Association of Regimens of Hormone Replacement Therapy to Prognostic Factors among Women Diagnosed with Breast Cancer Aged 50–64 Years

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Abstract

This study was conducted to assess the histopathological features of breast cancers in women diagnosed with breast cancer at 50–64 years of age who have and have not used hormone replacement therapy (HRT). A case-case analysis of the tumors from women aged 50–64 years who participated in a multicenter population-based case-control study of invasive breast cancer was conducted. In-person interviews collected a detailed history of all episodes of hormone use. Information was collected on selected tumor characteristics from 2346 women with breast cancer. Polytomous logistic regression was used to calculate the odds ratios (ORs) and 95% confidence intervals (CIs), contrasting the histopathological characteristics of the tumors of women who used various regimens of HRT with those of women who have never used HRT. The tumors of cases who used each regimen of HRT were smaller and of earlier stage than those of non-HRT users. Adjustment for screening diminished the magnitude of the effect, and only cases who used estrogen alone (estrogen replacement therapy) had reduced odds of being diagnosed with later-stage disease (regional or distant) than cases who never used HRT (OR, 0.7; 95% CI, 0.6–0.9). Higher proportions of estrogen receptor (ER)- and progesterone receptor (PR)-positive tumors were seen in cases who used any regimen of HRT *versus* those who did not use HRT. However, after adjustment for age and race, only the tumors of cases who used continuous combined HRT remained more likely to be ER+ and PR+ [OR ER− = 0.6 (95% CI, 0.4–0.9) and OR PR− = 0.5 (95% CI, 0.4–0.7)]. The tumors of women with breast cancer who used HRT have some better prognostic factors than those of women who have not used HRT. However, with the exception of the results noted above, this advantage may be due to the racial and age differences in those who use the various regimens of HRT and the effect of more frequent screening among HRT users, leading to earlier diagnosis.

Introduction

Accumulating evidence indicates a more favorable tumor biology among women who develop breast cancer who are either current or past users of HRT.[11] In the meta-analysis conducted by the Collaborative Group in Hormone Factors and Breast Cancer (1), HRT use was associated with an increased risk of localized breast tumors. The influence of HRT on clinical and prognostic factors as well as survival has been investigated by others (2–7), with most, but not all studies (8), showing better prognostic profiles and survival advantages among women diagnosed with breast cancer who have used HRT.

The relationship of various regimens of HRT to tumor characteristics has been investigated in a few previous studies (9–11). Prior studies have focused on the risk of developing a breast cancer with certain histological characteristics among postmenopausal women who used various regimens of HRT.

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[11] The abbreviations used are: HRT, hormone replacement therapy; OR, odds ratio; CI, confidence interval; ERT, estrogen replacement therapy; ER, estrogen receptor; PR, progesterone receptor; CHRT, combined HRT; C-CHRT, continuous CHRT; S-CHRT, sequential CHRT; CARE, Contraceptive and Reproductive Experience; ICD-O, International Classification of Diseases for Oncology.

Recently, we reported that combined HRT (CHRT) increased the risk of lobular and mixed lobular-ductal tumors but not ductal breast cancer risk among postmenopausal women who participated in the Women's Contraceptive and Reproductive Experience (CARE) Study (12). Here we explore how ever use of various regimens of HRT relates to selected tumor features among all patient participants of the Women's CARE Study who were diagnosed with breast cancer at ages 50–64 years. In particular, we address the following questions. (a) Are the tumors of HRT users smaller or of an earlier stage than those of patients who never used HRT, and, if they are, is this prognostic advantage due to the possible direct effect of HRT on cancer development, or is it attributable to more frequent screening of women who use HRT? (*b*) Are tumors of HRT users more likely to be ER+ and PR+ than tumors of nonusers, and, if they are, is this truly an effect of HRT use, or is it an artifact of racial distributions or histological profiles [because lobular tumors are more likely to be ER+ and PR+ (13)] of HRT users?

Materials and Methods

A detailed description of the methods used in the Women's CARE Study appears elsewhere (14, 15). Briefly, this population-based case-control study was conducted in five geographic areas: Atlanta; Detroit; Los Angeles; Philadelphia; and Seattle. The Centers for Disease Control served as the data coordinating center. Protocols were approved by the institutional review committees of each center.

