Published in final edited form as:

Breast Cancer Res Treat. 2014 June ; 145(2): 481–489. doi:10.1007/s10549-014-2960-4.

Use of menopausal hormone therapy and risk of ductal and lobular breast cancer among women 55–74 years of age

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Abstract

Background—The Women’s Health Initiative (WHI) randomized trials found that use of combined estrogen and progestin menopausal hormone therapy (CHT) increases breast cancer risk, but use of unopposed estrogen hormone therapy (EHT) does not. However, several questions regarding the impact of hormone use on risk of different types of breast cancer and what thresholds of use confer elevations in risk remain.

Methods—We conducted a population-based case-control study among women 55–74 years of age to assess the association between menopausal hormone use and risk of invasive ductal and invasive lobular breast carcinomas. Associations were evaluated using polytomous logistic regression and analyses included 880 ductal cases, 1,027 lobular cases, and 856 controls.

Results—Current EHT and CHT use were associated with 1.6-fold [95% confidence interval (CI): 1.1–2.2] and 2.3-fold (95% CI: 1.7–3.2) increased risks of lobular breast cancer, respectively, but neither was associated with risk of ductal cancer. Lobular cancer risk was increased after nine years of EHT use, but after only three years of CHT use.

Discussion—Evidence across more than a dozen studies indicates that lobular carcinoma is the type of breast cancer most strongly influenced by menopausal hormones. Here we characterize what thresholds of duration of use of both EHT and CHT that confer elevations in risk.

Impact—Despite the rapid decline in hormone therapy use the WHI results were published, study of the hazards associated with these medications remains relevant given the estimated 38 million hormone therapy prescriptions that are still filled in the United States annually.

Introduction

Results from the Women’s Health Initiative ([WHI](#)) randomized controlled trials of menopausal hormone therapy indicate that use of combined estrogen and progestin hormone therapy ([CHT](#))^[5] increases breast cancer risk, but that use of unopposed estrogen hormone therapy ([EHT](#)) does not. However, a now substantial number of studies indicate that the relationship between menopausal hormone therapy use and breast cancer risk varies by breast cancer type, with differences by histologic type observed most consistently. The two

most common histologic subtypes of breast cancer are invasive ductal carcinoma (IDC), which accounts for approximately 75% of postmenopausal breast cancers in the United States, and invasive lobular carcinoma (ILC), which accounts for 15–20% of cases.[12] Thirteen[3, 4, 6–10, 13, 15, 17–21] out of the sixteen[2, 11, 23] observational studies evaluating the relationship between menopausal hormone therapy use and ILC vs. IDC risk have shown that CHT use is more strongly related to risk of ILC than it is to risk of IDC. The thirteen studies reporting a difference in risk by histologic type (including four cohort studies and nine case-control studies) found that current CHT use results in 2.1–3.9 fold increases in the risk of ILC and lower or no increases in risk of IDC (relative risks of 0.7 to 2.0). The WHI trial had limited statistical power to assess this relationship as it included only 22 lobular cases in the CHT arm and 16 in the placebo arm.[5]

Despite the consistency of studies evaluating differences in risk according to histologic subtype, some key questions remain with regard to how duration of CHT use is related to risk and if this relationship varies whether the progestin component of CHT is used daily or for only a certain number of days per month. Though use of menopausal hormone therapy has declined sharply since the publication of the WHI trial results, these issues are of ongoing clinical and public health importance given that in the post-WHI era ~8% of women 40–80 years of age are CHT users and another ~9% are EHT users,[26] and an estimated 38 million hormone therapy prescriptions were filled in the United States in 2010. To evaluate the relationships between various menopausal hormone therapy regimens and risk of different histologic types of breast cancer we conducted a large scale population-based case-control study specifically focused on examining the etiologies of ILC vs. IDC.

Methods

We conducted a large population-based case-control study of lobular and ductal breast cancer among postmenopausal women 55 to 74 years of age living in the three county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties). This study was specifically designed to assess how use of menopausal hormone therapy influences risk of these two breast cancer subtypes.

