Hormone Replacement Therapy After a Diagnosis of Breast Cancer in Relation to Recurrence and Mortality

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Background: **Hormone replacement therapy (HRT) is typically avoided for women with a history of breast cancer because of concerns that estrogen will stimulate recurrence. In this study, we sought to evaluate the impact of HRT on recurrence and mortality after a diagnosis of breast cancer.** ***Methods:*** **Data were assembled from 2755 women aged 35–74 years who were diagnosed with incident invasive breast cancer while they were enrolled in a large health maintenance organization from 1977 through 1994. Pharmacy data identified 174 users of HRT after diagnosis. Each HRT user was matched to four randomly selected nonusers of HRT with similar age, disease stage, and year of diagnosis. Women in the analysis were recurrence free at HRT initiation or the equivalent time since diagnosis. Rates of recurrence and death through 1996 were calculated. Adjusted relative risks were estimated by use of the Cox regression model. All statistical tests were two-sided.** ***Results:*** **The rate of breast cancer recurrence was 17 per 1000 person-years in women who used HRT after diagnosis and 30 per 1000 person-years in nonusers (adjusted relative risk for users compared with nonusers = 0.50; 95% confidence interval [CI] = 0.30 to 0.85). Breast cancer mortality rates were five per 1000 person-years in HRT users and 15 per 1000 person-years in nonusers (adjusted relative risk = 0.34; 95% CI = 0.13 to 0.91). Total mortality rates were 16 per 1000 person-years in HRT users and 30 per 1000 person-years in nonusers (adjusted relative risk = 0.48; 95% CI = 0.29 to 0.78). The relatively low rates of recurrence and death were observed in women who used any type of HRT (oral only = 41% of HRT users; vaginal only = 43%; both oral and vaginal = 16%). No trend toward lower relative risks was observed with increased dose.** ***Conclusion:*** **We observed lower risks of recurrence and mortality in women who used HRT after breast cancer diagnosis than in women who did not. Although residual confounding may exist, the results suggest that HRT after breast cancer has no adverse impact on recurrence and mortality. [J Natl Cancer Inst 2001;93: 754–62]**

The use of hormone replacement therapy (HRT)—noncontraceptive estrogens with or without a progestogen—in women with a history of breast cancer is controversial *(1,2).* Estrogens have proliferative effects on the breast and are implicated in the development of breast cancer *(3).* In theory, breast cancer cells might grow and disseminate under the influence of estrogen. But whether HRT promotes the spread of established breast cancer is not known *(4).*

Breast cancer treatment can induce menopause or its symptoms. Adjuvant chemotherapy causes ovarian failure in many premenopausal patients *(5,6),* and tamoxifen often promotes vasomotor and vaginal symptoms *(7,8).* Although nonhormonal alternatives to HRT are available *(9–13),* at this time, none are known to be as effective as HRT in the management of menopausal symptoms *(12,13).* Selective estrogen receptor modulators, such as raloxifene, have beneficial effects on bone and lipid profiles *(11,14),* but they can aggravate menopausal symptoms *(14).* Thus, despite the potential for harm, HRT is used by some women after a diagnosis of breast cancer. The present study was designed to explore the influence of such use on recurrence and mortality.

Subjects and Methods

Study Population

This study was set within the Group Health Cooperative of Puget Sound, Seattle, WA, which is a health maintenance organization currently serving more than 400 000 residents of western Washington state. This record-based study was approved by the Institutional Review Board. Group Health Cooperative enrollees are representative of the surrounding population with respect to age, race/ethnicity, and marital status, although they have slightly higher levels of education on average *(15).* Female enrollees diagnosed with invasive carcinoma of the breast at ages 35–74 years from 1977 through 1994 were identified retrospectively in the records of the Cancer Surveillance System, a population-based cancer registry operating as part of the Surveillance, Epidemiology, and End Results (SEER) Program[1] of the National Cancer Institute. We excluded women with distant metastatic disease at diagnosis and women with a prior diagnosis of *in situ* or invasive breast cancer. The cohort comprised 2755 women who met these criteria.

Data Collection

The Cancer Surveillance System provided data on tumor characteristics at diagnosis, including the site, histology, and extent of disease (tumor size, extension, and lymph node status) and the first course of cancer treatment (surgery, radiation therapy, chemotherapy, and/or hormonal therapy). The Cancer Surveillance System was our primary source of vital status data, including date of death, cause of death from death certificates, or date of last physician contact. Cause-of-death information was available for 91% of women in the cohort who died by the end of 1996.

Group Health Cooperative pharmacy data were used to ascertain the use of HRT after a diagnosis of breast cancer. The pharmacy database contains records of all prescriptions filled at Group Health Cooperative outpatient pharmacies since 1977. Survey data show that 96% of female enrollees fill their prescriptions at these pharmacies *(15).* Pharmacy data were also obtained on tamoxifen and HRT use before diagnosis. The chronic disease score, a proxy measure of comorbidity based on 6 months of prescription data *(16,17),* was calculated as of 1 year before diagnosis.

