

# Menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer (United States)

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This study examines the relationship between menopausal estrogen and estrogen-progestin replacement therapy and risk of breast cancer, focusing on whether associations differ according to whether the tumors are *in situ* or invasive. Data are from a prospective study conducted 1980-89 on 49,017 selected participants in the Breast Cancer Detection Demonstration Project, a five-year screening program conducted between 1973 and 1980 in the United States. Overall, the rate ratio for estrogen-only use compared with no-hormone use was 1.0, and that for the estrogen-progestin combination was 1.2 (95 percent confidence interval [CI] = 1.0-1.6). However, the associations differed according to whether the tumors were *in situ* or invasive. The rate ratios of *in situ* breast cancer associated with use of estrogens alone and the combination regimen were 1.4 (CI = 1.0-2.0) and 2.3 (CI = 1.3-3.9), respectively. Duration of estrogen-only use also was associated with risk of *in situ* tumors, with users for 10 or more years at twice the risk of nonusers ( $P$ -value for trend test = 0.02). Duration of use was not associated with risk of invasive cancer. Our results are consistent with the hypothesis that hormone replacement therapy is related to earlier-stage breast cancer; however, the possibility that the results reflect increased breast cancer surveillance among those taking hormones cannot be ruled out. *Cancer Causes and Control* 1994, 5, 491-500

**Key words:** Breast cancer, estrogens, hormone replacement therapy, progestins, United States.

## Introduction

Estrogen replacement therapy (ERT) has been used commonly in the United States for the treatment of menopausal symptoms since the 1960s. By 1990, Premarin, a conjugated estrogen, was the fourthmost prescribed drug in the US,<sup>1</sup> with 32 percent of women aged 50 to 65 years reporting current use in one survey.<sup>2</sup> In the past decade, there has been a trend toward the concomitant use of progestins to offset the increased risk of endometrial cancer associated with ERT. By 1986,

28 percent of oral estrogens were prescribed in combination with a progestin.<sup>3</sup>

Although exogenous menopausal estrogens have been suspected of increasing the risk of breast cancer, numerous studies have failed to resolve the relationship. Some, but not all, studies<sup>4-10</sup> have reported relative risks ranging from 1.3 to 2.3 for 10 to 15 or more years of estrogen use. A case-control study<sup>5</sup> of women with breast cancer diagnosed during the Breast Cancer

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Detection Demonstration Project reported a stronger association with duration of use for *in situ* than invasive breast cancer. Recently, current use of estrogens was found to be a stronger predictor of risk than duration of use.<sup>11</sup>

Due to the more recent popularity of the use of estrogens in combination with progestins, only limited data regarding the effect of combined menopausal estrogen-progestin replacement therapy (EPRT) on the risk of breast cancer are available. However, there is some suggestion that the combined regimen may affect risk of breast cancer more adversely than estrogens alone.<sup>8</sup>

In the present analysis, the relationship between menopausal estrogen and EPRT and risk of breast cancer was examined in a follow-up study of 49,017 participants in a breast-cancer screening program. The large size of the study afforded the opportunity to examine different parameters of estrogen and estrogen-progestin use, including duration and currency of use, and to examine associations separately for *in situ* and invasive tumors.

### Materials and methods

The study subjects were participants in the Breast Cancer Detection Demonstration Project (BCDDP), a breast-cancer screening program conducted between 1973 and 1980. Sponsored by the American Cancer Society and the US National Cancer Institute (NCI),

the BCDDP provided up to five, annual, breast examinations to 283,222 women at 29 screening centers in 27 cities throughout the US. A follow-up study of a subset of the BCDDP participants was begun by the NCI in 1979 (Table 1). It included: (i) all participants who received a diagnosis of breast cancer during the five-year BCDDP screening program ( $n = 4,275$ ); (ii) all who underwent breast surgery during the screening period, with no evidence of malignant breast disease ( $n = 25,114$ ); (iii) all who had recommendations by the Project for a surgical consultation, but did not have either a biopsy or aspiration performed ( $n = 9,628$ ); and (iv) a sample of women who had neither surgery nor recommendation for surgical consultation during screening participation ( $n = 25,165$ ).

