Relationship Between Long Durations and Different Regimens of Hormone Therapy and Risk of Breast Cancer

Christopher I. Li, MD, PhD
Kathleen E. Malone, PhD
Peggy L. Porter, MD
Noel S. Weiss, MD, DrPH
Mei-Tzu C. Tang, PhD
Kara L. Cushing-Haugen, MS
Janet R. Daling, PhD

There is considerable evidence from observational studies, and now from a randomized controlled trial, the Women’s Health Initiative (WHI), that use of combined estrogen and progestin hormone replacement therapy (CHRT) is associated with an increased risk of breast cancer. Specifically, a pooled analysis of 51 observational studies found that current users of CHRT or progestin alone for 5 years or longer had a 53% increase in risk of breast cancer, and after 5.2 years of follow-up the WHI reported that CHRT was associated with a statistically nonsignificant 26% increase in breast cancer risk.

However, few studies have evaluated the effects of very long durations (≥15 years) of CHRT use on breast cancer risk. Two studies found that use of CHRT for 5 years or longer was associated with an increased risk of breast cancer (although use for 10 years or longer did not further increase the magnitude of these risks), but another reported that only use of CHRT for 10 years or longer was associated with an increase in risk. Also, the WHI evaluated use of the progestin component of CHRT in a continuous (daily) manner, and thus its results may not pertain to other patterns of CHRT use.
While many users of CHRT in the United States may have used the progestin component of CHRT continuously (70% of the population-based controls who were ever users of CHRT in our study herein had ever used the progestin component continuously), many may also have used it in a sequential manner (ie, for a certain number of days per month), since 33% of the controls who ever used CHRT in our study had at some time used it sequentially. However, few studies have assessed how such use is related to risk of breast cancer, although some that have assessed such use suggest that continuous use of progestin is more strongly associated with risk of breast cancer than is sequential use.6,7

Five recent studies also have reported that CHRT is associated with a 2.0- to 3.9-fold increased risk of invasive lobular carcinoma (ILC), the second most common histological type of breast cancer, but generally not with the risk of invasive ductal carcinoma (IDC), the most common histological type.6-10 In the 3 studies that evaluated duration of use, each found that ILC risk increased as duration of CHRT use increased.6,7,10 However, some of these reports have been limited by relatively small numbers of women with lobular cancer, and none has been able to evaluate the possible impact of very long-duration hormone replacement therapy (HRT).

Etiologic differences between the 2 major histological types of breast cancer are suggested by the observations that ILCs are more likely than IDCs to be hormone receptor–positive,11 and that incidence rates of ILC have increased steadily since 1977 among women 50 years of age and older in the United States, while incidence rates of IDC have remained largely constant since 1987.12,13 Distinguishing between breast carcinomas by histological type is also clinically important because ILCs have a better prognosis than do IDCs,14 although they also are more difficult to detect by mammography and clinical breast examinations.15,16

Although there appears to be variation in the associations between breast cancers with different hormone receptor profiles and hormonally related risk factors for breast cancer,16 limited data are available regarding associations between use of HRT and risk of breast cancer by estrogen receptor (ER) and progesterone receptor (PR) status. In one case series it was reported that users of HRT were more likely to have breast tumors that were ER positive (+) and PR+ compared with never users,17 while another found that women currently using HRT were more likely to have PR+ tumors but to have equal numbers of ER+ tumors compared with never users.18 Alternatively, a prospective study found that ever use of noncontraceptive estrogens was not associated with breast tumors with any particular combination of ER and PR status.18 However, none of these studies specified the type of HRT that participants had used.

Because many women have now used different types of HRT for long durations and some of these regimens have been associated with an increased risk of breast cancer, we assessed the relationships between various HRT regimens and different types of invasive breast cancer among participants in a population-based case-control study. Specifically, we evaluated both use of unopposed estrogen replacement therapy (ERT) and use of CHRT, use of sequential CHRT and of continuous CHRT, and short- and long-term use of these regimens, all with respect to risks of invasive ILC, IDC, ER+/PR+, ER+/PR− (−), and ER−/PR− breast carcinomas.

METHODS
We conducted a population-based case-control study of women 65 to 79 years of age living in the 3-county Seattle-Puget Sound metropolitan area.

