Published in final edited form as:
Pharmacoepidemiol Drug Saf. 2010 May ; 19(5): 440–447. doi:10.1002/pds.1941.

Hormone Therapy and Fatal Breast Cancer

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Abstract

Purpose—Among unanswered questions is whether menopausal use of estrogen therapy (ET) or estrogen-plus-progestin therapy (CHT) increases risk of developing fatal breast cancer, i.e developing *and* dying of breast cancer. Using a population-based case-control design, we estimated incidence rate ratios of fatal breast cancer in postmenopausal hormone therapy (HT) users compared to non-users by type, duration, and recency of HT use.

Methods—HT use prior to breast cancer diagnosis in 278 women who died of breast cancer within 6 years of diagnosis (cases) was compared with use in 2,224 controls never diagnosed with breast cancer using conditional logistic regression. Measures taken to address potential bias and confounding inherent in case-control studies included collecting and adjusting for detailed data on demographic and other factors potentially associated both with hormone therapy use and breast cancer.

Results—Fifty-six percent of cases and 68% of controls reported HT use. Among current 3+ year HT users, odds ratios and 95% confidence intervals for death were 0.83 (0.50, 1.38) and 0.69 (0.44, 1.09), respectively, for exclusive use of CHT or of ET, and were 0.94 (0.59, 1.48) and 0.70 (0.45, 1.07) for any use of CHT or of ET regardless of other hormone use.

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The findings and conclusions in this article are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

Conclusion—Point estimates suggest no increased risk of fatal breast cancer with HT use, although 50% increases in risk in longer-term current CHT users cannot be ruled out.

Keywords

Hormone replacement therapy; estrogen replacement therapy; estrogen progestin combination therapy; breast neoplasms; death; menopause; case-control

INTRODUCTION

Hormone therapy (HT) remains the most effective method for reducing menopausal hot flashes and night sweats.[1–3] HT use plummeted after the termination in 2002 of the estrogen-plus-progestin (CHT) arm of the Women's Health Initiative (WHI).[4–12] Yet many women who discontinued use have resumed HT for symptom relief.[13–16]

For assessing tradeoffs between risk and benefit of short-term menopausal HT therapy, the WHI offered limited information. Participants were well past menopause (mean age 63 years); 26% had used HT before enrolling; and only 12% had moderate/severe vasomotor symptoms at enrollment.[4] Results and recommendations from the WHI relate to HT use and incident breast cancer. Unanswered is whether HT increases risk of fatal breast cancer. At its termination, there were only 8 deaths from breast cancer in the WHI, 4 in each arm, among the 16,000 women randomized to CHT or placebo (RR 0.95: 95% CI 0.24, 3.81).[17] The other randomized study designed to investigate risk of fatal breast cancer with HT use in healthy women, the Women's International Study of Long Duration Oestrogen after Menopause (WISDOM), did not achieve recruitment goals.[18,19] Among prior observational studies of HT and fatal breast cancer reviewed by Nanda and colleagues,[20] none provided data separately for estrogen therapy (ET) and CHT, nor did the more recently published prospective Million Women Study.[21]

We reported previously the results of a case-control study suggesting a positive association between continuous combined HT and breast cancer incidence among current, longer term users.[22,23] Building upon that study, we then asked whether HT users were more likely to develop fatal breast cancer, i.e. to develop *and* die of breast cancer, than never users of HT.

METHODS

Study design

This study relies on the Women's Contraceptive and Reproductive Experiences (Women's CARE) Study, a population-based, multicenter case-control study of risk factors for invasive breast cancer conducted in metropolitan areas of Atlanta, Georgia; Detroit, Michigan; Los Angeles, California; Philadelphia, Pennsylvania; and Seattle, Washington. Details on Women's CARE Study methods have appeared previously.[22,24,25] The Women's CARE protocol was approved by the institutional review boards of the participating institutions. All study subjects provided written informed consent.

