinical data were obtained from detailed questionnaires filled out at the time of diagnosis, and review of the electronic medical records. This study was approved by the Institutional Review Board and was compliant with the standards of the Health Insurance Portability and Accountability Act.

Patients included in this study were enrolled in the Breast Cancer Database between January 2010 and February 2016. The BCD was queried for all patients who had reported menopause following BSO (which may have been performed for reasons including malignancy, benign diagnosis or preventative with BRCA diagnosis or family history of malignancy), prior to diagnosis of malignancy and then were subsequently diagnosed with invasive breast cancer. BSO may have occurred with or without concurrent hysterectomy. Patients were considered as being on HRT if by questionnaire or on chart review they reported taking any type of HRT: combined, or estrogen or progestin only. Women who had a history of HRT usage without history of BSO were excluded from the analyses. Demographic information, indication for the examination and information including mammographic density and BI-RADS assessment was obtained from the electronic medical record.

Statistical Analyses

Patients who had BSO were categorized into three groups: 1) BSO with no HRT 2) BSO with prior HRT usage or 3) BSO and current use of HRT at the time of diagnosis. The patients who had BSO were then compared to patients who had never taken HRT and reported natural (non-surgical) menopause. The variables of interest included clinical and tumor characteristics and mammographic breast density at the time of malignancy diagnosis. Pearson's chi-square and Fisher's exact tests were used to assess differences in stage, histology, ER/PR/HER2 positivity and breast density between those who had never taken HRT and those who were on HRT at the time of cancer diagnosis with a significance level of 0.05. The same analysis was completed for those who had never taken HRT and those who had previously taken HRT but were not on HRT at the time of diagnosis. All analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC).

Results

During the study period, a total of 1106 women with breast cancer were eligible for analysis. The median age was 59 years (39-95 years). The majority of women were Caucasian (74%). Of these, 976 (88%) women had natural menopause with no HRT, 63 (6%) underwent a BSO with no HRT, 51 (5%) had a BSO with previous history of HRT, and 16 (1%) had a BSO and were using HRT at time of cancer diagnosis. Patients who used HRT were using combined estrogen and progesterone (63%) or estrogen only (25%) (Table 1). There was no statistically significant difference in age of diagnosis between the groups. However, we found that women in the BSO groups underwent menopause at earlier ages (47,46,47 years) compared to the natural menopause group (51 years) (Table 1). The majority of patients (73% and 94% in previous and current users respectively), reported use of HRT for >1 year.

Though not statistically significant, women with BSO and current HRT use had more dense breasts (69% heterogeneously or extremely dense) compared to women who had natural meno-

pause with no HRT (44% heterogeneously or extremely dense). However, women with BSO and past HRT use had significantly less dense breasts (67%) compared to women who underwent natural menopause without HRT usage (56%) ($p=0.007$).

Women with BSO and no HRT use had a significantly higher proportion of mammographically occult malignancies compared to patients in other groups ($p=.0006$). In this group, only 49% of patients had malignancies detected on mammogram and 29% were detected with self or clinical breast exam, which is significantly different from the other groups ($p=.0001$).

We found no statistical difference between all patients for tumor characteristics including stage of diagnosis, histology and hormone receptor status among the four groups (Table 2). Patients with BSO and no HRT usage were significantly more likely to have BRCA mutation than patients without BSO or HRT usage and were more likely to have used chemoprevention prior to malignancy diagnosis. The majority of patients were diagnosed with early stage 0,1 disease (65-82%).

Discussion

In our study population, women with current HRT usage at time of cancer diagnosis had a higher breast density compared to women who had never reported use of HRT. HRT use in women with natural menopause has been shown to result in an increase in mammographic breast density [9-12]. Even in patients with BSO, the trend was persistent towards increased breast density with use of exogenous hormonal therapy. This is a surprising finding, as the doses of exogenous hormone given to women with BSO are much lower than basal levels of ovarian hormone production would have been had surgical menopause not occurred [11].

However, women with BSO and previous HRT use had remarkably less dense breast tissue than patients who had natural menopause and never used HRT. This surprising finding could indicate that the effects of HRT in this patient population did

not persist past the discontinuation of this therapy. Indeed, past studies on patients who took HRT for natural menopause have shown the effects on mammographic density did not persist at 5 years from time of discontinuation [1].

Surprisingly, despite increased breast density, patients who used HRT did not have more mammographically occult malignancies than patients who did not use HRT. Additionally, patients had malignancies which did not differ in histology or stage irrespective of past HRT usage. This may indicate that despite the use of HRT, patients are not at higher risk for more advanced stage malignancies. This is a surprising finding as the 2003 WHI trial indicated that HRT users are more likely to be diagnosed at later stages [9]. This may reflect an increased commitment to screening in our HRT patient population. Hormone receptor positivity was also similar for patients who had ever taken HRT and those who had never taken HRT.

