Postmenopausal Estrogen and Progestin Use in Relation to Breast Cancer Risk[1]

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Abstract

Epidemiological evidence now consistently supports a modest increase in breast cancer risk among women using postmenopausal hormones, usually estrogens. Less is known regarding how the addition of progestin affects breast cancer risk. The objective of this study was to investigate the type and duration of postmenopausal therapy and breast cancer risk. We performed a multicenter population-based case-control study set in Massachusetts, New Hampshire, and Wisconsin. The subjects were 5298 postmenopausal women (age range, 50–79 years) with a new diagnosis of invasive breast cancer from statewide tumor registries. For comparison, 5571 controls were randomly selected from population lists. Participants completed a structured telephone interview covering hormone use and breast cancer risk factors. Multivariable regression models were used to estimate relative risks (RRs) and 95% confidence intervals (CIs). The RR for breast cancer increased with longer durations of hormone use, about 2%/year for estrogen alone (RR, 1.02; 95% CI, 1.01–1.03) and 4%/year for estrogen-progestin use (RR, 1.04; 95% CI, 1.01–1.08). Estrogen-progestin use that was both recent and long term (>5 years in duration) was more strongly associated with breast cancer risk (RR, 1.57; 95% CI, 1.15–2.14) than similar use of estrogen alone (RR, 1.39; 95% CI, 1.17–1.65). In estrogen-progestin users, risks were similar for sequential and continuous use regimens but perhaps stronger for lobular than ductal breast cancer. Use of progestin alone was associated with a doubling of risk (RR, 2.09; 95% CI, 1.07–4.07 for ever use *versus* nonuse). Estrogen-progestin use, both sequential and continuous, appears to be more strongly associated with risk of breast cancer than use of estrogen alone.

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Introduction

Postmenopausal hormone use has been consistently associated with a modest increase in breast cancer risk, about 35% for current users of ≥5 years, that dissipates after discontinuation (1–3). This risk profile is reassuring to women who use hormone therapy for the control of acute menopausal symptoms, but troubling for those who use long-term hormone therapy for its bone and potential cardiovascular benefits (4). More information is needed to identify patterns of use that are associated with greater risk, particularly the increasingly common addition of progestin to the estrogen regimen. Several studies have provided evidence that estrogen-progestin use is associated with greater increases in risk than estrogen alone, but these studies have been limited by the types of preparations used, the relatively small numbers of exposed women, and the short durations of use (5–9). Recent reports have also suggested that this association may differ according to histological type (9–11).

To estimate more precisely the breast cancer risks associated with combined estrogen-progestin use, we conducted a multicenter case-control study in middle-aged and older women.

Materials and Methods

Selection of Cases. All female residents of Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire with a new diagnosis of invasive breast cancer at 50–79 years of age were eligible for this study. Cases were identified by each state's cancer registry from January 1992 through December 1994. From each state registry, information was available on cancer site, histology, extent of disease, and follow-up physician. According to an institutionally approved protocol, the physician of record for each eligible case was contacted by mail to obtain permission to approach the subject. Eligibility was limited to cases with listed telephone numbers and drivers' licenses by self-report (if < 65 years old). Between 1992 and 1994, we identified 6839 eligible breast cancer cases. Of these cases, physicians refused contact for 158 (2.3%), 293 (4.3%) were deceased, 83 (1.2%) could not be located, and 620 (9.1%) refused to participate. Thus, data for 5685 case women (83%) were available for general analysis.

Selection of Controls. In each state, community controls were randomly selected from lists of licensed drivers (age 50–64 years) and from rosters of Medicare beneficiaries provided by the Health Care Financing Administration (age 65–79 years). Computer files of potential controls were obtained annually. Controls were selected at random within 5-year age strata to

yield an age distribution similar to that of the cases enrolled in each state. Eligible controls reported no previous diagnosis of breast cancer during the study interview and had a listed telephone number. Of the 7655 potential controls identified, 183 (2.4%) had died, 124 (1.6%) could not be located, and 1397 (18.2%) refused to participate. Thus, 5951 control women (78%) completed the study interview.

