Relationship between Menopausal Hormone Therapy and Risk of Ductal, Lobular, and Ductal-Lobular Breast Carcinomas

Christopher I. Li,[1] Kathleen E. Malone,[1] Peggy L. Porter,[1,2,3] Thomas J. Lawton,[3] Lynda F. Voigt,[1] Kara L. Cushing-Haugen,[1] Ming Gang Lin,[1,2] Xiaopu Yuan,[1,2] and Janet R. Daling[1]

Divisions of [1]Public Health Sciences and [2]Human Biology, Fred Hutchinson Cancer Research Center; [3]Department of Pathology, School of Medicine, and University of Washington, Seattle, Washington

Abstract

Combined estrogen and progestin hormone therapy (CHT) increases breast cancer risk, but this risk varies by breast cancer type. Several studies indicate that CHT is more strongly related to lobular carcinoma risk than to ductal carcinoma risk, but these studies have been limited in their assessments of recency and duration of use, and none included a centralized pathology review. We conducted a population-based case-control study consisting of 324 lobular, 196 ductal-lobular, and 524 ductal cases diagnosed from 2000 to 2004 and 469 controls ages 55 to 74 years old. Tissue specimens were centrally reviewed for 83% of cases. Associations between hormone use and breast cancer risk were evaluated using polytomous logistic regression. Current CHT users had 2.7-fold [95% confidence interval (95% CI), 1.7-4.2] and 3.3-fold (95% CI, 2.0-5.7) elevated risks of lobular and ductal-lobular carcinomas, respectively, regardless of tumor stage, size, or nodal status. Elevations in risk were observed only among users of CHT for ≥3 years. Among ductal-lobular cases, CHT increased risk of tumors that were ≥50% lobular (odds ratio, 4.8; 95% CI, 2.1-11.1) but not tumors that were <50% lobular (odds ratio, 1.9; 95% CI, 0.9-4.1). Current CHT users for ≥3 years have a substantially increased risk of lobular carcinomas. Although lobular carcinomas are less common than ductal carcinomas (~16% versus 70% of all invasive breast cancers in the United States), this duration is shorter than the 5 years of use widely cited to be needed to confer an increased risk of breast cancer overall. Further studies focusing on the etiology of lobular carcinomas are needed. (Cancer Epidemiol Biomarkers Prev 2008;17(1):43–50)

Introduction

The Women's Health Initiative (WHI) randomized controlled trials of combined estrogen and progestin hormone therapy (CHT) (ref. 1) and unopposed estrogen hormone therapy (EHT) clearly show that current CHT use increases breast cancer risk but EHT does not. However, a growing number of studies have suggested or indicated that the relationship between CHT and breast cancer risk varies by breast cancer type. Differences by histologic type have been observed most consistently. Nine (2-10) of 11 (11, 12) observational studies have shown that CHT use is more strongly related to risk of invasive lobular carcinoma (ILC) and/or invasive ductal-lobular carcinoma (IDLC) than it is to risk of invasive ductal carcinoma (IDC). These studies included anywhere from 58 to 1,526 ILC and/or IDLC, although all but the Million Women's Study included less than 308 lobular cases. Specifically, the nine studies reporting a difference in risk by histologic type find that CHT use results in 2.0- to 3.9-fold increases in the risk of ILC and/or IDLC and lower or no increases in risk of IDC (relative risks, 0.7-2.0). The WHI CHT trial did not find a difference in risk by histology, although the trial was underpowered to assess this relationship given that it accrued only 38 ILC cases and 23 IDLC cases across both arms of the study (1).

ILC and IDLC are breast cancer subtypes of growing public health importance in the United States given their rapidly rising incidence rates over the past several years. ILC and IDLC rates increased 52% and 96%, respectively, from 1987 to 1999, whereas rates of IDC increased only 3% over this period (13). Whereas IDC is still the most common histologic type of breast cancer accounting for ~70% of all cases, together ILC and IDLC now account for ~16% of all invasive breast cancers diagnosed in the United States (13). Given the evidence that CHT use is strongly related to risk of ILC and IDLC, one of the most likely etiologic factor accounting for the rapid rise in ILC and IDLC rates is CHT use. Prior studies of the relationship between CHT use and breast cancers with a lobular component have been limited by the lack of a centralized pathology review, and almost all have been limited by relatively small numbers of ILC and IDLC cases. As a result, prior studies have not been able to assess in detail how both timing and duration of CHT use are related to risk of both ILC and IDLC.

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Requests for reprints: Christopher I. Li, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, 1100 Fairview Avenue North, M4-C308, P.O. Box 19024, Seattle, WA 98109-1024. E-mail: cili@fhcrc.org

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The results reported here are from the first study specifically designed to evaluate the relationship between CHT and lobular cancers. It was comprehensive in its ascertainment of CHT exposure and it involved a centralized pathology review of all available tumor tissue specimens from cases enrolled. Despite the sharp 38% to 68% declines (14-16) in CHT use rates in the United States following the publication and dissemination of the results of the WHI CHT trial (17), this study is still of considerable public health importance given the estimated 57 million prescriptions for menopausal hormone therapy that continue to be filled in the United States (18).