Cases were women 55 to 74 years old diagnosed with a primary invasive breast cancer between January 2000 and December 2008 with no prior history of *in situ* or invasive breast cancer. This study was funded in two continuous phases, and data from the first phase based on cases enrolled from January 2000 to March 2004 were published previously.[13] Breast cancer patients were identified through the Cancer Surveillance System (CSS), the population-based tumor registry that serves the 13 counties of western Washington state and participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute (though this study was restricted to residents of King, Pierce, and Snohomish counties). All women diagnosed with an invasive breast cancer with a lobular component based on ICD-O codes 8520, 8522, and 8524 assigned by CSS were potentially eligible as lobular cases. Thus, lobular, ductal-lobular, and lobular tumors with an other non-lobular histology present were grouped together consistent with several prior studies.[3, 4, 6, 8, 11, 14] Given the greater frequency of IDC, a random sample of ~25% IDC cases was selected for recruitment. IDC cases were frequency matched to the ILC case group by 5-year

age group. The pathology reports of all of these cases were then centrally reviewed to confirm eligibility and reclassify histology assignments as necessary. Since controls were ascertained via random digit dialing of landline home telephone numbers, to be eligible all cases were also required to have a landline home telephone. Of the 2,495 eligible cases identified, 1,984 (80%) were interviewed including 1,068 ILC and 916 IDC cases. Of those not enrolled, 442 (18%) refused to be interviewed or could not be located and 77 (3%) died before an interview could be conducted. In addition to basic information on breast cancer diagnosis, we obtained information on tumor characteristics from the cancer registry and from a centralized review of pathology reports. This includes data on estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (HER2) status, and tumor stage, size, and nodal status.

We used the Mitofsky-Waksberg[25] method of random digit dialing to identify potential controls from the general population of female residents of King, Pierce, and Snohomish counties. Controls were frequency matched within 5-year age groups to the cases using onestep recruitment. As the study progressed, we reduced our clustering factor from five to one in order to ensure timely completion of our calling. Up to nine calls were made to each number at various times of the day and days of the week. Numbers were recontacted three months later if all attempts were answered by an answering machine, or if a respondent refused to answer the screening questions. Numbers were recontacted again three months later if all attempts in the second contact round were answered by machine. A total of 79,559 numbers were dialed; 55,576 were nonworking, business, cellular, paging, dedicated facsimile, or data line numbers. 4,464 numbers were never answered, and thus their residential status could not be determined. Prior studies suggest that only about 20% of such numbers are indeed residential.[24] Of the 19,519 residential or presumed residential numbers, 15,695 were successfully screened for eligibility. Of the remainder, 1868 were answering machines, 1,552 reached a respondent who refused to answer the screening questions, and for 404 there were language or other communication barriers. Of the 1,313 eligible controls identified, 902 (69%) were interviewed.

Data Collection

The study protocol was approved by the Fred Hutchinson Cancer Research Center Institutional Review Board, and written informed consent was obtained from all study subjects. Cases and controls were interviewed in-person. Through a series of structured questions, detailed histories of all episodes of menopausal hormone therapy use, including beginning and ending dates, brand, dose, route of administration, and pattern of use (number of days per month) were obtained. To enhance recall, a photo book containing pictures of pills and packages of commonly used hormonal preparations was used along with a show card listing the brand and generic names of various prescription hormonal medications. Additionally, all participants were queried about their reproductive history, body size, medical history, and family history of cancer. Our questioning was limited to exposures that occurred before each participant's reference date. The reference date used for each woman with breast cancer was her diagnosis date. Control reference dates were assigned to reflect the expected distribution of reference dates among the cases.

Statistical Analysis

Women who never used any type of prescription menopausal hormone therapy served as the reference category. We assessed patterns of CHT use by categorizing women who used estrogen daily and progestin for ≥ 25 days per month as continuous CHT users and those used estrogen daily and progestin for <25 days per month as sequential CHT users, consistent with prior studies.[6, 13, 16]

