Effect of Hormone Replacement Therapy on Breast Cancer Risk: Estrogen Versus Estrogen Plus Progestin

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Background: **Hormone replacement therapy (HRT) given as unopposed estrogen replacement therapy (ERT) gained widespread popularity in the United States in the 1960s and 1970s. Recent prescribing practices have favored combination HRT (CHRT), i.e., adding a progestin to estrogen for the entire monthly cycle (continuous combined replacement therapy [CCRT]) or a part of the cycle (sequential estrogen plus progestin therapy [SEPRT]). Few data exist on the association between CHRT and breast cancer risk. We determined the effects of CHRT on a woman's risk of developing breast cancer in a population-based, case–control study.** ***Methods:*** **Case subjects included those with incident breast cancers diagnosed over 4½ years in Los Angeles County, CA, in the late 1980s and 1990s. Control subjects were neighborhood residents who were individually matched to case subjects on age and race. Case subjects and control subjects were interviewed in person to collect information on known breast cancer risk factors as well as on HRT use. Information on 1897 postmenopausal case subjects and on 1637 postmenopausal control subjects aged 55–72 years who had not undergone a simple hysterectomy was analyzed. Breast cancer risks associated with the various types of HRT were estimated as odds ratios (ORs) after adjusting simultaneously for the different forms of HRT and for known risk factors of breast cancer. All *P* values are two-sided.** ***Results:*** **HRT was associated with a 10% higher breast cancer risk for each 5 years of use (OR_5 = 1.10; 95% confidence interval [CI] = 1.02–1.18). Risk was substantially higher for CHRT use (OR_5 = 1.24; 95% CI = 1.07–1.45) than for ERT use (OR_5 = 1.06; 95% CI = 0.97–1.15). Risk estimates were higher for SEPRT (OR_5 = 1.38; 95% CI = 1.13–1.68) than for CCRT (OR_5 = 1.09; 95% CI = 0.88–1.35), but this difference was not statistically significant.** ***Conclusions:*** **This study provides strong evidence that the addition of a progestin to HRT enhances markedly the risk of breast cancer relative to estrogen use alone. These findings have important implications for the risk–benefit equation for HRT in women using CHRT. [J Natl Cancer Inst 2000; 92:328–32]**

Hormone replacement therapy (HRT) in the form of unopposed (without progestins) estrogen replacement therapy (ERT) gained widespread popularity in the United States in the 1960s and early 1970s. In the peak year of 1974, 28 million prescriptions were filled for noncontraceptive use of estrogens *(1)*. The first definitive studies *(2,3)* demonstrating a causal relationship between endometrial cancer and ERT were published in 1975. The increased incidence of endometrial cancer among women using ERT led initially to a marked decline in the number of prescriptions of this category of drugs, followed by increases when new strategies for delivering HRT were defined to protect the endometrium from the carcinogenic effects of unopposed estrogen. Accordingly, combination hormone replacement therapy (CHRT), in which a progestin is given with an estrogen either sequentially or continuously during a monthly cycle, has grown rapidly in popularity *(4)*.

The use of CHRT has necessitated a re-examination of the risk–benefit equation associated with HRT *(5)*. We recently provided *(6)* the most definitive results to date that CHRT, whether given as continuous combined therapy (CCRT, estrogen and progestin prescribed together during each day of the monthly cycle in which HRT is taken) or sequential estrogen and estrogen plus progestin therapy (SEPRT), with the progestin given for 10