The follow-up study was carried out in two phases (Table 1). The first phase was conducted between 1979 and 1986 and involved the administration of a baseline telephone interview and up to six, but usually four, annual telephone interviews by personnel at the BCDDP screening centers. The second phase involved the administration of one mailed questionnaire between 1987 and 1989. Nonrespondents to the mailed questionnaire were interviewed by telephone, if possible.

Information collected at the baseline interview included recognized breast-cancer risk-factors, breast cancer screening by physical examination and mammography since the end of the BCDDP, and breast procedures undergone since the last examination by

**Table 1. Breast Cancer Detection Demonstration Project**

Recruitment (1973-75)	283,222 Screenees				
	Cancers	Benigns	Recommended	Normals	
Selected for follow-up →	4,275	25,114	9,628	25,165	= 64,182
Answered Phase I baseline Interview (1979-80) →	3,729	24,405	9,103	24,197	= 61,434
Annual Interviews (1980-86)					
Eligible for continuation of follow-up →	3,382	23,992	8,913	23,789	= 60,076
Completed phase II Interview (1987-89) →	2,773	20,908	7,390	20,623	= 51,694

the screening program. In addition, information was collected on duration of, and age at first use of, birth control pills and female hormones other than birth control pills (excluding creams). Annual telephone interviews updated the information collected in the previous interview. During the second phase of the study, information was collected on breast procedures since the previous interview and risk factor information collected previously was updated; in addition, information was collected on ever-use of menopausal estrogens and progestins in the same month, duration of use of estrogens in combination with progestins, age at first use of progestins, and number of days in the month progestins were used. Thus, data on progestin use were available only for women who completed the second-phase interview. Information on physical and mammographic examinations of the breast was not obtained during the second phase of the study. Level of education, income, and measured height and weight were available from forms completed during the screening program.

The present analysis was limited to women who did not have a menstrual period for at least three months prior to an interview for one of the following reasons: a natural menopause; a bilateral oophorectomy with or without hysterectomy; or a hysterectomy with at least one ovary retained. Women with uncertain ages at menopause or types of menopause were excluded (two percent of the cohort). Also excluded were those who reported bilateral prophylactic mastectomies or a diagnosis of breast cancer before the start of follow-up. Thus, cases of breast cancer diagnosed during the BCDDP ( $n = 4,275$ ), which were included in the analysis of Brinton *et al.*,<sup>3</sup> were excluded from the present analysis. Also excluded were cases of breast cancer diagnosed between the end of the screening program and the start of the follow-up study, including those diagnosed among women who had a recommendation by the BCDDP for surgical consultation, but did not have surgery performed. Premenopausal cases of breast cancer also were excluded. The majority of the study subjects were White (89 percent), with small percentages of Blacks (five percent) and Asian-Americans (five percent).

After all exclusions, 49,017 subjects were available for analysis. A total of 42,020 of these (86 percent of non-cases; 85 percent of cases) completed a second-phase interview. Interviews were not completed by four percent of subjects due to death; one percent due to illness; three percent due to refusal; five percent because interviews were not completed before the close of the study (June 1989); and one percent who could not be located.

During the follow-up period, 1,185 cases of breast

cancer were identified among the study subjects through self-reports and reports of breast cancer on death certificates; pathology reports were obtained on ninety-two percent. Pathology reports were not obtained for eight percent of the self-reported cases largely due to nonresponse by hospitals and physicians. Because the accuracy of self-reporting was high among those with pathology reports (97 percent were confirmed), self-reported cancers without pathology reports were included in the analyses as invasive cancers. A total of 13 percent of the identified cancers were *in situ* and 87 percent invasive. Due to considerable missing data on tumor size, we were unable to determine stage of the invasive cancers.

Incidence rates of breast cancer were calculated with person-years (PY) of follow-up as the denominator. Follow-up was started at the date of the baseline interview or the date of menopause, whichever was later. For women who stopped menstruating because of a hysterectomy, but who retained at least one ovary, the date of menopause was defined as the date of hysterectomy or the date associated with the median age at natural menopause in the cohort (52.75 years), whichever was later. Person-years accrued until the earliest of the following dates: diagnosis of breast cancer; a second prophylactic mastectomy; death; or date of last contact.

Rate ratios (RR) and 95 percent confidence intervals (CI) were estimated by Poisson regression. The potential confounding variables shown in Table 2 were included in particular models only if they changed the estimates associated with hormone use. For all analyses, the following variables were considered time-dependent: age; use of female hormones for menopausal reasons; presence of benign breast disease; and mammographic examinations of the breast.