Medical records at the Group Health Cooperative were reviewed to ascertain the following factors: parity, gravidity, and age at first full-term pregnancy; age at menarche; age at and reason for cessation of menses; menopausal symptoms; hysterectomy; oophorectomy; smoking history at diagnosis; family history of breast cancer; height and weight at diagnosis; and HRT use before diagnosis, including age started and duration of use. We ascertained

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See "Notes" following "References."

whether the breast cancer was first suspected on mammographic screening. Results from estrogen and progesterone receptor assays were abstracted and classified as positive or negative as interpreted by the laboratory or physician. When a summary interpretation was not available, we classified the result as positive if the receptor was measured in concentrations of at least 10 fmol/mg or at least 3% of cells were positive. Treatments received for the initial breast cancer were ascertained.

Women who had a hysterectomy without bilateral oophorectomy or prior natural menopause were classified as postmenopausal if age 50 years or older. Age 50 years was chosen in accord with the median age of menstrual cessation among women in the cohort known to have had a natural menopause. Women who had menstruated within the previous 6 months were classified as premenopausal, unless they were also using HRT. Because HRT users may experience cycling due to the drug, their menopausal status is difficult to determine. Women with recent menstruation who were using HRT were classified as postmenopausal if 50 years old or older, as were women whose charts did not contain sufficient data to classify age at menopause.

Medical charts were our primary source of data on breast cancer recurrence. Recurrence was defined as invasive disease confined to the ipsilateral breast (22% of diagnosed recurrences) or metastasis. New primary contralateral breast cancers were not included in this definition.

Use of HRT After Breast Cancer

We assessed the impact of HRT use in women with a history of breast cancer who appeared to be free of disease. Women who used HRT during the period from diagnosis to the first medical recognition of invasive recurrent breast cancer, or the end of 1996, were included. To be considered a user, the woman was required to have filled at least two prescriptions for an HRT medication containing estrogen within a 6-month interval, any time after her initial diagnosis and before diagnosed recurrence. HRT initiation was defined to occur on the date that the second prescription was filled. The presence of a second fill within 6 months increases our confidence that the drug was actually taken. According to pharmacy data, 206 women (7.5% of the cohort) met this definition of HRT use; 32 of these women were ineligible for the following reasons found on chart review: 18 had recurrent breast cancer diagnosed before HRT initiation, four took HRT as part of an experimental treatment for locally advanced breast cancer, six had prior breast cancer not already identified, three had charts that were missing, and the source of the primary tumor was undetermined for one. Thus, we identified 174 eligible HRT users.

The cumulative use of HRT since diagnosis was estimated. A run-out time for each oral HRT prescription was determined on the basis of the number of pills dispensed and the prescribing instructions. Run-out times were summed to yield total months of use. Because entry into observation occurred at the second of two prescriptions, users entered with the duration accrued since the first prescription. Adherence to the prescribed regimen was assumed. The cumulative dose of oral HRT was estimated in a similar manner. Prescription doses were converted to conjugated-estrogen dose equivalents. [Equivalence to 0.625 mg of conjugated estrogens has been determined at 0.625 mg for esterified estrogens and 0.05 mg for ethinyl estradiol *(18).*] Cumulative use of vaginal HRT was measured by summing the number of tubes of estrogen cream dispensed from the pharmacy.

Nonusers

A comparison group of nonusers of HRT was randomly selected from the cohort. Because users were required to be enrolled in the Group Health Cooperative and to be free of diagnosed recurrence when they initiated HRT, we required that nonusers meet the same conditions at the equivalent time since diagnosis. To do this, we matched a set of four nonusers to each user at a defined reference date marking the start of observation. For users, the reference date was the date of HRT initiation. For nonusers, the reference date was based on the interval between diagnosis and HRT initiation in the matched user. Thus, nonusers were restricted to those with a recurrence-free interval at least as long as the interval from diagnosis to HRT initiation in the matched user. With this approach, we sought to maintain comparability between users and nonusers with respect to lack of disease progression at the start of follow-up. Users and nonusers were also matched on age at diagnosis (35–44 years, 45–54 years, 55–64 years, or 65–74 years), year of diagnosis (1977–1982, 1983–1988, or 1989–1994), and stage at diagnosis (I, II, or III) *(19).* Of 793 potential nonusers selected at random (within matching criteria), the following 98 were excluded for reasons found on medical chart review: 55 had recurrent breast cancer diagnosed before reference, 27 had prior breast cancer not already identified, 12 had charts that were missing, three were found to have breast cancers that were not carcinomas, and one chart noted the patient's refusal to participate in research. This left 695 matched nonusers for analysis.

Statistical Analysis

We compared users and nonusers of HRT after breast cancer with respect to breast cancer recurrence, breast cancer mortality, and total mortality. Follow-up began at the reference date. For the analysis of recurrence, observations were censored at the time of death, disenrollment from the Group Health Cooperative, or the end of 1996. For mortality analyses, observations were censored at the end of 1996 or, for breast cancer mortality analyses, at the time of death from another cause. Women were followed for a median of 3.7 years for recurrence and 4.6 years for mortality.