Cases
Women aged 65 to 79 years with no prior history of in situ or invasive breast cancer when diagnosed with invasive breast cancer from April 1, 1997, through May 31, 1999, were eligible as cases. The Cancer Surveillance System (CSS), 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,19 was used to identify these women. More than 95% of all incident cancer cases in the area covered by the CSS are entered into the registry within 6 months following the calendar year of their diagnosis.20 To be eligible for the study, the women with breast cancer had to live in King, Pierce, or Snohomish counties and have a Health Care Financing Administration (HCFA) record, since these records were used to identify controls and this helps ensure a population-based sample. Of the 1210 eligible cases identified, 975 (80.6%) were interviewed. Eligible cases were approached through their physicians. Patients for whom physicians gave permission to contact were invited to participate in the study through a mailed letter describing the study as an investigation of causes of breast cancer in older women. Fourteen percent of eligible cases refused to be interviewed, 4% died before an interview could be conducted, 1% moved away from the area, and the physicians treating 1% of cases refused to allow contact with their patients. Information on tumor histology was ascertained from the CSS, which abstracts data on tumor characteristics from pathology reports from institutions serving the area. The CSS classifies histological types using International Classification of Diseases for Oncology codes.21 We divided cases into 2 groups, with codes 8520 and 8522 used to define the 196 ILC cases and code 8500 used to define the 656 IDC cases. The 123 women with a tumor of other (n=114) or unspecified (n=9) histological type were excluded from the analyses of ILC and IDC. Information on ER/PR status was also ascertained from the CSS, which abstracts results of ER/PR testing for cases of breast cancer from participants’ medical records. Of the 975 cases, 646 were ER+/PR+, 147 were ER+/PR−, and 101 were ER−/PR−. The 6 women whose tumors were ER−/PR+ and the 75 women with an unknown ER and/or PR status were excluded from analyses by ER/PR status (the group of 6 women was excluded because of small numbers).
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Controls
The HCFA records were used to identify women from the general population of female residents of King, Pierce, and Snohomish counties who were the same ages as cases to serve as controls. Once identified, eligible controls were sent a letter similar to the one sent to cases that described the study and invited them to participate. Of the 1365 eligible women selected as controls, 1007 (73.8%) were interviewed. Twenty-two percent of eligible controls refused to be interviewed, 2% died after selection but before they could be interviewed, 2% moved away, and 1% could not be located.

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 participants. Cases and controls were interviewed in person in their homes by a trained interviewer, and a standardized structured questionnaire was used to ask them about their reproductive history, body size, medical history, and family history of cancer. Additionally, detailed histories of all episodes of HRT use, including beginning and ending dates, total duration, 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 date of diagnosis was used as the reference date for each woman with breast cancer. Controls were assigned reference years so that the distribution of control reference years would be similar to the distribution of case diagnosis years, in an attempt to control for recall bias. Reference months were then randomly assigned to controls.

Analysis
In our HRT analyses, the referent category consisted of women who had never used any type of HRT. Excluded from the analysis were women whose only use of HRT consisted of 6 or more months’ use of shots, creams, or suppositories (3 controls, 5 cases). Our analysis of ever use of ERT was restricted to women who were exclusive users of ERT, e.g., women who also had never used CHRT for 6 months or longer (thus, 69 controls [15%] and 95 cases [21%] who were ever users of ERT were excluded). This restriction was made because CHRT has been observed to be more strongly associated with risk of breast cancer than is ERT.1,3,4 With regard to patterns of CHRT use, estrogen users who took progesterin for fewer than 25 days per month were considered users of sequential CHRT, and those who used progesterin for 25 days per month or longer were considered users of continuous CHRT (consistent with a prior report). Additionally, the 74 controls and 68 cases (including 44 IDC cases and 12 ILC cases) who used CHRT for less than 6 months were excluded from our analyses. Since the risks of breast cancer associated with use of CHRT were similar among exclusive ever users of CHRT and ever users of CHRT who also may have used ERT (see below), we considered our estimates using all ever users of CHRT to be the most reliable since they were based on a larger number of cases and controls. Thus, our evaluations of recency of CHRT use, patterns of CHRT use, and associations between use of CHRT and risk of breast cancer by ER/PR status were each based on all ever users of CHRT, rather than being restricted only to exclusive ever users of CHRT.

We compared all breast cancer cases with controls using unconditional logistic regression22 and compared ILC and IDC cases with controls, and cases with different ER/PR profiles with controls, using polytomous logistic regression.23 All analyses were conducted using Stata version 7.0 (Stata Corp, College Station, Tex). Both statistical approaches were used to calculate odds ratios (ORs) as an estimate of the relative risk and to compute 95% confidence intervals (CIs) and associated P values; P <.05 was used to determine statistical significance. Multiple variables were evaluated as potential confounders, including family history of breast cancer (first-degree, no first-degree), type of menopause (natural, induced, simple hysterectomy [hysterectomy without a bilateral oophorectomy]), age at menopause (5-year categories), parity, body mass index 1 year prior to reference date (quartiles of control population), mean daily alcohol use during the 20 years prior to reference date (none, ≤8.1 g, ≥8.2 g), and oral contraceptive use (never, <5 years, ≥5 years). Only adjustment for type of menopause changed the risk estimates of the ORs of interest by more than 10%. Type of menopause was likely a confounder because ERT is associated with an increased risk of endometrial cancer but CHRT is not, and therefore ERT is more likely to be considered for women who have had a hysterectomy and CHRT for those with an intact uterus.23 Thus, all analyses were adjusted both for type of menopause and for age (continuous), since cases and controls were matched on age.

RESULTS
The age distribution of ILC and IDC cases was similar to that of controls (Table 1). Controls were more likely than cases to be nonwhite. Also, based on the proportions of participants exposed to risk factors shown in Table 1, both ILC and IDC cases were somewhat more likely than controls to have a first-degree family history of breast cancer and to have higher levels of alcohol consumption. The IDC cases were more likely never to have used oral contraceptives, while ILC cases were more likely to have used oral contraceptives for 5 years or longer compared with controls.

Women who had received ERT but not CHRT had a risk of breast cancer similar to that of women not using HRT, irrespective of recency or duration of use (Table 2). For example, 10.8% of cases and 12.3% of controls used ERT for 25 years or longer (OR, 1.0; 95% CI, 0.7-1.4). This lack of association remained irrespective of histological type,
Table 1. Distribution of Demographic Characteristics and Risk Factors for Women With Invasive Breast Carcinoma and for Controls

<table>
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<tr>
<th>Characteristic</th>
<th>Controls (n = 1007)</th>
<th>All Cases (n = 975)</th>
<th>P Value, Controls vs Cases</th>
<th>IDC Cases (n = 656)</th>
<th>ILC Cases (n = 196)</th>
<th>P Value, IDC vs ILC</th>
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<td>15/112 (13.4)</td>
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(continued)
though in some instances the ORs for ERT use were not inconsistent with a possible small effect, particularly for ILC.