We used polytomous logistic regression to calculate odds ratios (ORs) and their associated 95% confidence intervals (CIs) to compare IDC and ILC cases to controls.[1] All analyses were conducted using Stata/SE version 11.2 (StataCorp LP, College Station, TX). All models were adjusted for age (five year categories), reference year (continuous), and county since controls were matched to cases on these factors. Several potential confounders and effect modifiers of the relationship between menopausal hormone therapy use and breast cancer risk were assessed including: type of menopause, first degree family history of breast cancer, body mass index one year prior to reference date, alcohol consumption, and smoking history. Only type of menopause changed our risk estimates by more than 10% when added to the model, and so only it was added as a covariate to our final statistical models. Excluded from all analyses were the 46 controls, 36 IDC cases, and 41 ILC cases missing data on either menopausal hormone therapy use and/or type of menopause leaving a final analytic sample size of 856 controls, 880 IDC cases, and 1,027 ILC cases. In addition, none of the covariates were found to be a statistically significant effect modifier based on likelihood ratio testing including body mass index (all p-values for interaction were >0.05). We also calculated case-case differences in models that excluded controls and used the IDC cases as the referent comparison group in order to quantify the magnitude and statistical significance of the case-case differences observed. In addition, we assessed whether or not risk estimates differed among women with invasive lobular (ICD-O codes 8520 and 8524) versus invasive ductal-lobular (ICD-O code 8522) carcinomas. No appreciable differences in the magnitudes of risk were observed when the analysis was stratified in this way and none of the p-values comparing lobular versus ductal-lobular risk estimates were statistically significant (data not shown). Thus lobular and ductal-lobular tumors were grouped together in all analyses. Lastly, we conducted analyses restricted to ER+ cases and also stratified results according to tumor stage, size, and nodal status.

Results

Control women and IDC and ILC cases had similar age and annual household income distributions (Table 1). Compared to control women and IDC cases, ILC cases were somewhat less likely to be African American, more likely to be college graduates, less likely to be obese (have a body mass index ≥ 30.0 kg/m²), and more likely to consume one or more alcoholic beverages per day. Both IDC and ILC cases were more likely to have a first-degree family history of breast cancer, to have had a natural menopause, and to have a later age at menopause compared to control participants. With respect to tumor characteristics lobular cases were somewhat more likely than ductal cases to be stage III/IV, >5.0 cm in size, and lymph node positive.

Use of both EHT and CHT dropped considerably over the course of this study (Table 2). Among controls with 2000–2002 reference dates, 32.7% were current EHT users and 25.4% were current CHT users. However, by 2007–2008 only 10.6% of controls were current EHT users and 4.4% were current CHT users.

Neither short-term nor former use of menopausal hormone therapy was associated with risk of either IDC or ILC (Table 3). This included former users of EHT and CHT who stopped using these medications within two years of their reference date. Current use of both EHT and CHT overall was associated with an elevated risk of ILC (OR=1.6, 95% CI: 1.1–2.2 and OR=2.3, 95% CI: 1.7–3.2, respectively), but neither was associated with risk of IDC even among current users of these regimens for 10 years or longer; these differences between IDC and ILC were statistically significant. With respect to CHT use, for each interval of duration of current use assessed, the corresponding ILC and IDC risk estimates were also statistically different. Duration of CHT use was relevant to ILC risk. For EHT, ILC risk was only elevated among women who currently used EHT for nine years (OR=1.8, 95% CI: 1.3–2.6) or longer with no appreciable increase in risk observed for shorter durations of use. This threshold of nine years of use was determined by evaluating risks over one year intervals and the risk estimates for 8–8.9, 9–9.9, and 10–10.9 years of use were 0.9, 1.7, and 2.1, respectively. In contrast, for CHT ILC risk was appreciably elevated with only three years of current use (OR for 3–4.9 years of current use=3.0, 95% CI: 1.5–6.1) and the magnitude of risk then remained essentially constant across longer durations of current use. The three year threshold was also established by evaluating risks over one year intervals and the risk estimates for 2–2.9, 3–3.9, and 4–4.9 years of use were 1.0, 2.4, and 3.5, respectively. With respect to pattern of CHT use, both current use of continuous and sequential CHT for 3 years or longer were associated with appreciable increases in risk of ILC, but neither was associated with IDC risk.

Given that lobular carcinomas are more frequently ER+ compared to ductal carcinomas we also evaluated risks in analyses restricted to ER+ cases (Table 4). 94% of ILC cases were ER+ and consequently the risk estimates for ER+ ILC were essentially unchanged from those from our overall analyses of ILC. 82% of IDC cases were ER+ and similar to the overall analysis neither current EHT or current CHT use were associated with IDC risk, and users of continuous CHT for 10 years or longer had an increased risk of IDC (OR=1.7, 95% CI: 1.1–2.6), though this risk estimate was statistically lower than that for ILC (p-value for comparison=0.037).