Ascertainment of Hormone Use and Other Exposures. Cases and controls were interviewed by telephone from July 1992 through July 1995. The 45-min interview elicited information on known or suspected risk factors for breast cancer including hormone use before diagnosis for cases or, for controls, before an assigned reference date that was based on the average date of diagnosis for similarly aged cases. For each postmenopausal hormone used, the date started, date stopped, total duration, and type of preparation were ascertained. To facilitate recall, women received a pictorial display of common preparations before the interview (12). The interview also covered reproductive experiences, physical activity, alcohol use history, selected dietary elements, height and weight, medical history, and demographic factors. Information about the women's screening practices, and personal and family histories of breast cancer was obtained at the end of the interview to maintain blinding. The interviewers remained unaware of the case-control status of the subjects until the end of the interview for 87% of cases and 96% of controls.

Reliability Substudy. To assess the reliability of the questionnaire, a sequential sample of case and control women from Wisconsin and Massachusetts was reinterviewed. After an average of 3.4 months (range, 2–6 months), 154 cases (71% of those asked to be reinterviewed) and 153 controls (71%) were successfully recontacted and reinterviewed. Cohen's κ and 95% CIs[3] measured the reliability of ever/never hormone use, and the intraclass correlation coefficient measured the reproducibility of reported duration (continuously) of hormone use. The κ for ever/never use of hormone therapy was 0.92 (95% CI, 0.86–0.99) among case women and 0.89 (95% CI, 0.82–0.97) among controls. The intraclass correlation coefficient for duration of hormone use was 0.83 (95% CI, 0.78–0.88) among cases and 0.86 (95% CI, 0.83–0.89) among controls.

Statistical Analyses. Postmenopausal hormone use was defined as the use of oral or transdermal noncontraceptive hormones, including estrogens and/or progestins, for 6 cumulative months or more. A woman was defined as a current user if she reported an episode of use of at least 6 months in duration within the 12-month-period prior to the reference date.

A subject was deemed "postmenopausal" if she reported a natural menopause or a bilateral oophorectomy before the diagnosis or reference date. Women who reported hysterectomy alone were considered as postmenopausal if their reference age was older than or equal to the 90th percentile of age at natural menopause for the control group (55 years for both smokers and nonsmokers). Menopausal status was considered unknown for women with hysterectomy without bilateral oophorectomy if their reference age was 50–54 years. Women who began postmenopausal hormone use before the cessation of menses were considered postmenopausal with unknown age at menopause.

ORs and 95% CIs obtained from logistic regression models were used to estimate RRs. Conditional logistic regression models were stratified on age (in years) and state; the covariates included were age at menopause (eight categories), type of menopause (natural, bilateral oophorectomy, other), age at first full-term pregnancy (four categories, plus nulliparous), body mass index (quartiles), family history of breast cancer (absent, present, unknown), education (four categories), mammography history (three categories), recent alcohol consumption (six categories), personal history of benign breast disease (absent, present, unknown), age at menarche (five categories), and recent physical activity (four categories). Tests of the difference in the RRs for estrogen only *versus* estrogen-progestin use were evaluated by the change in log likelihood of adding the cross-product of an indicator for progestin use and a term for duration of hormone use, expressed continuously, to a model including the continuous hormone duration term and all other covariates. Only women who used these regimens exclusively (and nonusers) were included in these analyses. Tests of the heterogeneity in the RR for duration of postmenopausal hormone use according to other variables (evaluated continuously) were conducted by comparing the change in log likelihoods in models with and without appropriate cross-product terms (13).

Subjects for Analysis. Hormone use was unknown for 239 cases and 215 controls, and these women were excluded. Women who reported an episode of use before 40 years of age without menopause (67 cases and 73 controls) were excluded. Women who reported unspecified injections (38 cases and 46 controls) and women with hormone use consisting only of hormone injections (17 cases and 23 controls) were excluded from analysis. Twenty-six case interviews and 23 control interviews considered unreliable by the interviewers were also omitted. After these exclusions, 5298 cases and 5571 controls were available for analysis.