The risks of breast cancer associated with use of CHRT were similar among exclusive ever users of CHRT and all ever users of CHRT (which includes CHRT users who also had used ERT) (Table 3). For example, exclusive users of CHRT had a 1.8-fold (95% CI, 1.3-2.5) increased risk of breast cancer overall, and all ever users of CHRT had a 1.7-fold (95% CI, 1.3-2.2) increased risk. When examined by histological type, all ever users of CHRT had increases in risks of both IDC and ILC (OR, 1.5; 95% CI, 1.1-2.0; and OR, 1.7; 95% CI, 1.1-2.6; and OR, 1.5; 95% CI, 1.1-2.0, respectively) that generally increased in magnitude as duration of use increased. Similarly, ever use of sequential CHRT and continuous CHRT were associated with increases in risk of breast cancer of all histological types, of ductal, and of lobular breast cancer, respectively.

The increases in risk associated with ever and current use of CHRT differed little by the pattern of progestin use (Table 4). Specifically, ever use of both sequential CHRT and continuous CHRT were associated with increases in risk of breast cancer of all histological types (OR, 1.8; 95% CI, 1.2-2.7; and OR, 1.6; 95% CI, 1.2-2.2, respectively) that generally increased in magnitude as duration of use increased. Similarly, ever use of sequential CHRT and continuous CHRT were associated with increased risks of both IDC (OR, 1.7; 95% CI, 1.1-2.6; and OR, 1.5; 95% CI, 1.1-2.0, respectively) and ILC (OR, 2.8; 95% CI, 1.5-5.4; and OR, 2.7; 95% CI, 1.6-4.4, respectively).

When subdivided by ER/PR status, 66.3% (n=646) of cases were ER+/PR+, 15.1% (n=147) were ER+/PR−, 10.4% (n=101) were ER−/PR+, 0.6% (n=6) were ER−/PR−, and 7.7% (n=75) had an unknown ER/PR status. Ever, former, and current use of ERT were not associated with altered risks of ER+/PR+, ER+/PR−, or ER−/PR− breast cancers (Table 5). Use of ERT for 15 through 24.9 years was associated with an increased risk of ER+/PR+ breast cancer (OR, 1.6; 95% CI, 1.1-2.3), but use for 25 years or longer was not (OR, 1.0; 95% CI, 0.7-1.5). Otherwise, duration of ERT use did not alter risk of breast cancer by ER/PR status. Ever, former, and current use of CHRT were each associated with increased risk of ER+/PR+ breast cancers (OR, 1.6; 95% CI, 1.1-2.3), but use for 25 years or longer was not (OR, 1.0; 95% CI, 0.7-1.5). The increases in risk associated with ever and current use of CHRT differed little by the pattern of progestin use (Table 4). Specifically, ever use of both sequential CHRT and continuous CHRT were associated with increases in risk of breast cancer of all histological types (OR, 1.8; 95% CI, 1.2-2.7; and OR, 1.6; 95% CI, 1.2-2.2, respectively) that generally increased in magnitude as duration of use increased. Similarly, ever use of sequential CHRT and continuous CHRT were associated with increased risks of both IDC (OR, 1.7; 95% CI, 1.1-2.6; and OR, 1.5; 95% CI, 1.1-2.0, respectively) and ILC (OR, 2.8; 95% CI, 1.5-5.4; and OR, 2.7; 95% CI, 1.6-4.4, respectively). The increases in risk associated with ever and current use of CHRT differed little by the pattern of progestin use (Table 4). Specifically, ever use of both sequential CHRT and continuous CHRT were associated with increases in risk of breast cancer of all histological types (OR, 1.8; 95% CI, 1.2-2.7; and OR, 1.6; 95% CI, 1.2-2.2, respectively) that generally increased in magnitude as duration of use increased. Similarly, ever use of sequential CHRT and continuous CHRT were associated with increased risks of both IDC (OR, 1.7; 95% CI, 1.1-2.6; and OR, 1.5; 95% CI, 1.1-2.0, respectively) and ILC (OR, 2.8; 95% CI, 1.5-5.4; and OR, 2.7; 95% CI, 1.6-4.4, respectively) and of lobular and ductal tumors separately. Specifically, current use of CHRT was associated with 1.9-fold (95% CI, 1.4-2.6), 1.7-fold (95% CI, 1.2-2.4), and 3.1-fold (95% CI, 1.9-5.2) increases in risk of all histological types of breast cancer, of ductal, and of lobular breast cancer, respectively.