Rates of recurrence and death were calculated among users and nonusers by dividing the number of events by the total person-time at risk. Because time at risk began at the reference date, rates were calculated among women who had remained free of recurrence as of that date. Unadjusted relative risks (rate ratios) were obtained by dividing the event rate in users by that in nonusers. Multivariate associations were estimated by using the Cox regression model *(20).* Relative risks (hazard ratios) and 95% confidence intervals (CIs) were calculated, adjusting for influential factors. To assess confounding, we added a factor to the model and examined its effect on the relative risk associated with HRT use. Potentially confounding or modifying factors examined included the following: age, year, and disease stage at diagnosis; age at reference; time from diagnosis to reference; characteristics of the initial tumor including lymph node involvement, size, histology (ductal or other), and estrogen and progesterone receptor status; whether the cancer was first identified by screening; treatments received for the initial cancer, including surgery, radiation therapy, chemotherapy, and hormonal therapy; height; weight; body mass index; smoking status; marital status; family history of breast cancer; race/ethnicity; age at menarche; number of prior pregnancies and full-term pregnancies; age at first full-term pregnancy; hysterectomy; oophorectomy; menopausal status, age at menopause, and time since menopause; prior HRT use, its duration, and age at first use; and the chronic disease score. We adjusted for matching by using risk set stratification, which allows baseline hazards to vary freely between matched sets. A global test of the proportional hazards assumption that the relative risks are constant over time was performed *(21).*

Because oral HRT and vaginal HRT may represent different exposures, we analyzed the data comparing nonusers with users of any HRT, users of any oral HRT, and users of vaginal HRT only. For analyses of dose and duration, HRT was modeled as a time-dependent covariate for which cumulative use was updated at each prescription date. Categories of cumulative use for analysis were chosen on the basis of approximate equivalence of person-years between categories.

Nonusers were sampled without regard to HRT use after the reference date; we required only that a nonuser had not used HRT after diagnosis and before her assigned reference date. Thirty-two women randomly selected as nonusers went on to use HRT. At HRT initiation, each of these women was censored from her original, nonusing matched set. She then re-entered the analysis as a user and was matched to her own set of nonusers. Thus, her contribution to the analysis as a nonuser stops at the time that she initiated HRT. Her subsequent follow-up experience reflects her new status as a user. By not omitting subsequent users from the pool of nonusers for comparison, we avoided exaggerating any underlying differences between exposure groups. A selected nonuser also remained in the pool of potential matches for other HRT users. Random sampling resulted in 120 women serving as matched nonusers for more than one user. Analyses included these women in each matched set for which they were selected. In Cox models, variances for the estimated parameters were adjusted to account for data clustering from this source *(21).* Stata *(21)* and SAS *(22)* data management and statistical software were used. All statistical tests were two-sided.

RESULTS

More than 1900 prescriptions for HRT were filled after breast cancer diagnosis by the 174 HRT users identified (Table 1). Vaginal preparations accounted for 38% of HRT prescriptions. Among the users, 41% obtained only oral HRT, 43% obtained only vaginal HRT, and 16% obtained both oral and vaginal HRT. The extent of HRT use after breast cancer is

Table 1. Hormone replacement therapy (HRT) prescriptions filled after a diagnosis of breast cancer and before diagnosed recurrence (Group Health Cooperative, 1977–1996)

Route of HRT administration	Estrogen type	No. of prescriptions* (% of total)
Oral		1182 (62)
	Conjugated	562
	Esterified	543
	Ethinyl estradiol	77
Vaginal		728 (38)
	Conjugated	442
	Dienestrol	286
Topical	Estradiol	3 (<1)
Total		1913 (100)

*Prescriptions filled after the initial breast cancer diagnosis and before diagnosed recurrence (or the end of 1996) among 174 women who used HRT after breast cancer.

summarized in Table 2. The median duration of oral HRT use during follow-up was 15 months. Estrogens were unopposed by progestogens for 79% of the users; the rest combined a progestogen with estrogen for at least one monthly cycle.

The characteristics of the women who did and did not use HRT after breast can-

Table 2. Extent of hormone replacement therapy (HRT) use after a diagnosis of breast cancer (Group Health Cooperative, 1977–1996)

Oral HRT	Duration, mo*	% of oral users
	1–6	16
	7–12	20
	13–24	29
	25–60	22
	>60	12
	Total dose, mg†	**% of oral users**
	>0–150	24
	>150–300	32
	>300–600	20
	>600–900	9
	>900	14
Vaginal HRT	**No. of tubes‡**	**% of vaginal users**
	2	19
	3–4	25
	5–9	35
	10–19	11
	>19	11

*Estimated total duration of oral estrogen use accrued during follow-up by each of the 98 users of oral HRT.

†Estimated total dose of oral estrogens taken during follow-up by each of the 98 users of oral HRT, in conjugated-estrogen dose equivalents *(18).*

‡Number of tubes of vaginal estrogen cream dispensed during follow-up to each of the 75 users of only vaginal HRT.