Results

Compared with controls, women with breast cancer were more likely to have later age at menopause, later age at first birth or to be nulliparous, heavier body mass, a family history of breast cancer, higher educational attainment, and benign breast disease (Table 1). Overall, postmenopausal hormone users tended to be younger, of higher education, lower body mass, and more physically active than nonusers. Hormone users were also much more likely to report a history of recent mammography.

Ever Use of Estrogens. Among all breast cancer cases, 28% had ever used postmenopausal hormones, and in controls, the age-adjusted frequency was 25%. Most cases had used estrogen only (70%). The primary type of estrogen specified was conjugated estrogen (79% used Premarin). Compared with women who had never used postmenopausal hormones, the multivariate adjusted estimated RR for ever use of unopposed estrogen only use was 1.23 (95% CI, 1.09–1.39; Table 2). Risk for estrogen-only users was similar in women who reported a natural menopause.

Ever Use of Progestin. Of the estrogen-progestin users, most (73% of cases and 72% of controls) used only this combined regimen; 27% of cases and 28% of controls had used both unopposed estrogen and combined estrogen-progestin. Progestin was almost exclusively identified by participants as medroxyprogesterone acetate (86% reported Provera). Compared with women who never used postmenopausal hormones, the RR for ever use of estrogen-progestin only was 1.43 (95% CI, 1.18–1.74). RRs associated with estrogen-progestin use among women who had a natural menopause were slightly greater than those for the full study group (Table 2).

Among combined estrogen-progestin users, most women (85% of cases and 86% of controls) used progestins 10 or more

[3] The abbreviations used are: CI, confidence interval; RR, relative risk; OR, odds ratio; SE, standard error.

Table 1 Age-standardized[a] characteristics (%) of women with breast cancer and controls age 50–79 years, 1992–1994

Characteristic	Cases		Controls	
	Users (N = 1471)	Nonusers (N = 3827)	Users (N = 1439)	Nonusers (N = 4132)
Age (yrs)				
50–59	36	23	40	28
60–69	38	40	38	41
70–79	26	37	22	31
Age at menopause (yrs)[b]				
<45	26	18	33	22
45–54	52	60	47	58
≥55	10	14	10	13
Unknown	12	8	10	7
Type of menopause				
Natural	48	74	44	72
Surgical	50	20	54	22
Premenopausal	2	6	2	6
Age at first full-term pregnancy (yrs)				
≤19	13	12	14	15
20–29	66	66	69	66
≥30	9	10	7	9
Nulliparous	12	12	10	10
Body mass index quartile (kg/m^2)				
1 (13.2–22.6)	26	19	27	24
2 (22.7–25.3)	26	23	29	24
3 (25.4–29.0)	24	25	24	25
4 (29.1–56.7)	24	33	20	27
Family history of breast cancer				
No	79	78	86	86
Yes	21	23	14	14
Education				
No high school diploma	12	21	14	20
High school diploma	45	47	45	48
At least some college	43	32	41	32
Screening mammography history[c]				
Never	10	30	8	23
Less than annual	33	35	40	45
At least annual	57	35	52	32
Benign breast disease				
No	71	78	78	83
Yes	29	22	22	17
Recent alcohol intake (drinks/day)				
0	17	25	18	26
<1	65	58	64	60
≥1	18	17	18	14
Recent recreational physical activity				
None	23	30	17	27
Occasional/moderate	48	43	48	43
Frequent/vigorous	29	27	35	30
Age at menarche (yrs)				
<12	20	19	19	17
12	27	26	24	26
>12	53	55	57	57

[a] Control frequencies were adjusted to the age distribution of cases.
[b] Among postmenopausal women only.
[c] For the 5-year time period before the reference age.

days per month. Progestin added >21 days each cycle ("continuous" use) was associated with a RR of 1.54 (95% CI, 1.15–2.07), which was similar to the risk associated with sequential progestin added <10 days each cycle (RR, 1.57; 95% CI, 0.95–2.60). Women taking progestin only (without estrogen) had an almost 2-fold greater risk of breast cancer (RR, 2.09; 95% CI, 1.07–4.07).