To analyze use of hormones in a time-dependent manner, periods of use were reconstructed using dates of interview. Use of female hormones other than birth control pills that occurred more than five years before the date of menopause (reported by eight percent of the cohort) was considered unrelated to menopause and was evaluated as a separate variable. Adjustment for this variable did not change the estimates associated with menopausal hormone use. Analyses were done both excluding and including study subjects with hormone use that occurred five years or less before the start of menopause. Because analyses limiting study subjects to nonusers and those who started using hormones after their date of menopause were similar to those that included study subjects with hormone use that occurred five years or less before the start of menopause, only the latter are presented. For deceased subjects and subjects who were known to be alive at the

end of follow-up but who did not complete a mailed questionnaire, information on exposure to hormones was not ascertained between the last interview date and the exit date. Hormone status subsequent to the last interview was assumed to be the same as that last reported for nonusers or past users of hormones. For 'current' users of menopausal hormones at their last Phase I interview who did not complete a mailed questionnaire, PYs subsequent to the last interview were classified as 'unknown' for currency and duration of use.

Person-time was allocated initially into the following exposure categories: non-hormone use; use of estrogens only; use of estrogens combined with progestins; use of estrogens with progestin use uncertain; and use of estrogens with progestin use not ascertained. Cases and PYs with uncertain or unascertained progestin use had a similar distribution to those associated with estrogen only use according to type of menopause and currency of hormone use. Therefore, these categories of cases and PYs were included in the estrogen-only category. Thus, progestin use was not ascertained for 11 percent of the PYs in the estrogen-only category and was uncertain for 16 percent. Among the cases in this category, progestin use was not ascertained for 13 percent and was uncertain for 21 percent. Results regarding estrogen-only use were unchanged when these PYs and cases were excluded. In addition, results essentially were unchanged when women who did not complete a Phase II interview were excluded from the analyses.

To include exposure most likely to have been causal, exposure was assessed up until one year prior to the diagnosis of breast cancer for the cases and the equivalent age for non-cases for all time-dependent variables except mammographic breast examinations. Mammographic breast examinations were ascertained until diagnosis for breast cancer cases and the equivalent time for non-cases. Thus, current users of hormones were defined as those reporting use one year prior to a diagnosis of breast cancer or the equivalent age for non-cases.

To assess the extent to which the associations with hormone use were modified by other breast cancer risk-factors, observed RRs at each level of hormone use and the potential effect modifiers were compared with those expected under an additive model.

## Results

A total of 313,902 PYs were accumulated for the 49,017 study subjects. The mean duration of follow-up was 6.4 years, with a median of 7.2 years, a maximum of

**Table 2.** Prevalence of estrogen and estrogen-progestin use according to selected factors

Risk factor	No hormone use	Estrogen only	Estrogen-progestin	Total
	%	%	%	Person-years
<b>Age</b>				
< 55 years	53	39	8	70,157
55-64 years	45	47	7	151,056
65-74 years	41	53	5	71,180
75+ years	54	41	2	21,508
<b>Menopause type<sup>a</sup></b>				
Natural	61	32	6	189,290
Hysterectomy	31	58	6	58,477
Bilateral oophorectomy	20	73	7	66,135
<b>Age at menopause<sup>a</sup></b>				
< 40 years	29	65	6	44,453
40-44 years	34	59	6	50,070
45-49 years	47	46	6	99,925
50-54 years	58	35	7	103,261
≥ 55 years	63	30	6	16,190
<b>Biopsied benign breast disease<sup>a</sup></b>				
No	47	46	6	112,665
Biopsy recommended	51	42	6	35,579
≥ 1 biopsy	45	48	7	165,657
<b>First-degree family-history of breast cancer<sup>a</sup></b>				
No	46	47	6	237,255
Yes	47	46	6	56,922
<b>Education<sup>a</sup></b>				
Post-graduate work	45	45	9	26,713
College graduate	47	44	9	33,519
Some college	43	49	7	72,312
High school	47	47	5	131,688
< High school	49	46	4	47,296
<b>Age at first livebirth<sup>a</sup></b>				
< 20 years	43	48	5	39,550
20-24 years	45	47	6	120,779
25-29 years	48	44	7	76,143
≥ 30 years	53	40	6	30,668
Nulliparous	45	47	6	46,383

<sup>a</sup> Percentages for this variable are age-standardized to the distribution of person-years in the total study population.