Materials and Methods

We conducted a population-based case-control study of women 55 to 74 years old living in the three-county Seattle-Puget Sound metropolitan area (King, Pierce, and Snohomish counties). The study consisted of three case groups defined based on histology (IDC, ILC, and IDLC) and a common control group.

Cases. Women 55 to 74 years old with no prior history of *in situ* or invasive breast cancer when diagnosed with invasive breast cancer between January 1, 2000 and March 31, 2004 were eligible as cases. The Cancer Surveillance System, the population-based tumor registry that serves the Seattle-Puget Sound region of Washington State and participates in the Surveillance, Epidemiology, and End Results program of the National Cancer Institute, was used to identify these women. All ILC and IDLC cases diagnosed in the registry over this period were considered eligible. Given that IDC is much more common than both ILC and IDLC, a random sample of ~25% of otherwise eligible IDC cases was selected and also targeted for recruitment. These IDC cases were frequency matched 1:1 to the combined ILC and IDLC case group by 5-year age group. Because controls were ascertained via random-digit dialing of landline home telephone numbers, to be eligible all cases also needed to have a landline home telephone. Of the 1,251 eligible cases identified, 1,044 (83%) were interviewed, including 524 IDC cases, 324 ILC cases, and 196 IDLC cases. Fourteen percent of eligible cases refused to be interviewed or could not be located, 2% died before an interview could be conducted, and the physicians treating 1% of cases refused to allow contact with their patients.

Information on tumor histology was collected through two sources, a centralized review of pathology reports and a centralized review of available tumor tissue specimens. A review of pathology reports was conducted on all cases. Histology of invasive tumor tissue was classified according to the diagnoses and descriptions contained in each report. For this review, the histology of any *in situ* disease present was noted but not factored into the final histology call made. For example, cases with IDC and lobular carcinoma *in situ* were classified as IDC cases ($n = 61$), and cases with ILC and ductal carcinoma *in situ* were classified as ILC cases ($n = 63$). Only tumors with both invasive lobular and invasive ductal components were classified as IDLC cases. The majority of cases had multiple pathology reports, most commonly one for an initial biopsy and then one for a lumpectomy or mastectomy. When there were discrepancies between the histology calls made on a biopsy compared to a lumpectomy/mastectomy, the call made on the tumor specimen of the largest size was given priority.

At the conclusion of the interview conducted on all participants, cases were asked to sign a tumor tissue release form granting us access to their stored paraffin-embedded tissue specimens for our centralized pathology review. One thousand and two (96%) cases signed this release form. We attempted to obtain tumor tissue specimens for all 1,002 cases from local hospitals and were able to obtain tissue for 869 (83%) cases. The pathology reports and histology slides for all of these cases underwent expert pathology review by the study pathologists (P.L.P., M.G.L., X.Y., and T.J.L.). Tumors were classified as IDC or ILC according to WHO recommendations (19). For this study, IDLC tumors comprised two categories: (*a*) tumor areas of distinct ILC and IDC in the same breast and (*b*) tumors with lobular and ductal features intermixed in a single tumor. In the first category, the percent of the total tumor area of each tumor type was recorded; in the second category, the tumor was designated 100% ''mixed'' type. After agreement by all four study pathologists on diagnostic criteria, the histology of each case was assessed by review of all submitted slides by one of two staff pathologists (M.G.L. and X.Y.). A second review of the diagnosis and histologic grade of every case was done by the study pathologist (P.L.P.). Discrepancies between the initial and the second assessments were resolved by consensus review or submitted for additional review by the study's consulting pathologist (T.J.L.). All of these reviews were conducted prior to reviewing the diagnosis recorded in the clinical pathology reports or the calls made by the other study pathologists. Sixty-one cases, representing discrepancies either between the pathology report review and the study diagnosis or between the study pathologists, were reviewed by the consulting pathologist to reach consensus of diagnosis.

Final categorizations of histology were based on the histology call made by the centralized review. For our categorizations of IDC, ILC, and IDLC tumors, there was strong agreement between the pathology report reviews and the centralized reviews as the two had an overall 94% agreement with an associated κ statistic of 0.91. The histology of the 175 cases whose tissue was not obtained was based on our review of their pathology reports.