Duration of Use. The average duration of use of estrogen alone (cases, 10.1 years; controls, 9.2 years) was greater than that of use of estrogen-progestin (cases, 4.7 years; controls, 4.5 years). Risk of breast cancer increased with duration of use of each type of hormone regimen (Table 3); the RR was 1.02 for unopposed estrogen use per year, with the 95% CI = 1.01–1.03 (*i.e.*, an increase of 2%/year). The increase in risk was greater among women who used estrogen in combination with progestin (P = 0.10), where each year of use was associated with a 4% increase in risk (95% CI, 1.01–1.08). These RRs were similar in ever users and current users. RRs diminished with increasing time since last use for estrogen-only users, and were not statistically significantly elevated after 5 years since last use

Table 2 RR of breast cancer according to ever use of postmenopausal hormones

Hormone use	All women				Women with natural menopause		
	Cases	Controls	RR[a] (95% CI)	RR[a,b] (95% CI)	Cases	Controls	RR[a,b] (95% CI)
Nonusers	3827	4132	1	1	2780	2919	1
Any use	1471	1439	1.14 (1.04–1.26)	1.28 (1.16–1.43)	691	616	1.32 (1.14–1.52)
Estrogen alone only	1007	1027	1.07 (0.97–1.19)	1.23 (1.09–1.39)	308	303	1.11 (0.92–1.34)
Estrogen with progestin only	315	286	1.36 (1.14–1.64)	1.43 (1.18–1.74)	279	245	1.51 (1.21–1.88)
Progestin added (days/month)[c]							
<10	39	36	1.52 (0.93–2.49)	1.57 (0.95–2.60)	33	29	1.69 (0.95–2.99)
10–21	90	127	0.92 (0.68–1.23)	0.96 (0.70–1.31)	81	106	1.04 (0.74–1.46)
>21	131	102	1.48 (1.12–1.97)	1.54 (1.15–2.07)	115	96	1.45 (1.06–1.99)
Both estrogen alone and estrogen with progestin	119	110	1.17 (0.88–1.56)	1.22 (0.91–1.64)	81	59	1.68 (1.15–2.46)
Progestin only	30	16	2.26 (1.17–4.34)	2.09 (1.07–4.07)	23	9	3.04 (1.31–7.03)

[a] Logistic regression models conditional on age and state.
[b] RRs have been adjusted for age at menopause, type of menopause, age at first full-term pregnancy, body mass index, family history of breast cancer, education, screening mammography history, recent alcohol consumption, history of benign breast disease, age at menarche, and recent physical activity.
[c] Determined by current regimen else highest number of days/month in former users.

Table 3 RR of breast cancer according to timing of postmenopausal hormone use

	Estrogen only			Estrogen with progestin only		
	Cases	Controls	RR[a] (95% CI)	Cases	Controls	RR[a] (95% CI)
Duration of use (yrs)						
All users						
<5	402	449	1.08 (0.92–1.27)	198	193	1.36 (1.07–1.73)
≥5	605	578	1.36 (1.17–1.58)	117	93	1.58 (1.16–2.15)
Continuous (per yr)[b,c]			1.02 (1.01–1.03)			1.04 (1.01–1.08)
			$P < 0.001$			$P = 0.005$
Current users						
<5	157	192	1.07 (0.84–1.37)	163	170	1.32 (1.02–1.70)
≥5	443	449	1.34 (1.12–1.59)	107	91	1.50 (1.09–2.06)
Continuous (per yr)[b]			1.02 (1.01–1.02)			1.04 (1.01–1.07)
			$P = 0.002$			$P = 0.01$
Time since last use (yrs)						
Current user	600	641	1.25 (1.08–1.45)	270	261	1.39 (1.12–1.71)
<5	84	53	1.76 (1.21–2.56)	31	19	1.71 (0.92–3.18)
5–9	54	50	1.22 (0.80–1.87)			
10–19	161	162	1.12 (0.87–1.43)	14	6	2.38 (0.82–6.87)[d]
≥20	107	112	1.04 (0.77–1.40)			
Continuous (per yr)[b]			0.99 (0.99–1.00)			0.98 (0.97–0.99)
			$P < 0.001$			$P < 0.001$

