Hormone Replacement Therapy and Risk of Breast Cancer With a Favorable Histology

Results of the Iowa Women's Health Study

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Context Long-term, postmenopausal use of hormone replacement therapy (HRT) appears to increase breast cancer risk. Whether the effect of HRT use on risk of breast cancer varies among histological types of invasive carcinoma is unknown.

Objective To determine associations between HRT use and risk of ductal carcinoma in situ (DCIS), invasive carcinoma with favorable histology, and invasive ductal or lobular carcinoma.

Design Prospective cohort study whose participants were followed up continuously for 11 years from January 1986 to December 1996.

Setting and Participants Iowa Women's Health Study, a population-based random sample of postmenopausal women aged 55 to 69 years in 1986. A total of 1520 incident breast cancer cases occurred in the at-risk cohort of 37 105 women.

Main Outcome Measures Multivariate-adjusted relative risk (RR) of tumor-specific breast cancers associated with duration of ever, current, or past HRT use.

Results Duration of ever HRT use was associated with risk of invasive carcinoma with a favorable histology, with an RR of 1.81 (95% confidence interval [CI], 1.07-3.07) for those who used HRT 5 or fewer years vs an RR of 2.65 (95% CI, 1.34-5.23) for those who used HRT for more than 5 years (*P* for trend = .005) after adjustment for age and other breast cancer risk factors. There was no association between ever HRT use and the incidence of DCIS or invasive ductal or lobular carcinoma. Among current hormone users, after adjusting for age and other breast cancer risk factors, the RRs (95% CIs) of invasive carcinoma with a favorable histology were 4.42 (2.00-9.76) and 2.63 (1.18-5.89) for 5 or fewer years of use and for more than 5 years of use, respectively. Risk of invasive ductal or lobular carcinoma was associated with current use (≤5 years) of HRT with an RR of 1.38 (95% CI, 1.03-1.85).

Conclusions Exposure to HRT was associated most strongly with an increased risk of invasive breast cancer with a favorable prognosis. These data add important clinical information for assessing the risks and benefits of HRT use.

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DESPITE THE WELL-DOCUMENTED effects of hormone replacement therapy (HRT) on reducing menopausal symptoms,[1] and risk of osteoporosis,[2] and a potentially beneficial effect on the primary prevention of coronary heart disease,[3,4] concerns about breast cancer cause many women to avoid taking estrogens. Recent studies demonstrating that the selective estrogen receptor modulators tamoxifen[5] and raloxifene[6] reduce the incidence of hormone receptor–positive breast cancer have focused new attention on associations between hormones and breast cancer risk.

Whether HRT use increases risk of breast cancer is controversial. A considerable amount of epidemiological data supports a modest increase in risk of breast cancer with long-term hormone use. For example, in a combined analysis of 51 studies, the relative risk (RR) of breast cancer was 1.35 (95% confidence interval [CI], 1.21-1.49) for women who used HRT for 5 years or more compared with never-users.[7] However, Shairer et al[8] proposed that postmenopausal hormone exposure specifically promotes the growth of less aggressive, slow-growing tumors. Although two[8,9] of three[10] studies reported differences in the association between HRT use and risk of invasive vs in situ breast cancer, it has not been determined whether the effect of HRT use on breast cancer incidence varies among histological types of invasive carcinomas. Clinically, significant differences in prognosis exist between infiltrating ductal and lobular carcinomas, which account for 85% to 90% of invasive tumors,[11,12] and the less common medullary, papillary, tubular, and

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mucinous tumors that have a lower risk of axillary node metastases and a more favorable prognosis.[12,13] Information regarding differences in HRT-associated risk across histological types of breast cancer could have implications for determining the risks and benefits of hormonally related disease prevention strategies.

Using data from a large cohort of postmenopausal women, we examined whether the association between HRT use and breast cancer incidence differs among 3 histologically defined groups of breast tumors: ductal carcinoma in situ (DCIS), invasive carcinomas with favorable histologies, and invasive ductal and/or lobular carcinoma.

METHODS

The Iowa Women's Health Study is a prospective cohort study designed to examine the effect of several risk factors on the incidence of cancer in postmenopausal women aged 55 to 69 years at baseline. Detailed methods for recruitment and data collection were published previously.[14,15] Briefly, potential participants were selected randomly from the 1985 Iowa Department of Transportation driver's license list. The list contained approximately 94% of all Iowa women in the target age range. In January 1986, 98 029 eligible women were mailed a 16-page, self-administered questionnaire, and 41 837 eligible women completed and returned the questionnaire, yielding a response rate of 42.7%. From the information available on the driver's license list and the 1980 US Census for Iowa, it was determined that responders were approximately 3 months older, were 0.4 kg/m^2 lower in body mass index (BMI), and slightly more likely to live in rural counties. However, we have shown that the incidence of breast cancer is similar among respondents and nonrespondents (RR, 1.01; 95% CI, 0.9-1.1).[15]

The population at risk for developing breast cancer excluded women who at baseline (1) were premenopausal (n = 569), (2) reported a previous total or partial mastectomy (n = 1870), or (3) reported a personal history of nonskin cancer (n = 2293). The at-risk cohort included 37 105 women.