The increases in risk associated with ever and current use of CHRT differed little by the pattern of progestin use (Table 4). Specifically, ever use of both sequential CHRT and continuous CHRT were associated with increases in risk of breast cancer of all histological types (OR, 1.8; 95% CI, 1.2-2.7; and OR, 1.6; 95% CI, 1.2-2.2, respectively) that generally increased in magnitude as duration of use increased. Similarly, ever use of sequential CHRT and continuous CHRT were associated with increased risks of both IDC (OR, 1.7; 95% CI, 1.1-2.6; and OR, 1.5; 95% CI, 1.1-2.0, respectively) and ILC (OR, 2.8; 95% CI, 1.5-5.4; and OR, 2.7; 95% CI, 1.6-4.4, respectively).
for the ER+/PR+ group. The increases in risk of ER+/PR+ tumors for ever and current users of CHRT were limited primarily to those using CHRT for 5 or more years. Similarly, ever and current use of sequential CHRT and continuous CHRT were associated with increases in risks of ER+/PR+ tumors, but were not associated with increased risks of ER−/PR− or ER−/PR− tumors. Ever users of these regimens for 5 years or longer had higher risks of ER+/PR+ tumors than did users for less than 5 years, but we were not able to evaluate duration of use among current users of these regimens because of sample size limitations. Neither ever use of sequential CHRT and continuous CHRT for more than 5 years, nor for less than 5 years, was associated with altered risks of invasive ER+/PR− or ER−/PR− breast carcinomas.

**COMMENT**

Certain limitations of our study should be considered when interpreting the results. We did not perform independent or centralized pathology reviews or hormone receptor evaluations of the tumors, but instead relied on the diagnoses and tests performed by numerous pathologists and laboratories in the Seattle-Puget Sound area. Misclassification of tumor histological type and ER/PR status may have resulted in some instances. Additionally, we were able to interview only 80.6% of all eligible cases and 73.8% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to type of hormones used or to the timing and duration of hormone therapy. We also relied on participants’ recall of the types of hormone therapy used as well as on the source of hormone therapy used. However, studies have shown reasonable agreement between reports from postmenopausal women and physicians’ records. All but one of the eligible controls used HRT. This meta-analysis was limited, though, in that data on the type of hormone therapy used were only available for 39% of the eligible women, and because the analysis was not restricted to women who had ever used CHRT in our study were unable to interview 12% of all eligible cases and 25% of all eligible controls. Our results could be biased if the women we were unable to interview differed from those who did participate with regard to type of hormone therapy used.

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ers\(^1\)\(^4\) have found that CHRT use is a stronger risk factor for breast cancer than is ERT use. In a prior meta-analysis that was based primarily on studies conducted before widespread use of CHRT, use of ERT for 10 years or longer was associated with a 15% to 49% increased risk of breast cancer.\(^2\)\(^9\)

It is noteworthy that results from the Nurse’s Health Study from 1976 to 1986, a time period prior to the widespread use of CHRT, are consistent with our results, because both found that use of ERT lasting 15 years or longer was not associated with an increased risk of breast cancer.\(^10\) This specific report was not included in the meta-analysis by Steinberg et al,\(^26\) as they included results from the Nurse’s Health Study that were published later\(^11\) and included a larger proportion of ERT users who later also received CHRT. Also, few studies have focused on older women, and none of the studies described above looked specifically at use of ERT lasting 25 years or longer.

The results of our study are in partial agreement with the 5 studies that have evaluated associations between use of HRT and the occurrence of ILC and IDC.\(^6\)\(^\_\)\(^10\) Our findings are consistent with 4 of these 5 studies in finding that ERT is not associated with an increase in risk of ILC\(^10\) or IDC.\(^6\)\(^\_\)\(^10\) It also has been observed in these studies that use of CHRT is associated with a 2.0- to 3.9-fold increased risk of ILC. Similarly, we found that ever use of CHRT is associated with a 2.7-fold increase in risk of ILC. Although in each of these studies it was observed that use of CHRT is more strongly associated with ILC than with IDC, similar to only 1 of the previous 5 studies\(^6\) we observed that use of CHRT is also associated with a 1.5-fold increased risk of IDC. However, there are also some important differences between our study and these prior reports. Four of these 5 studies only included cases diagnosed before 1995, and they all included younger postmenopausal women. Our study focused on older women who were diagnosed in more recent years (1997-1999), resulting in a relatively high prevalence of HRT use for long durations. This provided us with greater power to measure the relationships between long duration of CHRT use and risks of ILC and IDC.

Consistent with the hypothesis that use of CHRT may have a different effect on the risk of ILC and IDC, lobular carcinomas are more likely to be both ER+ and PR+ compared with ductal carcinomas,\(^11\) suggesting that the former are more likely to be hormonally responsive. Our findings with respect to IDC are also consistent with ecological data indicating that incidence rates of LC have increased at the same time that rates of CHRT use have increased.\(^12\)\(^13\) These ecological data also indicate that rates

### Table 3. Use of Combined Estrogen and Progestin Hormone Replacement Therapy (CHRT) and Risk of Overall and Specific Histological Types of Invasive Breast Carcinoma\(^*\)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Controls, No. (%)</th>
<th>All Cases (n = 975)</th>
<th>IDC Cases (n = 656)</th>
<th>ILC Cases (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7)</td>
<td>284 (29.1)</td>
<td>Reference</td>
<td>199 (30.3)</td>
</tr>
<tr>
<td>Ever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>96 (9.5)</td>
<td>136 (13.9)</td>
<td>1.8 (1.3-2.5)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5-14 y</td>
<td>37 (3.7)</td>
<td>57 (5.8)</td>
<td>2.0 (1.3-3.2)</td>
<td>.004</td>
</tr>
<tr>
<td>≥15 y</td>
<td>30 (3.0)</td>
<td>49 (5.0)</td>
<td>2.0 (1.3-3.3)</td>
<td>.01</td>
</tr>
</tbody>
</table>