Cases. Caucasian and African-American women aged 35–64 years residing in one of the five geographic areas, with no history of *in situ* or invasive breast cancer when diagnosed with invasive breast cancer between July 1, 1994 and April 30, 1998 were eligible as cases. The Surveillance, Epidemiology, and End Results Registry at each site (except Philadelphia) was used to identify cases. In Philadelphia, cases were ascertained by field staff contacting the hospitals in the study area. Because one goal of the study was to maximize the number of African-American women participating in the study, African-American women were oversampled. Both African-American and Caucasian women were randomly selected to provide, if possible, approximately equal numbers of women in each 5-year age category. Only patients born in the United States were considered eligible.

Of the 5982 eligible patients identified and selected, 4575 (76.5%) were interviewed.

Data Collection. In-person interviews were conducted with all study subjects, usually in the woman's home. We obtained a detailed history of all episodes of hormone use, including beginning and ending dates, total duration, brand, dose, and pattern of use (number of days per month) for each formulation used up until diagnosis of breast cancer. In addition, we asked questions about each woman's reproductive history, health history, oral contraceptive use, and family history of cancer. A life events calendar and a photo book of hormone replacement medications marketed in the United States were used to enhance recall.

The pathology information available for this study included histological classification [ICD-O codes (16)], extent of disease, tumor size, and ER and PR status. These data were extracted from Surveillance, Epidemiology, and End Results registry files at all sites except Philadelphia, where data were collected from pathology reports, medical records, and hospital registry abstracts.

Analysis. The analyses are based on all 2346 women aged 50–64 years at breast cancer diagnosis who participated in the Women's CARE Study. For analysis, the tumors were grouped into four histological groups: (*a*) all histologies ($n = 2346$); (*b*) ductal ($n = 1722$) ICD-O code 8500; (*c*) lobular ($n = 177$) ICD code 8520 or mixed lobular-ductal ($n = 154$) ICD-O code 8522; and (*d*) all other histologies ($n = 293$).

Estrogen users who took a progestin 5 to <25 days/month were considered sequential combined HRT (S-CHRT) users, whereas those who used progestin ≥25 days/month were considered continuous combined HRT (C-CHRT) users. Women who used HRT but did not use any regimen in this analysis for 6 or more months were excluded from analyses of HRT use ($n = 250$). Women who used more than one regimen were classified as users of each regimen ($n = 231$), provided they used the regimen for at least 6 months.

Polytomous logistic regression was used in this case-case analysis to calculate ORs and compute 95% CIs, contrasting the histopathological characteristics of the tumors of cases who have used various regimens of HRT with those of cases who have never used HRT. The dependent (outcome) variables in the different models were tumor size (with <2 cm as the referent category), stage (with local stage as the referent category), histology (with ductal as the referent category), and ER/PR status (with positive receptor status as the referent category). Therefore, the ORs presented in this paper are the odds of exposure to HRT among women with certain tumor characteristics (*i.e.*, tumor size ≥ 5 cm), relative to the odds of exposure to HRT among women with the referent tumor characteristic (*i.e.*, tumor size < 2 cm). All analyses were adjusted for age, race, and study site. In addition, analyses of tumor size and stage of disease were also adjusted for whether or not a patient had a screening mammogram in the 2 years before her breast cancer diagnosis.

Results

Ever use of specific regimens of HRT for 6 months or longer among women with breast cancer in this study varied by age ($P < 0.01$), race ($P < 0.01$), and the presence of a screening mammogram in the 2 years before diagnosis ($P < 0.01$; Table 1).

Among women with breast cancer who had used C-CHRT, 20.5% developed a tumor of either lobular or mixed lobular/ductal histology compared with 12.1% of women who had never used any HRT (OR, 1.7; 95% CI, 1.2–2.4; Tables 1 and 2). Although lobular-type carcinoma and tumors of histologies other than ductal were more frequent among ERT and S-CHRT users, the odds of this occurring were within the limit of chance.

