

# Menopausal Estrogen and Estrogen-Progestin Replacement Therapy and Breast Cancer Risk

Catherine Schairer, PhD

Jay Lubin, PhD

Rebecca Troisi, ScD

Susan Sturgeon, DrPH

Louise Brinton, PhD

Robert Hoover, MD

**I**N A RECENT COLLABORATIVE RE-analysis of more than 90% of the world's epidemiological data on the relationship between menopausal hormone replacement therapy (HRT) and breast cancer risk, it was found that longer durations of recent, but not past, use of HRT increased breast cancer risk, particularly among leaner women and for tumors that were less clinically advanced.<sup>1</sup> Unresolved issues include the extent to which the findings were due to a biological effect of hormones rather than issues of screening and ascertainment. The data were also insufficient to determine whether a combined estrogen-progestin regimen increased risk beyond that associated with estrogen alone.

In 1994, we published data on HRT and breast cancer risk from a follow-up study conducted among former participants in a breast cancer screening program.<sup>2</sup> Cases were diagnosed through 1989. Those data were included in the collaborative analysis.<sup>1</sup> In this article, we expand our previous analysis to include cases diagnosed in the follow-up study through 1995, almost doubling the total number of cases. The collection of additional data on mammographic screening and use of the combined estrogen-progestin regimen allowed us to address some issues left unresolved.

**For editorial comment see p 534.**

**Context** Whether menopausal hormone replacement therapy using a combined estrogen-progestin regimen increases risk of breast cancer beyond that associated with estrogen alone is unknown.

**Objective** To determine whether increases in risk associated with the estrogen-progestin regimen are greater than those associated with estrogen alone.

**Design** Cohort study of follow-up data for 1980-1995 from the Breast Cancer Detection Demonstration Project, a nationwide breast cancer screening program.

**Setting** Twenty-nine screening centers throughout the United States.

**Participants** A total of 46 355 postmenopausal women (mean age at start of follow-up, 58 years).

**Main Outcome Measure** Incident breast cancers by recency, duration, and type of hormone use.

**Results** During follow-up, 2082 cases of breast cancer were identified. Increases in risk with estrogen only and estrogen-progestin only were restricted to use within the previous 4 years (relative risk [RR], 1.2 [95% confidence interval {CI}, 1.0-1.4] and 1.4 [95% CI, 1.1-1.8], respectively); the relative risk increased by 0.01 (95% CI, 0.002-0.03) with each year of estrogen-only use and by 0.08 (95% CI, 0.02-0.16) with each year of estrogen-progestin-only use among recent users, after adjustment for mammographic screening, age at menopause, body mass index (BMI), education, and age. The *P* value associated with the test of homogeneity of these estimates was .02. Among women with a BMI of 24.4 kg/m<sup>2</sup> or less, increases in RR with each year of estrogen-only use and estrogen-progestin-only use among recent users were 0.03 (95% CI, 0.01-0.06) and 0.12 (95% CI, 0.02-0.25), respectively. These associations were evident for the majority of invasive tumors with ductal histology and regardless of extent of invasive disease. Risk in heavier women did not increase with use of estrogen only or estrogen-progestin only.

**Conclusion** Our data suggest that the estrogen-progestin regimen increases breast cancer risk beyond that associated with estrogen alone.

*JAMA.* 2000;283:485-491

www.jama.com

## METHODS

### Follow-up Study

Study subjects were participants in the Breast Cancer Detection Demonstration Project (BCDDP) conducted between 1973 and 1980. We previously described a follow-up study begun in 1979 involving a subset of BCDDP participants.<sup>2</sup> In brief, the follow-up study included (1) all screening participants who underwent breast surgery during the screening period, with no evidence of malignant disease (n = 25 114); (2) all subjects who had recommenda-

tions by the project for a surgical consultation but did not have either a biopsy or aspiration performed (n = 9628); and (3) a sample of women who had neither surgery nor recommendation for

**Author Affiliations:** National Cancer Institute, Division of Cancer Epidemiology and Genetics, Rockville, Md (Drs Schairer, Lubin, Troisi, Sturgeon, Brinton, and Hoover); Social and Scientific Systems Inc, Bethesda, Md (Dr Troisi); and the Department of Biostatistics and Epidemiology, University of Massachusetts, Amherst (Dr Sturgeon).

**Corresponding Author and Reprints:** Catherine Schairer, PhD, National Cancer Institute, Division of Cancer Epidemiology and Genetics, 6120 Executive Blvd, EPS Room 7080-MSC 7234, Rockville, MD 20852-7234 (e-mail: schairec@exchange.nih.gov).

surgical consultation during screening participation (n = 25 165). The follow-up study was approved by the Institutional Review Board at the National Cancer Institute. Informed consent was obtained from participants.

The follow-up study was carried out in 3 phases. Our previous analysis involved the first 2 phases of the study, in which annual telephone interviews were conducted between 1979 and 1986 and 1 mailed questionnaire was administered between 1987 and 1989.<sup>2</sup> The current analysis includes data from these earlier phases as well as from the latest phase of the study, during which 1 mailed questionnaire was administered between 1993 and December 1995 to study subjects not known to be deceased and who completed a questionnaire in 1987-1989. Nonrespondents to the mailed questionnaire were interviewed by telephone, if possible.