Stratified by tumor stage and nodal status, the relationship between current EHT use and ILC risk was restricted to elevations in risk of early stage disease (stage I and II) and node negative disease, with less variation in risk according to tumor size (Table 5). Current EHT use was not related to risk of any clinical subgroup of IDC with the exception of a reduced risk of stage III/IV ductal cancer (OR=0.4, 95% CI: 0.2–0.9). In contrast, current CHT use was associated with statistically significant elevated risks of ILC across all tumor stage, size, and nodal status categories. However, for IDC and for ER+ IDC specifically, current CHT use was only associated with an increased risk of tumors that were early stage, small, and node negative. Additionally, all ILC current CHT use risk estimates were statistically greater than their corresponding IDC current CHT use risk estimates.

Discussion

This study adds to the now substantial body of evidence indicating that current EHT and CHT use are more strongly related to risk of ILC compared to IDC. The most consistent observation across the 16 studies[2–4, 6–11, 13, 15, 17–21, 23] evaluating these relationships is that current CHT use is associated with a greater risk of ILC than IDC as demonstrated in 13 of these studies.[3, 4, 6–10, 13, 15, 17–21] The other associations though are less consistent as 10 of the 16 find that CHT use is positively associated with IDC risk,[2, 3, 7, 8, 10, 11, 16, 18, 20, 21] 6 of the 16 find that EHT use is positively associated with ILC risk,[4, 7, 10, 19–21] and 5 of the 15 find that EHT use is positively associated with IDC risk.[10, 11, 18, 20, 21] The only randomized trial data on these relationships comes from WHI. In the WHI CHT trial no difference in the distributions of histology were observed between cases diagnosed in the CHT vs. placebo users (p-value=0.89). However the trial had limited statistical power to identify differences given that only 22 and 16 lobular cases were diagnosed in the CHT and placebo arms, respectively.[5] Some of the discrepancies across studies may relate to the populations studied and the durations of hormone use participants experienced. The results here support the evidence that EHT use increases ILC risk, but that this elevation in risk is only observed among long term current EHT users for nine years or longer. With respect to CHT use and IDC risk, while we did not find CHT use to be related to IDC risk overall, it was positively related to risk of IDC tumors that were early stage, small, and node negative. Consequently, in studies that are not population-based and/or in which screening is more common than in the general population, and consequently include a disproportionate number of early stage breast cancer, the observed positive association between CHT use and IDC risk may in part be influenced by surveillance bias. Other sources of variation also likely relate to the relatively smaller sample sizes of many or most of these studies as 13 of the 16 included less than 500 ILC cases, and 7 included less than 300. Thus, few had the ability to evaluate the impact of duration of use on these risks or to stratify results according to tumor characteristics.

One manner in which this study expands our knowledge of these relationships is through greater characterization of thresholds of duration of use that are associated with risk. Specifically, we observed that recent CHT use for as short as three years confers a three-fold increased risk of ILC while shorter term use was not related to risk. Recent EHT use confers an 80% increased risk of ILC, but this increase is observed only after nine or more years of use. Only a handful of studies have characterized the relationship between different durations of current use and ILC and IDC risk. Two of the cohort studies evaluated duration among current users using categories spanning 5 year increments.[3, 20] Both studies found that current CHT use for less than five years was associated with elevations in risk of both ILC and IDC, and the magnitudes of these risk estimates were higher for ILC (2.5 and 1.9) than for IDC (1.7 and 1.5). They did not evaluate shorter intervals of use as we did here to determine if shorter term use is also associated with risk. Evaluating this component is important because current clinical practice recommends that women who do decide to use menopausal hormone therapy use it for the shortest duration possible. However, the length of what a relatively safe short-term duration of use is remains unclear. The data presented here suggest that duration of CHT and EHT use do not appear to impact risk of IDC, but that

use of CHT for at least three years and use of EHT for at least nine years may be thresholds past which ILC risk is elevated.

Consistent with prior studies, a higher proportion of our ILC cases compared to our IDC cases were ER+ (94% vs. 82%). Given that the impact of menopausal hormone therapy on breast cancer risk is largely hormonally mediated, varying distributions of ER positivity between ILC and IDC cases could potentially account for some of the differences observed. Further supporting etiologic distinctions between ILC and IDC are results from our analyses restricted to ER+ cases that also indicate that while current EHT use and current CHT use are associated with risk of ER+ lobular cancer, neither is associated with ER+ ductal breast cancer risk (with the exception of current users of continuous CHT for ≥ 10 years).