Controls. Controls from the general population of female residents of King, Pierce, and Snohomish counties were identified using random-digit dialing according the Mitosky-Waksberg method with a clustering factor (denoted as ''k'' by Waksberg) of 5 (20). Controls were frequency matched 1:1 to the ILC and IDLC case group combined within 5-year age groups using one-step recruitment (21). A total of 29,735 random telephone numbers were called. Up to nine calls were made to each number at different times of the day and week before the number was abandoned. Telephone numbers that were always answered by machine or that were answered by a respondent who refused to answer the screening questions were recontacted by a different interviewer 3 months after the initial call. A total of 17,398 of the numbers called were found to be nonworking, business, cellular, paging, dedicated facsimile, or

data line numbers. We were unable to determine the residential status of 2,461 (8%) telephone numbers because they were never answered. Only about 20% of such numbers have been found previously to be residential (22). A total of 9,876 of the telephone numbers were either verified as residential or presumed to be residential. Eighty-seven percent of these were successfully screened for study eligibility. The reasons for unsuccessful screening were that telephone calls to the number were always answered by machine (n = 572), the respondent refused to answer screening questions (n = 484), or the household could not be screened because of language or communication barriers (n = 216). Six hundred and sixty eligible controls were identified and 469 of these were interviewed (71%).

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 and were asked about their reproductive history, body size, medical history, and family history of cancer. Additionally, detailed histories of all episodes of menopausal hormone therapy use, including beginning and ending dates, brand, dose, and pattern of use (number of days per month), were obtained. A life events calendar and a photo book of hormone replacement medications used in the United States were used to enhance recall. 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. The reference category consisted of women who never used any type of hormone therapy. Women whose only hormone therapy use was for less

Table 1. Distribution of selected characteristics among controls and cases

Characteristic	Controls (n = 428), n (%)	Ductal cases (n = 468), n (%)	Lobular and ductal-lobular cases (n = 481), n (%)	Lobular cases (n = 299), n (%)	Ductal-lobular cases (n = 182), n (%)
Age (y)					
55-59	122 (28.5)	130 (27.8)	148 (30.8)	89 (29.8)	59 (32.4)
60-64	116 (27.1)	124 (26.5)	123 (25.6)	74 (24.7)	49 (26.9)
65-69	105 (24.5)	113 (24.1)	119 (24.7)	78 (26.1)	41 (22.5)
70-74	85 (19.9)	101 (21.6)	91 (18.9)	58 (19.4)	33 (18.1)
Race/ethnicity					
Non-Hispanic white	387 (90.4)	420 (89.7)	448 (93.1)	281 (94.0)	167 (91.8)
African American	7 (1.6)	11 (2.4)	9 (1.9)	7 (2.3)	2 (1.1)
Asian/Pacific Islander	9 (2.1)	17 (3.6)	8 (1.7)	3 (1.0)	5 (2.7)
Native American	9 (2.1)	11 (2.4)	3 (0.6)	2 (0.7)	1 (0.5)
Hispanic White	16 (3.7)	9 (1.9)	13 (2.7)	6 (2.0)	7 (3.8)
Education					
Less than high school	21 (4.9)	32 (6.8)	26 (5.4)	19 (6.4)	7 (3.8)
High school graduate	115 (26.9)	131 (28.0)	117 (24.3)	75 (25.1)	42 (23.1)
Some college/technical school	168 (39.3)	165 (35.3)	164 (34.1)	98 (32.8)	66 (36.3)
College graduate	124 (29.0)	140 (29.9)	174 (36.2)	107 (35.8)	67 (36.8)
Annual household income					
<$20,000	34 (9.4)	52 (13.2)	50 (12.2)	31 (12.4)	19 (11.9)
$20,000-34,999	70 (19.3)	77 (19.6)	86 (21.0)	53 (21.2)	33 (20.8)
$35,000-69,999	150 (41.3)	140 (35.6)	129 (31.5)	75 (30.0)	54 (34.0)
$70,000-89,999	43 (11.8)	45 (11.5)	69 (16.9)	44 (17.6)	25 (15.7)
≥$90,000	66 (18.2)	79 (20.1)	75 (18.3)	47 (18.8)	28 (17.6)
Missing	65	75	72	49	23
First-degree family history of breast cancer					
No	359 (83.9)	366 (78.2)	367 (76.3)	228 (76.3)	139 (76.4)
Yes	69 (16.1)	102 (21.8)	114 (23.7)	71 (23.7)	43 (23.6)
Type of menopause					
Natural	241 (57.7)	304 (66.2)	316 (67.8)	192 (66.2)	124 (70.5)
Induced	105 (25.1)	95 (20.7)	80 (17.2)	57 (19.7)	23 (13.1)
Simple hysterectomy	72 (17.2)	60 (13.1)	70 (15.0)	41 (14.1)	29 (16.5)
Missing	10	9	15	9	6
Age at menopause (y)					
≤44	53 (17.7)	41 (11.8)	27 (7.6)	17 (7.9)	10 (7.2)
45-49	66 (22.1)	87 (25.1)	101 (28.5)	65 (30.2)	36 (25.9)
50-52	83 (27.8)	102 (29.5)	91 (25.7)	53 (24.7)	38 (27.3)
53-55	55 (18.4)	68 (19.7)	87 (24.6)	51 (23.7)	36 (25.9)
≥56	42 (14.0)	48 (13.9)	48 (13.6)	29 (13.5)	19 (13.7)
Missing	129	122	127	84	43
BMI (kg/m^2)					
<23.4	107 (25.1)	121 (26.1)	148 (31.1)	90 (30.3)	58 (32.4)
23.4-26.4	107 (25.1)	114 (24.6)	101 (21.2)	57 (19.2)	44 (24.6)
26.5-31.0	108 (25.3)	111 (23.9)	136 (28.6)	90 (30.3)	46 (25.7)
≥31.1	105 (24.6)	118 (25.4)	91 (19.1)	60 (20.2)	31 (17.3)
Missing	1	4	5	2	3