Information collected from phase 1 of the study included recognized breast cancer risk factors; breast cancer screening practices, including number of mammograms for a routine reason or because of a problem since the last interview; and breast procedures undergone since the last examination by the screening program or the last interview. In addition, information was collected on age at first use and duration of use of female hormones (excluding creams) other than oral contraceptives. Information was not obtained on type of hormone used. During phase 2 of the study, information on breast procedures and previously collected risk factors was updated. Information was obtained on use of menopausal hormones in the form of shots, creams, patches, or pills since the last interview; those who had used pills provided information on ever use of menopausal estrogens and progestins in the same month, duration of use of estrogens and progestins, and number of days in the month progestins were used. Information on breast cancer screening practices was not collected during phase 2. In phase 3 of follow-up, previously collected information, including use of estrogens and progestins, was

updated; information was also collected on mammographic and physical examinations of the breast for a routine reason or because of a problem in the 5 years prior to the interview.

Level of education was recorded on a form completed at entry to the screening program. Height and weight measurements were recorded on forms at each screening visit. Current height and weight measurements were available from the 1987-1989 questionnaire.

#### Analytic Data Set

This analysis was limited to women who were menopausal before the start of the follow-up period or who became menopausal during the course of the study. Menopausal women were defined as those who did not have a menstrual period for at least 3 months prior to an interview because of natural menopause or a bilateral oophorectomy. In addition, women who stopped menstruating because of a hysterectomy but who retained at least 1 ovary or whose ovarian status was uncertain were considered to have reached menopause by age 57 years (the 75th percentile for age at menopause in the study population) or their age at hysterectomy, whichever was later. However, they were assigned an unknown value for their specific ages at menopause in the analyses. Those reporting prophylactic bilateral mastectomies or a diagnosis of breast cancer before the start of follow-up were excluded. Those reporting use of menopausal hormones in the form of shots, patches, or creams (n = 6212) were also excluded because detailed information regarding timing of use was not available. Most study subjects (86%) were white. There were small percentages of black (5%), Hispanic (2%), and Asian American (5%) women, as well as those with other or unknown race/ethnicity (1%).

After all exclusions, 46 355 subjects were available for analysis. A total of 39 427 (85%) of these subjects completed a phase 2 questionnaire; 33 004 (84%) of those who completed a phase 2 questionnaire also completed a phase 3 questionnaire. Phase 3 question-

naires were not completed by those who completed phase 2 for reasons including death (6%); loss to follow-up (0.5%); and illness, refusal, or because contact with study subjects at a current telephone number was not made by the end of the study period (9.5%).

During follow-up, 2082 breast cancer cases were identified in study subjects through self-reports or reports of breast cancer on death certificates; 1054 of these cases were included in our previous analysis.<sup>2</sup> Pathology reports were obtained for 1713 of these cases (82%); reports were not obtained for 237 cases (11%) because they were not received before the end of the study period, because of nonresponse of physicians or hospitals, or because permission to retrieve medical records was not received from the study subject. Pathology reports for the 132 cases (6%) identified by death certificate also were not retrieved. A total of 255 (15%) cancers for which pathology reports were available were in situ and 1456 (85%) were invasive. It was uncertain whether 2 cases were in situ or invasive. Invasive tumors were further classified into 2 groups based on histology: (1) mucinous, medullary, tubular, or papillary carcinomas (n = 76) or (2) ductal or lobular carcinomas (n = 916). A total of 788 in the second group were ductal carcinomas, 104 were lobular carcinomas, and 24 were comedocarcinomas or Paget disease with infiltrating ductal carcinoma. Histology was not available for 464 invasive cases, largely from those whose disease was diagnosed during phase 1 of the study, because pathology reports were no longer available from which to code histology. Because the accuracy of self-reporting was high among those with pathology reports (97% were confirmed as cancers), cancers without pathology reports (n = 369) were included in the analyses but were not categorized as in situ or invasive.

Nodal status was available for 1253 (86%) of the invasive cases; 903 (72%) were node negative and 350 were (28%) node positive. Tumor size was available for 1041 (71%) of invasive cases:

680 (65%) were smaller than 2 cm and 361 (35%) were 2 cm or larger.

### Analysis

Follow-up began at the date of the baseline interview or date of menopause, whichever was later. Person-years accrued until the earliest of the following dates: diagnosis of breast cancer, a second prophylactic mastectomy, death (including cases identified by death certificate), or date of last contact.

Data were analyzed using Poisson regression methods. We calculated relative risks (RRs) and 95% confidence intervals (CIs) for categorized variables using standard likelihood ratio methods.<sup>3</sup> For a continuous variable (eg, duration of estrogen use), the RR was modeled as a linear excess RR (ERR) as follows:  $\lambda(t, z, d) = \lambda(t, z, 0) (1 + \beta d)$ , where  $d$  is duration of hormone use, the parameter  $\beta$  is the change in the ERR (RR - 1) per unit  $d$ ,  $\lambda(t, z, 0)$  is the risk at time  $t$  for those with covariate vector  $z$  and no hormone use, and  $\lambda(t, z, d)$  is the risk at time  $t$  for those with covariate vector  $z$  and  $d$  years of hormone use. The background risk  $\lambda(t, z, 0)$  was modeled by means of stratification. Likelihood-based methods were used to obtain CIs for the linear ERR model.<sup>4</sup> Score tests were used to test for the statistical significance of trends and to assess quadratic departures from linearity in the linear ERR model. No such departures were detected. Tests of homogeneity of the effects of estrogen and estrogen-progestin were assessed by score tests in which the effects of the 2 regimens were first assumed to be the same and then were allowed to vary. Similarly, score tests were used to assess the homogeneity of hormonal effects by categories of body mass index (BMI).