HRT use was associated with smaller tumor size (Tables 1 and 2). Adjusted for age, race, and study site and compared with cases who never used any HRT, the relative odds of a patient having a 5+ cm tumor were respectively 0.6 (95% CI, 0.4–0.9), 0.5 (95% CI, 0.3–0.8), and 0.4 (95% CI, 0.2–0.7) for ever users of ERT, S-CHRT, and C-CHRT. After additional adjustment for presence of a screening mammogram within the prior 2 years, the OR estimates were attenuated for each regimen and were no longer statistically significant. Specifically, the ORs for a 5+ cm tumor in relation to use of ERT, S-CHRT, and C-CHRT compared with never use of HRT were 0.9 (95% CI, 0.6–1.4), 0.9 (95% CI, 0.5–1.7), and 0.7 (95% CI, 0.4–1.3), respectively, when adjusted for age, race, study site, and screening history. Similarly, HRT was associated with reduced odds of more advanced disease [OR = 0.6 (95% CI, 0.5–0.8), OR = 0.6 (95% CI, 0.5–0.8), and OR = 0.7 (95% CI, 0.5–0.9) for ERT, S-CHRT and C-CHRT users, respectively]. Again, however, adjustment for screening history diminished these effects.

Table 1 Relationship of age, race, screening history, and tumor characteristics to type of HRT regimen among women diagnosed with breast cancer ages 50–64 years

Variable	All women with breast cancer (N = 2346)	Use of pill or patch HRT[a]			
		Never used HRT (N = 935)	Used ERT[b] (N = 635[c])	Used S-CHRT[d] (N = 381[c])	Used C-CHRT[e] (N = 385[c])
	N (%)	N (%)	N (%)	N (%)	N (%)
Age at diagnosis (yrs)					
50–54	844 (36.0)	387 (41.3)	176 (27.7)	123 (32.3)	101 (26.2)
55–59	770 (32.8)	261 (27.9)	233 (36.7)	139 (36.5)	150 (39.0)
60–64	732 (31.2)	287 (30.7)	226 (35.6)	119 (31.2)	134 (34.1)
P[f]			<0.001	0.002	<0.001
Race					
White	1535 (65.4)	470 (50.3)	447 (70.4)	332 (87.1)	338 (87.8)
Black	811 (34.6)	465 (49.7)	188 (29.6)	49 (12.9)	47 (12.2)
P[f]			<0.001	<0.001	<0.001
Screening mammogram in 2 yrs before ref.					
No	558 (23.8)	329 (35.2)	102 (16.1)	35 (9.2)	44 (11.4)
Yes	1788 (76.2)	606 (64.8)	533 (83.9)	346 (90.8)	341 (88.6)
P[f]			<0.001	<0.001	<0.001
Histology					
Ductal	1722 (73.4)	712 (76.1)	462 (72.8)	270 (70.9)	272 (70.6)
Any lobular	331 (14.1)	113 (12.1)	92 (14.5)	63 (16.5)	79 (20.5)
All other	293 (12.5)	110 (11.8)	81 (12.8)	48 (12.6)	34 (8.8)
Tumor size					
<2 cm	1316 (59.1)	464 (53.0)	387 (63.3)	240 (65.9)	252 (67.0)
2 to <5 cm	733 (32.9)	317 (36.2)	184 (30.1)	104 (28.6)	106 (28.2)
5+ cm	177 (8.0)	94 (10.7)	40 (6.5)	20 (5.5)	18 (4.8)
Missing	120	60	24	17	9
Stage					
Local	1492 (64.3)	537 (58.1)	433 (68.8)	267 (70.6)	262 (68.8)
Regional/Dist	830 (35.7)	387 (41.9)	196 (31.2)	111 (29.4)	119 (31.3)
Missing	24	11	6	3	4
ER/PR status					
ER+	1470 (72.9)	524 (67.8)	411 (73.0)	262 (76.8)	286 (82.7)
ER−	547 (27.1)	249 (32.2)	152 (27.0)	79 (23.2)	60 (17.3)
Missing	329	162	72	40	39
PR+	1216 (63.8)	431 (59.0)	338 (62.6)	213 (64.7)	250 (76.9)
PR−	690 (36.2)	299 (41.0)	202 (37.4)	116 (35.3)	75 (23.1)
Missing	440	205	95	52	60
ER+/PR+	1136 (59.9)	396 (54.5)	319 (59.4)	196 (59.8)	235 (73.0)
ER+/PR−	233 (12.3)	92 (12.7)	71 (13.2)	54 (16.5)	29 (9.0)
ER−/PR+	74 (3.9)	32 (4.4)	19 (3.5)	16 (4.9)	13 (4.0)
ER−/PR−	452 (23.9)	206 (28.4)	128 (23.8)	62 (18.9)	45 (14.0)
Missing	451	209	98	53	63