NOTE: Excluded are the 41 controls, 56 IDC cases, 27 ILC cases, and 14 IDLC cases who used hormone therapy for less than 6 mo, had missing current hormone therapy use data, or had missing family history data.

Table 2. Recency of hormone use and risk of breast cancer risk by histologic type

Recency of use of menopausal hormone therapy	Controls (n = 428)	Ductal cases (n = 468)		Lobular and ductal-lobular cases (n = 481)		P for comparison with ductal cases
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	
Never use	92 (21.5)	117 (25.0)	1.0 (Reference)	78 (16.2)	1.0 (Reference)	
Former use	102 (23.8)	74 (15.8)	0.6 (0.4-0.9)†	65 (13.5)	0.8 (0.5-1.2)	0.221
Current EHT use	145 (33.9)	123 (26.3)	0.7 (0.5-1.0)†	126 (26.2)	1.1 (0.7-1.5)	0.027
<3 y	8 (1.9)	4 (0.9)	0.4 (0.1-1.3)	3 (0.6)	0.4 (0.1-1.7)	0.903
3-4.9 y	7 (1.6)	7 (1.5)	0.8 (0.3-2.2)	6 (1.2)	0.9 (0.3-2.9)	0.694
5-9.9 y	32 (7.5)	15 (3.2)	0.4 (0.2-0.7)†	23 (4.8)	0.8 (0.5-1.6)	0.023
≥10 y	98 (22.9)	97 (20.7)	0.8 (0.3-2.0)	94 (19.5)	1.2 (0.8-1.8)	0.0666
Current CHT use	89 (20.8)	154 (32.9)	1.4 (1.0-2.1)	212 (44.1)	2.9 (1.9-4.3)†	<0.0001
<3 y	11 (2.6)	11 (2.4)	0.8 (0.3-2.0)	14 (2.9)	1.5 (0.6-3.7)	0.136
3-4.9 y	8 (1.9)	15 (3.2)	1.5 (0.6-3.7)	28 (5.8)	4.2 (1.8-9.8)†	0.004
5-9.9 y	27 (6.3)	43 (9.2)	1.3 (0.7-2.2)	68 (14.1)	3.1 (1.8-5.4)†	<0.0001
≥10 y	43 (10.0)	85 (18.2)	1.6 (1.0-2.5)	102 (21.2)	2.9 (1.8-4.6)†	0.004
Current continuous CHT use	75 (17.6)	134 (28.9)	1.4 (1.0-2.2)	182 (38.4)	2.9 (1.9-4.4)†	<0.0001
<3 y	8 (1.9)	8 (1.8)	0.8 (0.3-2.2)	12 (2.7)	1.7 (0.7-4.5)	0.115
≥3 y	67 (16.2)	126 (28.1)	1.5 (1.0-2.3)	170 (37.7)	3.0 (2.0-4.6)†	<0.0001
Current sequential CHT use	13 (3.0)	16 (3.4)	1.0 (0.5-2.3)	23 (4.9)	2.2 (1.0-4.6)†	0.038
<3 y	3 (0.9)	2 (0.6)	0.6 (0.1-4.0)	2 (0.7)	0.9 (0.1-5.3)	0.777
≥3 y	10 (2.8)	14 (4.2)	1.2 (0.5-2.8)	21 (7.2)	2.6 (1.1-5.8)†	0.042

*All ORs are adjusted for age, year, and first-degree family history of breast cancer.
† $P < 0.05$.

than 6 months (6 controls, 11 IDC cases, 9 ILC cases, and 3 IDLC cases) or who had missing data on current hormone therapy use (22 controls, 32 IDC cases, 10 ILC cases, and 7 IDLC cases) were excluded from all analyses. With regard to patterns of CHT use, estrogen users who took progestin for <25 days per month were considered sequential CHT users, and those who used progestin for ≥25 days per month were considered continuous CHT users (consistent with previous reports; refs. 3, 6).