Variables included as time-dependent factors were attained age, BMI, use of female hormones for menopausal reasons, and mammographic examinations of the breast. Hormone use was calculated to 1 year prior to attained (or current) age to eliminate exposure that was most likely not causal. Data on BMI and mammographic examinations were calculated to attained age.

Because information on progestin use was not collected until the 1987-1989 interview, progestin use was unknown for the 6928 subjects who did not answer this interview. For these subjects and those who were uncertain whether they had used progestins, person-years and cases associated with estrogen use were included in the *estrogen (progestin unknown)* category if the subject had undergone a natural menopause; otherwise, they were included in the *estrogen only* category because women with a surgical menopause were less likely to have used progestins. Information on episodes of hormone use that occurred before breast cancer diagnosis may have been reported by study subjects after diagnosis. For instance, a subject may have reported on a 1994 interview that she had been diagnosed as having breast cancer in 1993 and that she had used hormones between 1991 and 1992 (before diagnosis). For this same study subject, all hormone use that was reported on interviews completed prior to 1993 would have been reported before breast cancer diagnosis. An individual who responded to the 1994 interview but did not report breast cancer on that interview would have reported any hormone use in a manner similar to this hypothetical case.

We assessed the influence of mammographic screening (ie, mammograms as part of routine screening rather than for a problem) during the follow-up period by categorizing person-years and cases in a time-dependent manner into 1 of the following 4 groups: (1) no mammographic screening, defined as the period of time from the start of the follow-up study to the first screening mammogram during the follow-up study; (2) sporadic mammographic screening, defined as the period of 1 year following the first screening mammogram and subsequent periods more than 1 year after a screening mammogram; (3) annual mammographic screening, defined as the period of time within 1 year of the second and subsequent screening mammograms; and (4) unknown mammographic screening type. We chose to adjust for mammographic

screening in this manner, rather than controlling for number of screening mammograms, because cancer detection rates associated with the first mammogram during the BCDDP screening program were markedly higher than those associated with subsequent mammograms, while cancer detection rates were remarkably constant for the second and subsequent mammograms.<sup>5</sup> A similar variable was created for clinical breast examinations by a health care professional during the follow-up period.

For the follow-up period until the 1987-1989 questionnaire, we calculated BMI from information obtained from the screening visit closest in time to the baseline follow-up interview; for the subsequent period we calculated BMI from current height and weight from the 1987-1989 questionnaire.

For analytic purposes, BMI data were grouped into quintiles. Because there was virtually no difference in the prevalence of hormone use in the lowest 2 quintiles, they were combined in the analyses. To control as completely as possible for the confounding effects of age at menopause, we created narrow categories for the most commonly reported ages at menopause and broader categories for the less commonly reported ages. We performed selected analyses excluding subjects with unknown age at menopause to address theoretical concerns that including these women would seriously underestimate the risk associated with HRT.<sup>6</sup>

## RESULTS

The mean duration of follow-up was 10.2 years, with a median of 12.3 years, a maximum of 16.0 years, and a minimum of less than 1 year. During follow-up, 473 687 person-years were accumulated for the 46 355 subjects. The average age at start of follow-up was 58 years.

Forty-two percent of person-years were associated with no use of hormones, 38% with estrogen-only use, 4% with combined estrogen-progestin-only use, 6% with estrogen-progestin use among those who also used estrogen alone, 5% with estrogen use with uncertain or unascertained progestin

use, 1% with progestin-only use or progestin use with uncertain estrogen use, and 5% with uncertain hormone use. The primary type of estrogen used was conjugated estrogens (Premarin) and the primary progestin was medroxyprogesterone acetate.

### Ever Use and Recency of Use

Relative risks associated with ever use of different hormone regimens after adjustment for attained age, age at menopause, education, BMI, and mammographic screening are shown in TABLE 1. Adjustment for race, period of follow-up, age at first live birth, family history of breast cancer, history of benign breast disease, and clinical breast examinations did not alter these estimates. There were slight increases in risk associated with all regimens of use except progestin only. Most subsequent analyses are restricted to non-hormone use, use of estrogen only, and use of estrogen-progestin only.

Increases in risk associated with use of estrogen only and estrogen-proges-

tin only were largely restricted to recent use of hormones (defined as current use and past use occurring within the previous 4 years) (TABLE 1). Relative risks were 1.2 (95% CI, 1.0-1.4) and 1.4 (95% CI, 1.1-1.8), respectively. The mean person-year weighted duration of combined estrogen-progestin use among recent users was less than half that among recent users of estrogens alone (3.6 vs 10.3 years).

### Duration of Use

Observed and predicted RRs associated with duration of estrogen-only use and estrogen-progestin-only use among recent users are shown in the FIGURE. Based on the linear excess risk model, the RR of breast cancer increased by 0.01 (95% CI, 0.002-0.03) for each year of estrogen-only use ( $P = .01$  for trend) and by 0.08 (95% CI, 0.02-0.16) for each year of estrogen-progestin-only use ( $P = .01$  for trend). The  $P$  value for the test of homogeneity of these estimates was .02. Results were similar when analyses were restricted to the cat-

egory of annual mammographic screening, which included 24% of the person-years in the study.