10.3 years and a minimum of less than one year. The average age at start of follow-up was 57.4 years.

Forty-six percent of the PYs in this study were associated with non-hormone use, 46 percent with estrogen-only use, and six percent with combined estrogen-progestin use. As shown in Table 2, the percentage of PYs associated with hormone use (combination of estrogen-only use and estrogen plus progestin use) varied substantially by type of menopause and age at menopause, with higher percentages of PYs associated with surgical menopause or meno-

**Table 3.** Rate ratios (RR) of breast cancer associated with ever-use and duration of estrogen and estrogen-progestin use

	Person-years	All cases			<i>In situ</i>			Invasive <sup>a</sup>		
		No.	RR	(CI) <sup>b</sup>	No.	RR	(CI) <sup>b</sup>	No.	RR	(CI) <sup>b</sup>
Ever-use <sup>c,d</sup>										
No	145,550	519	1.0	—	54	1.0	—	465	1.0	—
Estrogens only	145,940	566	1.0	(0.9-1.2)	78	1.4	(1.0-2.0)	488	1.0	(0.9-1.1)
Estrogens and progestins	19,969	90	1.2	(1.0-1.6)	18	2.3	(1.3-3.9)	72	1.1	(0.9-1.4)
Duration of estrogen-only use <sup>e,f,g</sup>										
< 5 years	73,345	276	1.0	(0.9-1.2)	30	1.1	(0.7-1.7)	246	1.0	(0.9-1.2)
5-9 years	28,780	105	1.0	(0.8-1.2)	16	1.5	(0.8-2.6)	89	1.0	(0.8-1.2)
10-14 years	20,393	76	1.0	(0.8-1.3)	17	2.1	(1.2-3.7)	59	0.9	(0.6-1.1)
15-19 years	8,597	51	1.2	(0.9-1.6)	8	1.8	(0.9-3.9)	43	1.1	(0.8-1.5)
≥ 20 years	3,978	41	1.2	(0.8-1.6)	7	2.0	(0.9-4.5)	34	1.1	(0.8-1.5)
Duration of estrogen-progestin use <sup>e,h,i</sup>										
< 2 years	8,633	47	1.5	(1.1-2.1)	11	3.3	(1.7-6.3)	36	1.3	(0.9-1.9)
2-3 years	3,345	12	1.0	(0.6-1.8)	5	3.9	(1.5-9.7)	7	0.7	(0.3-1.4)
≥ 4 years	3,805	20	1.4	(0.9-2.2)	1	0.7	(0.1-4.7)	19	1.5	(0.9-2.4)

<sup>a</sup> Includes cases not confirmed by pathology report.

<sup>b</sup> CI = 95% confidence interval.

<sup>c</sup> Excludes 10 cases (2 *in situ*, 8 invasive) and 2,440 person-years with uncertain hormone use.

<sup>d</sup> Adjusted for attained age and education.

<sup>e</sup> Reference group is no hormone use.

<sup>f</sup> Excludes 17 cases (all invasive) and 3,978 person-years with unknown duration of use.

<sup>g</sup> Adjusted for attained age.

<sup>h</sup> Excludes 11 cases (1 *in situ*, 10 invasive) and 4,185 person-years with unknown duration of use.

pause at early ages also associated with hormone use. Notably, a higher percentage of the PYs associated with hormone use among those undergoing surgical menopause compared with natural menopause involved estrogen-only use. The percentage of total PYs associated with estrogen-progestin use varied inversely with age (falling from eight percent among those less than 55 years to two percent in those 75 years of age or older) and directly with level of education (falling from nine percent among college graduates to four percent in those with less than a high school education). Hormone use did not vary substantially according to other factors; thus, only age, education, type of menopause, and age at menopause were evaluated as potential confounders in the analyses.

Overall, there was no association between ever-use of estrogens alone or estrogens used in combination with progestins and risk of breast cancer after adjustment for attained age and education (Table 3). However, the associations differed according to whether the tumors were *in situ* or invasive. Both estrogens alone and the combined regimen were associated with increased risk of *in situ* tumors (RR = 1.4 and 2.3, respectively), but not invasive tumors. Further adjustment for type of menopause and age at menopause did not alter these results.