Briefly, from 1994–1998 the Women's CARE Study randomly sampled black and white women aged 35–64 years with incident invasive breast cancer along with a control group of women identified by random-digit-dialing who had never been diagnosed with breast cancer. Among these original Women's CARE cases, black women and younger women were oversampled. Rates of control recruitment corresponded over time to frequencies of case recruitment, and cases and controls were frequency matched on age in five-year categories, race, and study site. In-person interviews obtained information on exposures prior to the reference date, i.e., the date of breast cancer diagnosis for cases or the date at

which the control was identified by random digit dialing. Interview response rates were similar for case (76.5%) and control (78.6%) women.

The present study used an efficient population-based case-control design[26] to estimate incidence rate ratios of fatal breast cancer in HT users compared to non-users. Case-control studies of fatal outcomes generally identify cases at death. However, next-of-kin or medical records cannot adequately provide detailed information on type, duration and recency of HT use as well as relevant confounders. The appropriate HT exposure period for determining risk of fatal breast cancer associated with HT use is before the cancer has been diagnosed. To obtain this exposure information directly from the respondents soon after these exposures occurred, we built upon the Women's CARE study to define as cases all postmenopausal women with fatal breast cancer. These women had incident breast cancer (discovered in the CARE study) who, based upon our follow-up, died from their breast cancer within six years after diagnosis. Among the 2,137 postmenopausal incident breast cancer cases in the original Women's CARE Study, 278 women satisfied these conditions and served as cases for the present study of hormone therapy. The exposure history of the control group represented the HT exposure history of the underlying population giving rise to these cases when newly diagnosed with breast cancer. In theory, the ideal control group would include women diagnosed with breast cancer but who did not die of the disease, along with those never diagnosed with breast cancer in 1994–1998, each group in their proportions in the source population. For practical reasons we used only the 2,224 population-based postmenopausal controls without breast cancer in the parent CARE study. Because breast cancer is rare (approximately 1 – 4 per 1000 women per year in this age group), very few women with breast cancer, regardless of outcome, would have been included in a random sample of the general population of women aged 35–64 years, and estimates of hormone exposure history for our control group would be unaffected.[27]

Interview data collection

We used a mixture of recall and recognition techniques (structured questionnaire, response cards, color pictures of hormone preparations, and a life-events calendar)[22,28,29] to ascertain HT exposures. The questionnaire covered other known and purported risk factors for breast cancer that might confound the association between HT use and breast cancer.

Analysis variables

HT exposure—HT use before the reference date was defined either as: 1) exclusive use of either CHT or ET; 2) any use of CHT even if ET was used at another time, or, conversely, any use of ET even if CHT was also used; or 3) any HT regardless of type for separate analyses. HT exposure was restricted to pills or patches, since 93.6% of the months of HT use consisted of pill or patch delivery. Sixty-one controls and 5 cases who only used HT creams, shots, implants, suppositories, unopposed progestin or unknown type of HT were excluded from the analysis. In addition to type of HT, we distinguished four subgroups of exposure based on recency and duration of use: Current user, <3 years of use; current user, 3+ years of use; former user, <3 years of use; former user, 3+ years of use. Current use was defined as use up to or within 6 months of the reference date. We defined longer-term use as 3+ years to distribute observations relatively equally within strata of HT users. Sensitivity analyses redefined longer-term use as 5+ years.

Menopause—Our analysis was restricted to postmenopausal women. Only 2% (5/324) of premenopausal Women's CARE cases who died and 5% (97/1976) of premenopausal Women's CARE controls used CHT or ET pills and patches. We included menopausal women who 1) were naturally menopausal; 2) had induced menopause; 3) were known to be menopausal but with unknown type; and 4) women age 50 or older whose menopausal status

was unclassifiable due to a simple hysterectomy or to start of HT before menopause. We performed sensitivity analyses excluding women with unclassifiable menopausal status.