Results from analyses stratified by tumor stage, size, and nodal status are further revealing in that elevations in risk of IDC associated with CHT use (but not EHT use) were noted only for tumors that were early stage, small, and node negative. In contrast, CHT was positively associated with risk of ILC regardless of tumor stage, size, and nodal status. These results are strikingly similar to the only other study to conduct a similar analysis, a large population-based case-control study in Germany.[22] In this study, CHT use was only associated with risk of ER+ and/or PR+ IDCs that were <2.0 cm or node negative, while CHT use was associated with elevated risks of ER+ and/or PR+ ILC regardless of tumor size and nodal status. These observations suggest that the association between CHT use and IDC may be primarily explained by more frequent access to medical care and consequently to more frequent access to breast cancer screening. Such surveillance bias though appears to be entirely absent with respect to the CHT and ILC relationship.

Potential limitations of this study relate to its case-control design in that recall bias is a potential concern. However, the differences seen according to breast cancer subtype are very unlikely to be affected by recall bias since this would require one assuming that ductal breast cancer patients recalled exposures differently than did lobular cancer patients. Also, two factors enhance the generalizability of this study, one is its population-based design and the second is its high overall response rates from both cases and controls. Other major strengths of this study are its detailed collection of episodes of menopausal hormone therapy use, substantial sample size, and centralized review of pathology reports to categorize the histology of breast cancer cases.

Despite the dramatic decline in use of menopausal hormone therapy regimens following the publication of the Women's Health Initiative randomized trials demonstrating that the harms of these regimens outweigh their benefits, among women 40–80 years of age in the United States ~8% are CHT users and another ~9% are EHT users,[26] and in 2010 an estimated 38 million hormone therapy prescriptions were filled in the United States based on data from the IMS National Prescription Audit PlusTM (<http://www.menopause.org/hormonetherapystats.aspx>). Efforts to further clarify the breast cancer related harms of these medications thus remain clinically important, particularly with respect to defining what types of hormones and durations of use may be safer than others. It is clear based on both the WHI trial data and the large body of observational study data that CHT is more strongly related to risk of breast cancer than is EHT. The data presented here are also consistent with

the large majority of studies evaluating risk according to histologic subtype in finding that CHT and EHT use are more strongly related to risk of ILC than to risk of IDC. Our results add to this literature by suggesting that with respect to ILC, current use of CHT for as short as 3 years confers an approximately three-fold increase in risk, while only current EHT use for 9 years or longer is related to ILC risk. At present our understanding of the biological mechanisms underlying the strong relationship between CHT use and ILC remains quite limited. Further mechanistic studies are warranted as they could lead to the identification of novel pathways and targets through which this form of breast cancer could be prevented.

Acknowledgments

Grant Support: This study was funded by the National Cancer Institute (R01-CA105041) and the Department of Defense (W81XWH-05-1-0482) (all authors)

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Table 1

Selected characteristics of population-based controls, invasive ductal carcinoma cases, and invasive lobular carcinoma cases

Characteristic	Controls (n=856)		Ductal cases (n=880)		Lobular cases (n=1,027)	
	n	%	n	%	n	%
Age						
55–59	248	29.0	248	28.2	303	29.5
60–64	226	26.4	244	27.7	293	28.5
65–69	211	24.6	209	23.8	236	23.0
70–74	171	20.0	179	20.3	195	19.0
Race/ethnicity						
Non-Hispanic white	758	88.8	796	90.6	944	92.0
African American	27	3.2	20	2.3	16	1.6
Asian/Pacific Islander	17	2.0	35	4.0	22	2.1
Native American	24	2.8	16	1.8	22	2.1
Hispanic white	28	3.3	12	1.4	22	2.1
Missing	2		1		1	
Education						
<High school	39	4.6	48	5.5	60	5.8
High school graduate	204	23.9	207	23.5	217	21.1
Some college/technical school	335	39.2	332	37.7	361	35.2
College graduate	277	32.4	293	33.3	389	37.9
Missing	1		0		0	
Annual household income						
<\$20,000	82	10.9	98	12.5	102	11.3
\$20,000–\$34,999	138	18.3	132	16.9	170	18.8
\$35,000–\$69,999	284	37.6	272	34.8	295	32.7
\$70,000–\$89,999	85	11.3	101	12.9	131	14.5
\$90,000	166	22.0	179	22.9	204	22.6
Missing	101		98		125	
Type of menopause						
Natural menopause	457	53.4	563	64.0	681	66.3