[a] Excludes women who use HRT for <6 months.
[b] ERT, unopposed estrogen.
[c] The sum of users in each category does not equal the total number of HRT users because some women used more than one regimen.
[d] S-CHRT, sequential estrogen plus progestin use (5–24 days/month).
[e] C-CHRT, continuous combined estrogen plus progestin use (25+ days/month).
[f] P (χ^2 test) for relationship of variable to HRT regimen.

After additionally adjusting for screening, only the tumors of patients who used ERT retained a substantive reduced relative odds of advanced disease stage [OR = 0.7 (95% CI, 0.6–0.9)].

Breast cancer cases who had used HRT had proportionately more ER+ and PR+ tumors than did cases who never used HRT (Table 1). However, after adjusting for age, race, and study site, only the relationship between C-CHRT and ER/PR status remained statistically significant. Among breast cancer patients who had used C-CHRT, 82.7% had ER+ tumors, and 76.9% had PR+ tumors, compared with 67.8% ER+ tumors and 59.0% PR+ tumors among patients who had never used HRT. The age-, race-, and study site-adjusted odds for ER− and PR− tumors associated with C-CHRT use were OR = 0.6 (95% CI, 0.4–0.9) and OR = 0.5 (95% CI, 0.4–0.7), respectively (Table 2).

Because lobular type tumors are more likely to be ER+ and PR+ (in this study, 89.9% and 83.1% of lobular tumors were ER+ and PR+, respectively, compared with 71.3% and 61.7% of ductal tumors) and to be related to CHRT use (9, 11, 12, 17), we investigated the relationship of HRT use to tumor size, stage, and ER and PR status separately for tumors of ductal and lobular histology (Tables 3 and 4).

Among women with breast cancer of ductal histology, those who used any regimen of HRT presented with smaller and earlier stage tumors than women who had never used HRT (Table 3). However, after adjustment for the presence of a screening mammogram in the 2 years before reference date, these differences diminished, and none remained statistically significant. The proportion of ductal tumors that were either ER− or PR− did not differ substantively between breast cancer

Table 2 Associations of Regimens of HRT use with prognostic factors

Variable	Used ERT[a]		Used S-CHRT[c]		Used C-CHRT[d]	
	OR[b]	(95% CI)	OR[b]	(95% CI)	OR[b]	(95% CI)
Histology						
Ductal	1.0	Ref.[e]	1.0	Ref.	1.0	Ref.
Any lobular	1.2	0.9–1.7	1.3	0.9–1.9	1.7	1.2–2.4
All other	1.3	0.9–1.8	1.4	0.9–2.0	0.9	0.6–1.5
Tumor size						
<2 cm	1.0	Ref.	1.0	Ref.	1.0	Ref.
2 to <5 cm	0.7	0.6–0.9	0.8	0.6–1.0	0.7	0.5–1.0
5+ cm	0.6	0.4–0.9	0.5	0.3–0.8	0.4	0.2–0.7
Tumor size[f]						
<2 cm	1.0	Ref.	1.0	Ref.	1.0	Ref.
2 to <5 cm	1.0	0.7–1.2	1.1	0.8–1.5	1.0	0.7–1.4
5+ cm	0.9	0.6–1.4	0.9	0.5–1.7	0.7	0.4–1.3
Stage						
Local	1.0	Ref.	1.0	Ref.	1.0	Ref.
Regional/distant	0.6	0.5–0.8	0.6	0.5–0.8	0.7	0.5–0.9
Stage[f]						
Local	1.0	Ref.	1.0	Ref.	1.0	Ref.
Regional/distant	0.7	0.6–0.9	0.8	0.6–1.1	0.9	0.6–1.2
ER/PR status						
ER+	1.0	Ref.	1.0	Ref.	1.0	Ref.
ER−	1.0	0.7–1.2	0.8	0.6–1.2	0.6	0.4–0.9
PR+	1.0	Ref.	1.0	Ref.	1.0	Ref.
PR−	1.0	0.8–1.3	1.0	0.7–1.3	0.5	0.4–0.7
ER+/PR+	1.0	Ref.	1.0	Ref.	1.0	Ref.
ER+/PR−	1.0	0.7–1.5	1.4	0.9–2.2	0.6	0.4–1.0[g]
ER−/PR+	1.1	0.6–2.0	1.5	0.7–2.9	1.2	0.6–2.5
ER−/PR−	1.0	0.7–1.3	0.8	0.6–1.2	0.5	0.3–0.8