This study has several limitations since it is a retrospective review. We did not have available information for many patients on time between HRT discontinuation and malignancy diagnosis, which may play a role in mammographic density. This study was not sufficiently powered to examine the effects of race and BMI on mammographic breast density.

Conclusion

In our study cohort, women with history of surgical menopause who were on HRT at the time of breast cancer diagnosis had a trend towards increased breast density. Surprisingly, women who were prior users of HRT who were not on HRT at the time of malignancy diagnosis had less dense breasts than women who never used HRT. Despite the change observed in breast density, the tumor characteristics do not differ with HRT usage, suggesting that variability in breast density did not correlate with stage of disease at presentation. Further research is warranted in looking at the effects of HRT usage in the population of women with BSO and the impact on long term outcomes, including breast cancer recurrences.

Tables

Table 1: Clinical Characteristics

Variables	Natural menopause, no HRT (N=976, 88%)		BSO, no HRT (N=63, 6%)		p-value*	BSO, prior HRT (N=51, 5%)		p-value*	BSO, current HRT (N=16, %)		p-value*
		%		%			%			%	
Median age at diagnosis, years	64 (39-95)		64 (39-93)		0.48	65 (45-83)		0.34	62 (41-77)		0.17
Median age at menopause, years	51 (33-62)		47 (32-60)		<0.0001	46 (30-59)		<0.0001	47 (39-55)		<0.0001
Family history of breast cancer											
Yes	273	28	25	40	0.06	15	29	0.87	3	19	0.58
No	703	72	38	60		36	71		13	81	
BRCA1 or 2 mutation											
Yes	19	10	10	43	0.0002	2	20	0.30	1	100	0.11
No	165	91	13	57		8	80		0	0	
Unknown or not tested	792	-	40	-		41	-		15	-	

Chemoprevention											
Yes	51	5	9	14	0.008	5	10	0.19	0	0	1.00
No	925	95	54	86		46	90		16	100	
HRT duration											
≤1 year					0.0001	13	27	0.43	1	6	0.13
>1 year						36	73		15	94	
Unknown						2	-		0		
Method of detection											
Self or clinical breast exam	289	30	18	29	0.0001	10	20	0.43	4	25	0.13
Mammogram	620	64	31	49		37	73		9	56	
Ultrasound	36	4	4	6		3	6		1	6	
MRI	21	2	9	14		1	2		2	13	
Other	10	1	1	2		0	0		0	0	
Mammo occult											
Yes	43	4	10	16	0.0006	5	10	0.08	1	6	0.52
No	933	96	53	84		46	90		15	94	
Breast density											
Entirely fatty	94	10	5	8	0.95	0	0	0.007	0	0	0.17
Scattered fibroglandular	448	46	30	47		34	67		5	31	
Heterogeneously dense	393	40	25	40		16	31		11	69	
Extremely dense	41	4	3	5		1	2		0	0	

Table 2: Tumor Characteristics

Variables	Natural menopause, no HRT (N=976, 88%)	%	BSO, no HRT (N=63, 6%)	%	p-value*	BSO, prior HRT (N=51, 5%)	%	p-value*	BSO, current HRT (N=16, 1%)	%	p-value*
Clinical stage											
0	194	20	16	25	0.42	17	33	0.24	6	38	0.41
I	489	50	25	40		20	39		7	44	
IIA, IIB	217	22	15	24		11	22		3	18	
IIIA, IIIB, IIIC	73	8	7	11		3	6		0	0	
IV	3	0.3	0	0		0	0		0	0	
Histology											
DCIS (including microinv)	209	21	17	27	0.49	17	33	0.28	6	38	0.37
IDC	623	64	35	55		29	57		8	50	
ILC	92	10	85	13		3	6		1	6	
Other invasive	52	5	3	5		2	4		1	6	
ER											
Negative	165	17	13	21	0.39	12	24	0.26	3	20	0.73
Positive	798	83	48	79		39	76		12	80	
Unknown	13	-	2	-		0	-		1	-	

PR											
Negative	320	33	22	36	0.68	23	45	0.09	5	36	0.78
Positive	643	67	39	64		28	55		9	64	
Unknown	13	-	2	-		0	-		2	-	
Her2Neu											
Negative	652	85	43	96	0.21	29	85	0.92	10	100	0.71
Positive	95	12	2	4		4	12		0	0	
Equivocal	20	3	0	0		1	3		0	0	
Unknown/ NA	209	-	18	-		17	-		6	-	

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