Table 3. Characteristics of 174 users and 695 nonusers of hormone replacement therapy (HRT) after a diagnosis of breast cancer (Group Health Cooperative, 1977–1996)

Characteristic	Users, No. (%)*	Nonusers, No. (%)*
Age at diagnosis, y		
35–44	20 (11)	80 (12)
45–54	36 (21)	144 (21)
55–64	54 (31)	216 (31)
65–74	64 (37)	255 (37)
Age at reference, y		
<50	20 (11)	88 (13)
50–59	42 (24)	159 (23)
60–69	54 (31)	212 (31)
⩾70	58 (33)	236 (34)
Time from diagnosis to reference, y		
<1	47 (27)	188 (27)
1–2	46 (26)	184 (26)
3–7	44 (25)	175 (25)
⩾8	37 (21)	148 (21)
Year of diagnosis		
1977–1982	49 (28)	196 (28)
1983–1988	70 (40)	280 (40)
1989–1994	55 (32)	219 (32)
Stage at diagnosis		
I	91 (52)	403 (58)
II	51 (29)	246 (35)
I/II†	20 (11)	3 (<1)
III	10 (6)	42 (6)
II/III†	2 (1)	1 (<1)
Lymph nodes involved	31 (18)	175 (25)
Missing data	15 (9)	50 (7)
Tumor size >2 cm	40 (23)	206 (30)
Missing data	24 (14)	16 (2)
Ductal histology	130 (75)	540 (78)
Estrogen receptor positive at diagnosis	84 (48)	409 (59)
Missing data	51 (29)	149 (21)
Progesterone receptor positive at diagnosis	71 (41)	311 (45)
Missing data	58 (33)	178 (26)
Cancer first identified on screening mammogram	41 (24)	159 (23)
Missing data	1 (1)	6 (1)
Mastectomy (total or radical)	87 (50)	300 (43)
Radiation therapy	99 (57)	419 (60)
Chemotherapy	30 (17)	153 (22)
Tamoxifen	23 (13)	167 (24)
History of breast cancer in mother, sister, or daughter noted in medical chart	36 (21)	136 (20)
Median chronic disease score‡	*1091*	*1044*
Missing data	18 (10)	85 (12)
Current smoker at diagnosis	37 (21)	160 (23)
Missing data	1 (1)	10 (1)
Median body mass index, kg/m^2	*24.0*	*24.7*
Missing data	0 (0)	4 (1)
Hysterectomy before reference date	89 (51)	228 (33)
Bilateral oophorectomy before reference date	43 (25)	108 (16)
Before diagnosis	32 (18)	100 (14)
After diagnosis	11 (6)	8 (1)
Menopause induced by radiation therapy or chemotherapy	7 (4)	39 (6)
Missing data	6 (3)	65 (9)
Age at natural menopause, y		
<47	25 (14)	88 (13)
47–51	30 (17)	148 (21)
⩾52	25 (14)	122 (18)
Missing data	2 (1)	4 (1)

(Table continues)

Table 3 (continued). Characteristics of 174 users and 695 nonusers of hormone replacement therapy (HRT) after a diagnosis of breast cancer (Group Health Cooperative, 1977–1996)

Characteristic	Users, No. (%)*	Nonusers, No. (%)*
Age at induced menopause, y		
<47	20 (11)	73 (11)
47–51	11 (6)	29 (4)
⩾52	7 (4)	13 (2)
Menopausal symptoms noted in medical chart		
Hot flashes	79 (45)	187 (27)
Sweats	28 (16)	53 (8)
Irregular menstrual or vaginal bleeding	25 (14)	73 (11)
Vaginal dryness or atrophy	96 (55)	216 (31)
HRT use before diagnosis	119 (68)	337 (48)
Missing data	10 (6)	31 (4)
Duration of HRT use before diagnosis, y		
0	45 (26)	327 (47)
>0–5	30 (17)	173 (25)
6–10	24 (14)	55 (8)
>10	40 (23)	66 (9)
Missing data	35 (20)	74 (11)
Age at first use if HRT used before diagnosis, y		
<45	33 (19)	87 (13)
45–54	45 (26)	152 (22)
⩾55	15 (9)	50 (7)
Missing data	26 (15)	48 (7)
Median age at menarche, y	*12*	*12*
Missing data	8 (5)	54 (8)
Nulliparous at diagnosis	24 (14)	91 (13)
Missing data	1 (1)	10 (1)
Median age at first full-term pregnancy if parous, y	*24*	*24*
Missing data	4 (2)	17 (2)
White	169 (97)	646 (93)
Missing data	2 (1)	10 (1)

*The number (%) of individuals missing data is shown. Median values are shown in *italic type*, where indicated.

†Data were insufficient to resolve stage into a single category. These women were matched to women in either of the appropriate adjacent stage groups. For example, women of stage "I/II" could be matched to women of stage I, II, or I/II.

‡The chronic disease score is a proxy measure of comorbidity based on prescription data *(16,17)*.

cer are described in Table 3. Regional lymph node involvement and large tumor size at diagnosis were somewhat less common in users than in nonusers. Estrogen receptor assays were positive for 48% of the users and for 59% of the nonusers with available results. (Estrogen receptor status was known for 71% of the users and 79% of the nonusers.) Mastectomy was performed in a greater proportion of users than nonusers; chemotherapy and tamoxifen were used less often. Similar proportions received radiation therapy. Prior hysterectomy and bilateral oophorectomy were more common in users than in nonusers. HRT was used before diagnosis by 68% of HRT users after diagnosis and by 48% of nonusers, and the duration of prior HRT use was greater among users.