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or more days per month, are associated with little or no increased risk of endometrial cancer. Although CHRT is more widely prescribed to women with an intact uterus, it is sometimes prescribed to women who have had hysterectomy, possibly because of the belief that progestins will also negate any carcinogenic effects of estrogens on the breast *(7)*. Studies *(8)* of mitotic activity in the breast during the normal menstrual cycle cast doubt on this premise, however, since mitotic activity peaks at the time of maximum serum progesterone. Direct evidence that progestins may actually be harmful in terms of breast cancer risk was first presented in the mid-1980s, when results from a cohort study of Swedish women were published suggesting that women who received CHRT for more than 6 years had a 4.4-fold increased risk of breast cancer *(9)*. No increased risk was observed with shorter term use, however, and the 4.4-fold increased risk was based on only 10 patients and did not achieve statistical significance. A subsequent report on this cohort with more precise risk estimates showed a more modest 1.6-fold increase in risk with more than 6 years of CHRT use *(10)*. There have been additional papers describing results on CHRT use and breast cancer risk but none with substantial statistical power or great detail on CHRT usage patterns *(11)*.

We have conducted a population-based, case–control study designed primarily to determine the effects of CHRT use on breast cancer risk. We report here the results based on interviews of 2653 breast cancer patients and 2429 control subjects. This study provides the most definitive and detailed data yet available on the relationship between CHRT use and breast cancer risk.

Subjects and Methods

For this study, breast cancer patients were identified by the Cancer Surveillance Program (CSP), the population-based cancer registry of Los Angeles County, CA. Registration is estimated to be more than 98% complete *(12)*. Since June 1987, the CSP has been part of the statewide California Cancer Registry, whose methodology for ascertainment and quality control has been previously described *(13)*. In 1992, the CSP became part of the National Surveillance, Epidemiology, and End Results (SEER)[1] Program of the U.S. National Cancer Institute, Bethesda, MD.

Qualifying case subjects included female patients with a diagnosis of breast cancer of epithelial origin registered by the CSP who were English-speaking residents of Los Angeles County. Cases were ascertained in three diagnostic periods. Group I case subjects were first diagnosed during the period from March 1, 1987, through December 31, 1989; these case subjects were white (including Hispanic); were born in the United States, Canada, or Western Europe; and were aged 55–64 years at first diagnosis. Group II case subjects were first diagnosed during the period from January 1, 1992, through December 31, 1992; these case subjects were also white (including Hispanic) or African-American, were born in the United States, and were aged 55–69 years at first diagnosis. Group III case subjects were first diagnosed during the period from September 1, 1995, through April 30, 1996; these case subjects were white (including Hispanic) or African-American, were born in the United States, and were aged 55–72 years at first diagnosis. This sequence of data collection was adopted to make maximal use of personnel and other resources. Since CHRT first became popular in the late 1970s and early 1980s, changing the targeted age range over time also maximized the likelihood of long-term use of CHRT. Interviews were completed with 2653 of the 3976 qualifying patients. We sought physician approval before initiating patient contact, but 144 physicians (4%) refused, as did 794 patients (20%) themselves. An additional 385 patients (10%) had died or were too ill to participate at the time we contacted them (Table 1). All patients were generally interviewed within 1 year of diagnosis.

Control women were individually matched to case subjects by age (±3 years), race–ethnicity, and neighborhood of residence (hence, roughly by social class). These neighborhood control subjects were identified by "control walkers" who followed a predetermined algorithm beginning with a residence bearing a specific relationship to the residence of the patient at her time of diagnosis. The walkers proceeded though a sequence of houses, canvassing each until a matched control subject was identified. Matched control subjects were interviewed for 2429 patients (Table 1); no matched control subject was found for 224 patients. The first qualifying control subject refused to participate in 536 instances and an additional matched control subject was sought. The median number of households canvassed before a qualifying control subject was identified was 33.

Data Collection

Each participant was interviewed in person in her home. Each case–control pair was generally interviewed by the same interviewer. The interview took about three quarters of an hour to complete, was highly structured, and obtained information on demographics, physical characteristics, menstrual and reproductive experiences, physical exercise activity, benign breast disease history, family history of breast cancer, use of mammographic screening, history of smoking, alcohol and caffeine consumption, and a detailed history of use of HRT and oral contraceptives. Exposure histories were ascertained up to 1 year before the diagnosis date (reference date) of the breast cancer patient, both for the patient herself and for her matched control subject. An album of color photographs of exogenous hormones marketed in the United States was available as an aid to facilitate recall of specific hormone preparations used by the respondent. The respondents were asked to sign an informed consent form outlining the study's purpose, procedures, benefits, and risks that was reviewed and approved on an annual basis by the federally designated University of Southern California School of Medicine Institutional Review Board.