There was also no association between duration of use of estrogens alone and risk of breast cancer in the

aggregate (Table 3). However, risk of *in situ* breast cancer rose with increasing duration of hormone use, with users for 10 or more years being at twice the risk of nonusers (*P*-value for the trend test 0.02). Long duration of use of estrogens alone was not associated with a significantly increased risk of invasive breast cancer. There was no alteration in these results after adjustment for type of menopause, age at menopause, and education.

For the total case series as well as for *in situ* and invasive tumors separately, there were no clear patterns of risk associated with duration of estrogen-progestin use, although the maximum duration of use that could be evaluated was only four or more years (Table 3).

In order to determine whether the increased risk of *in situ* breast cancer associated with the combined regimen actually reflected long-term estrogen use, we limited the analyses to those who had used estrogens for less than 10 years (this included 72 percent of *in situ* cases who had used the combined regimen). Among these women, the RR of *in situ* breast cancer associated with estrogen-progestin use was 2.1 (CI = 1.1-3.9), indicating that the increased risk associated with the combined regimen did not solely reflect risk associated with long-term estrogen use. Similarly, the RR associated with estrogen-progestin use among invasive cases who had used estrogens for less than 10 years was the same as that presented in Table 3.

**Table 4.** Rate ratios (RR) of breast cancer associated with estrogen and estrogen-progestin use

	Person-years	All cases			<i>In situ</i>			Invasive <sup>a</sup>		
		No.	RR <sup>b</sup>	(CI) <sup>c</sup>	No.	RR <sup>b</sup>	(CI)	No.	RR <sup>b</sup>	(CI) <sup>c</sup>
Recency of use <sup>a</sup>										
No	145,550	519	1.0	—	54	1.0	—	465	1.0	—
Estrogens only										
Current use	44,940	205	1.3	(1.1-1.5)	30	1.8	(1.1-2.7)	175	1.2	(1.0-1.5)
Past use	89,600	322	0.9	(0.8-1.1)	45	1.3	(0.9-1.9)	277	0.9	(0.8-1.1)
Estrogens and progestins										
Current use	11,728	49	1.2	(0.9-1.6)	11	2.4	(1.2-4.7)	38	1.0	(0.7-1.4)
Past use	7,101	37	1.4	(1.0-2.0)	6	2.3	(1.0-5.4)	31	1.3	(0.9-1.9)

<sup>a</sup> Includes cases not confirmed by pathology report.

<sup>b</sup> Adjusted for attained age and education.

<sup>c</sup> CI = 95% confidence interval.

<sup>d</sup> Excludes an additional 43 cases (4 *in situ*, 39 Invasive) and 12,538 person-years with uncertain recency of hormone use.

**Table 5.** Rate ratios (RR) of breast cancer associated with current and past duration of estrogen only use

	Person-years	All cases			<i>In situ</i>			Invasive <sup>a</sup>		
		No.	RR <sup>b</sup>	(CI) <sup>c</sup>	No.	RR <sup>b</sup>	(CI) <sup>c</sup>	No.	RR <sup>b</sup>	(CI) <sup>c</sup>
Current duration of estrogen-only use										
No hormone use	145,550	519	1.0	—	54	1.0	—	465	1.0	—
< 5 years	13,786	61	1.4	(1.1-1.8)	7	1.4	(0.6-3.1)	54	1.4	(1.1-1.9)
5-9 years	10,722	43	1.2	(0.9-1.7)	5	1.3	(0.5-3.2)	38	1.2	(0.9-1.7)
10-14 years	9,546	40	1.2	(0.8-1.6)	8	2.3	(1.1-4.8)	32	1.0	(0.7-1.5)
≥ 15 years	10,885	61	1.4	(1.1-1.8)	10	2.4	(1.2-4.9)	51	1.3	(1.0-1.7)
<i>P</i> -value for trend						0.04				
Past duration of estrogen-only use										
No hormone use	145,550	519	1.0	—	54	1.0	—	465	1.0	—
< 5 years	56,006	206	1.0	(0.8-1.2)	21	1.0	(0.6-1.6)	185	1.0	(0.8-1.2)
5-9 years	16,757	56	0.9	(0.7-1.2)	10	1.5	(0.8-3.0)	46	0.8	(0.6-1.1)
10-14 years	9,753	33	0.9	(0.6-1.2)	9	2.3	(1.1-4.7)	24	0.7	(0.5-1.1)
≥ 15 years	7,082	27	0.9	(0.6-1.4)	5	1.8	(0.7-4.4)	22	0.8	(0.5-1.3)
<i>P</i> -value for trend						0.11				

<sup>a</sup> Includes cases not confirmed by pathology report.