[a] Relative to nonusers (3827 cases and 4132 controls). Logistic regression models conditional on age and state. RRs were adjusted for age at menopause, type of menopause, age at first full-term pregnancy, body mass index, family history of breast cancer, education, screening mammography history, recent alcohol consumption, history of benign breast disease, age at menarche, and recent physical activity. Women who used both unopposed estrogen and estrogen-progestin are excluded.
[b] Includes nonusers.
[c] In the test of the difference in RRs for the duration of estrogen-only *versus* estrogen-progestin use, $\chi^2 = 2.64$, 1 degrees of freedom, $P = 0.10$. Among users of estrogen with progestin added <10 days/month, RR, 1.05; 95% CI, 0.99–1.12, $P = 0.1$, 10–21 days/month, RR, 1.03, 95% CI, 0.98–1.09, $P = 0.3$; >21 days/month, RR, 1.05, 95% CI, 1.00–1.10, $P = 0.05$.
[d] Estimate for time since last use ≥5 years.

(Table 3). This pattern could not be evaluated in combined therapy users because nearly all estrogen-progestin use was recent (only 14 cases discontinued use ≥5 years ago).

Variation by Other Risk Factors. Women who were at low risk of breast cancer (because of younger age, lean body mass, no family history of breast cancer, or low intake of alcoholic beverages) had slightly greater RRs of breast cancer associated with recent, long-term unopposed estrogen use than women in the higher risk categories (Table 4). The same patterns held for estrogen-progestin use as for estrogen-only use, except that the association appeared stronger in regular consumers of alcohol.

Histology and Extent of Disease. The RRs associated with ever use of estrogen and progestin were somewhat greater ($P = 0.006$) for lobular (RR, 2.01; 95% CI, 1.25–3.22) than for ductal disease (RR, 1.43; 95% CI, 1.14–1.79; Table 5), whereas RRs for estrogen-only use were similar for lobular (RR, 1.19) and ductal (RR, 1.22) histology. Use of estrogen alone and estrogen-progestin similarly increased risk of both localized breast cancer and more advanced disease. The increase in RR of localized breast cancer per year of estrogen-progestin use was greater than that for each year of estrogen-only use ($P = 0.05$).

Discussion

In this large case-control study, women who took combined estrogen-progestin regimens had a greater increase in breast cancer risk than users of estrogen alone. The increase in risk with each year of use was about twice as great for estrogen-

Table 4 RR of breast cancer associated with recent use of postmenopausal hormones (within 5 years of the reference age) and duration of use ≥5 years *versus* never use

	Estrogen only				Estrogen with progestin only			
	Cases	Controls	RR[a] (95% CI)	P^b	Cases	Controls	RR[a] (95% CI)	P^b
Overall	489	477	1.39 (1.17–1.65)		114	93	1.57 (1.15–2.14)	
Reference age (yrs)								
50–59	133	170	1.49 (1.12–1.98)		66	48	1.91 (1.25–2.90)	
60–69	222	198	1.41 (1.11–1.80)		41	36	1.35 (0.82–2.23)	
70–79	134	109	1.27 (0.95–1.71)	0.4	7	9	0.88 (0.31–2.49)	0.01
Body mass index quartile (kg/m^2)								
1 (13.2–22.6)	126	127	1.66 (1.22–2.25)		33	30	1.74 (1.00–3.04)	
2 (22.7–25.3)	121	123	1.26 (0.93–1.72)		32	29	1.51 (0.87–2.64)	
3 (25.4–29.0)	109	122	1.17 (0.85–1.60)		19	14	1.35 (0.63–2.89)	
4 (29.1–56.7)	110	83	1.46 (1.04–2.05)	0.3	24	16	1.50 (0.76–2.98)	0.8
Family history								
No	391	413	1.39 (1.16–1.67)		91	76	1.67 (1.18–2.35)	
Yes	94	63	1.33 (0.91–1.93)	0.8	23	17	1.25 (0.64–2.44)	0.9
Recent alcohol intake (drinks/day)								
None	96	85	1.71 (1.21–2.42)		12	11	1.35 (0.56–3.27)	
<1	306	306	1.46 (1.19–1.79)		75	67	1.49 (1.03–2.16)	
≥1	86	86	0.94 (0.65–1.35)	0.07	27	15	2.08 (1.05–4.11)	0.2
Self-reported screening mammography in the past 5 yrs								
Never	40	26	1.19 (0.69–2.06)		0	4	1.59 (0.90–2.83)[c]	
Less than annual	166	184	1.63 (1.26–2.11)		26	28		
At least annually	280	266	1.27 (1.02–1.58)	0.8	67	81	1.56 (1.08–2.24)	0.3