We used polytomous logistic regression to calculate odds ratios (OR) and their associated 95% confidence intervals (95% CI) to compare IDC, ILC, and IDLC cases to controls (23). All analyses were conducted using Stata/SE version 9.2 (StataCorp LP, College Station, TX). All models were adjusted for age (5-year categories) and reference year (continuous). Several self-reported variables were evaluated as potential confounders, including education, income, first-degree family history of breast cancer (yes/no), type of menopause [natural, induced, simple hysterectomy (hysterectomy without a bilateral oophorectomy)], age at menopause, and body mass index (BMI) 1 year prior to reference date (quartiles of control population). (Note: Women who were using hormone therapy at reference date and still having periods and women who had a hysterectomy without bilateral oophorectomy were considered postmenopausal at reference date because they were all 55 years or older. These women were also considered to have unknown age at menopause.) Only first-degree family history of breast cancer changed the ORs of interest by more than 10%; thus, only it was included in our final statistical models along with age and reference year. As a result, the 13 controls, 13 IDC cases, 6 ILC cases, and 4 IDLC cases with missing first-degree family history data were excluded from all analyses. We calculated two-sided Ps for the comparison between our lobular case group risk estimates and our IDC risk estimates using unconditional logistic regression models that treated the IDC group as the reference category and excluded the controls.

Results

Greater than 90% of participants in the control group and each case group were non-Hispanic whites (Table 1). ILC and IDLC cases were somewhat more likely than controls and IDC cases to be college graduates. Somewhat higher proportions of the participants in each case group had an annual household income of less than $20,000 compared with controls. Higher proportions of cases had a first-degree family history of breast cancer and underwent a natural menopause compared with controls. ILC and IDC cases were less likely to have a very young age at menopause compared with controls and IDC cases and also tended to have a lower BMI.

Compared with never users of hormone therapy, current EHT users and former hormone therapy users of any type had reduced risks of IDC (OR, 0.7; 95% CI, 0.5-1.0 and OR, 0.6; 95% CI, 0.4-0.9, respectively) but not of ILC/IDLC, ILC, or IDLC (Table 2). The risk estimates for current EHT use for IDC was statistically different from the risk estimate for ILC/IDLC (P = 0.027). Current CHT users had a 2.9-fold (95% CI, 1.9-4.3) increased risk of ILC/IDLC, with a 2.7-fold (95% CI, 1.7-4.2) increased risk of ILC and a 3.3-fold (95% CI, 2.0-5.7) increased risk of IDLC. These risk estimates were highly statistically different from the risk estimate for IDC ($P \leq 0.002$). Elevations in risks of both ILC and IDLC were only observed among current CHT users for 3 years or longer, and they did not further increase with longer durations of use. Both current continuous CHT use and current sequential CHT use were also associated with risk of ILC/IDLC (OR, 2.9; 95% CI, 1.9-4.4 and OR, 2.2; 95% CI, 1.0-4.6, respectively). Again, these elevations in risk were limited to women who used continuous or sequential CHT for 3 years or longer. Current CHT use, even for 10 years or longer, was not associated with IDC risk.

Table 2. Recency of hormone use and risk of breast cancer risk by histologic type (Cont'd)

Recency of use of menopausal hormone therapy	Lobular cases (n = 299)		P for comparison with ductal cases	Lobular and ductal-lobular cases (n = 182)		P for comparison with ductal cases
	n (%)	OR* (95% CI)		n (%)	OR* (95% CI)	
Never use	51 (17.1)	1.0 (Reference)		27 (14.8)	1.0 (Reference)	
Former use	40 (13.4)	0.7 (0.4-1.2)	0.415	25 (13.7)	0.9 (0.5-1.6)	0.220
Current EHT use	82 (27.4)	1.0 (0.7-1.6)	0.052	44 (24.2)	1.0 (0.6-1.8)	0.121
<3 y	1 (0.3)	0.2 (0.0-1.9)	0.628	2 (1.1)	0.8 (0.2-4.0)	0.433
3-4.9 y	3 (1.0)	0.7 (0.2-2.9)	0.947	3 (1.6)	1.4 (0.3-5.7)	0.406
5-9.9 y	15 (5.0)	0.9 (0.4-1.8)	0.035	8 (4.4)	0.8 (0.3-2.0)	0.104
≥10 y	63 (21.1)	1.2 (0.7-1.9)	0.081	31 (17.0)	1.1 (0.6-2.0)	0.276
Current CHT use	126 (42.1)	2.7 (1.7-4.2)†	0.002	86 (47.3)	3.3 (2.0-5.7)†	0.001
<3 y	9 (3.0)	1.6 (0.6-4.1)	0.176	5 (2.7)	1.5 (0.5-4.8)	0.279
3-4.9 y	13 (4.3)	3.0 (1.2-7.9)†	0.095	15 (8.2)	6.3 (2.4-16.6)†	0.001
5-9.9 y	46 (15.4)	3.3 (1.8-6.0)†	0.001	22 (12.1)	2.7 (1.3-5.6)†	0.029
≥10 y	58 (19.4)	2.5 (1.5-4.2)†	0.059	44 (24.2)	3.6 (1.9-6.5)†	0.004
Current continuous CHT use	107 (36.3)	2.7 (1.7-4.2)†	0.005	75 (41.9)	3.4 (2.0-5.9)†	0.001
<3 y	7 (2.5)	1.6 (0.5-4.7)	0.214	5 (2.9)	1.9 (0.6-6.5)	0.147
≥3 y	100 (35.7)	2.8 (1.7-4.4)†	0.005	70 (40.9)	3.5 (2.0-6.1)†	0.002
Current sequential CHT use	15 (5.1)	2.2 (1.0-5.1)†	0.060	8 (4.5)	2.2 (0.8-5.8)	0.131
<3 y	2 (1.1)	1.4 (0.2-8.9)	0.455	0 (0.0)	0.0	
≥3 y	13 (6.9)	2.4 (1.0-5.9)	0.096	8 (7.7)	2.9 (1.0-8.2)†	0.079