<sup>b</sup> Adjusted for attained age.

<sup>c</sup> CI = 95% confidence interval.

Risk associated with number of days in the month that progestins were used could not be evaluated effectively due to considerable missing data.

Overall, there was a 30 percent increase in the risk of breast cancer associated with current use of estrogens alone, but no increase in risk associated with past use (Table 4). The risk associated with current use derived more from the association with *in situ* (RR = 1.8) than invasive (RR = 1.2) breast cancer. There were no clear patterns of risk associated with recency of use of estrogens in combination with progestins.

RRs of breast cancer associated with duration of estrogen-only use among current and past users were examined to disentangle the effects of duration and currency of use (Table 5). Overall, risk of breast cancer was elevated slightly for all durations of use among current users but not among past users, suggesting a currency effect. However, risk of *in situ* breast cancer

rose with increasing duration of use among current users (*P*-value for trend test = 0.04), suggesting a duration effect. There was also some suggestion of a trend in risk with increasing duration among past users (*P*-value for trend test = 0.11). As with the total case series, the patterns of risk of invasive breast cancer suggested a currency rather than duration effect.

There were no clear trends in risk associated with age at first hormone use or years since first use. The RRs of *in situ* cancer associated with age at first use of hormones compared with nonuse were 1.0, 1.9, 1.4, 1.5, and 2.1 for less than 40 years, 40-44 years, 45-49 years, 50-54 years, and 55 years of age, respectively. Those for invasive cancer were 0.8, 0.8, 1.1, 1.2, and 1.0. RRs of *in situ* breast cancer associated with years since first use of hormones compared with nonuse were 2.1, 1.1, 1.5, 1.8, 0.9, 1.9, for less than five years, five to nine years, 10-14, 15-19, 20-24, and 25 or more years, respectively. Those

for invasive cancer were 1.2, 1.2, 0.9, 1.1, 1.0, and 0.9.

For invasive breast cancer, associations with ever-use of estrogens-only did not vary substantially according to a family history of breast cancer, a history of biopsied benign-breast disease, type of menopause, Quetelet's Index ( $\text{wt}[\text{kg}]/\text{ht}[\text{m}]^2$ ), or age. Numbers of cases were too few to evaluate interactions adequately for estrogen-progestin use or for *in situ* disease.

To address the possibility of increased surveillance and detection of breast cancer among hormone users, we examined the relationship between hormone use and mammographic screening in the five years following the screening phase of the BCDDP. After standardizing the percentages to the age distribution of the cohort, 29 percent of the PYs associated with nonuse of hormones occurred among those who had at least one screening mammogram during this period, compared with 31 percent of the PYs associated with estrogen-only use, and 40 percent of those associated with estrogen-progestin use. However, among those reporting at least one screening mammogram, the average number of such mammograms reported during Phase I of the study did not vary according to hormone use. When examined according to currency of hormone use, 36 percent of the PYs associated with current hormone use occurred among those who had at least one screening mammogram since the end of the BCDDP, compared with 29 percent of those associated with past hormone use; again, the average number of mammograms among those with at least one screening mammogram did not vary by hormone use. When analyses were limited to those reporting at least one screening mammogram during the five years following the screening phase of the BCDDP, results regarding ever-use (Table 6) and currency of use (Table 6) were generally similar to those for the entire dataset. In addition, duration of estrogen-only use among this subgroup was associated with risk of *in situ* breast cancer (RRs

were 1.1, 1.1, 1.7, for less than five years of use, five to nine years of use, and 10 or more years of use, respectively), but not invasive disease (RRs = 1.2, 0.8, 1.0).