**Exclusive Ever Use of CHRT†**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Controls, No. (%)</th>
<th>All Cases (n = 975)</th>
<th>IDC Cases (n = 656)</th>
<th>ILC Cases (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7)</td>
<td>284 (29.1)</td>
<td>Reference</td>
<td>199 (30.3)</td>
</tr>
<tr>
<td>Ever</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>166 (16.4)</td>
<td>232 (23.8)</td>
<td>1.7 (1.3-2.2)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>5-14 y</td>
<td>60 (6.0)</td>
<td>65 (6.7)</td>
<td>1.3 (0.9-2.0)</td>
<td>.18</td>
</tr>
<tr>
<td>≥15 y</td>
<td>42 (4.2)</td>
<td>66 (6.8)</td>
<td>1.8 (1.2-2.7)</td>
<td>.004</td>
</tr>
</tbody>
</table>

**Ever Use of CHRT†**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Controls, No. (%)</th>
<th>All Cases (n = 975)</th>
<th>IDC Cases (n = 656)</th>
<th>ILC Cases (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 1007)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>No. (%)</td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>No. (%)</td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7)</td>
<td>284 (29.1)</td>
<td>Reference</td>
<td>199 (30.3)</td>
</tr>
<tr>
<td>Current</td>
<td>115 (11.4)</td>
<td>178 (18.3)</td>
<td>1.9 (1.4-2.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>32 (3.2)</td>
<td>31 (3.2)</td>
<td>1.2 (0.7-2.1)</td>
<td>.44</td>
</tr>
<tr>
<td>5-14 y</td>
<td>50 (5.0)</td>
<td>87 (8.9)</td>
<td>2.2 (1.5-3.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>≥15 y</td>
<td>33 (3.3)</td>
<td>60 (6.2)</td>
<td>2.2 (1.4-3.5)</td>
<td>.001</td>
</tr>
</tbody>
</table>

**Reccency of CHRT‡**

Abbreviations: CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OR, odds ratio.

*All models are adjusted for age of women at their reference date (see “Methods” section) and type of menopause. Analyses among all cases (including IDC cases, ILC cases, and cases with other or unspecified histological types) compared with controls were conducted using unconditional logistic regression. Analyses comparing IDC and ILC cases with controls were conducted using polytomous logistic regression. Separate categories of 15-24.9 years and ≥25 years are not given because of small numbers. Evaluation of recency of CHRT use is based on all ever users of CHRT, rather than being restricted only to exclusive ever users of CHRT.

†Ever users defined as women never using any type of hormone replacement therapy (HRT); former users defined as those using CHRT for ≥6 months with last use ≥6 months prior to reference date who are not current ERT users; current users defined as those using CHRT for ≥6 months with last use within the 6 months prior to reference date.

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of IDC have remained largely constant over this same time period, which is somewhat incongruous with our finding herein that use of CHRT is also associated with an increased risk of IDC. However, the associations with IDC are more modest than those with ILC, and perhaps other ecological trends that have not been identified that are related to the risk of IDC may explain why IDC rates have remained relatively constant. In 2 of the 5 studies, risk of breast cancer by different patterns of CHRT use was reported. In 1 study, it was found that sequential CHRT and continuous CHRT use were both associated with an increased risk of ILC and with an increased risk of nonlobular carcinomas that was within the limits of chance (P > .05),6 while in the other study, which was restricted to women younger than 65 years, it was observed that only continuous CHRT was associated with an increased risk of ILC.7 Similar to the former study, our results suggest that use of sequential CHRT and of continuous CHRT increase ILC risk and (to a lesser extent) IDC risk. One limitation of the WHI is that it only evaluated use of continuous CHRT, and thus conclusions regarding the effect of SCHRT or other CHRT regimens on risk of breast cancer could not be drawn. However, our data and the data from Chen et al6 suggest that sequential CHRT and continuous CHRT are equivalent with respect to the risks of breast cancer associated with their use.

Few studies have examined whether the potential influence of HRT use on incidence of breast cancer varies by ER/PR status. While in a prospective study it was observed that these associations were similar irrespective of ER/PR status,16 in 2 case series it was reported that HRT users were more likely to have hormone receptor-positive tumors.17,18 However, these studies did not differentiate between types of HRT used. We observed that

### Table 4. Relationship of Sequential and Continuous Regimens of Combined Estrogen and Progestin Hormone Replacement Therapy (CHRT) to Risk of Overall and of Histological Types of Invasive Breast Carcinoma, by Duration*