Statistical Analyses

Women undergoing a hysterectomy without oophorectomy (simple hysterectomy) before menopause were excluded from all analyses related to HRT, since we have demonstrated that alternative methods for assigning an age at menopause to such women will lead to substantially biased estimates of

Table 1. Summary of results of recruitment of breast cancer case patients and control subjects in the study

No. of case patients eligible		3976	No. of control subjects sought		2653
Died or too ill to participate	385		None found	224	
Physician refusal	144		Interviewed		2429
Patient refusal	794		1st match	1893	
Interviewed		2653	2nd match	394	
No. excluded from final analysis			3rd match	142	
Premenopausal at reference date	104		(median household units walked = 33)*		
Simple hysterectomy	599		Excluded from final analysis		
Last menstrual period, age <35 y	29		Premenopausal at reference date	67	
Radiotherapy to pelvic area	3		Simple hysterectomy	537	
Missing key data/other	21		Last menstrual period, age <35 y	23	
Total analyzed		1897	Radiotherapy to pelvic area	1	
			Missing key data/other	18	
			Aged <55 y or >72 y	146	
			Total analyzed		1637

*The median number of households canvassed before a qualifying control subject was identified was 33.

HRT effects on breast cancer risk *(14)*. Premenopausal women were also excluded.

Age at last menstrual period cannot be used to uniformly estimate age at menopause, since women who use SEPRT usually continue to have monthly menstrual periods, irrespective of their ovarian function, and women on ERT and CCRT can rarely distinguish breakthrough bleeding from ovarian function-determined menses. For a woman taking HRT before her reported age at last menstrual period, we set her age of menopause as the year in which she began HRT use *(6)*, with the rationale that HRT use was started because of menopausal symptoms. For women taking oral contraceptives, age at menopause was taken as the end of the period of oral contraceptive use, if no natural menstruation occurred thereafter. Natural menstruation was taken to mean menstruating and not using oral contraceptives or HRT at the time. This is the same schema to approximate age at menopause as we used in our earlier study of HRT and endometrial cancer *(6)*.

Statistical analyses were conducted using standard conditional multivariate logistic regression techniques *(15)* by use of the EPILOG statistical package program (Epicenter Software, Pasadena, CA). Although the study was designed as a matched case–control study, because of the large number of exclusions, we report results using a stratified analytic approach by use of strata formed from 2-year "age at reference date" by 2-year "year of birth" by four "socioeconomic status" divisions (based on the average educational and income levels in the geographic area of residence) and three ethnicity groupings. Because of this strategy, control subjects under the age of 55 years and over the age of 72 years were also excluded. Matched analyses of the case–control pairs in which both were eligible for inclusion produced similar risk estimates to the stratified risk estimates reported here. All of the reported risk estimates were adjusted for the major risk factors of breast cancer: type of menopause (natural versus bilateral oophorectomy), age at natural menopause (continuous variable), age at bilateral oophorectomy (continuous variable), age at menarche (continuous variable), family history of breast cancer in mother or daughter (yes/no), personal history of benign breast disease (yes/no), nulliparity (yes/no), age at first full-term pregnancy (continuous variable), duration of oral contraceptive use (continuous variable), weight (continuous variable), and drinks of alcohol per week (continuous variable). All *P* values determining statistical significance are two-sided.

Tumor stage was determined by a review of all original pathology reports and cancer registry abstracts, both of which are routinely collected by the CSP.