## Discussion

In this study, we found elevations in the risk of *in situ* breast cancer with extended durations of menopausal estrogen use. For invasive cancers, there was no relationship with duration of use, consistent with some,<sup>4,12-15</sup> but not all studies.<sup>5,7-8,10-11,16-18</sup> There was a slight increase in the risk of invasive cancer with current estrogen use, as has been reported from several other cohort studies,<sup>11,15</sup> but only one<sup>10</sup> of a number of case-control studies.<sup>4,6-7,9,12-13</sup> The finding of a predilection of hormones to early-stage cancers is consistent with results from a case-control study based on cases diagnosed during the BCDDP screening program,<sup>5</sup> in which estrogen effects predominated among *in situ* tumors and smaller invasive tumors.

We found higher relative risks of *in situ* cancer associated with estrogen-progestin use than with use of estrogens alone. On the other hand, risk of invasive cancer was not associated with the combined regimen. Data on the effects of combination estrogen-progestin therapy are limited, and, to our knowledge, no other results regarding risk of *in situ* breast cancer have been published. However, several reports have suggested that the combined regimen is associated with a higher risk of invasive breast cancer<sup>8</sup> or breast cancer in general<sup>7,19</sup> than are estrogens alone. These include a study from Sweden,<sup>8</sup> where the most commonly used progestins are related structurally to testosterone rather than progesterone, as in North America. Other studies have reported a protective effect of the combined estrogen-progestin regimen,<sup>20-21</sup> no increase in risk with the combined regimen,<sup>9-10,22</sup> similar increases in risk with the combined regimen and estrogens

**Table 6.** Rate ratios (RR) of *in situ* and invasive breast cancer associated with menopausal estrogen and estrogen-progestin use among those who had at least one screening mammogram during phase I of the follow-up study

	Person-years	<i>In situ</i>			Invasive <sup>a</sup>		
		No.	RR <sup>b</sup>	(CI) <sup>c</sup>	No.	RR <sup>b</sup>	(CI) <sup>c</sup>
Hormone use							
No	42,466	20	1.0	—	153	1.0	—
Estrogens only	45,176	28	1.3	(0.7-2.3)	177	1.0	(0.8-1.3)
Current use	15,119	11	1.5	(0.7-3.1)	71	1.3	(1.0-1.7)
Past use	26,178	17	1.3	(0.7-2.6)	94	0.9	(0.7-1.2)
Estrogens and progestins	8,026	13	3.0	(1.5-6.1)	34	1.1	(0.8-1.6)
Current use	5,110	9	3.2	(1.4-7.2)	20	1.1	(0.7-1.7)
Past use	2,498	3	2.4	(0.7-8.3)	14	1.5	(0.9-2.6)

<sup>a</sup> Includes cases not confirmed by pathology report.

<sup>b</sup> Adjusted for attained age and education.

<sup>c</sup> CI = 95% confidence interval.

alone,<sup>11</sup> or higher risks with estrogens alone than with the combined regimen.<sup>18</sup>

Our observations of higher hormone-associated risks for *in situ* than invasive cancer and for the further enhancement of risk with combined estrogen-progestin therapy as compared with use of estrogens alone could reflect either surveillance bias, a latency effect, or biologic differences between the tumor types.

Although mammographic screening was more common among hormone users than nonusers in this study, results among those with at least one screening mammogram in the first five years of the follow-up study were similar to those for the entire dataset, suggesting that surveillance bias does not account totally for our findings. Further arguing against bias as an explanation for our findings is that our results regarding estrogen-only use are consistent with those from an analysis of cases detected during the BCDDP screening program, where all participants underwent mammographic screening.<sup>5</sup> However, without a complete screening history and information regarding the method of breast cancer detection, this potential bias cannot be ruled out.

Because the development of invasive cancer may follow *in situ* disease, the relative lack of association with invasive cancer may be due to an inadequate latency period, especially for combined therapy, which is a relatively recent exposure. The slightly increased risk of invasive breast cancer among past users of the combined regimen supports this interpretation.