Whereas age at menopause is a documented confounder of the relationship between hormone use and breast cancer risk in some studies (24), this was not the case here. When our main analyses were additionally adjusted for age at menopause, the risk estimates for both current EHT use and current CHT use were quite similar to those unadjusted for age at menopause [current EHT use: OR (95% CI), 0.6 (0.4-0.99) for IDC and 1.2 (0.7-2.0) for ILC/IDLC; current CHT use: OR (95% CI), 1.2 (0.8-1.8) for IDC and 2.8 (1.8-4.3) for ILC/IDLC]. Recently, Reeves, et al. (9) also observed that BMI was an effect modifier of the relationship between hormone use and risk of ductal and lobular carcinomas. Here we found no evidence of this when BMI was considered as an effect modifier of the relationships between current EHT or current CHT use and risks of IDC and ILC/IDLC (for IDC: Ps for interaction = 0.94 for current EHT use and 0.32 for current CHT use; for ILC/IDLC: Ps for interaction = 0.97 for current EHT use and 0.39 for current CHT use). In analyses stratified by BMI using three categories (<25.0, 25.0-29.9, and ≥30.0 kg/m^2), current CHT use was associated with statistically significant increases in risk of ILC/IDLC across all three BMI categories [OR (95% CI), 4.2 (2.0-4.4), 2.0 (1.0-4.1), and 2.9 (1.3-6.2), respectively] but not with increases in risk of IDC [OR (95% CI), 1.6 (0.8-3.1), 0.9 (0.5-1.9), and 1.6 (0.8-3.5), respectively]. Current EHT use was associated with 0.5- to 0.7-fold reductions in risk of IDC across these three BMI categories, but all of these risk estimates were within the limits of chance. However, this study had limited power to detect an interaction with BMI due to its sample size.

We further examined risk of mixed ductal-lobular tumors in relation to hormone therapy use according to the proportion of the tumor that was lobular. Compared with never users of hormone therapy, CHT users had a 4.8-fold (95% CI, 2.1-11.1) increased risk of IDLC tumors that were ≥50% lobular, but only a 1.9-fold (95% CI, 0.9-4.1) increased risk of IDLC tumors that were <50% lobular that was within the limits of chance (Table 3). This difference in risk estimates for current CHT use was statistically significant (P = 0.04). In addition, current CHT use was associated with a 7.7-fold (95% CI, 1.7-34.8) elevated risk of tumors that we classified as being 100% mixed, meaning that lobular and ductal features were intermixed in the same tumor.

Current CHT users had elevated risks of IDC that were stage I, ≤2.0 cm in size, and node negative [OR (95% CI), 1.8 (1.2-2.8), 1.8 (1.2-2.8), and 1.6 (1.1-2.5), respectively] but no elevations in their risks of other types of IDC

Table 3. Recency of hormone use and risk of ductal-lobular breast cancer risk by proportion of the tumor that is lobular

Recency of use of menopausal hormone therapy	Controls (n = 428)	<50% Lobular (n = 58)		≥50% Lobular (n = 70)		Lobular and ductal features intermixed in the same tumor (n = 37)		P for comparison of <50% vs ≥50% lobular cases
	n (%)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	n (%)	OR* (95% CI)	
Never use	92 (21.5)	12 (21.8)	1.0 (Reference)	8 (12.1)	1.0 (Reference)	2 (5.7)	1.0 (Reference)	
Former use	102 (23.8)	9 (16.4)	0.7 (0.3-1.7)	3 (4.5)	0.4 (0.1-1.4)	9 (25.7)	4.6 (1.0-22.0)	0.60
Current EHT use	145 (33.9)	12 (21.8)	0.6 (0.3-1.5)	18 (27.3)	1.4 (0.6-3.4)	8 (22.9)	2.6 (0.5-12.8)	0.08
Current CHT use	89 (20.8)	22 (40.0)	1.9 (0.9-4.1)	37 (56.1)	4.8 (2.1-11.1)†	16 (45.7)	7.7 (1.7-34.8)†	0.04

*All ORs are adjusted for age, year, and first-degree family history of breast cancer.
† $P < 0.05$.