RESULTS

HRT was used by 54% of the 1897 breast cancer patients included in the analysis and by 52% of the 1637 control subjects. The 1897 patients averaged 46.3 months of HRT use compared with 42.9 months for control subjects. The majority of HRT use was unopposed ERT, with conjugated equine estrogen in relatively low doses ($\leq$0.625 mg/day) being the most popular formulation and dose. Combination therapy was more commonly prescribed sequentially, usually in combination with 0.625 mg of conjugated equine estrogen. Sequential use was roughly 50% more common among control women in this population than continuous combined therapy. Medroxyprogesterone acetate comprised the great majority of all progestin use.

The association between breast cancer risk and months of use of any form of HRT is shown in Table 2. Breast cancer risk increased 10% per 5 years of use of HRT (odds ratio $[OR]_5 = 1.10$; 95% confidence interval [CI] = 1.02–1.18; $P = .015$). Although the observed risk did not increase monotonically with increasing months of use, the data are compatible with a steady increase in risk with increasing duration of HRT use. After 15 years of use, the observed breast cancer risk was increased 36%.

ERT use was not associated with breast cancer risk except in long-term users (OR for $\geq$15 years of use = 1.24; Table 2). The data are, however, compatible with a steady increase in risk of 6% per 5 years of ERT use ($OR_5 = 1.06$; 95% CI = 0.97–1.15; $P = .18$), although this result is not statistically significant. Relative risks were higher in thin women than in heavy women (data not shown).

Breast cancer risk was increased much more substantially, however, with the use of CHRT (Table 2). Risk increased consistently with increasing duration of CHRT use, with an OR of 1.51 associated with use for 10 or more years. The estimated risk per 5 years of use was 1.24 (95% CI = 1.07–1.45; $P = .005$).

Risk appeared to be higher with SEPRT than with CCRT, but the difference was not statistically significant (Table 3). For SEPRT, the observed risk associated with 10 or more years of use was 1.79; the comparable risk for CCRT was 1.23. The OR per 5 years of SEPRT use was 1.38 (95% CI = 1.13–1.68; $P = .0015$) compared with 1.09 (95% CI = 0.88–1.35; $P = .44$) for CCRT, but this difference was not statistically significant.

Among the 1897 breast cancer patients, 186 presented with *in situ* disease, 1116 had their cancer confined to the breast at the time of diagnosis, 566 had regional lymph node involvement or metastatic disease, and 29 had unknown stage. Risks per 5 years of use of various HRT categories by pathologic stage are shown in Table 4. For ERT, excess risk was confined almost entirely to *in situ* disease ($OR_5 = 1.41$; 95% CI = 1.18–1.69). On the other hand, for CHRT, risks were comparable across all stages at presentation. We also included mammographic screening (never, within 1 year, and >1 year ago) as a covariate in our risk estimate models as an alternative method of determining whether observed risk differences might be due to different screening behaviors in HRT users and nonusers.

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer in relation to duration of use of any HRT and to duration of use of ERT and CHRT*

HRT type	Months of use	No. of case patients	No. of control subjects	OR	Two-sided *P*†
No HRT		873	784	1.00 (referent)	
Any HRT‡	1–60	475	406	1.07	
	61–120	236	186	1.21	
	121–180	151	140	1.14	
	$\geq$181	162	121	1.36	
			Per 5 y	1.10 (95% CI = 1.02–1.18)	.015
ERT§	1–60	353	304	1.02	
	61–120	151	136	0.94	
	121–180	105	105	0.93	
	$\geq$181	133	103	1.24	
			Per 5 y	1.06 (95% CI = 0.97–1.15)	.18
CHRT§	1–60	277	224	1.11	
	61–120	98	66	1.51	
	$\geq$121	50	34	1.51	
			Per 5 y	1.24 (95% CI = 1.07–1.45)	.005

*HRT = hormone replacement therapy; ERT = estrogen replacement therapy; and CHRT = combination hormone replacement therapy.

†*P* value ascertained from the difference in log-likelihood with and without variable of interest.