[a] ERT, unopposed estrogen.
[b] Relative to never users of HRT and adjusted for age, race, and study site.
[c] S-CHRT, sequential estrogen plus progestin use (5–24 days/month).
[d] C-CHRT, continuous combined estrogen plus progestin use (25+ days/month).
[e] Ref., referent.
[f] Relative to never users of HRT and adjusted for age, race, study site, and screening mammogram in 2 years before reference (yes/no).
[g] 95% CI does not include 1.0.

cases who had never used HRT and those who had used any regimen, with the exception of PR status among C-CHRT users. Only 27.0% of women with ductal tumors who had used C-CHRT had PR− tumors compared with 41.6% of women with ductal tumors who never used any form of HRT [OR = 0.7 (95% CI, 0.5–1.0)].

Among cases with lobular histology, after adjustment for screening, the tumors of women who used HRT were somewhat larger than those of women who had never used HRT, but these differences were consistent with chance (Table 4). The odds of having an ER− and PR− tumor among women who had used ERT or S-CHRT was not increased relative to women who had never used HRT. However, compared with the tumors of never users with lobular cancer, the lobular tumors of women who used C-CHRT were less likely to be PR−. Only 9.5% of the lobular tumors of C-CHRT users were PR− compared with 21.6% of never users [OR = 0.2 (95% CI, 0.1–0.6)]. Although the relative odds of an ER− tumor among C-CHRT users who had lobular tumors (7.1%) was reduced (OR, 0.5; 95% CI, 0.1–1.6), the estimate was imprecise.

Discussion

Some limitations to this study should be considered. We did not conduct an independent pathology review of the tumors but depended on the diagnosis made by numerous pathologists serving the five geographic areas in the study. The determination of ER/PR status was not conducted in one central laboratory using the same method. In addition, ER status was not available for 14.0% of the patients in our study, and PR status was not available for 18.8% of the patients in our study. Almost twice as many African-American women had ER/PR status missing (27%) compared with Caucasian women (15%).

We were only able to interview 76.5% of all eligible cases. It is likely that some women refused because they were too ill to participate. Hence, the distribution of tumor characteristics may be slightly more favorable than that which would have occurred had we been able to interview all eligible women and ascertain their tumor characteristics and relationship to HRT.

In this study, 84.0% of estrogen use was conjugated estrogen, and 94.0% of progestin use was medroxyprogesterone-acetate. For our analyses, we did not differentiate between these preparations and other types such as those predominant in Europe (*i.e.*, 17β-estradiol and the testosterone-derived progestens). We relied on a woman's ability to recall the types of HRT used. However, the majority of women who used HRT for 6 months or more in our study were current users (70.9% of ERT users and 80.0% of CHRT users), which would increase their ability to report accurately the specific HRT type and regimen used. We chose to use ever use of a HRT regimen for 6 months or more (women who used HRT for less than 6 months were excluded), rather than current use or use for 5 or more years (ERT, 58.0%; S-CHRT, 48.4%; C-CHRT 39.8% had used the specific regimen for 5 or more years), as our measure of exposure. However, the results of an analysis of