Characteristic	Controls (n=856)		Ductal cases (n=880)		Lobular cases (n=1,027)	
	n	%	n	%	n	%
Simple hysterectomy	206	24.1	187	21.3	165	16.1
Surgical menopause	193	22.5	130	14.8	181	17.6
First-degree family history of breast cancer						
No	677	81.7	648	76.9	764	76.6
Yes	152	18.3	195	23.1	233	23.4
Missing	27		37		30	
Body mass index, kg/m ² at reference date						
<25.0	257	30.3	278	31.6	358	35.0
25.0–29.9	291	34.3	280	31.8	341	33.3
30.0	300	35.4	322	36.6	325	31.7
Missing	8		0		3	
Alcohol use at reference date						
None	433	50.9	419	48.1	476	46.7
<1 drink/day	288	33.8	305	35.0	344	33.7
1 drink/day	130	15.3	148	17.0	200	19.6
Missing	5		8		7	
Smoking status at reference date						
Never	423	49.5	436	49.5	492	47.9
Former	344	40.2	343	39.0	410	39.9
Current	88	10.3	101	11.5	125	12.2
Missing	1		0		0	
AJCC stage						
I	N/A		503	57.62	487	48.22
II	N/A		292	33.45	397	39.31
III/IV	N/A		78	8.9	126	12.48
Missing	N/A		7		17	
Tumor size (cm)						
2.0	N/A		636	73.44	604	60.4
2.1–5.0	N/A		203	23.44	303	30.3
>5.0	N/A		27	3.1	93	9.3

Characteristic	Controls (n=856)		Ductal cases (n=880)		Lobular cases (n=1,027)	
	n	%	n	%	n	%
Missing	N/A		14		27	
Nodal status						
Negative	N/A		606	69.1	658	64.7
Positive	N/A		271	30.9	359	35.3
Missing	N/A		3		10	

Table 2

Recent use of menopausal hormone therapy among controls by reference year

	Reference years							
	2000–2002		2003–2004		2005–2006		2007–2008	
	n	%	n	%	n	%	n	%
Recency of use of menopausal hormone therapy								
Never use	53	17.5	46	22.0	47	25.7	43	26.7
Short-term use	18	5.9	8	3.8	10	5.5	7	4.4
Former use	56	18.5	70	33.5	89	48.6	87	54.0
Current EHT use	99	32.7	61	29.2	25	13.7	17	10.6
Current CHT use	77	25.4	24	11.5	12	6.6	7	4.4

Table 3

Recency of menopausal hormone therapy use and risk of invasive ductal and invasive lobular breast cancer

Recency of use of menopausal hormone therapy	Controls (n=856)				Ductal cases (n=880)				Lobular cases (n=1,027)				p-value for ductal vs. lobular comparison
	n	%	n	%	n	%	OR*	95% CI	n	%	OR*	95% CI	
Never use	189	22.1	230	26.1	1.0	ref			185	18.0	1.0	ref	
Short-term use	43	5.0	59	6.7	1.1	0.7–1.7			54	5.3	1.3	0.8–2.0	0.485
Former use	302	35.3	262	29.8	0.7	0.6–1.0 [†]			261	25.4	0.9	0.7–1.2	0.107
Last used EHT 6–23 months prior	16	1.9	17	1.9	1.1	0.5–2.3			12	1.2	1.0	0.5–2.3	0.840
Last used EHT 24 months prior	137	16.0	103	11.7	0.7	0.5–1.0 [†]			96	9.4	0.9	0.6–1.2	0.312
Last used CHT 6–23 months prior	24	2.8	19	2.2	0.7	0.4–1.3			16	1.6	0.7	0.3–1.3	0.973
Last used CHT 24 months prior	99	11.6	90	10.3	0.7	0.5–1.0 [†]			113	11.0	1.0	0.7–1.5	0.016
Current EHT use	202	23.6	162	18.4	0.9	0.6–1.2			224	21.8	1.6	1.1–2.2 [†]	<0.001
<3 years	9	1.1	7	0.8	0.8	0.3–2.1			6	0.6	0.8	0.3–2.3	0.947
3–4.9 years	9	1.1	9	1.0	1.1	0.4–3.0			7	0.7	1.2	0.4–3.3	0.996
5–8.9 years	33	3.9	20	2.3	0.7	0.4–1.3			26	2.5	1.1	0.6–2.0	0.020
9 years	150	17.5	125	14.2	0.9	0.6–1.3			185	18.0	1.8	1.3–2.6 [†]	<0.001
Current CHT use	120	14.0	167	19.0	1.1	0.8–1.5			303	29.5	2.3	1.7–3.2 [†]	<0.001
<3 years	14	1.6	10	1.1	0.6	0.3–1.4			21	2.0	1.5	0.7–3.0	0.032
3–4.9 years	11	1.3	18	2.1	1.3	0.6–2.9			35	3.4	3.0	1.5–6.1 [†]	0.009
5–9.9 years	35	4.1	40	4.6	0.9	0.5–1.5			93	9.1	2.4	1.5–3.8 [†]	<0.001
10 years	60	7.0	98	11.2	1.3	0.9–1.9			152	14.8	2.3	1.6–3.4 [†]	<0.001
Current continuous CHT use	101	11.8	145	16.5	1.1	0.8–1.6			253	24.7	2.3	1.7–3.2 [†]	<0.001
<3 years	17	2.0	14	1.6	0.7	0.3–1.4			30	2.9	1.7	0.9–3.2	0.010
3–4.9 years	14	1.6	21	2.4	1.2	0.6–2.5			37	3.6	2.5	1.3–4.8 [†]	0.015
5–9.9 years	32	3.7	34	3.9	0.8	0.5–1.4			83	8.1	2.3	1.5–3.8 [†]	<0.001
10 years	38	4.4	75	8.5	1.5	1.0–2.4			102	10.0	2.5	1.6–3.8 [†]	0.010
Current sequential CHT use	17	2.0	16	1.8	0.8	0.4–1.6			37	3.6	2.0	1.1–3.8 [†]	0.002
<3 years	9	1.1	3	0.3	0.3	0.1–1.0 [†]			3	0.3	0.3	0.1–1.1	0.883