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Controls, No. (%) (n = 1007)</th>
<th>IDC Cases (n = 656)</th>
<th>ILC Cases (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>P Value</td>
<td>OR (95% CI)</td>
</tr>
<tr>
<td>Ever use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7) 284 (29.1) Reference</td>
<td>199 (30.3) Reference</td>
<td>47 (24.0) Reference</td>
</tr>
<tr>
<td>Ever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>55 (5.5) 80 (8.2) 1.8 (1.2-2.7)</td>
<td>.002 52 (7.9) 1.7 (1.1-2.6)</td>
<td>.02 19 (9.7) 2.8 (1.5-5.4)</td>
</tr>
<tr>
<td>5-14.9 y</td>
<td>22 (2.2) 26 (2.7) 1.5 (0.8-2.8)</td>
<td>.18 17 (2.6) 1.4 (0.7-2.8)</td>
<td>.31 6 (3.1) 2.2 (0.8-5.9)</td>
</tr>
<tr>
<td>≥15 y</td>
<td>9 (0.9) 21 (2.2) 2.9 (1.3-6.6)</td>
<td>.01 14 (2.1) 2.7 (1.1-6.4)</td>
<td>.02 5 (2.6) 4.6 (1.4-14.6)</td>
</tr>
<tr>
<td>Current use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>35 (3.5) 50 (5.1) 1.7 (1.1-2.8)</td>
<td>.02 32 (4.9) 1.6 (0.9-2.7)</td>
<td>.08 13 (6.6) 2.9 (1.4-6.1)</td>
</tr>
<tr>
<td>Current</td>
<td>20 (2.0) 30 (3.1) 2.0 (1.1-3.7)</td>
<td>.03 20 (3.0) 1.8 (1.0-3.6)</td>
<td>.07 6 (3.1) 2.6 (1.0-7.1)</td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>4 (0.4) 3 (0.3) 1.2 (0.2-6.2)</td>
<td>.80 2 (0.3) 1.2 (0.2-7.0)</td>
<td>.88 1 (0.5) 2.7 (0.3-26.5)</td>
</tr>
<tr>
<td>≥5 y</td>
<td>16 (1.6) 27 (2.8) 2.1 (1.1-4.1)</td>
<td>.02 18 (2.7) 2.0 (1.0-4.1)</td>
<td>.06 5 (2.6) 2.6 (0.9-7.8)</td>
</tr>
<tr>
<td>Continuous CHRT (Use of Progestin for ≥ 25 d/mo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7) 284 (29.1) Reference</td>
<td>199 (30.3) Reference</td>
<td>47 (24.0) Reference</td>
</tr>
<tr>
<td>Ever</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>116 (11.5) 159 (16.3) 1.6 (1.2-2.2)</td>
<td>.001 102 (15.5) 1.5 (1.1-2.0)</td>
<td>.02 40 (20.4) 2.7 (1.6-4.4)</td>
</tr>
<tr>
<td>5-14.9 y</td>
<td>52 (5.2) 57 (5.8) 1.3 (0.9-2.0)</td>
<td>.21 41 (6.3) 1.3 (0.8-2.1)</td>
<td>.24 13 (6.6) 1.9 (1.0-3.9)</td>
</tr>
<tr>
<td>≥15 y</td>
<td>43 (4.3) 69 (7.1) 2.0 (1.3-3.0)</td>
<td>.002 40 (6.1) 1.6 (1.0-2.6)</td>
<td>.06 19 (9.7) 3.5 (1.9-6.8)</td>
</tr>
<tr>
<td>Current use†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>26 (2.6) 22 (2.3) 1.0 (0.6-1.8)</td>
<td>.99 15 (2.3) 1.0 (0.5-1.9)</td>
<td>.94 5 (2.6) 1.5 (0.5-4.3)</td>
</tr>
<tr>
<td>Current</td>
<td>90 (8.9) 137 (14.1) 1.8 (1.3-2.5)</td>
<td>&lt;.001 87 (13.3) 1.6 (1.1-2.3)</td>
<td>.01 35 (17.9) 3.1 (1.8-5.3)</td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>35 (3.5) 41 (4.2) 1.4 (0.9-2.3)</td>
<td>.15 31 (4.7) 1.5 (0.9-2.6)</td>
<td>.13 8 (4.1) 1.8 (0.8-4.3)</td>
</tr>
<tr>
<td>≥5 y</td>
<td>55 (5.5) 96 (9.8) 2.2 (1.5-3.2)</td>
<td>&lt;.001 56 (8.5) 1.7 (1.1-2.7)</td>
<td>.01 27 (13.8) 4.0 (2.2-7.3)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; OR, odds ratio.

*All models are adjusted for age of women at their reference date (see "Methods" section) and type of menopause. Analyses among all cases (including IDC cases, ILC cases, and cases with other or unspecified histological types) compared with controls were conducted using unconditional logistic regression. Analyses comparing IDC and ILC cases with controls were conducted using polytomous logistic regression. Evaluation of patterns of CHRT use is based on all ever users of CHRT, rather than being restricted only to exclusive ever users of CHRT. Separate categories of 15-24.9 years and ≥25 years are not given because of small numbers.

†Never used defined as women never using any type of hormone replacement therapy (HRT); ever used defined as those using sequential CHRT (or continuous CHRT) for ≥6 months.‡Ever used defined as women never using HRT; former used defined as those using sequential CHRT (or continuous CHRT) for ≥6 months with last use >6 months prior to reference date who are not current users of estrogen replacement therapy; current users defined as those using sequential CHRT (or continuous CHRT) for ≥6 months with last use within the 6 months prior to reference date. Information on whether CHRT use was sequential or continuous was missing for 32 participants (13 controls and 19 cases); these participants were excluded from analyses.

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use of ERT was not associated with risk of breast cancer of any ER/PR profile, but we did find that use of CHRT (including use of sequential CHRT and of continuous CHRT) was associated with increases in risks of ER+/PR+ tumors, and that the magnitude of these risks increased as duration of CHRT use increased. Use of CHRT was not associated with risks of either ER+/PR− or ER−/PR− tumors, although caution is warranted in interpretation of the findings due to limited statistical power to detect differences. Although these findings need to be confirmed by others.