Table 3 Relationship of regimens of HRT to prognostic factors among women with ductal breast cancer

Variable	Never used HRT (N = 712)	Used ERT[a] (N = 462[b])			Used S-CHRT[c] (N = 270[b])			Used C-CHRT[d] (N = 272[b])		
	N (%)	N (%)	OR	95% CI	N (%)	OR	95% CI	N (%)	OR	95% CI
Tumor size[e]										
<2 cm	357 (52.7)	283 (64.0)	1.0	Ref.[g]	173 (67.6)	1.0	Ref.	185 (69.3)	1.0	Ref.
2 to <5 cm	257 (37.9)	141 (31.9)	0.7	0.6–1.0[h]	75 (29.3)	0.7	0.5–1.0	75 (28.1)	0.7	0.5–0.9
5+ cm	64 (9.4)	18 (4.1)	0.4	0.2–0.7	8 (3.1)	0.3	0.1–0.7	7 (2.6)	0.3	0.1–0.6
Tumor size[f]										
<2 cm	357 (52.7)	283 (64.0)	1.0	Ref.	173 (67.6)	1.0	Ref.	185 (69.3)	1.0	Ref.
2 to <5 cm	257 (37.9)	141 (31.9)	1.0	0.7–1.3	75 (29.3)	1.0	0.7–1.5	75 (28.1)	0.9	0.6–1.3
5+ cm	64 (9.4)	18 (4.1)	0.6	0.4–1.2	8 (3.1)	0.6	0.3–1.5	7 (2.6)	0.5	0.2–1.1
Stage[e]										
Local	416 (59.2)	309 (67.8)	1.0	Ref.	189 (70.5)	1.0	Ref.	187 (69.3)	1.0	Ref.
Regional/distant	287 (40.8)	147 (32.2)	0.6	0.5–0.8	79 (29.5)	0.6	0.4–0.9	83 (30.7)	0.7	0.5–0.9
Stage[f]										
Local	416 (59.2)	309 (67.8)	1.0	Ref.	189 (70.5)	1.0	Ref.	187 (69.3)	1.0	Ref.
Regional/distant	287 (40.8)	147 (32.2)	0.8	0.6–1.0	79 (29.5)	0.8	0.6–1.1	83 (30.7)	0.8	0.6–1.2
ER/PR status[e]										
ER+	396 (67.2)	221 (72.2)	1.0	Ref.	104 (73.8)	1.0	Ref.	198 (79.2)	1.0	Ref.
ER−	193 (32.8)	113 (27.8)	1.0	0.7–1.3	64 (26.2)	1.0	0.7–1.5	52 (20.8)	0.8	0.5–1.2
PR+	326 (58.4)	236 (60.2)	1.0	Ref.	147 (62.3)	1.0	Ref.	173 (73.0)	1.0	Ref.
PR−	232 (41.6)	156 (39.8)	1.1	0.8–1.5	89 (37.7)	1.0	0.8–1.5	64 (27.0)	0.7	0.5–1.0[h]

[a] ERT, unopposed estrogen.
[b] Women could have used more than one regimen.
[c] S-CHRT, sequential estrogen plus progestin use (5–24 days/month).
[d] C-CCRT, continuous combined estrogen plus progestin use (25+ days/month).
[e] Used ≥6 months relative to never users of HRT; adjusted for age, race, and study site.
[f] Used ≥6 months relative to never users of HRT; adjusted for age, race, study site, and screening mammogram in 2 years before reference.
[g] 95% CI does not include 1.0.
[h] Ref., referent.

current users or use of 5 years or more did not differ substantially from that of ever users.

Our measure of screening may seem rather crude (*i.e.*, screening mammogram in 2 years before diagnosis), yet it did affect the magnitude of our estimates. This is not surprising because having a screening mammogram in the last 2 years (72.5% of women) was highly correlated to tumor size. Of the women with a screening mammogram in the last 2 years, 66.8% had a tumor <2 cm in size compared with 33.7% of the tumors of women who had not been recently screened. Our results varied little when the number of mammograms in the last 5 years was used for our adjustments.