[a] Relative to nonusers (3827 cases and 4132 controls). Logistic regression models were conditional on age and state. RR was adjusted for age at menopause, type of menopause, age at first full-term pregnancy, body mass index, family history of breast cancer, education, history of screening mammography, recent alcohol consumption, history of benign breast disease, age at menarche, and recent physical activity. Women who used both unopposed estrogen and estrogen-progestin are excluded.
[b] Evaluated continuously when appropriate with hormone use represented by a continuous linear duration term. Tests include users with all durations and timings of use.
[c] Estimate for mammography never and less than annually combined.

progestin use as it was for estrogen-only use. Also, the risks associated with combined use were greater for lobular than for ductal histologies.

Our results for current or recent users of unopposed estrogen are consistent with the recent pooled analysis of 51 epidemiological studies of postmenopausal hormone use and breast cancer, which showed that the RR of breast cancer was slightly elevated and increased by 2.3% (95% CI, 1.1–3.6) for each year of use (1). No increased risk was observed for past users. In a recent population-based case-control study in Sweden (14), current use of estrogen alone was associated with a 2-fold elevation in risk, with a 2% increase/year of use; in follow-up of the Breast Cancer Detection Demonstration Project, there was a more modest RR of 1.20 (95% CI, 1.0–1.4) for recent users (5). In contrast, Ross *et al.* (8) reported no association with estrogen only, except in users with ≥15 years of use.

Estrogen-progestin use was uncommon in most earlier epidemiological studies that were included in the pooled analysis; hence, this large evaluation could not provide firm evidence of a relationship (1). Recent studies with more substantial combined use now show increased risk associated with the addition of progestin. In a preliminary analysis from the Nurses' Health Study, a greater annual increase in risk (9%; SE = 2.5) was associated with current use of estrogen-progestin combinations than with use of estrogen only (3.3%; SE = 0.84; Ref. 6). The recent Breast Cancer Detection Demonstration Project study reported significantly stronger effects among estrogen-progestin users than among estrogen-only users (P = 0.02), with an annual increase per year for recent estrogen-progestin users of 8% (95% CI, 0.02–0.16; Ref. 5). A slightly lower increase was reported in the case-control study of Ross *et al.* (RR, 1.24; 95% CI, 1.07–1.45 for 5 years of use; Ref. 8). Scandinavian studies also found significant additional risks associated with estrogen-progestin use (7, 14). The risk differential in these Scandinavian reports, however, was only observed in users of testosterone-derived progestins, usually in combination with higher-dose synthetic estrogens, which have a greater potency than natural estrogens and are not commonly prescribed in the United States (15). Increases in risk associated with use of combined hormones have not been observed in other reports (16–21), although all these studies included few women with sufficient long-term use to evaluate this association.

Our study is one of the few to examine the risks associated with the use of continuous *versus* sequential progestin regimens. Whereas we observed similar positive effects with both regimens, Ross *et al.* (8) reported that risk was higher with sequential regimens (OR, 1.38; 95% CI, 1.13–1.65) than with continuous regimens (OR, 1.09; 95% CI, 0.88–1.3). We did not observe an elevated RR associated with intermediate progestin use (10–21 days/cycle); however, the CI does not rule out a risk increase. In a Danish study, increased rates among users of combined sequential therapy were found, but not among those using other regimens (22). In contrast, another Scandinavian study reported evidence that continuous use was associated with greater breast cancer incidence than sequential use, although different preparations limit direct comparisons (14).