Age at menopause was known for all with induced menopause, and for none with menopause of unknown type or unknown menopausal status. For women with natural menopause, age was known for 92% of deceased cases and 90% of controls. When age at menopause was not known, it was imputed with age at bilateral oophorectomy or, if none, with age at first use of any HT, or, if none, age at last menstrual period.

Follow-up for vital status

All breast cancer cases aged 35–64 interviewed for the Women's CARE Study were followed annually for vital status, and, if deceased, date and cause of death as recorded in the state death certificate. The four Women's CARE field centers covered by Surveillance Epidemiology and End Results (SEER) registries used standard SEER follow-up procedures, primarily passive linkage with state death records. SEER registries are required to achieve 95% follow-up for vital status, and all involved in this study were compliant. For the Pennsylvania site, state death records were used. All five sites verified that follow-up for vital status was complete through 2004 deaths. Because case ascertainment for the Women's CARE Study spanned 1994 – 1998, all Women's CARE cases were followed for at least 6 years.

Data analysis

We report odds ratios (ORs) and 95% confidence intervals (CIs) as estimates of incidence rate ratios of developing and then dying from breast cancer within 6 years of diagnosis in HT users compared to women who never used HT. To control for frequency matching by race, study area, and 5-year age categories in the parent Women's CARE study, we used conditional logistic regression stratified on these factors. To assess additional confounding, we included in the base model three variables, age at menopause (continuous), type of menopause (induced vs other), and at least one screening mammogram within two years before the reference date (yes or no), which, based on the literature[30] or our own data,[31] qualified *a priori* as potential confounders. Other variables subsequently added individually to the base models and assessed individually were body mass index, family history of breast cancer, education, marital status, parity, alcohol consumption, smoking status, number of pre-existing medical conditions, use of oral contraceptives, and less than twice the federal poverty threshold for household income. Among these, only poverty level led to a >5% change in the ratio of ORs (ratio 1.052) in an adjusted model compared to the base model. However, because missing data on household income resulted in loss of 72 women from our models, we did not include poverty in the main analyses but performed sensitivity analyses instead. Analyses were done using Stata's program clogit 8.1 (Stata Corp, College Station, TX).

RESULTS

Fifty-six percent of the 278 cases and 68% of the 2,224 controls reported HT use prior to the reference date (Table 1). Type of HT used varied by type of menopause, as expected (Table 1). Most menopausal HT use began at menopause (72% –73% of users) or within five years before (4%) or after menopause (13%), but the start differed by type of menopause. About one-third of naturally menopausal HT users began use at or before menopause, and two-thirds after menopause. Among women with induced or unclear type of menopause, about 9 of 10 began use at or before menopause.

Among HT users, 73% of cases and 61% of controls reported use only for symptoms, with an additional 16% of cases and 28% of controls using HT for symptoms and to prevent osteoporosis or heart disease. Only 7% of cases and controls used HT exclusively to prevent osteoporosis or heart disease.

Table 2 reports the association of recency and duration of HT use with fatal breast cancer, adjusting for age and type of menopause and at least one screening mammogram within the past two years Most exposed cases and controls were current 3+ year users; the number exposed in other recency-duration subgroups was often small. Point estimates for all CHT exposures were below 1.0 or, in one instance, barely exceeded 1.0, regardless of duration or recency of use. For current 3+ year users, the upper bounds of the CIs were 1.38 for women who used CHT exclusively compared to never users and 1.48 for any use of CHT. For ET, all ORs were below 1.0 except in the small group of former 3+ year users. Among current 3+ year ET users, point estimates were 0.69 (exclusive users) and 0.70 (any users). Upper bounds of the CIs were 1.09 and 1.07, respectively. When users of any HT were compared with never users (last data rows in Table 2), as in most prior studies, the results were between those for any CHT use and any ET use.