Possible biologic explanations for our findings of an elevated risk of early-stage tumors in association with hormone replacement therapy may relate to differences in the presence of hormone receptors, through which hormones modulate cell activity.<sup>30</sup> Although estrogen-receptor status has not been linked consistently to tumor size and stage at diagnosis,<sup>30</sup> there have been reports of a decline in estrogen- and progesterone-receptor positive tumors with increasing advance of disease.<sup>31</sup> In addition, there is some evidence that *in situ* tumors are more frequently progesterone-receptor positive than invasive tumors.<sup>32</sup> Although ERT has not been associated with estrogen-receptor-positive tumors, this may be because the routinely used ligand-binding techniques to measure steroid receptors detect only those that are unbound to hormones.<sup>33</sup> To date, there are no data regarding the relationship between combined estrogen-progestin replacement therapy and risk of receptor-positive breast tumors. Further studies using monoclonal antibody techniques, which measure both bound and unbound receptors,<sup>30</sup> and which define receptor-positive tumors by the presence of both estrogen and progesterone receptors may assist in the interpretation of hormone-disease relationships.

In attempting to determine why the combined estrogen-progestin therapy might be related more adversely to breast cancer risk than estrogens alone, note must be made of the fact that hormones may increase the risk of breast cancer through enhanced cell proliferation, a feature common to all stages of the carcinogenic process.<sup>23</sup> Thus, hormones may increase the number of normal cells that are potential targets for initiating agents, the proliferation of initiated cells, or the growth of established cancer cells. Most studies have shown that breast cell proliferation is greatest during the luteal phase of the menstrual cycle, when levels of progesterone are at their highest.<sup>24-29</sup>

Other issues that bear on the interpretation of our results include the fact that self-reported estrogen and progestin use was not validated against medical records. Further, data regarding progestin use were collected after the diagnosis of breast cancer, raising the possibility that cases recalled their progestin use differently from non-cases. However, validation of other types of hormone use in several case-control studies indicates no differential misclassification by case-control status.<sup>34-35</sup> It is also unlikely that differential recall was a major factor in the finding of a stronger association with combined estrogen-progestin use for *in situ* than invasive breast cancer. However, the magnitude of the association of the combined regimen with *in situ* cancer would be attenuated if substantial numbers of those who reported that they were uncertain whether they had ever used progestins or whose progestin use was not ascertained had actually used progestins. In the extreme, if all person-years and the two '*in situ*' cases in the 'uncertain' progestin category were classified as combined estrogen-progestin users rather than estrogen-only users, the RR for *in situ* cancer associated with the combined regimen would be approximately the same as that associated with estrogen-only use. More realistically, if 16 percent of the PYs in this 'uncertain' category were classified in the estrogen-progestin category (*i.e.*, the percentage of PYs associated with progestin use among estrogen users whose progestin use was ascertained), the increased risk of *in situ* cancer associated with the combined regimen would still be approximately twofold.

It is also notable that the study cohort was at 30 percent higher risk of breast cancer than would be expected based on rates derived from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, largely reflecting the high prevalence in the cohort of women with a history of benign breast disease. The study subjects also had a higher prevalence of a family history of breast cancer than the general population. However, the associations between estrogen-only use and invasive breast cancer

did not differ according to either of these variables, suggesting that these results are applicable to other populations. Due to small numbers of cases, it was difficult to evaluate interactions adequately for *in situ* breast cancer and for combined estrogen-progestin use; thus, it is possible that these findings may not be generalizable.

Another issue that needs to be considered is the possibility of diagnostic inaccuracies in the classification of *in situ* breast cancer and certain benign lesions, specifically hyperplasia with and without atypia.<sup>36-37</sup> However, it is unlikely that misclassification of this sort would be differential according to hormone regimen.

Finally, in view of the small number of *in situ* cases, particularly those who had used estrogens in combination with progestins, our results must be interpreted cautiously and in conjunction with results from other studies.

The results of this study underscore the complexity of assessing the risks and benefits of hormone replacement therapy. Any increased risk of breast cancer associated with EPRT must be weighed against the beneficial effect of the combined regimen on the risk of endometrial cancer. The beneficial effects of hormone replacement therapy on bone loss after menopause and possibly on cardiovascular disease also need to be considered. Although there is some evidence that hormone-associated breast cancers have a relatively favorable prognosis, treatment for early stage breast cancer, even *in situ* tumors, is not trivial. In the past, mastectomy has been the standard treatment for ductal carcinoma *in situ*, with survival rates approaching 100 percent. With the advent of lumpectomy as a treatment option for invasive cancer, the management of carcinoma *in situ* has become more controversial.<sup>38</sup> Thus, to understand better the risks associated with hormone replacement therapy, future research should include evaluation of breast cancer risk by stage of disease.

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