Breast cancer recurrence was diagnosed in 16 HRT users (9%) and in 101 nonusers (15%) (Table 4). The rate of recurrence was 17 per 1000 person-years in users (95% CI = 11 to 29) and 30 per 1000 person-years in nonusers (95% CI = 25 to 37). Comparison of rates yielded an unadjusted relative risk associated with ever use of HRT after breast cancer of 0.58 (95% CI = 0.34 to 0.98). Adjusting for bilateral oophorectomy, hysterectomy, mastectomy, tamoxifen, and the matching variables in a Cox model resulted in a relative risk of 0.50 (95% CI = 0.30 to 0.85). Further adjustments did not appreciably change the results. The relative risk was similar when restricting to users of unopposed estrogens only. Risks associated with oral HRT and vaginal HRT differed little. Relative risks of recurrence associated with a longer duration or larger cumulative dose of HRT were closer to 1 than in the lower dose and duration groups.

Five HRT users (3%) and 59 nonusers (8%) died of breast cancer during follow-up (Table 5). The breast cancer mortality rate was five per 1000 person-years in users (95% CI = 2 to 11) and 15 per 1000 person-years in nonusers (95% CI = 12 to 20). The unadjusted relative risk associated with ever use was 0.31 (95% CI = 0.13 to 0.78). Adjusting for body mass index, positive lymph nodes at diagnosis, and the matching variables resulted in a relative risk of 0.34 (95% CI = 0.13 to 0.91). Other adjustments made little difference. The relative risks were low for both oral HRT use and vaginal HRT use.

During the follow-up period, 17 users (10%) and 115 nonusers (17%) died (Table 6). The total mortality rate was 16 per 1000 person-years in HRT users (95% CI = 10 to 26) and 30 per 1000 person-years in nonusers (95% CI = 25 to 36). The unadjusted relative risk associated with ever use was 0.54 (95% CI = 0.33 to 0.90). Adjusting for matching reduced the relative risk to 0.48 (95% CI = 0.29 to 0.78). Essentially no confounding was found with additional adjustments. Oral HRT use and vaginal HRT use were each associated with a low relative risk of total mortality. The relative risk did not vary appreciably by the cumulative dose or the duration of oral HRT.

Risks associated with HRT after breast cancer were especially low early in the follow-up period. During the first year after the reference date, the adjusted relative risk of recurrence was 0.13 (95% CI = 0.02 to 1.00), whereas afterward the relative risk rose to 0.73 (95% CI = 0.41 to 1.29). No users and six nonusers died during the first year after reference, so the relative risk of mortality was zero in that interval. Beyond the first year, the adjusted relative risks were 0.37 (95% CI = 0.13 to 1.04) for breast cancer mortality and 0.50 (95% CI = 0.31 to 0.83) for total mortality.

Among women with estrogen receptor-positive tumors, the unadjusted relative risks associated with use of HRT after diagnosis were 0.31 for recurrence (95% CI = 0.10 to 0.98), 0.16 for breast cancer mortality (95% CI = 0.02 to 1.19), and 0.30 for total mortality (95% CI = 0.11 to 0.82). The respective relative risks in estrogen receptor-negative women were 0.81 (95% CI = 0.30 to 2.17), 0.56 (95% CI = 0.12 to 2.53), and 0.59 (95% CI = 0.20 to 1.71).

Table 4. Recurrence of breast cancer in relation to the use of hormone replacement therapy (HRT) after a diagnosis of breast cancer (Group Health Cooperative, 1977–1996)

	Person-years	No. of recurrences	Rate per 1000 person-years* (95% CI)	Unadjusted relative risk† (95% CI)	Adjusted relative risk‡ (95% CI)
Any HRT					
Never	3356	101	30 (25 to 37)	1 (referent)	1 (referent)
Ever	916	16	17 (11 to 29)	0.58 (0.34 to 0.98)	0.50 (0.30 to 0.85)
Unopposed estrogens only§					
Never	2690	81	30 (24 to 37)	1 (referent)	1 (referent)
Ever	770	14	18 (11 to 31)	0.60 (0.34 to 1.07)	0.51 (0.28 to 0.93)
Estrogen with ⩾1 cycle of progestogen§					
Never	475	15	32 (19 to 52)	1 (referent)	1 (referent)
Ever	121	2	17 (4 to 66)	0.53 (0.12 to 2.30)	0.42 (0.15 to 1.22)
Oral HRT‖					
Never	1750	46	26 (20 to 35)	1 (referent)	1 (referent)
Ever	453	8	18 (9 to 35)	0.67 (0.32 to 1.42)	0.57 (0.28 to 1.16)
Duration, mo¶					
0	1792	46	26 (19 to 34)	1 (referent)	1 (referent)
1–12	213	3	14 (5 to 44)	0.55 (0.17 to 1.77)	0.41 (0.14 to 1.23)
⩾13	195	5	26 (11 to 62)	1.00 (0.40 to 2.52)	0.91 (0.37 to 2.23)
Dose, mg¶,#					
0	1792	46	26 (19 to 34)	1 (referent)	1 (referent)
>0–225	206	4	19 (7 to 52)	0.76 (0.27 to 2.10)	0.52 (0.21 to 1.31)
>225	201	4	20 (7 to 53)	0.78 (0.28 to 2.15)	0.76 (0.25 to 2.26)
Vaginal HRT only**					
Never	1589	53	33 (25 to 44)	1 (referent)	1 (referent)
Ever	457	8	18 (9 to 35)	0.53 (0.25 to 1.10)	0.46 (0.21 to 1.01)
Tubes of cream					
2–4	229	3	13 (4 to 41)	0.39 (0.12 to 1.26)	0.29 (0.09 to 0.93)
⩾5	228	5	22 (9 to 53)	0.66 (0.26 to 1.65)	0.70 (0.26 to 1.92)