We examined the robustness of our findings in sensitivity analyses (Table 3). ORs were similar to those in Table 2 after we adjusted for poverty level in addition to the other potential confounders (Table 3, Row B) and after we defined longer-term use of HT as 5+ years (Row D). When women with unclassifiable menopausal status were excluded (Row C), ORs increased and upper bounds of CIs increased predictably with the marked decreases in sample size.

DISCUSSION

We used a population-based observational design to estimate relative rates of fatal breast cancer, i.e. developing and dying from breast cancer, in HT users compared to non-users. Point estimates of the association between CHT or ET and fatal breast cancer were generally below 1.0, although, given fairly wide CIs, increases in risk of up to 50% or more could not be excluded for some CHT exposures.

The few previous studies of HT use and incidence of fatal breast cancer in healthy users have had mixed results and did not publish results by type of HT. The prospective Million Women Study reported that current users of HT at the beginning of follow-up were at 22% increased risk for breast cancer death after 4.1 years (RR 1.22, 95% CI: 1.05, 1.41).[21] The prospective Kuopio Osteoporosis Risk Factor and Prevention Study found an elevated risk of breast cancer death after 7 years of follow-up among women who used HT more than 5 years compared to non-users (HR 2.62, 95% CI 0.98, 7.00).[32] Most of the 10 studies reviewed by Nanda and colleagues [20] found a reduced risk of death from breast cancer in users. In four of these studies, the reduced risk decreased with duration of use, duration of follow-up, and years since last use. The two studies showing an increased risk of death with HT use had wide confidence intervals. Adjustment for confounding varied across the studies; only two studies reported data on mammography screening, which, in our study, was a strong confounder whose control attenuated observed protection for HT use against death, especially for CHT.

CHT use has been more often linked to an increased risk of breast cancer incidence in postmenopausal women than ET.[22,23,30] Observational studies of HT use and prognostic factors at breast cancer diagnosis suggest that HT users present with tumors that are smaller with less lymph node involvement compared to non-users, and that HT use is associated with less aggressive histology.[33] However, results have not been consistent,[34] and few

studies have provided data by HT regimen, duration and recency of use. Tumors in the CHT arm of the WHI were larger than those in the placebo group and were diagnosed at a later stage.[35] In our Women's CARE dataset, among all breast cancer cases HT users appeared to have more favorable tumor characteristics than non-users, with a greater likelihood of lobular as opposed to ductal histology,[23] a higher proportion of ER and PR positive tumors, and a lower proportion of late-stage disease[36] but adjustment for recent screening attenuated some of these effects.

Among the study's strengths is the efficient population-based case-control design which allows timely collection of information on HT use and potential confounders directly from the study subject. Our data included start and stop dates of use, type of regimen and reasons for starting and stopping use. Unlike the women studied in the WHI, about 90% of our study participants began HT use at or within 5 years of menopause, and around 90% of use was for relief of menopausal symptoms, exposures of primary interest. HT use was assessed between 1994 and 1998, before the results of the WHI were publicized, and over a narrow period in which prescribing patterns were relatively constant.

Our study has several limitations. First, with a case-control design, our outcome was limited to death from breast cancer, in contrast to prospective studies, which can examine the entire range of disease outcomes, such as venous thromboembolism, stroke and coronary heart disease, that can be affected by HT use. Second, with 278 cases an up to 50% increase in risk of fatal breast cancer with CHT use for menopausal symptoms could not be excluded. Third, although our case group captured fatal breast cancers occurring within 6 years after breast cancer diagnosis, longer follow-up may have been needed to reveal an association between HT and fatal breast cancer, especially since HT use has been associated with less aggressive histology in some studies. Finally, potential limitations of any case-control study include selection bias, recall bias and confounding. Interview response rates for the Women's CARE Study were similar for case and control subjects and were within the ranges reported by other recent studies.[25] Bias could result if study participants differed from non-participants. However, we have no reason to believe that decisions to participate were based on hormone history, or that there was differential participation of cases and controls in the CARE Study related to hormone use. Exposures to HT and other potential confounders were obtained from face-to-face interviews,[22] and most HT users were current users at the reference date (Table 2), aiding HT recall. Agreement between self-reported HT use and prescription data in the Million Women Study was high overall and for the hormonal constituents of the preparations, for both current and former users.[37] We lacked information on exposures after diagnosis that could affect survival, including possible continued HT use as well as cancer treatment and access to care. Estimates of HT use after breast cancer diagnosis suggest that it is low.[38,39] We adjusted for education, income, and screening mammography, all related to access to care. While unmeasured confounding remains possible, we explored a wide variety of potential confounders, and we deemed, conservatively, a 5% or greater change in the ratio of adjusted to crude ORs minimally important in this particular setting with ORs often close to the null.