The relation we observed between postmenopausal hormones and breast cancer risk was generally similar in subgroups of women using postmenopausal hormones. Unlike previous evaluations that suggested the association with postmenopausal hormones was generally stronger in older age groups (8, 23–25), we found some evidence that the relationship was stronger in younger women, particularly for combined estrogen-progestin use. Because our response rates were notably lower among older women, this observation could be artifactual. However, a recent Swedish case-control study showed

Table 5 RR of breast cancer associated with use of postmenopausal hormone use according to tumor characteristics

Characteristic	Nonusers	Estrogen only		Estrogen with progestin only		*P*
	Cases	Cases	RR[a] (95% CI)	Cases	RR[a] (95% CI)	
Histology						
Ductal						
Ever hormone use[b]	2446	659	1.22 (1.06–1.41)	208	1.43 (1.14–1.79)	
Duration of use—all users (continuous per year)[c]			1.02 (1.01–1.03) $P = 0.001$		1.04 (1.00–1.08) $P = 0.03$	0.2
Duration of use—current users (continuous per year)[c]		393	1.01 (1.00–1.03) $P = 0.008$	173	1.03 (1.00–1.07) $P = 0.07$	
Lobular						
Ever hormone use[b]	319	89	1.19 (0.88–1.61)	32	2.01 (1.25–3.22)	
Duration of use—all users (continuous per year)[c]			1.03 (1.01–1.05) $P = 0.01$		1.04 (0.97–1.11) $P = 0.3$	0.7
Duration of use—current users (continuous per year)[c]		57	1.02 (1.00–1.05) $P = 0.02$	30	1.04 (0.97–1.12)[d] $P = 0.3$	
Extent of disease at diagnosis						
Local or stage I						
Ever hormone use[b]	2342	655	1.20 (1.04–1.38)	213	1.47 (1.18–1.84)	
Duration of use—all users (continuous per year)[c]			1.02 (1.01–1.03) $P = 0.001$		1.05 (1.02–1.09) $P = 0.002$	0.05
Nonlocalized or stage II–IV						
Ever hormone use[b,e]	1128	256	1.22 (1.01–1.47)	83	1.50 (1.12–2.02)	
Duration of use—all users (continuous per year)[c]			1.02 (1.00–1.03) $P = 0.01$		1.01 (0.96–1.06) $P = 0.7$	0.9

[a] Logistic regression models were conditional on age and state. RR was adjusted for age at menopause, type of menopause, age at first full-term pregnancy, body mass index, family history of breast cancer, education, screening mammography history, recent alcohol consumption, history of benign breast disease, age at menarche, and recent physical activity. Women who used both unopposed estrogen and estrogen-progestin are excluded.
[b] Reference category is nonusers including 4132 controls; 1027 controls used estrogen only, and 286 controls used estrogen and progestin only.
[c] Includes nonusers.
[d] In the test of the difference in RRs for the duration of current estrogen-progestin use in relation to ductal *versus* lobular breast cancer, $\chi^2 = 3.35$, 1 degree of freedom, $P = 0.07$.
[e] Model adjusted for all factors except screening mammography: estrogen alone only, RR, 1.09; 95% CI, 0.90–1.31; estrogen and progestin, RR, 1.26; 95% CI, 0.94–1.68. In the test of the difference in the RRs for the duration of estrogen only *versus* estrogen-progestin use.

similar age-specific patterns (14). We found some evidence, as have others, that the risk associated with use of both estrogen only and estrogen-progestin was slightly greater among women with lean body mass (1, 9). The recent study of Schairer *et al.* (5) observed that the use of estrogen alone was associated with an increased risk only among lean women, and not among heavy women, whereas associations with combined use did not vary by weight. Our finding that estrogen and estrogen-progestin effects may be modified by alcohol is an interesting finding that merits further attention. Several earlier studies have shown that heavy alcohol consumption is associated with an increased risk of breast cancer (26–28).