### Table 5. Relationship of Various Hormone Replacement Therapy Regimens to Risk of Invasive Breast Carcinoma, by Combined Estrogen Receptor (ER) and Progesterone Receptor (PR) Status*

<table>
<thead>
<tr>
<th>Regimen†</th>
<th>Controls, No. (%) (n = 1007)</th>
<th>ER+/PR+ (n = 646)</th>
<th>ER+/PR− (n = 147)</th>
<th>ER−/PR− (n = 101)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) OR (95% CI) P Value</td>
<td>No. (%) OR (95% CI) P Value</td>
<td>No. (%) OR (95% CI) P Value</td>
<td></td>
</tr>
<tr>
<td><strong>CHRT Use</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7) 170 (26.3) Reference</td>
<td>54 (36.7) Reference</td>
<td>35 (34.7) Reference</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>397 (39.4) 243 (37.6) 1.1 (0.8-1.5) .46</td>
<td>46 (31.3) 0.8 (0.5-1.3) .32</td>
<td>40 (39.6) 1.0 (0.6-1.7) .98</td>
<td></td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>113 (11.2) 51 (7.9) 0.9 (0.6-1.3) .52</td>
<td>12 (8.2) 0.7 (0.4-1.4) .31</td>
<td>12 (11.9) 1.0 (0.5-2.1) .92</td>
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<tr>
<td>5-14.9 y</td>
<td>83 (8.2) 60 (9.3) 1.3 (0.9-2.0) .21</td>
<td>12 (8.2) 1.0 (0.5-2.0) .90</td>
<td>10 (9.9) 1.1 (0.5-2.5) .76</td>
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<tr>
<td>15-24.9 y</td>
<td>77 (7.6) 65 (10.1) 1.6 (1.1-2.5) .03</td>
<td>8 (5.4) 0.8 (0.3-1.8) .56</td>
<td>8 (7.9) 1.0 (0.4-2.4) .95</td>
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<tr>
<td>≥25 y</td>
<td>124 (12.3) 67 (10.4) 1.0 (0.7-1.5) .97</td>
<td>14 (9.5) 0.7 (0.3-1.8) .42</td>
<td>10 (9.9) 0.8 (0.3-1.8) .59</td>
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<tr>
<td>Former</td>
<td>123 (12.2) 83 (12.8) 1.2 (0.9-1.7) .26</td>
<td>17 (11.6) 0.8 (0.5-1.6) .60</td>
<td>12 (11.9) 1.0 (0.5-2.0) .97</td>
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<td>Current</td>
<td>274 (27.2) 160 (24.8) 1.0 (0.8-1.4) .81</td>
<td>29 (19.7) 0.7 (0.4-1.3) .28</td>
<td>28 (27.7) 1.0 (0.5-1.9) .98</td>
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<tr>
<td>6 mo-4.9 y</td>
<td>42 (4.2) 12 (1.9) 0.5 (0.3-1.1) .08</td>
<td>3 (2.0) 0.6 (0.2-2.0) .37</td>
<td>3 (3.0) 0.7 (0.2-2.6) .62</td>
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<tr>
<td>5-14.9 y</td>
<td>49 (4.9) 29 (4.5) 1.1 (0.6-1.9) .71</td>
<td>7 (4.8) 1.2 (0.5-3.1) .65</td>
<td>8 (7.9) 1.7 (0.7-4.2) .26</td>
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<tr>
<td>≥15 y</td>
<td>183 (18.2) 119 (18.4) 1.2 (0.8-1.8) .27</td>
<td>19 (12.9) 0.8 (0.4-1.7) .60</td>
<td>17 (16.8) 1.1 (0.5-2.4) .79</td>
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<tr>
<td><strong>Sequential CHRT Use</strong></td>
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</tr>
<tr>
<td>Never</td>
<td>339 (33.7) 170 (26.3) Reference</td>
<td>54 (36.7) Reference</td>
<td>35 (34.7) Reference</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>165 (16.4) 165 (25.5) 2.0 (1.5-2.7) &lt;.001</td>
<td>31 (21.1) 1.3 (0.8-2.2) .29</td>
<td>17 (16.8) 0.9 (0.5-1.8) .86</td>
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<tr>
<td>6 mo-4.9 y</td>
<td>60 (6.0) 42 (6.5) 1.4 (0.9-2.2) .13</td>
<td>12 (8.2) 1.4 (0.7-2.9) .32</td>
<td>6 (5.9) 0.9 (0.3-2.2) .77</td>
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<tr>
<td>5-14.9 y</td>
<td>63 (6.3) 71 (11.0) 2.3 (1.8-3.2) &lt;.001</td>
<td>12 (8.2) 1.3 (0.7-2.7) .41</td>
<td>7 (6.9) 1.0 (0.4-2.5) .94</td>
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<tr>
<td>≥15 y</td>
<td>42 (4.2) 52 (8.0) 2.4 (1.5-3.8) &lt;.001</td>
<td>7 (4.8) 1.1 (0.5-2.7) .79</td>
<td>4 (4.0) 0.9 (0.3-2.7) .87</td>
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</tr>
<tr>
<td>Former</td>
<td>20 (2.0) 23 (3.6) 2.3 (1.2-4.4) .01</td>
<td>6 (4.1) 2.1 (0.8-5.6) .13</td>
<td>2 (2.0) 1.0 (0.2-4.3) .96</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>115 (11.4) 127 (19.7) 2.3 (1.6-3.2) &lt;.001</td>
<td>22 (15.0) 1.4 (0.8-2.4) .26</td>
<td>13 (12.9) 1.1 (0.5-2.2) .78</td>
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</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>32 (3.2) 22 (3.4) 1.4 (0.8-2.6) .22</td>
<td>5 (3.4) 1.1 (0.4-3.1) .79</td>
<td>2 (2.0) 0.6 (0.1-2.7) .52</td>
<td></td>
</tr>
<tr>
<td>5-14.9 y</td>
<td>50 (5.0) 57 (8.8) 2.4 (1.5-3.7) &lt;.001</td>
<td>12 (8.2) 1.8 (0.9-3.7) .12</td>
<td>7 (6.9) 1.4 (0.6-3.4) .50</td>
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<tr>
<td>≥15 y</td>
<td>33 (3.3) 48 (7.4) 2.9 (1.8-4.8) &lt;.001</td>
<td>5 (3.4) 1.1 (0.4-2.9) .89</td>
<td>4 (4.3) 1.2 (0.4-3.8) .76</td>
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<tr>
<td><strong>Continuous CHRT Use</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>339 (33.7) 170 (26.3) Reference</td>
<td>54 (36.7) Reference</td>
<td>35 (34.7) Reference</td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>55 (5.5) 54 (8.4) 2.1 (1.3-3.2) &lt;.001</td>
<td>10 (6.8) 1.4 (0.6-2.9) .42</td>
<td>8 (7.9) 1.3 (0.6-3.1) .52</td>
<td></td>
</tr>
<tr>
<td>6 mo-4.9 y</td>
<td>22 (2.2) 14 (2.2) 1.4 (0.7-2.8) .37</td>
<td>5 (3.4) 1.7 (0.6-4.8) .31</td>
<td>2 (2.0) 0.8 (0.2-3.8) .81</td>
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</tr>
<tr>
<td>≥5 y</td>
<td>33 (3.3) 40 (6.2) 2.5 (1.5-4.2) &lt;.001</td>
<td>5 (3.4) 1.1 (0.4-3.1) .81</td>
<td>6 (5.9) 1.6 (0.6-4.3) .31</td>
<td></td>
</tr>
<tr>
<td>Former</td>
<td>35 (3.5) 35 (5.4) 2.0 (1.2-3.4) .01</td>
<td>7 (4.8) 1.5 (0.6-3.6) .38</td>
<td>3 (3.0) 0.7 (0.2-2.6) .64</td>
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<tr>
<td>Current</td>
<td>20 (2.0) 19 (2.9) 2.1 (1.1-4.1) .03</td>
<td>3 (2.0) 1.2 (0.3-4.1) .83</td>
<td>5 (5.0) 2.5 (0.8-7.3) .10</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CHRT, combined estrogen and progesterone hormone replacement therapy; CI, confidence interval; ERT, estrogen replacement therapy; NA, not available; OR, odds ratio.