To assess the impact of excluding women with an unknown age at menopause on the analysis, we restricted data to recent users with a known age at menopause. Relative risks were changed only slightly; in contrast with estimates of 0.01 and 0.08 for all data, the increase in RR for each year of estrogen-only use was 0.02 (95% CI, 0.002-0.04) and for each year of estrogen-progestin-only use was 0.06 (95% CI, -0.002 to 0.15). The  $P$  value for the test of homogeneity of these associations was .23. We also examined associations among women with a known age at menopause but unadjusted for age at menopause; the increase in RR for each year of estrogen-only use was 0.01 (95% CI, 0.002-0.24) and for estrogen-progestin-only use was 0.07 (95% CI, 0.001-0.16), suggesting that ignoring age at menopause entirely had little effect on the estimates.

When analyses included all recent users of estrogen-progestin (ie, including those who also used estrogen alone and those with an unknown age at menopause), the RR increased by 0.05 (95% CI, 0.003-0.11) with each year of use. The  $P$  value associated with the test of homogeneity of this estimate and that associated with duration of use of estrogen alone was .07.

There was no association between duration of use of estrogen alone and risk of breast cancer among past users.

### Duration by Days in the Month Progestins Were Used

Among recent users who used progestins for fewer than 15 days per month, the RRs associated with less than 4 and 4 or more years of use of estrogen-progestin only were 1.1 (95% CI, 0.8-1.7) and 1.5 (95% CI, 1.0-2.4), respectively, based on 26 and 22 cases. The median number of days progestins were used in this group was 10.

There were too few cases who had used progestins for 15 or more days per month ( $n = 12$ ) to derive stable estimates according to duration of use. A substantial number of cases ( $n = 33$ )

**Table 1.** Relative Risk of Breast Cancer Associated With Use of Estrogen and Estrogen-Progestin Replacement Therapy

	No. of Person-Years	No. of Cases	RR (95% CI)*
Ever use			
No use	196 666	761	1.0 (Referent)
Estrogen only	179 401	805	1.1 (1.0-1.3)
Estrogen-progestin only	17 428	101	1.3 (1.0-1.6)
Estrogen alone and estrogen-progestin	29 564	162	1.2 (1.0-1.5)
Progestin only	3 048	11	0.9 (0.5-1.6)
Estrogen (progestin unknown)	24 757	130	1.3 (1.0-1.5)
Progestin (estrogen unknown)	151	0	... †
Unknown use	22 669	112	1.3 (1.0-1.5)
Years since last use			
Estrogen only			
Current	55 008	243	1.1 (1.0-1.3)
1-2	15 533	77	1.4 (1.1-1.8)
>2-4	12 171	55	1.2 (0.9-1.6)
>4-6	10 463	35	0.9 (0.6-1.3)
>6	67 836	309	1.1 (0.9-1.2)
Estrogen-progestin only			
Current	11 780	77	1.4 (1.1-1.9)
1-2	1 899	9	1.2 (0.6-2.4)
>2-4	1 388	7	1.2 (0.5-2.5)
>4-6	579	2	0.6 (0.2-2.6)
>6	1 779	6	0.6 (0.3-1.6)

\*RR indicates relative risk; CI, confidence interval. Data are adjusted for attained age, education, body mass index, age at menopause, and mammographic screening.

†Ellipses indicate data not applicable.



were uncertain how many days in the month they had used progestin.

**Variation by BMI**

Associations with duration of estrogen-only use among recent users varied significantly according to BMI ( $P = .002$  for score test), with increases in risk evident only in women with a BMI of 24.4 kg/m<sup>2</sup> or less (TABLE 2). The RRs increased by 0.03 (95% CI, 0.01-0.06) for each year of estrogen-only use in this group.

Associations with duration of estrogen-progestin-only use among recent users did not vary significantly according to BMI ( $P = .42$  for score test), although there was a significant increase in risk among lean women but not heavier women. The RR among lean women increased by 0.12 (95% CI, 0.02-0.25) for each year of use. The  $P$  value associated with the test of homogeneity of this estimate and that associated with estrogen-only use in lean women was .06.

When those with an unknown age at menopause were excluded, the RR increased by 0.05 for each year of estrogen-only use (95% CI, 0.02-0.08) among lean

women; the increase in the RR for each year of estrogen-progestin-only use in lean women was 0.11 (95% CI, 0.01-0.27). The  $P$  value associated with the test of homogeneity of these estimates was .36.