‡Adjusted for type of menopause and age at menopause, age at menarche, family history of breast cancer, history of benign breast disease, nulliparity, age at first full-term pregnancy, use of oral contraceptives, body weight, and alcohol use.

§Additionally adjusted simultaneously for ERT and CHRT use.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer in relation to duration of use of SEPRT and CCRT*

HRT type	Months of use	No. of case patients	No. of control subjects	OR	Two-sided *P*†
No HRT		873	784	1.00 (referent)	
SEPRT‡	1–60	218	166	1.19	
	61–120	75	48	1.58	
	⩾121	27	14	1.79	
			Per 5 y	1.38 (95% CI = 1.13–1.68)	.0015
CCRT‡	1–60	59	58	0.88	
	61–120	23	18	1.28	
	⩾121	23	20	1.23	
			Per 5 y	1.09 (95% CI = 0.88–1.35)	.44

*HRT = hormone replacement therapy; SEPRT = sequential estrogen plus progestin replacement therapy; and CCRT = continuous combined replacement therapy.

†*P* value ascertained from the difference in log-likelihood with and without variable of interest.

‡Adjusted for type of menopause and age at menopause, age at menarche, family history of breast cancer, history of benign breast disease, nulliparity, age at first full-term pregnancy, use of oral contraceptives, body weight, and alcohol use and adjusted simultaneously for each type of HRT use shown and ERT use.

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs) for breast cancer per 5 years of use of different types of HRT in relation to pathologic stage at diagnosis*

	Stage			
HRT type	All	*In situ*	Localized	Advanced
No. of case patients†	1897	186	1116	566
HRT, OR (95% CI)‡	1.10 (1.02–1.18)	1.36 (1.15–1.61)	1.08 (0.99–1.18)	1.03 (0.92–1.15)
ERT, OR (95% CI)§	1.06 (0.97–1.15)	1.41 (1.18–1.69)	1.03 (0.94–1.13)	0.98 (0.87–1.11)
CHRT, OR (95% CI)§	1.24 (1.07–1.45)	1.10 (0.76–1.60)	1.26 (1.06–1.49)	1.22 (0.98–1.51)
SEPRT, OR (95% CI)¶	1.38 (1.13–1.68)	1.07 (0.64–1.79)	1.44 (1.16–1.78)	1.32 (0.99–1.76)
CCRT, OR (95% CI)¶	1.09 (0.88–1.35)	1.14 (0.69–1.88)	1.03 (0.80–1.33)	1.12 (0.83–1.52)

*HRT = hormone replacement therapy; ERT = estrogen replacement therapy; CHRT = combination hormone replacement therapy; SEPRT = sequential estrogen plus progestin replacement therapy; and CCRT = continuous combined replacement therapy.

†Twenty-nine patients had disease of unknown stage.

‡Adjusted for type of menopause and age at menopause, age at menarche, family history of breast cancer, history of benign breast disease, nulliparity, age at first full-term pregnancy, use of oral contraceptives, body weight, and alcohol use.

§Additionally adjusted simultaneously for ERT and CHRT use.

¶Additionally adjusted simultaneously for ERT, SEPRT, and CCRT use.

The OR for CHRT (per 5 years of use) actually increased slightly (from 1.24 to 1.27).

We explored whether the effect of CHRT on breast cancer risk might be restricted to current users, as has been suggested by others concerning ERT use *(16)*. CHRT is a relatively recent phenomenon so that most users were either current users or had ceased usage only in the recent past. Nonetheless, there was no clear difference in risk level between current users and those who had stopped use at least 2 years previously (data not shown).

There were substantial missing data on progestin dose, but data on conjugated equine estrogen dose were quite complete. Risks were generally modestly higher with increasing estrogen dose (data not shown).