Table 4. Risk of ductal versus lobular carcinomas by various tumor characteristics among current CHT users versus never users of hormone therapy

Clinical tumor characteristic	Ductal, OR* (95% CI)	Lobular or ductal-lobular, OR* (95% CI)	*P* for comparison with ductal cases	Lobular, OR* (95% CI)	*P* for comparison with ductal cases	Ductal-lobular, OR* (95% CI)	*P* for comparison with ductal cases
All cases	1.4 (1.0-2.1)	2.9 (1.9-4.3) †	<0.0001	2.7 (1.7-4.2) †	0.002	3.3 (2.0-5.7) †	0.001
Stage							
I	1.8 (1.2-2.8) †	3.6 (2.2-5.9) †	0.009	3.4 (1.9-6.4) †	0.048	3.8 (1.9-7.5) †	0.032
II	1.1 (0.6-1.8)	2.4 (1.4-3.9) †	0.011	2.1 (1.2-3.8) †	0.039	2.8 (1.3-6.1) †	0.025
III/IV	0.5 (0.2-1.1)	3.3 (1.3-8.5) †	0.001	3.6 (1.2-10.7) †	0.002	2.7 (0.5-14.7)	0.03
Size (cm)							
≤2.0	1.8 (1.2-2.8) †	3.1 (2.0-4.9) †	0.024	2.9 (1.7-5.1) †	0.095	3.4 (1.8-6.2) †	0.053
2.1-5.0	0.6 (0.3-1.1)	2.2 (1.3-3.8) †	0.001	1.9 (1.0-3.7) †	0.004	2.9 (1.2-6.9) †	0.002
>5.0	0.3 (0.1-1.3)	7.5 (2.1-26.7) †	0.003	6.1 (1.6-22.3) †	0.005	‡	
Nodal status							
Negative	1.6 (1.1-2.5) †	3.3 (2.1-5.2) †	0.002	2.9 (1.7-4.9) †	0.033	4 (2.2-7.5) †	0.004
Positive	1.1 (0.6-1.8)	2.7 (1.6-4.7) †	0.006	2.7 (1.4-5.1) †	0.013	2.8 (1.2-6.7) †	0.068

*All ORs compare current CHT use with never use of hormone therapy and are adjusted for age, year, and first-degree family history of breast cancer.
† $P < 0.05$.
‡ Could not be calculated because there were no ductal-lobular cases with a tumor size more than 5.0 cm who never used hormone therapy.

based on stage, tumor size, and nodal status (Table 4). Current CHT users had elevated risks of ILC/IDLC, ILC, and IDLC regardless of tumor stage, tumor size, and nodal status. Nearly all of the comparisons between the risk estimates for IDC and those for ILC/IDLC, ILC, and IDLC were statistically significant.

Discussion

Before interpreting the results of this study, it is important to acknowledge some of its limitations. We interviewed 83% of eligible cases and 71% of eligible controls. If the eligible women not interviewed for this study are different from those we did interview with respect to their use of hormone therapy, then our results could be biased. However, our comparisons across case groups are unlikely to be effected by any such differences given that it is unlikely that the proportions of hormone therapy use among the cases not interviewed for this study would vary considerably by case type. All exposure data used in this study were based on self-report so recall bias is also a concern. With respect to our main exposure or interest, current hormone therapy use, prior studies suggest that there is reasonably high agreement between data on hormone therapy use reported by postmenopausal women and data ascertained from medical records (25-27). Several strategies were also used to enhance recall at the time of the interview, including lists and photographs of commonly used brands and types of hormone therapy, review of any current prescription medication bottles or packages, and a life events calendar containing important milestones and life events. Given that 76% of controls and 82% of cases who were ever users of hormone therapy reported being current users of hormone therapy at their reference date, this increases the likelihood that the majority of women included were able to accurately report the type of hormone therapy they were currently using. In addition, it is not conceivable that recall among cases would differ according to histology. Lastly, we were unable to assess the relationship between time since last use among former users of EHT and CHT due to sample size limitations.

The results reported here are from the first epidemiologic study specifically designed to investigate the etiology of lobular carcinomas and is the first to incorporate a centralized review of pathology reports and tumor tissue. We confirmed the result of the majority of studies (2-10) evaluating the relationship between hormone therapy use and risk of different histologic types of breast cancer in finding that CHT use is more strongly related to risk of tumors with an invasive lobular component than it is to risk of IDC. This study expands on previous work by documenting that current CHT use for only 3 years or longer is sufficient to increase risks of both ILC and IDLC tumors about 3- to 4-fold. This duration is shorter than the widely cited duration of 5 years required to see an overall increase in breast cancer risk observed in the pooled analysis of 51 epidemiologic studies reported by the Collaborative Group on Hormonal Factors in Breast Cancer (28) and in the WHI CHT trial (1). Our result needs to be interpreted cautiously because only 8 controls, 15 IDC cases, and 28 ILC/IDLC cases used CHT for 3.0 to 4.9 years. However, this result is consistent with the elevation in overall breast cancer risk observed after 4 years of use in a subanalysis of the WHI CHT trial results, which was limited to women without prior menopausal hormone use. The five prior studies evaluating duration of CHT use with respect to lobular carcinoma risk were somewhat limited in their assessment of the relationship between duration of CHT use and lobular carcinoma risk, particularly for intervals under 5 years. One study evaluated use for a duration of less than 5 years, and it found that women who had used CHT for at least 13 months in the past 5 years had an increased risk of lobular tumors but not of nonlobular tumors (2). The remaining four studies all found that the risk of lobular carcinoma was higher among women who used CHT for 5 years or longer compared with women who used CHT for less than 5 years, but three (3, 9, 10) of these four (6) studies did find an elevation in lobular carcinoma risk among CHT users for less than 5 years, including one that included 166 lobular cases that were current users of CHT for less than 5 years (9). However, none of these four studies evaluated risk within finer