*Rates were calculated from the reference date (i.e., the date of HRT initiation in users or the quivalent date since diagnosis in matched nonusers). CI = confidence interval.

†Relative risk (rate ratio) comparing users with nonusers. Users and nonusers were matched on age at diagnosis (35–44, 45–54, 55–64, and 65–74 years), year of diagnosis (1977–1982, 1983–1988, and 1989–1994), stage (I, II, and III), and time from diagnosis to the reference date (months).

‡Relative risk (hazard ratio) from Cox regression models. Adjusted for bilateral oophorectomy, hysterectomy, mastectomy, tamoxifen, and matching.

§Analysis excluded 17 nonusers of HRT (with estrogens) who used progestins, i.e., filled two or more prescriptions for a progestin within 6 months, some time after diagnosis and before any recurrence. Six HRT users who used progestins but did not receive progestins concurrently with an estrogen were also excluded, along with their matched nonusers.

‖Includes 98 users of oral HRT and their matched nonusers.

¶Cumulative use. Total person-years for the zero category differs from that for the "never" category because some oral users entered analysis having used only vaginal HRT to that time, whereas the time at risk among users in this analysis reflects oral use only. Person-years in the nonzero categories of use likewise reflect oral use only; thus, they do not sum to the total years in the "ever" category.

#Dose in conjugated-estrogen dose equivalents *(18).*

**Includes 75 users of vaginal, but not oral, HRT and their matched nonusers.

DISCUSSION

We observed that women who used HRT after a diagnosis of breast cancer had lower risks of recurrence, breast cancer mortality, and total mortality than nonusers. Whether the relations represent a true benefit of HRT after breast cancer is not clear. The actions of estrogen in established breast cancer appear to be complex and are poorly understood. Estrogens can stimulate the growth of breast cancer cells in tissue culture at low doses but can inhibit growth at high doses *(23).* Breast tumors can regulate and maintain internal levels of estradiol independent of levels outside the tumor *(24),* so exogenous estrogens may have relatively little effect on tumor growth *(10).*

The potential for confounding is of crucial concern in observational studies of HRT use after breast cancer. The reasons women seek HRT or other correlates of use may favor improved prognosis apart from any effect of HRT itself. In this study, HRT users and nonusers are known to have differed in several ways. The low relative risks of recurrence and death associated with HRT persisted after adjustment for those factors in the analysis. An important strength of this study is that both HRT users and nonusers were free of diagnosed recurrence at reference (HRT initiation or the equivalent time since diagnosis), when survival comparisons began. Without this feature, nonusers of HRT with recurrent breast cancer would have been compared with users who, by definition, were free of recurrence at the start of follow-up, and relative risks would have been falsely low. Confounding by indication for the use of HRT may nonetheless exist in our data. Most of the users sought HRT after breast cancer to treat symptoms of menopause. Menopausal symptoms are associated with low circulating levels of endogenous estrogens *(25).* If estrogens contribute to breast cancer progression, then the users may have been at lower underlying risk than the nonusers because of lower underlying estrogen levels. To explore this issue, we analyzed our data restricted to the 122 users who reported starting HRT to treat menopausal symptoms and their matched nonusers. With this restriction, the relative risk of recurrence dropped

Table 5. Breast cancer mortality in relation to the use of hormone replacement therapy (HRT) after a diagnosis of breast cancer (Group Health Cooperative, 1977–1996)

	Person-years	No. of deaths from breast cancer	Rate per 1000 person-years* (95% CI)	Unadjusted relative risk† (95% CI)	Adjusted relative risk‡ (95% CI)
Any HRT					
Never	3855	59	15 (12 to 20)	1 (referent)	1 (referent)
Ever	1050	5	5 (2 to 11)	0.31 (0.13 to 0.78)	0.34 (0.13 to 0.91)
Unopposed estrogens only§					
Never	3077	49	16 (12 to 21)	1 (referent)	1 (referent)
Ever	883	4	5 (2 to 12)	0.29 (0.10 to 0.79)	0.31 (0.10 to 0.96)
Estrogen with ⩾1 cycle of progestogen§					
Never	561	7	12 (6 to 26)	1 (referent)	—
Ever	141	1	7 (1 to 50)	0.57 (0.07 to 4.61)	—‖
Oral HRT¶					
Never	2011	21	10 (7 to 16)	1 (referent)	1 (referent)
Ever	523	1	2 (<1 to 14)	0.18 (0.03 to 1.36)	0.21 (0.06 to 0.82)
Vaginal HRT only#					
Never	1821	36	20 (14 to 27)	1 (referent)	1 (referent)
Ever	521	4	8 (3 to 20)	0.39 (0.14 to 1.09)	0.37 (0.11 to 1.21)
Tubes of cream					
2–4	248	2	8 (2 to 32)	0.41 (0.10 to 1.69)	0.26 (0.04 to 1.93)
⩾5	272	2	7 (2 to 29)	0.37 (0.09 to 1.54)	0.47 (0.11 to 1.92)

*Rates were calculated from the reference date (i.e., the date of HRT initiation in users or the equivalent date since diagnosis in matched nonusers). CI = confidence interval.