**Extent of Disease and Tumor Histology**

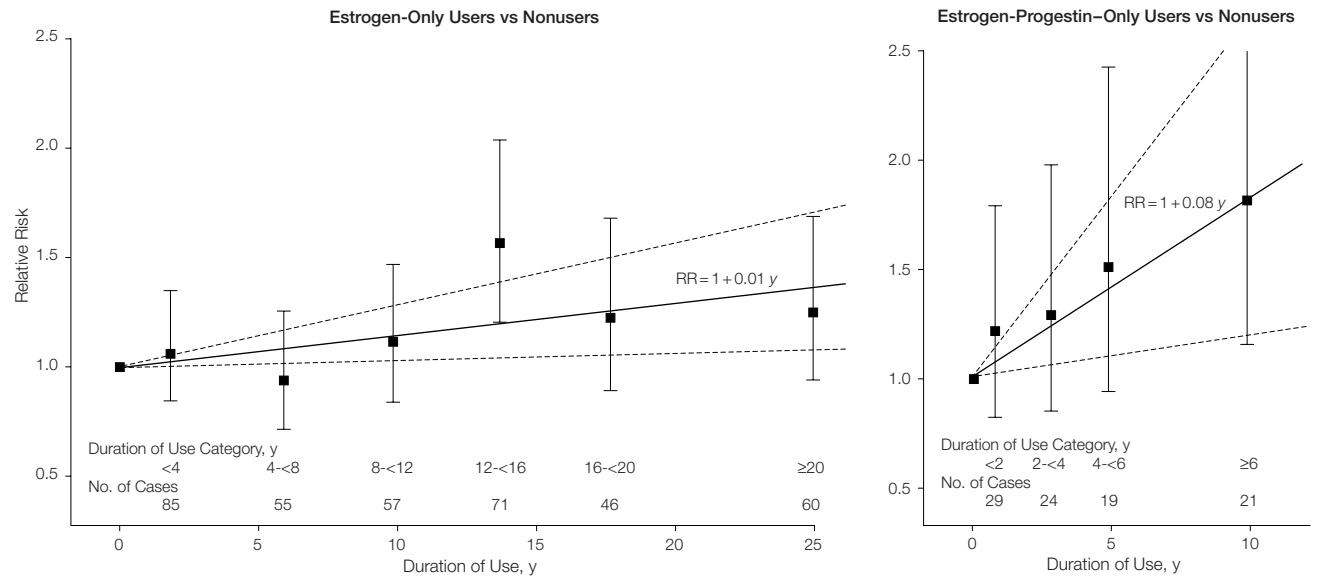
In recent estrogen-only users with BMI of 24.4 kg/m<sup>2</sup> or less, duration of use was associated with significant in-

**Table 2.** Relative Risks Associated With Duration of Estrogen-Only Use and Estrogen-Progestin-Only Use Among Recent Users by Body Mass Index (BMI)

Duration of Use, y	Body Mass Index (BMI)			
	≤24.4 kg/m <sup>2</sup>		>24.4 kg/m <sup>2</sup>	
	No. of Cases	RR (95% CI)*	No. of Cases	RR (95% CI)*
<b>Estrogen Only</b>				
No use	351	1.0 (Referent)	379	1.0 (Referent)
<8	80	1.0 (0.8-1.3)	55	1.0 (0.7-1.3)
8-<16	82	1.5 (1.2-2.0)	40	1.0 (0.7-1.4)
≥16	72	1.6 (1.2-2.2)	32	0.8 (0.6-1.3)
Increase in RR per year of use (95% CI)	0.03 (0.01-0.06)		-0.01 (-0.02 to 0.10)	
$P$ value for trend	.001		.46	
<b>Estrogen-Progestin Only</b>				
No use	351	1.0 (Referent)	379	1.0 (Referent)
<2	14	1.0 (0.6-1.8)	12	1.3 (0.7-2.3)
2-<4	12	1.1 (0.6-2.0)	10	1.5 (0.8-2.9)
≥4	26	2.0 (1.3-3.0)	13	1.3 (0.7-2.4)
Increase in RR per year of use (95% CI)	0.12 (0.02-0.25)		0.04 (-0.03 to 0.17)	
$P$ value for trend	.01		.28	

\*RR indicates relative risk; CI, confidence interval. Relative risks are adjusted for attained age, age at menopause, education, mammographic screening, and BMI.

**Figure.** Observed Relative Risks and Fitted Linear Excess Relative Risk Model Associated With Duration of Estrogen-Only and Estrogen-Progestin-Only Use Among Recent Users



Solid squares indicate observed relative risks (RRs); error bars, 95% confidence intervals (CIs). The solid line indicates the fitted linear excess RR; the dashed lines indicate 95% CIs. Observed RRs are plotted at the person-year weighted mean value for duration of use for categories of estrogen-only use and estrogen-progestin-only use. The number of cases in each category is also shown. For estrogen-progestin-only use, the upper limits of the 95% CIs for 10-year duration (2.86) and for the linear excess RR (2.64) are not shown.

**Table 3.** Relative Risks Associated With Estrogen-Only and Estrogen-Progestin-Only Use Among Recent Users With BMI ≤24.4 kg/m<sup>2</sup> According to Extent of Invasive Disease\*

Duration of Use, y	All Invasive		Invasive, Node Negative		Invasive, Node Positive		Invasive, <2 cm		Invasive, ≥2 cm	
	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
<b>Estrogen Only</b>										
No use	257	1.0 (Referent)	171	1.0 (Referent)	53	1.0 (Referent)	109	1.0 (Referent)	56	1.0 (Referent)
<8	56	1.0 (0.7-1.3)	34	0.9 (0.5-1.5)	19	1.7 (0.9-2.9)	23	1.1 (0.7-1.7)	19	1.3 (0.7-2.2)
8-<16	64	1.7 (1.2-2.3)	45	1.8 (1.3-2.6)	11	2.4 (0.7-3.0)	31	2.0 (1.3-3.2)	15	1.9 (1.0-3.6)
≥16	49	1.5 (1.1-2.2)	32	1.4 (0.9-2.1)	14	1.2 (0.5-2.0)	24	1.5 (0.9-2.6)	10	2.0 (0.9-4.4)
Increase in RR per year of use (95% CI)†	0.04 (0.01-0.06)		0.03 (0.004-0.06)		0.10 (0.03-0.22)		0.05 (0.01-0.10)		0.07 (0.01-0.16)	
<b>Estrogen-Progestin Only</b>										
No use	257	1.0 (Referent)	171	1.0 (Referent)	53	1.0 (Referent)	109	1.0 (Referent)	56	1.0 (Referent)
<4	20	1.1 (0.7-1.8)	11	0.9 (0.5-1.7)	3	0.7 (0.2-2.7)	13	1.4 (0.7-2.6)	4	1.2 (0.4-3.4)
≥4	18	1.9 (1.1-3.3)	9	1.3 (0.6-2.7)	5	2.4 (0.9-6.7)	14	3.1 (1.6-5.9)	0	...
Increase in RR per year of use (95% CI)†	0.13 (0.02-2.90)		0.02 (Undefined-0.19)		0.21 (0.003-0.65)		0.30 (0.09-0.65)		...	