Finally, our statistical power to determine the relationships between regimen of HRT used and the tumor characteristics of the lobular tumors was limited by the small number of lobular and mixed-lobular ductal cases available for analysis (n = 331). Nevertheless, this is the largest study to evaluate lobular tumors for the relationship of tumor characteristics to regimen of HRT.

Consistent with a growing number of reports of an association between CHRT and lobular breast cancer (9, 11, 12, 17, 18), we found that the odds of having pure lobular or mixed lobular histology tumors was related to combined HRT use and particularly C-CHRT use among women with breast cancer. This result is consistent with our recent case-control analysis showing an increased risk of developing lobular breast cancer among a subset of women from the CARE study (1749 women known to be postmenopausal or ≥55 years of age). In contrast, Ursin *et al.* (10) did not see any differences in risk for histological subtypes associated with the use of any regimen of HRT in a case-control study in Los Angeles.

Also consistent with past reports, we found that HRT use of each type was related to decreased odds of larger and later stage tumors. However, these associations diminished once we considered the effects of screening. Women who used HRT were more likely to have had a screening mammogram in the past 2 years, and tumor size was strongly related to having a screening mammogram in the last 2 years. Specifically, when we adjusted our results for the presence of a screening mammogram in the 2 years before diagnosis, the decreased risk of large tumor size and late-stage tumors associated with HRT use was no longer significant, with the exception that ERT users were at 30% reduced odds of being diagnosed with their cancer at later stage (regional or distant) relative to nonusers. Ross *et al.* (19), whose study included *in situ* cancers, found that ERT was inversely related to the risk of developing these late-stage tumors but found no effect of the regimen of CHRT on stage of disease. Magnusson *et al.* (5) found CHRT was related to reduced risk of developing larger and later stage tumors; however, they made no adjustment for screening practices.

In our study, breast cancer cases who had used HRT had proportionately more ER+ and PR+ tumors than never users. However, after adjusting for age, race, and study site in a multivariate analysis, those women who used ERT or S-CHRT were no more likely to be ER+ or PR+ than the cases who never used HRT. When analyses were conducted adjusting for age alone and for race alone, adjustment for race yielded a greater change in ORs (data not shown). The magnitude of the confounding effect of race in these data was likely due to the large proportion of women in our study who were African American (approximately one-third). African-American women are less likely to use HRT (see Table 1) and are more likely to have ER− and PR− tumors than Caucasian women (13). In our study, the proportion of patients that were ER− and PR− were as follows: African-American, ER− = 37.4% and PR− = 45.0%; and Caucasian, ER− = 22.5% and PR− = 32.2%. This illustrates the importance of considering the racial

Table 4 Relationship of regimens of HRT to prognostic factors among women with lobular breast cancer