†Relative risk (rate ratio) comparing users with nonusers. Users and nonusers were matched on age at diagnosis (35–44, 45–54, 55–64, and 65–74 years), year of diagnosis (1977–1982, 1983–1988, and 1989–1994), stage (I, II, and III), and time from diagnosis to the reference date (months).

‡Relative risk (hazard ratio) from Cox regression models. Adjusted for positive lymph nodes at diagnosis (yes/no), body mass index (dummy quartiles), and matching.

§Analysis excluded 17 nonusers of HRT (with estrogens) who used progestins, i.e., filled two or more prescriptions for a progestin within 6 months, some time after diagnosis and before any recurrence. Six HRT users who used progestins but did not receive progestins concurrently with an estrogen were also excluded, along with their matched nonusers.

‖Insufficient data for this adjustment.

¶Includes 98 users of oral HRT and their matched nonusers.

#Includes 75 users of vaginal, but not oral, HRT and their matched nonusers.

only slightly (from 0.54 to 0.45), in the expected direction if this form of confounding were present. The relative risks of breast cancer mortality and total mortality were essentially unchanged. Although confounding by indication may be present, it is unlikely that its magnitude is large enough to conceal a true adverse effect of HRT on recurrence and mortality.

The users of HRT after breast cancer were more likely than the nonusers to have used HRT before diagnosis. HRT users may be screened more aggressively for breast cancer than nonusers. Screen-detected cancers are identified at an earlier stage and are more amenable to treatment than are symptom-detected cancers. In this study, users and nonusers of HRT were matched on stage at diagnosis, and similar proportions had that diagnosis prompted by a screening mammogram. Relative risks held after adjustment for prior use of HRT and its duration, as well as for mode of detection of the initial breast cancer.

Matching on a recurrence-free interval since diagnosis and adjusting for other factors do not assure complete comparability between users and nonusers of HRT. Women with a history of breast cancer who seek HRT are likely to be thoroughly evaluated for recurrence. Nonusers are unlikely to undergo a similar evaluation at the equivalent time before an arbitrary reference date. A nonuser may enter the study with an undiagnosed recurrence, leaving her at higher risk than her matched user for a period of time. Differential screening of this sort may account for some of the reduced risk seen in users, especially early in follow-up *(26)*.

Published case series report low rates of recurrence and death in users of HRT after breast cancer *(27–32)*. Four *(33–36)* of five *(37)* cohort studies identified found no increased risk of recurrent breast cancer among users of HRT after diagnosis compared with nonusers. However, these studies tended to be small, relatively brief, and limited in their ability to control confounding. Of the two cohort studies that clearly matched on disease-free interval before HRT initiation, one *(37)* included only 21 users of estradiol (not commonly used in the United States) and found a relative risk of recurrence of 1.7 (95% CI = 0.3 to 8.9). The other study *(33)* included 90 users of various estrogens and reported a relative risk of recurrence of 0.4 (95% CI = 0.2 to 0.9).

The use of HRT at or shortly before a diagnosis of breast cancer represents exposure in the presence of the developing tumor. Such use may, therefore, be relevant to the question of HRT use after diagnosis. Most studies of HRT use before diagnosis find better prognosis in users than in nonusers *(38)*, although it is not clear why. Confounding may account for some of the difference. Another possibility is that HRT users develop breast tumors with favorable biologic features *(38–41)*.

Certain results of this study argue against a causal influence of HRT after breast cancer on recurrence and mortality. We found no evidence of improved disease-free or overall survival with greater cumulative use of HRT. The total duration of oral HRT use was relatively short

Table 6. Total mortality in relation to the use of hormone replacement therapy (HRT) after a diagnosis of breast cancer (Group Health Cooperative, 1977–1996)