\*RR indicates relative risk; CI, confidence interval; BMI, body mass index; and ellipses, data not applicable. Relative risks are adjusted for attained age, education, BMI, age at menopause, and mammographic screening.  
 †When CIs for increase in RR exclude 1.0, P values for trend are <.05.

**Table 4.** Relative Risks Associated With Duration of Estrogen-Only and Estrogen-Progestin-Only Use Among Recent Users With BMI ≤24.4 kg/m<sup>2</sup> According to Histology of Invasive Disease\*

Duration of Use, y	Tumor Histology			
	Ductal/Lobular		Ductal Only	
	No. of Cases	RR (95% CI)	No. of Cases	RR (95% CI)
<b>Estrogen Only</b>				
No use	145	1.0 (Referent)	128	1.0 (Referent)
<8	27	0.9 (0.6-1.4)	23	0.9 (0.6-1.4)
8-<16	36	1.7 (1.1-2.5)	32	1.6 (1.1-2.5)
≥16	32	1.5 (0.9-2.3)	28	1.5 (0.9-2.4)
Increase in RR per year of use (95% CI)	0.03 (0.01-0.07)		0.03 (0.001-0.07)	
P value for trend	.02		.04	
<b>Estrogen-Progestin Only</b>				
No use	145	1.0 (Referent)	128	1.0 (Referent)
<4	17	1.3 (0.8-2.3)	13	1.1 (0.6-2.1)
≥4	16	2.5 (1.4-4.4)	13	2.2 (1.2-4.2)
Increase in RR per year of use (95% CI)	0.17 (0.02-0.41)		0.17 (0.02-0.41)	
P value for trend	.002		.01	

\*RR indicates relative risk; BMI, body mass index; CI, confidence interval. Relative risks are adjusted for attained age, age at menopause, education, mammographic screening, and BMI.

creases in risk of both early- and later-stage invasive disease (TABLE 3). Estrogen-progestin-only use was also associated with significant increases in risk of invasive cancer, but numbers were too small to draw conclusions regarding associations according to extent of invasive disease. There were no significant increases in risk of in situ disease associated with either regi-

men, but the number of cases was small. In recent users with BMI of 24.4 kg/m<sup>2</sup> or less, use of estrogen only and estrogen-progestin only were both associated with significant increases in risk of invasive tumors with ductal and/or lobular histologies (TABLE 4). Similar associations were evident when analyses were limited to invasive tumors with ductal histology. There were too few

cases with other histologies to examine these associations.

**COMMENT**

Our results suggest that the combined estrogen-progestin regimen is associated with greater increases in breast cancer risk than estrogen alone. These results are consistent with those from the recent collaborative analysis, although in that analysis, the effect of the combined estrogen-progestin regimen was evaluated among women who may also have used estrogen alone.<sup>1</sup> Recently published data also support a more adverse effect on the breast with the estrogen-progestin regimen than with estrogen alone.<sup>7</sup>

Assessing the comparative risk of estrogen alone vs estrogen-progestin was complicated by the fact that use of estrogen alone was associated with increased risk in lean but not heavy women. We found differences between the 2 regimens among lean women but were unable to draw conclusions among heavier women. In the collaborative reanalysis, associations without regard to type of hormone were evident in lean but not heavy women.<sup>1</sup>

Among lean women, we found no evidence that associations differed according to extent of disease. In the collaborative reanalysis, increases in risk

were greater for localized than distant disease, but results according to extent of disease were not reported in lean women.<sup>1</sup> We also found significant increases in risk for the vast majority of invasive tumors classified as lobular and/or ductal carcinomas, results that are not consistent with those of Gapstur et al.<sup>8</sup> Their categories for duration of use ( $\leq 5$  or  $> 5$  years) may have obscured an effect of long-term use; in addition, they did not present results among lean women. In a survival analysis based on a different series of cases, we found that the reduction in breast cancer mortality among current hormone users at diagnosis was not due to earlier-stage disease or tumors with more favorable histologies in hormone users compared with nonusers,<sup>9</sup> consistent with the current analysis.