Our finding that combined postmenopausal hormone use is more strongly associated with lobular cancer has been suggested in three previous reports (9–11). In the recent record linkage study of Chen *et al.* (9), current use of combination therapy was associated with an OR of 3.91 (95% CI, 2.08–7.44) for lobular breast cancer, whereas the OR for nonlobular breast cancer was 1.25 (95% CI, 0.86–1.81). In a re-examination of our earlier case-control study of breast cancer (16), we found that combined estrogen and progestin regimen was associated with a 4-fold (95% CI, 1.8–5.3) increase in invasive lobular cancer risk, but no increased risk of ductal lesions was found (10). Another smaller case-control study (29) reported an OR for lobular carcinoma of 2.6 (95% CI, 1.1–5.8) among combination users but no increase in ductal carcinoma (OR, 0.7; 95% CI, 0.5–1.1). This association is consistent with the steady increase, since 1977, in incidence rates for lobular breast carcinoma in women ≥50 years (29), a group with increasing utilization of progestins (30). A recent report from the Iowa Women's Health Study suggests that the effects of postmenopausal hormones may depend upon histology (31), although an artifact of mammography screening could not be ruled out. Their results are not directly comparable to our own histology-specific analysis because most ductal and lobular histologies (95%) were combined in their data, and no consistent association with postmenopausal hormone use was observed.

Despite the coherence of our results and the precision of most of our estimates, it is possible that these associations are attributable to characteristics of hormone users, rather than the hormones themselves. In general, postmenopausal hormone users appear to be healthier than nonusers (32–34), and some of the measured indicators of "health" (younger age, lower weight, and high levels of physical activity) are associated with decreased breast cancer risk (35). There is evidence suggesting that women with menopausal symptoms also have lower estrogen levels than women without symptoms (36, 37), and thus they probably have lower inherent breast cancer risk (38). Indeed, in our study, postmenopausal women who reported menopausal symptoms were more likely to use postmenopausal hormones (33%) than women without symptoms (19%). In the aggregate, however, these characteristics have likely resulted in an *underestimation* in observational studies of the true risk associated with postmenopausal hormones (39). Confounding by unmeasured risk factors remains a concern, but because adjustment tended to reveal slightly higher risks, it is likely that any residual confounding would tend to attenuate rather than inflate the observed RRs.

Differences in recall of hormone use by cases and controls may have introduced bias, although self-reports of hormone use

are generally reproducible, as in this study, and valid (40–43). Of greater concern are disparities in participation by cases and controls. Although we enrolled a high proportion of cases and controls, there was some variability in control participation (Wisconsin, 84%; Massachusetts, 70%; New Hampshire, 69%). If control women who agreed to our interview were more likely to use hormones, this may have attenuated the apparent relation between postmenopausal hormones and breast cancer risk. Indeed, the RR for current use of any menopausal hormones in Wisconsin was 1.40 (95% CI, 1.20–1.64), but it was only 1.09 (95% CI, 0.86–1.38) in Massachusetts. Moorman *et al.* (44) observed that postmenopausal hormone use was 80% higher in participating controls than in nonparticipating controls. Selection bias might explain the generally null findings of other case-control studies of this issue of postmenopausal hormones as well (16, 19, 21, 45).

Our epidemiological findings are concordant with clinical and laboratory evidence that estrogen is a promoter of mammary tumors (15). Recent prospective epidemiological data also demonstrate that higher levels of circulating estrogens are associated with breast cancer risk (38), although there is little evidence that endogenous progesterone is directly associated with risk. *In vivo* and *in vitro* studies have demonstrated both antagonistic and synergistic effects of progesterone (15, 46–48) in the presence of estrogen. The effect of progestins on the postmenopausal breast is not well understood and may depend upon the drug formulation (49). Shi *et al.* (50) postulated that progestins may have adverse effects on the progression of early stages of breast carcinogenesis. One possible mode of adverse action of progesterone may be the conversion of estrones to the more potent estradiol through induction of 17β-hydroxysteroid dehydrogenase (51). Limited evidence supports a differential biological effect of postmenopausal hormones according to tissue type (52). Lobular tumors are more frequently estrogen and progesterone receptor positive than other histological types, suggesting perhaps greater hormone dependence (52, 53).

This large study confirms the modest increase in breast cancer risk associated with unopposed estrogens and supports recent data suggesting a greater increased risk associated with estrogen-progestin regimens, particularly among long-term users. Our findings also suggest that the increase in risk for estrogen-progestin use includes the use of progestin for >21 days of the cycle. This study raises the question of a specific enhancing effect of preparations containing progestin in the genesis of lobular carcinoma.

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