CONCLUSION

Despite lack of definitive answers, recommendations for short term HT use for intolerable menopausal symptoms occurring around the time of menopause have been emerging.[17,40–43] Our results on the association of HT use and risk of fatal breast cancer add to the body of evidence from prior studies representing diverse geographic areas, different populations and different rates of HT exposure. Though the present study suggests no increased risk of fatal breast cancer in recipients of either form of HT, the issue is by no means settled.

Acknowledgments

This study was funded by the Centers for Disease Control and Prevention (CDC), Division of Cancer Prevention and Control, through subcontracts to the Women's Contraceptive and Reproductive Experiences (CARE) Study through an interagency agreement with the National Institute of Child Health and Human Development (NICHD), and by CDC Division of Cancer Prevention and Control contract #200-2002-00370 with the University of Pennsylvania (Sandra A. Norman, P.I.). The Women's CARE Study was funded by the NICHD, with additional support from the National Cancer Institute, through contracts with Emory University (N01-HD-3-3168), Fred Hutchinson Cancer Research Center (N01-HD-2-3166), Karmanos Cancer Institute at Wayne State University (N01-HD-3-3174), the University of Pennsylvania (N01-HD-3-3176) and the University of Southern California (N01-HD-3-3175) and through an interagency agreement with CDC (Y01-HD-7022). CDC also contributed additional staff and computer support. General support was also provided through Surveillance, Epidemiology and End Results Program contracts N01-PC-67006 (Atlanta), N01-CN-65064 (Detroit), N01-PC-67010 (Los Angeles), and N01-CN-0532 (Seattle).

We thank Noel S. Weiss, MD, DrPH for his many helpful suggestions on drafts of the manuscript.

Abbreviations and acronyms

HT	Hormone therapy
CHT	Estrogen-plus-progestin hormone therapy
ET	Estrogen therapy
WHI	Women's Health Initiative
Women's CARE Study	Women's Contraceptive and Reproductive Experiences Study
SEER	Surveillance Epidemiology and End Results Program
OR	Odds ratio
CI	95% Confidence interval

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Pharmacoepidemiol Drug Saf. Author manuscript; available in PMC 2011 May 20.

Table 1

Type of Hormone Use (Number and Row Percentage) and Type of Menopausal Status in Cases and Controls. Women's CARE Study, 1994–1998

	Menopausal Cases, Deceased from Breast Cancer within 6 Years of Diagnosis					Menopausal Controls				
Menopausal status	**Never Any HT**	**ET only**	**CHT only**	**Both CHT & ET**	**Total**	**Never Any HT**	**ET Only**	**CHT Only**	**Both CHT & ET**	**Total**
All	122	83	46	27	278	717	772	484	251	2,224
	44%	30%	17%	10%	100%	32%	35%	22%	11%	100%
Natural	90	11	23	7	131	493	75	207	56	831
	69%	8%	18%	5%	100%	59%	9%	25%	7%	100%
Induced	6	33	1	4	44	67	312	13	67	459
	14%	75%	2%	9%	100%	15%	68%	3%	15%	100%
Known menopausal but unknown type	0	6	0	2	8	5	56	1	25	87
	0%	75%	0%	25%	100%	6%	64%	1%	29%	100%
Menopausal status unclassifiable and age 50 or older	26	33	22	14	95	152	329	263	103	847
	27%	35%	23%	15%	100%	18%	39%	31%	12%	100%
Simple hysterectomy	23	29	1	3	56	130	308	10	37	485
	41%	52%	2%	5%	100%	27%	63%	2%	8%	100%
Menopause obscured by HT use	0	4	20	11	35	0	6	247	60	313
	0%	11%	57%	31%	100%	0%	2%	79%	19%	100%