The biological mechanisms underlying an effect of exogenous hormones on the breast are complex. In a study of proliferation of normal human breast tissue implanted into athymic nude mice, there appeared to be a maximally effective dosage of estradiol in regard to breast cell proliferation beyond which higher dosages had no effect.<sup>10</sup> This phenomenon may explain the lack of effect of exogenous estrogen on breast cancer risk in heavy women, who have relatively higher endogenous estrogen levels than lean women due to nonovarian synthesis of estrone as a result of the peripheral conversion of androgens. The fact that progesterone does not down-regulate estrogen and progesterone receptors in the breast may contribute to its adverse effects.<sup>10,11</sup> Moreover, the isozyme of  $17\beta$ -hydroxysteroid dehydrogenase induced by progesterone in the breast predominantly catalyzes the conversion of the less potent estrone to the more potent estradiol.<sup>12</sup>

Several methodological issues need to be considered in interpreting our results. The pattern of greater increases in risk associated with the estrogen-progestin regimen than with estrogen alone was evident when subjects with an unknown age at menopause were both included and excluded, although

the disparity between the associations was slightly smaller when they were excluded. The lack of statistical significance for the test of the homogeneity of the associations of the 2 regimens after exclusion of those with an unknown age at menopause most likely resulted from the elimination of 17% of person-years and 20% of cases in the study, which reduced the information available for estimating increases in the RRs. We chose to present our main findings including women with an unknown age at menopause because age at menopause was not a substantial confounder of the hormone associations in these data and because excluding these women resulted in a substantial loss of information. Moreover, the estimates including and excluding these women were not meaningfully different, given the uncertainty in the estimates.

Although we were not able to completely account for differences in mammographic screening according to hormone use, it is reassuring that results were similar when we restricted analyses to those who had undergone annual mammographic screening. Moreover, similar differences have been noted in other populations where mammographic screening is widespread<sup>7</sup> or where differences in mammographic screening have been taken into account in assessing risk of HRT.<sup>13</sup>

Although our study may be subject to problems of recall in the reporting of menopausal hormone use,<sup>14</sup> such misclassification would most likely dilute the magnitude of the relationship between HRT and breast cancer risk. The fact that some episodes of hormone use that occurred before breast cancer diagnosis were reported after diagnosis raises the possibility of differential recall by cases and noncases. However, our results with regard to recency of use are very similar to those from a cohort study in which all hormone use was reported before diagnosis.<sup>13</sup> Moreover, in another cohort study in which all hormone use was reported before diagnosis, the estrogen-progestin regimen also was associated with greater increases in risk than estrogens alone.<sup>7</sup> Finally, in an early case-

control study based on this study population in which hormone use was validated, there was no evidence of differential reporting of hormone use by cases and controls.<sup>15</sup>

Our results, as well as those of others, suggest that in weighing the risks and benefits of menopausal HRT, it is important to consider the type of hormone regimen as well as individual characteristics of the woman, such as body mass index.

**Acknowledgment:** We are indebted to Leslie Carroll and Heather Clancey of IMS Inc, Rockville, Md, for computer support.

#### REFERENCES

1. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy. *Lancet*. 1997;350:1047-1059.
2. Schairer C, Byrne C, Keyl PM, et al. Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States). *Cancer Causes Control*. 1994;5:491-500.
3. Breslow NE, Day NE. *Statistical Methods in Cancer Research: The Design and Analysis of Cohort Studies*. Lyon, France: International Agency for Research on Cancer; 1987.
4. Preston DL, Lubin JH, Pierce DA, McConney ME. EPICURE [software]. Release 2.0. Seattle, Wash: HiroSoft International Corp; 1996.
5. Baker LH. Breast Cancer Detection Demonstration Project. *CA Cancer J Clin*. 1982;32:194-225.
6. Pike MC, Ross RK, Spicer DV. Problems involved in including women with simple hysterectomy in epidemiologic studies measuring the effects of hormone replacement therapy on breast cancer risk. *Am J Epidemiol*. 1998;147:718-721.
7. Persson I, Weiderpass E, Bergstrom R, Schairer C. Risks of breast and endometrial cancer after estrogen and estrogen-progestin replacement therapy. *Cancer Causes Control*. 1999;10:253-260.
8. Gapstur SM, Morrow M, Sellers TA. Hormone replacement therapy and breast cancer with a favorable pathology. *JAMA*. 1999;281:2091-2097.
9. Schairer C, Gail M, Byrne C, et al. Estrogen replacement therapy and breast cancer survival in a large screening study. *J Natl Cancer Inst*. 1999;91:264-270.
10. Laidlaw IJ, Clarke RB, Howell A, et al. The proliferation of normal human breast tissue implanted into athymic nude mice is stimulated by estrogen but not progesterone. *Endocrinology*. 1995;136:164-171.
11. Hargreaves DF, Knox F, Swindell R, Potten CS, Bundred NJ. Epithelial proliferation and hormone receptor status in the normal post-menopausal breast and the effects of hormone replacement therapy. *Br J Cancer*. 1998;78:945-949.
12. Poutanen M, Isomaa V, Peltoketo H, Vihko R. Role of  $17\beta$ -hydroxysteroid dehydrogenase type 1 in endocrine and intracrine estradiol biosynthesis. *J Steroid Biochem Mol Biol*. 1995;55:525-532.
13. Colditz GA, Hankinson SE, Hunter DJ, et al. The use of estrogens and progestins and the risk of breast cancer in postmenopausal women. *N Engl J Med*. 1995;332:1589-1593.
14. Greendale GA, James MK, Espeland MA, Barrett-Connor E, for the PEPI Investigators. Can we measure prior postmenopausal estrogen/progestin use? *Am J Epidemiol*. 1997;146:763-770.
15. Brinton LA, Hoover RN, Szklo M, et al. Menopausal estrogen use and risk of breast cancer. *Cancer*. 1981;47:2517-2522.

the cap, whether in quarterly or annually capped plans, we identified the first month of the year in which the capped limit was exceeded. Unlike Rector, we were not able to identify and exclude members who disenrolled nonvoluntarily. Like Rector, we used an extended Cox model with the internally defined time-dependent variable of reaching the cap to analyze the relationship between reaching the cap and disenrollment from the health plan.<sup>2</sup> Models were estimated for each plan and each year controlling for participant age, sex, and chronic disease score.<sup>3</sup>

**Results.** The percentages of members reaching their annual prescription cap for plans A, B, and C, respectively, were 22.6%, 0.7%, and 1.6% in 1997 and 12%, 4.1%, and 3.9% in 1998. Disenrollment rates among those enrolled in the first 3 months of each year for plans A, B, and C, respectively, were 19.3%, 28.9%, and 6.8% in 1997 and 10.4%, 22.9%, and 14.0% in 1998. Among those disenrolling in 1997, 21%, 7%, and 7%, respectively, re-enrolled in 1998.