	Person-years	No. of deaths	Rate per 1000 person-years* (95% CI)	Unadjusted relative risk† (95% CI)	Adjusted relative risk‡ (95% CI)
Any HRT					
Never	3855	115	30 (25 to 36)	1 (referent)	1 (referent)
Ever	1050	17	16 (10 to 26)	0.54 (0.33 to 0.90)	0.48 (0.29 to 0.78)
Unopposed estrogens only§					
Never	3077	96	31 (26 to 38)	1 (referent)	1 (referent)
Ever	883	15	17 (10 to 28)	0.55 (0.32 to 0.94)	0.48 (0.28 to 0.83)
Estrogen with ⩾1 cycle of progestogen§					
Never	561	13	23 (13 to 40)	1 (referent)	1 (referent)
Ever	141	2	14 (4 to 57)	0.61 (0.14 to 2.71)	0.50 (0.19 to 1.29)
Oral HRT‖					
Never	2011	46	23 (17 to 31)	1 (referent)	1 (referent)
Ever	523	6	11 (5 to 26)	0.50 (0.21 to 1.17)	0.35 (0.17 to 0.72)
Duration, mo¶					
0	2054	46	22 (17 to 30)	1 (referent)	1 (referent)
1–12	237	3	13 (4 to 39)	0.56 (0.18 to 1.81)	0.37 (0.10 to 1.41)
⩾13	240	3	12 (4 to 39)	0.56 (0.17 to 1.79)	0.35 (0.15 to 0.81)
Dose, mg¶,#					
0	2054	46	22 (17 to 30)	1 (referent)	1 (referent)
>0–225	235	3	13 (4 to 40)	0.57 (0.18 to 1.83)	0.39 (0.10 to 1.47)
>225	242	3	12 (4 to 38)	0.55 (0.17 to 1.78)	0.34 (0.15 to 0.80)
Vaginal HRT only**					
Never	1821	67	37 (29 to 47)	1 (referent)	1 (referent)
Ever	521	11	21 (12 to 38)	0.57 (0.30 to 1.09)	0.60 (0.31 to 1.16)
Tubes of cream					
2–4	248	4	16 (6 to 43)	0.44 (0.16 to 1.20)	0.41 (0.14 to 1.18)
⩾5	272	7	26 (12 to 54)	0.70 (0.32 to 1.52)	0.76 (0.33 to 1.73)

*Rates were calculated from the reference date (i.e., the date of HRT initiation in users or the equivalent date since diagnosis in matched nonusers). CI = confidence interval.

†Relative risk (rate ratio) comparing users with nonusers. Users and nonusers were matched on age at diagnosis (35–44, 45–54, 55–64, and 65–74 years), year of diagnosis (1977–1982, 1983–1988, and 1989–1994), stage (I, II, and III), and time from diagnosis to the reference date (months).

‡Relative risk (hazard ratio) from Cox regression models. Adjusted for matching.

§Analysis excluded 17 nonusers of HRT (with estrogens) who used progestins, i.e., filled two or more prescriptions for a progestin within 6 months, some time after diagnosis and before any recurrence. Six HRT users who used progestins but did not receive progestins concurrently with an estrogen were also excluded, along with their matched nonusers.

‖Includes 98 users of oral HRT and their matched nonusers.

¶Cumulative use. Total person-years for the zero category differs from that for the "never" category because some oral users entered analysis having used only vaginal HRT to that time, whereas the time at risk among users in this analysis reflects oral use only. Person-years in the nonzero categories of use likewise reflect oral use only; thus, they do not sum to the total years in the "ever" category.

#Dose in conjugated-estrogen dose equivalents *(18).*

**Includes 75 users of vaginal, but not oral, HRT and their matched nonusers.

on average. Also, we found that the relative risks associated with oral HRT and vaginal HRT were similar, within the limits of chance. While systemic absorption of estrogens delivered transvaginally can be substantial, serum estrogen levels following administration of conjugated estrogens by vaginal cream average only about one-fourth that of the same oral dose *(42).* Consensus is lacking on the degree to which vaginal HRT has systemic effects *(43,44).*

The risk of a second primary breast cancer is also of concern when considering the use of HRT after an initial diagnosis. Although this study was not designed to address that question, we collected data that may be relevant. Women who were diagnosed with contralateral breast cancer or who had a contralateral mastectomy before the reference date were excluded from this analysis. A new primary contralateral breast cancer was diagnosed after the reference date in 10 (6%) of 167 users and in 26 (4%) of 642 nonusers at risk. The rate of contralateral cancer was 12 per 1000 person-years in users (95% CI = 6 to 22) and eight per 1000 person-years in nonusers (95% CI = 6 to 12). The relative risk of contralateral breast cancer associated with ever use of HRT after the initial diagnosis was 1.42 (95% CI = 0.69 to 2.95) when unadjusted and 1.33 (95% CI = 0.66 to 2.68) when adjusted for bilateral oophorectomy, hysterectomy, positive lymph nodes at diagnosis, and the matching variables. Other adjustments had little effect. This result reinforces the need for caution in assessing the overall impact of HRT after breast cancer.

Additional evidence against a true benefit of the use of HRT is found in related breast cancer research. Tamoxifen has antiestrogenic effects on the breast and reduces risks of recurrence and death *(5,6).* Ovarian ablation by bilateral oophorectomy, pelvic irradiation, or drugs improves survival in young women with breast cancer *(5,6).* Postmenopausal patients with breast cancer who are obese experience worse survival than those who are lean *(45),* possibly because of higher estrogen levels in the obese women *(46).*

Our findings suggest that women who seek and use HRT after breast cancer do not have elevated risks of recurrence and

death. Given the limitations of this study and uncertainty about noncausal explanations, these results should be interpreted with caution. Additional observational studies are needed, especially those that are able to address potential biases with strategies similar to those used in this study and that are large enough to examine in detail issues of dose, duration, and regimen. We believe it would also be desirable to conduct randomized trials of HRT in women in remission after breast cancer who have symptoms of estrogen loss.

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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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