Recency of use of menopausal hormone therapy	Controls (n=856)			Ductal cases (n=880)			Lobular cases (n=1,027)			p-value for ductal vs. lobular comparison	
	n	%		n	%	OR*	95% CI	n	%		OR*
3 years	8	0.9	13	1.5	1.3	0.5-3.3	34	3.3	4.0	1.8-9.0 [†]	0.001

* All models are adjusted for age, reference year, county of residence, and hysterectomy/bilateral oophorectomy status.

[†] p<0.05.

Table 4
Current use of different menopausal hormone therapy regimens and risk of ER+ ductal and ER+ lobular breast cancer

Recency of use of menopausal hormone therapy	Controls (n=856)				ER+ ductal cases (n=719)				ER+ lobular cases (n=970)				p-value for ER+ ductal vs. ER+ lobular comparison
	n	%	n	%	n	%	OR*	95% CI	n	%	OR*	95% CI	
Never use	189	22.1	184	25.6	1.0	ref			175	18.0	1.0	ref	
Current EHT use	202	23.6	131	18.2	0.9	0.6–1.3			210	21.6	1.5	1.1–2.2 [†]	0.004
<3 years	9	1.1	7	1.0	1.0	0.3–2.7			5	0.5	0.7	0.2–2.1	0.541
3–4.9 years	9	1.1	7	1.0	1.1	0.4–3.2			6	0.6	1.0	0.3–3.0	0.799
5–8.9 years	33	3.9	18	2.5	0.8	0.4–1.5			25	2.6	1.1	0.6–2.1	0.087
9 years	150	17.5	98	13.6	0.9	0.6–1.3			174	18.0	1.8	1.3–2.6 [†]	<0.001
Current CHT use	120	14.0	151	21.0	1.2	0.9–1.7			284	29.3	2.4	1.7–3.2 [†]	<0.001
<3 years	14	1.6	9	1.3	0.7	0.3–1.7			17	1.8	1.3	0.6–2.7	0.176
3–4.9 years	11	1.3	18	2.5	1.7	0.8–3.7			33	3.4	3.1	1.5–6.3 [†]	0.060
5–9.9 years	35	4.1	37	5.2	1.1	0.6–1.8			89	9.2	2.5	1.6–4.0 [†]	<0.001
10 years	60	7.0	87	12.1	1.4	0.9–2.1			143	14.8	2.3	1.6–3.4 [†]	0.003
Current continuous CHT use	101	11.8	132	18.4	1.3	0.9–1.8			236	24.4	2.3	1.7–3.3 [†]	<0.001
<3 years	17	2.0	14	1.9	0.9	0.4–1.8			27	2.8	1.6	0.8–3.1	0.076
3–4.9 years	14	1.6	20	2.8	1.5	0.7–3.0			33	3.4	2.4	1.2–4.7 [†]	0.106
5–9.9 years	32	3.7	31	4.3	1.0	0.6–1.7			78	8.1	2.4	1.5–3.9 [†]	<0.001
10 years	38	4.4	67	9.3	1.7	1.1–2.6 [†]			97	10.0	2.5	1.6–3.9 [†]	0.037
Current sequential CHT use	17	2.0	13	1.8	0.8	0.4–1.7			35	3.6	2.1	1.1–3.8 [†]	0.004