The risk of disenrollment across all plans and both years was significantly associated with older age, greater disease burden (ie, higher chronic disease score), and reaching the cap. In 1997, the relative risks (RRs) of disenrollment in any given month for those reaching the cap for the 3 plans were 2.62 (95% confidence interval [CI], 2.15-3.19), 2.21 (95% CI, 1.70-2.88), and 2.24 (95% CI, 1.43-3.50); in 1998, the RRs of disenrollment were 3.04 (95% CI, 2.40-3.86), 1.79 (95% CI, 1.12-2.86), and 2.30 (95% CI, 1.86-2.86) in plans A, B, and C, respectively.

**Comment.** Exhaustion of prescription coverage, whether administered on a quarterly or annual basis, was associated with a 2- to 3-fold increase in the RR of disenrollment. These findings expand on those of Rector and suggest that this relationship holds under various scenarios including variation in underlying use, cap amounts, and cap administration.

Emily R. Cox, PhD  
Brenda R. Motheral, PhD  
Kathi Fairman, MA  
Express Scripts Inc  
Maryland Heights, Mo

**Funding/Support:** This research was funded by The Robert Wood Johnson Foundation's Changes in Health Care Financing and Organization (HCFO) Initiative.

1. Rector TS. Exhaustion of drug benefits and disenrollment of Medicare beneficiaries from managed care organizations. *JAMA*. 2000;283:2163-2167.
2. Crowley J, Hu M. Covariance analysis of heart transplant data. *J Am Stat Assoc*. 1977;72:27-36.
3. Clark DO, Korff MV, Saunders K, Baluch WM, Simon GE. A chronic disease score with empirically derived weights. *Med Care*. 1995;33:783-795.

## CORRECTIONS

**Incorrect Unit of Measure and Numbers:** In the Original Contribution entitled "Cognitive-Behavioral Therapy, Imipramine, or Their Combination for Panic Disorder" published in the May 17, 2000, issue of THE JOURNAL (2000;283:2529-2536), the units of measure for imipramine and desipramine should be ng/mL instead of ng/dL on page 2532 and ng/mL instead of mg/mL on page 2535. On page 2530 under "Study Design" patients randomized to CBT+placebo should number 5 per block of 24, not 25. In the "Treatment Conditions" section on page 2531, near the end of the third paragraph, ". . . the dosage [of imipramine] could be increased up to 300 mg/d by week 5" should read "week 7."

**Author Omitted:** In the Caring for the Critically Ill Patient article entitled "Ketoconazole for Early Treatment of Acute Lung Injury and Acute Respiratory Distress Syndrome" published in the April 19, 2000, issue of THE JOURNAL (2000;283:1995-2002), an author was inadvertently omitted from the ARDS Network listing on page 2002. Brian Christman, MD, should have been listed with the Vanderbilt University group and identified as an author.

**Acknowledgment Omission:** In the Original Contribution entitled "Menopausal Estrogen and Estrogen-Progestin Replacement Therapy and Breast Cancer Risk" published in the January 26, 2000, issue of THE JOURNAL (2000;283:485-491), acknowledgments were omitted. The authors wish to thank the Breast Cancer Detection Demonstration Project study participants as well as Susan Englehart, Cathy Ann Grundmayer, and the staff at Westat Inc, Rockville, Md, for conduct of the Breast Cancer Detection Demonstration Project Follow-up Study.

**Incorrect Data in Table:** In the Original Contribution entitled "Estrogen Replacement Therapy for Treatment of Mild to Moderate Alzheimer Disease: A Randomized Controlled Trial" published in the February 23, 2000, issue of THE JOURNAL (2000;283:1007-1015), incorrect data appeared in Table 3 on page 1013. In the placebo group column, the mean (SD) changes in scores at 12 months for the Emotional Face Recognition Test and the Grooved Pegboard Test should have been -5.7 (22.4) and -5.2 (42.4), respectively.

**Photo Misidentification:** In the Medical News & Perspectives article entitled "Psychiatrists Help Survivors in the Balkans" published in the March 8, 2000, issue of THE JOURNAL (2000;283:1277-1278), the photo on page 1278 identified as Ismet Ceric, MD, should have been identified as Vlado Jukić, MD.

**Acknowledgment Omission:** In the Original Contribution entitled "Vaginal Misoprostol Administered 1, 2, or 3 Days After Mifepristone for Early Medical Abortion: A Randomized Trial" published in the October 18, 2000, issue of THE JOURNAL (2000;284:1948-1953), an acknowledgment was omitted. The authors wish to acknowledge the contributions of Larry Lader, president of the Abortion Rights Mobilization, for making the study possible.