Variable	Never used HRT (N = 113)	Used ERT[a] (N = 92[b])			Used S-CHRT[c] (N = 63[b])			Used C-CHRT[d] (N = 79[b])		
	N (%)	N (%)	OR	95% CI	N (%)	OR	95% CI	N (%)	OR	95% CI
Tumor size[c]										
<2 cm	53 (52.0)	46 (51.1)	1.0	Ref.[f]	37 (59.7)	1.0	Ref.	42 (54.5)	1.0	Ref.
2 to <5 cm	36 (35.3)	31 (34.4)	1.0	0.5–2.0	19 (30.6)	1.0	0.4–2.1	25 (32.5)	1.0	0.5–2.0
5+ cm	13 (12.7)	13 (14.4)	1.1	0.4–2.9	6 (9.7)	0.5	0.2–1.6	10 (13.0)	0.8	0.3–2.1
Tumor size[g]										
<2 cm	53 (52.0)	46 (51.1)	1.0	Ref.	37 (59.7)	1.0	Ref.	42 (54.5)	1.0	Ref.
2 to <5 cm	36 (35.3)	31 (34.4)	1.5	0.7–3.0	19 (30.6)	1.6	0.7–3.8	25 (32.5)	1.3	0.6–2.7
5+ cm	13 (12.7)	13 (14.4)	2.3	0.8–6.6	6 (9.7)	1.5	0.4–5.8	10 (13.0)	1.5	0.5–4.8
Stage[e]										
Local	66 (58.9)	62 (67.4)	1.0	Ref.	44 (69.8)	1.0	Ref.	45 (57.7)	1.0	Ref.
Regional/distant	46 (41.1)	30 (32.6)	0.7	0.4–1.3	19 (30.2)	0.7	0.3–1.5	33 (42.3)	1.1	0.6–2.2
Stage[g]										
Local	66 (58.9)	62 (67.4)	1.0	Ref.	44 (69.8)	1.0	Ref.	45 (57.7)	1.0	Ref.
Regional/distant	46 (41.1)	30 (32.6)	0.9	0.5–1.8	19 (30.2)	1.1	0.5–2.6	33 (42.3)	1.6	0.8–3.2
ER/PR status[e]										
ER+	83 (88.3)	72 (85.7)	1.0	Ref.	48 (88.9)	1.0	Ref.	65 (92.9)	1.0	Ref.
ER−	11 (11.7)	12 (14.3)	1.5	0.5–4.2	6 (11.1)	0.6	0.2–1.9	5 (7.1)	0.5	0.1–1.6
PR+	69 (78.4)	65 (81.3)	1.0	Ref.	40 (78.4)	1.0	Ref.	57 (90.5)	1.0	Ref.
PR−	19 (21.6)	15 (18.8)	0.7	0.3–1.6	11 (21.6)	0.5	0.2–1.5	6 (9.5)	0.2	0.1–0.6

[a] ERT, unopposed estrogen.
[b] Women could have used more than one regimen.
[c] S-CHRT, sequential estrogen plus progestin use (5–24 days/month).
[d] C-CHRT, continuous combined estrogen plus progestin use (25+ days/month).
[e] Used ≥6 months relative to never users of HRT; adjusted for age, race, and study site.
[f] Ref., referent.
[g] Used ≥6 months relative to never users of HRT; adjusted for age, race, study site, and screening mammogram in 2 years before reference.

composition of the population studied when assessing the relationship of HRT use to tumor characteristics. The tumors of the women who used C-CHRT were more likely to be ER+ and PR+, as might be expected from the relationship of C-CHRT to tumors of lobular histology. However, when we stratified by histology and adjusted for age, study site, and race, both ductal and lobular type cancers were significantly more likely to be PR+ if the women had used C-CHRT. This was particularly true of lobular tumors, where >90% were PR+ among women who used C-CHRT compared with 78.4–81.3% of the lobular tumors of women who had never used HRT or had used ERT or S-CHRT. Although no other reports have addressed the relationship of estrogen and progesterone status of the breast tumors among women using combined HRT by the number of days progestin is taken, Ursin *et al.* (10) found an increasing risk of developing a PR+ tumor among women using any regimen of CHRT.

There is a growing need to determine the effects of progestin on mammary tissue. The pooled analysis of 51 epidemiological studies (1) and a number of recent studies indicate CHRT is related to an increased risk of developing breast cancer (9, 11, 12, 15, 17–21). The results of our Women's CARE Study and others indicate the resulting tumors are more likely to be of lobular or mixed lobular-ductal histology (9, 11, 12, 17, 18), a type of breast cancer with more favorable prognosis than ductal tumors (22). Our study also indicates that cases who had used continuous combined therapy are more likely to have ER+/PR+ tumors, even after adjustment for race and age. Furthermore, independently of the histological subtype, the tumors are more likely to be PR+. The mechanisms involved need to be determined, and ultimately, the survival by regimen needs to be assessed.

In summary, our study indicates that women who use HRT have tumors with good prognostic factors (*i.e.*, lobular histology, small tumor size, earlier stage, and ER/PR positivity). These characteristics make it more likely that women who have used HRT will have lower mortality associated with their disease. Our analysis found (with the few exceptions noted in "Results") that the association of HRT use with better prognostic features may be explained in part by racial differences in HRT use patterns and the effect of more frequent screening among HRT users, leading to earlier diagnosis.

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