* All models are adjusted for age, reference year, county of residence, and hysterectomy/bilateral oophorectomy status.

[†] p<0.05.

Table 5

Current use of menopausal hormone therapy and risk of ductal and lobular breast cancer according to tumor stage, size, and nodal status

Clinical tumor characteristics	Ductal			Lobular			ER+ ductal			ER+ lobular			p for comparison
	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	OR*	95% CI	
<i>Current EHT use</i>	0.9	0.6–1.2	1.6	1.1–2.2 [†]			<0.001	0.9	0.6–1.3	1.5	1.1–2.2 [†]		0.004
Stage													
I	1.0	0.7–1.5	1.7	1.1–2.5 [†]			0.049	1.0	0.6–1.5	1.6	1.0–2.5 [†]		0.055
II	0.9	0.6–1.4	2.0	1.3–3.1 [†]			0.005	1.0	0.6–1.6	2.0	1.3–3.1 [†]		0.021
III/IV	0.4	0.2–0.9 [†]	0.8	0.4–1.6			0.146	0.5	0.2–1.3	0.7	0.4–1.6		0.395
Size, cm													
2.0	1.0	0.7–1.5	1.7	1.1–2.5 [†]			0.037	1.0	0.7–1.5	1.6	1.1–2.4 [†]		0.052
2.1–5.0	0.7	0.4–1.1	1.5	0.9–2.4			0.008	0.8	0.4–1.5	1.5	0.9–2.5		0.073
>5.0	0.4	0.1–1.4	2.1	0.9–4.8			0.201	0.5	0.1–2.2	2.0	0.9–4.8		0.586
Nodal status													
Negative	0.9	0.6–1.3	2.1	1.4–3.1 [†]			<0.001	0.9	0.6–1.4	2.1	1.4–3.2 [†]		<0.001
Positive	0.9	0.5–1.5	1.3	0.8–2.0			0.158	1.0	0.6–1.8	1.2	0.7–1.9		0.492
<i>Current CHT use</i>	1.1	0.8–1.5	2.3	1.7–3.2 [†]			<0.001	1.2	0.9–1.7	2.4	1.7–3.2 [†]		<0.001
Stage													
I	1.6	1.1–2.2 [†]	2.6	1.8–3.8 [†]			0.009	1.7	1.2–2.5 [†]	2.6	1.8–3.8 [†]		0.042
II	0.8	0.5–1.2	2.2	1.5–3.3 [†]			<0.001	0.8	0.5–1.3	2.3	1.5–3.4 [†]		<0.001
III/IV	0.4	0.2–1.0 [†]	2.1	1.2–3.8 [†]			<0.001	0.6	0.2–1.4	2.5	1.4–4.5 [†]		0.001
Size, cm													
2.0	1.4	1.0–2.0	2.6	1.8–3.7 [†]			0.001	1.5	1.1–2.2 [†]	2.6	1.8–3.7 [†]		0.006
2.1–5.0	0.6	0.3–1.0	1.8	1.2–2.8 [†]			<0.001	0.7	0.4–1.3	1.8	1.2–2.8 [†]		0.004
>5.0	0.3	0.1–1.2	3.1	1.5–6.4 [†]			0.002	0.3	0.1–1.7	3.6	1.7–7.7 [†]		0.006
Nodal status													
Negative	1.3	0.9–1.9	2.7	1.9–3.8 [†]			<0.001	1.5	1.0–2.2 [†]	2.7	1.9–3.9 [†]		0.002
Positive	0.8	0.5–1.3	2.2	1.5–3.4 [†]			<0.001	0.9	0.5–1.5	2.3	1.5–3.5 [†]		0.001

* All models are adjusted for age, reference year, county of residence, and type of menopause.

[†] p<0.05.