Table 2

Association of type and duration of hormone therapy (HT) use with fatal breast cancer. Odds Ratios (OR) and 95% confidence intervals (95CI). Women's CARE Study, 1994–1998

		N cases/controls	OR (95CI)
Never Any HT		122 / 717	1.0 ref cat
Only CHT vs never any use of HT	Former, <3yr	8 / 78	.68 (.31, 1.46)
	Current, <3yr	12 / 136	.67 (.35, 1.30)
	Former, 3+ yr	2 / 16	1.02 (.23, 4.59)
	Current, 3+ yr	24 / 250	.83 (.50, 1.38)
Any CHT vs never any use of HT*	Former, <3yr	18 / 189	.72 (.42, 1.23)
	Current, <3yr	19 / 166	.95 (.54, 1.66)
	Former, 3+ yr	4 / 75	.47 (.17, 1.34)
	Current, 3+ yr	32 / 301	.94 (.59, 1.48)
Only ET vs never any use of HT	Former, <3yr	24 / 176	.90 (.55, 1.47)
	Current, <3yr	15 / 122	.87 (.47, 1.60)
	Former, 3+ yr	9 / 57	1.11 (.51, 2.41)
	Current, 3+ yr	35 / 416	.69 (.44, 1.09)
Any ET vs never any use of HT†	Former, <3yr	35 / 249	.97 (.64, 1.48)
	Current, <3yr	18 / 164	.82 (.46, 1.44)
	Former, 3+ yr	15 / 99	1.20 (.65, 2.22)
	Current, 3+ yr	42 / 510	.70 (.45, 1.07)
Any HT (CHT or ET) vs never any HT‡	Former, <3yr	33 / 277	.79 (.52, 1.21)
	Current <3yr	32 / 282	.86 (.54, 1.36)
	Former 3+yr	12 / 96	.96 (.50, 1.86)
	Current, 3+ yr	79 / 844	.81 (.57, 1.15)

*Includes women who used ET before or after CHT

†Includes women who used CHT before or after ET

‡Includes all who used CHT, ET, or both

Table 3

Sensitivity analyses for association between current longer-term use of any estrogen-plus-progestin therapy (CHT) or any estrogen therapy (ET) compared to never any use of hormone therapy (HT), and fatal breast cancer: Odds Ratios (OR) and 95% confidence intervals (95% CI). Women's CARE Study. 1994–1998, Atlanta, Seattle, Los Angeles, Detroit, Philadelphia.

		Any CHT		Any ET	
		N exposed* cases/controls	OR (95% CI)	N exposed* cases/controls	OR (95% CI)
A	Adjusted for age at menopause, type of menopause and screening, as presented in Table 2	32/301	0.94 (0.59, 1.48)	42/510	0.70 (0.45, 1.07)
B	A, also adjusted for <2 times federal poverty level for household income (y/n)	31/291	1.03 (0.64, 1.64)	40/495	0.73 (0.47, 1.13)
C	A, excluding women with unclassifiable menopausal status	10/86	1.16 (0.55, 2.42)	23/298	0.91 (0.47, 1.78)
D	A, but current longer-term use defined as 5+ years	24/220	1.00 (0.60, 1.66)	29/424	0.57 (0.35, 0.93)

* Rows A–C: Current 3+ years of HT use, Row D: Current 5+ years of HT use