*All models are adjusted for age of women at their first use (see “Methods” section) and type of menopause. All analyses were conducted using polytomous logistic regression.

†Six ER−/PR+ cases and 75 cases with an unknown ER/PR status were excluded from these analyses. Evaluation of risk of breast cancer by ER/PR status is based on all ever users of CHRT, rather than being restricted only to exclusive ever users of CHRT. Separate categories of 15-24.9 years and 25 years are not given for some regimens because of small numbers.

‡Odds ratio cannot be estimated because no ER−/PR− cases were former users of continuous CHRT.
they suggest that the progestin component of CHRT is particularly important with respect to altering the risk of breast cancer. Our observations suggest that CHRT may promote breast cancer through the stimulation of both ERs and PRs, and not through the ER alone, given that use of CHRT was associated with an increased risk of ER+/PR− tumors, but not with an increased risk of ER+/PR+ tumors (although ERs/PR− numbers were small). Furthermore, use of exogenous estrogens alone was not associated with risk of any ER/PR profile.

Evidence is mounting regarding the adverse impact on breast cancer risk of adding progesterin to HRT. This adverse impact appears to be manifest within several years of initiating use of CHRT, and to be similar in magnitude irrespective of the pattern of CHRT use (continuous or sequential). At least for the forms of CHRT used most commonly by US women in the latter part of the 20th century, including both sequential CHRT and continuous CHRT, an increased incidence of breast cancer must be tallied as a possible consequence.

Author Affiliations: Division of Public Health Sciences (Drs Li, Malone, Weiss, Tang, and Daling, and Ms Cushing-Haagen) and Division of Human Biology (Dr Porter), Fred Hutchinson Cancer Research Center, Seattle, Wash; and Department of Epidemiology, School of Public Health and Community Medicine (Drs Li, Malone, Weiss, and Daling) and Department of Pathology, School of Medicine (Dr Porter), University of Washington, Seattle.

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Author Contributions: Study concept and design; acquisition of data: Malone, Porter, Daling. Analysis and interpretation of data: critical revision of the manuscript for important intellectual content: Li, Malone, Porter, Weiss, Tang, Cushing-Haagen, Daling. Drafting of the manuscript: Li. Statistical expertise: Li, Tang, Cushing-Haagen. Obtained funding: Malone, Daling. Administrative, technical, or material support: Porter, Daling.

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REFERENCES