categories of duration of use for less than 5 years. In contrast to our ILC and IDLC findings, we observed that current CHT use, even for 10 years or longer, was associated with a much lower risk of IDC than it was with risks of both ILC and IDLC. The risk estimate for IDC among current CHT users for 10 years or longer neared but did not reach statistical significance (OR, 1.6; 95% CI, 1.0-2.5).

This is the first study to characterize IDLC tumors based on the proportion of the tumor that exhibits lobular features. We found a striking difference in the association between current CHT use and IDLC risk based on this proportion, as current CHT use was associated with a nonstatistically significant 1.9-fold increased risk of tumors that were <50% lobular but a 4.8-fold increased risk of tumors that were ≥50% lobular and a 7.7-fold increased risk of tumors that had intermixed ductal and lobular features. This further supports the role of CHT use in the etiology of tumors that have a substantial lobular component. We hypothesize that CHT use may stimulate the growth of foci of lobular carcinoma that would remain small or perhaps clinically undetectable in the absence of CHT exposure.

Additional evidence indicating that CHT use is involved in the etiology of lobular tumors are our observations that CHT use is related to risk of both ILC and IDLC regardless of various clinical tumor characteristics. In contrast, we found that CHT use was only related to risk of IDC tumors that were early stage, small, or node negative. This suggests that the association between CHT use and IDC may be partly explained by the more frequent access to medical care, and thus breast cancer screening services, that CHT users experience compared with women who do not use hormone therapy. The strong relationships between CHT use and risks of advanced-stage, large, and node-positive ILC and IDLC indicate that this type of surveillance bias does not have an important effect on the association between CHT use and risks of these breast cancer subtypes.

We also observed that current EHT use was associated with a reduced risk of IDC but not with reductions in risk of ILC or IDLC. The magnitude of this finding is consistent with the nearly statistically significant reduction in overall breast cancer risk (hazard ratio, 0.77; 95% CI, 0.59-1.01) observed among EHT users in the WHI unopposed estrogen trial (29). Given the consistency of this result with the WHI trial, this finding may not simply be due to chance. What accounts for a reduction in risk associated with EHT use is unclear, but it may be related to the earlier age at menopause EHT users experience given that it is only recommended for women who have had a hysterectomy. Also noteworthy was that long-term current use of EHT for 10 years or longer was not associated with elevations in risks of any of the histologic subtypes of breast cancer studied here.

Although rates of CHT use have dropped considerably since the publication of the WHI trials (14-16), studies of the risks associated with CHT use remain of critical importance given the estimated 57 million hormone therapy prescriptions that are still filled in the United States each year (18). The results of this study provide further evidence that CHT use increases the risk of ILC, and they indicate that current use of CHT for as little as 3 years may increase risk of these tumors substantially. Continued research aimed at identifying the biological basis for the relationship between CHT use and lobular carcinoma risk is warranted. Clinically, it is important to acknowledge that lobular carcinomas tend to be less aggressive than IDC, as data indicate that lobular tumors are more likely to be estrogen receptor positive (30) and are associated with an 11% lower risk of mortality compared with IDC (31). Further studies focusing on the etiology of different subtypes of breast cancer are needed to advance our understanding of this heterogeneous disease.

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Correction

Correction: Article on Hormone Therapy and Lobular Carcinoma Risk

In the article (1) on hormone therapy and lobular carcinoma risk in the January 2008 issue *Cancer Epidemiology, Biomarkers & Prevention*, there was an error in the grant support footnote on page 43. The last digit is missing. The correct number is R01-CA85913.

Reference

1. Li CI, Malone KE, Porter PL, et al. Relationship between menopausal hormone therapy and risk of ductal, lobular, and ductal-lobular breast carcinomas. Cancer Epidemiol Biomarkers Prev 2008;17:43–50.

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Relationship between Menopausal Hormone Therapy and Risk of Ductal, Lobular, and Ductal-Lobular Breast Carcinomas

Christopher I. Li, Kathleen E. Malone, Peggy L. Porter, et al.

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