DISCUSSION

The results of this study on the relationship between ERT and breast cancer are compatible with the conclusions of a recent meta-analysis *(11)* and other summary assessments *(17,18)* of the extensive literature on this subject. We designed this study to have high statistical power, to conduct careful adjustment for potential confounders, including especially age at menopause, to make careful and systematic collection of detailed exposure histories, and to make use of healthy and closely age-related population control subjects *(19)*. In particular, possible differences in HRT use by socioeconomic status, age, calendar year, or ethnicity were controlled in analysis by stratification.

This study provides detailed data on the effects of an added progestin on breast cancer risk. These data strongly refute the notion that progestins will be protective against breast cancer development *(20)*, a belief that has persisted despite the absence of any strong biologic rationale for an antiestrogenic, anticancer effect of progestins on the breast. In fact, this study provides the strongest evidence to date that progestins not only do not protect the breast from the carcinogenic effects of estrogen but also increase substantially the small ERT-related increase in breast cancer risk. The biologic effects of progestins on the breast, while not extensively studied, support the observations in this study that progestins may enhance breast cancer risk. As noted above, maximum mitotic activity in breast tissue occurs in the mid-to-late luteal phase of the menstrual cycle, at the time of maximum progesterone levels *(8)*. This situation is clearly different from that in the endometrium where the influence of progesterone during the luteal phase of the cycle is to inhibit any further mitotic activity.

The relationship between mammographic density patterns and breast cancer risk is well established *(21)*. Mammographic densities were measured as part of the Postmenopausal Estrogen/Progestin Interventions Trial *(22)*. In this trial, 875 postmenopausal women were assigned to either placebo or 0.625-mg conjugated equine estrogen alone or in combination with medroxyprogesterone acetate either as SEPRT or as CCRT. There was a much greater increase in mammographic densities in women treated with SEPRT or CCRT than in those treated with ERT. There was little difference between women on sequential versus continuous combined therapy, however. To the extent that mammographic densities are a reliable predictor of breast cancer, these data strongly support an added impact of progestin on the breast cancer risk associated with ERT.

Risks associated with CCRT in this study tended to be substantially less than those associated with SEPRT. However, these differences are compatible with chance, and the results of the Postmenopausal Estrogen/Progestin Intervention Trial described above found no differences between SEPRT and CCRT on mammographic densities. However, because the differences in the observed ORs in the current study are sufficiently large, it would seem prudent to consider the

possibility that these differences are real and have an underlying biologic basis. One explanation might be that standard regimens for CCRT call for lower daily doses of progestins (typically, 2.5 mg of medroxyprogesterone acetate) than sequential therapy (typically, 5–10 mg). Alternatively, these data suggest that the effect of added progestin on breast cancer risk might be greater after "priming" of tissue by unopposed estrogen. Estrogen stimulation *in vitro* results in increased cellular progesterone receptor content, whereas constant progesterone stimulation, even with estrogen present (as in CCRT), reduces progesterone receptor synthesis and/or increases progesterone receptor degradation *(23)*.

Even with a slight increased risk of breast cancer and a more substantial increased risk of endometrial cancer, the overall risk–benefit equation for ERT balances strongly on the side of benefit *(24)*, primarily because of the marked reduction in risk from cardiovascular disease. We have calculated that, for each incident case of breast cancer in women due to long-term ERT use, more than six deaths from heart disease are prevented; moreover, mortality overall is substantially reduced in women using ERT *(25)*. Unfortunately, the sparse available epidemiologic data, in particular with regard to heart disease risk, limit similar calculations for CHRT, but it is clear from the data presented here that the overall risk–benefit equation will be considerably less favorable than for ERT. If the main purpose for prescribing CHRT is to protect the endometrium from the carcinogenic effects of estrogen, then this study would argue that the adverse effect on the breast may outweigh the beneficial effect on the endometrium, at least in terms of cancer morbidity and mortality. Women who are candidates for HRT should be provided with this information as well as that on other established risks and benefits associated with various types of HRT and should also be told where uncertainty still exists in the risk–benefit equation.

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NOTES

[1]*Editor's note:* SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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