Risk Factor Assessment

Self-reported information ascertained from the baseline mailed questionnaire included birth date, education, cigarette smoking history, personal history of cancer, and history of cancer in female relatives (no information on the number of relatives affected or the relative's age at diagnosis was collected). Reproductive history included information on outcome of each pregnancy, length of each pregnancy, and age at beginning of each pregnancy. Women were asked whether they had ever used pills, other than birth control pills, that contain estrogen or other female hormones and how long they had used them. Participants also were asked to record their height, current weight, and weight at age 18 years; from this information, current BMI (calculated as weight in kilograms divided by the square of height in meters) and BMI at age 18 years were computed. To determine waist-to-hip ratio, a paper tape and detailed instructions for circumference measurements of the waist and hips were enclosed with the questionnaire. Kushi et al[16] verified the high validity and reliability of this approach to obtaining anthropometric data in this population. Information on menstrual history included age at menarche and age at menopause; menstruation in the last year; and the type of menopause (ie, natural, surgical, medical, or other). Usual alcohol consumption was assessed using the Harvard semiquantitative food frequency questionnaire developed by Willett et al,[17] and has been described in detail elsewhere.[18,19]

Four follow-up questionnaires were mailed in 1987, 1989, 1992, and 1997 to collect information on incident self-reported disease, vital status, and current residence. On the second follow-up survey, participants were asked whether they had ever undergone mammography and the length of time since last mammography.

Identification of Cases

The cohort has been followed up continuously for 11 years (January 1986-December 1996). Incident breast cancer cases among Iowa residents were identified using the Health Registry of Iowa, part of the National Cancer Institute's Surveillance, Epidemiology and End Results program. Each year, registry cases were matched with Iowa Women's Health Study participants using a combination of first, last, and maiden names, ZIP code, birth date, and Social Security number. Information on deaths was obtained from the State Health Registry of Iowa for residents, and from the National Death Index for women who did not respond to the 4 mail follow-up surveys. Vital status is known for more than 99% of the Iowa Women's Health Study participants.

Surveillance, Epidemiology and End Results personnel used a 6-digit code to record tumor morphology according to the *International Classification of Diseases for Oncology, Second Edition*. The first 4 digits of this code describe tumor histology, the fifth digit describes behavior (eg, 2 = carcinoma in situ, 3 = malignant, primary site), and the sixth digit describes histological grade. For these analyses, the first 5 digits were used to classify breast cancer cases into 4 groups: (1) DCIS, (2) invasive carcinoma with a favorable prognostic histology (ie, mucinous, medullary, tubular, papillary), (3) invasive ductal and/or lobular carcinoma, and (4) other (excluded from analysis).

Statistical Analysis

The type of HRT use was categorized as never use, 5 years or fewer or more than 5 years for ever-users, current users, and past users. Anthropometric risk factors were stratified into tertiles. Women who reported a mother, sister, or daughter with breast cancer were considered to have a positive family history of breast cancer. Alcohol abstainers were women whose reported alcohol intake was 0 g/d, and alcohol consumers were classified into 2 groups based on a median split of daily alcohol intake ($<$4.0 or $\geq$4.0 g/d). Other characteristics such as age at menarche, menopause, first live birth, parity, and type of menopause were classified into logical categories.

Person-years of follow-up were computed for each woman as the amount of time since completion of the baseline questionnaire to 1 of the following events: (1) breast cancer diagnosis, (2) death (if in Iowa), (3) a move out of Iowa (if date known), (4) midpoint of interval between last contact date and either date of next follow-up or December 31, 1996 (if date of move was unknown), and (5) midpoint of interval between date of last contact and date of death (for non-Iowa deaths). For women without 1 of these events, follow-up was to December 31, 1996.

Cox proportional hazards regression was used to determine age-adjusted and multivariate-adjusted associations between HRT use and breast cancer incidence. The RRs and 95% CIs were computed within categories of risk factors for each histological type of breast cancer. To compare respective regression coefficients across tumor types, multivariate polychotomous logistic regression was used to account simultaneously for the 4 possible outcomes (ie, noncase, DCIS, invasive carcinoma with a favorable histology, invasive ductal or lobular carcinoma). The dependent variable was treated as a polychotomous nominal variable, and the logit estimator always compared histologically defined cases (eg, DCIS) with noncases.[20] These regression coefficients agreed closely with those computed from the multivariate Cox proportional hazards analysis. Analyses were performed using PROC PHREG and PROC CATMOD of the SAS statistical software package (SAS Institute Inc, Cary, NC).

RESULTS

After 371 477 person-years of follow-up, 1520 incident breast cancer cases occurred in the at-risk cohort. The distribution of breast cancer cases by histology is shown in TABLE 1; 11.5% were DCIS, 5.4% were invasive breast cancer with a favorable histology, and 76.6% were infiltrating ductal or lobular carcinoma. Fifteen women diagnosed as having lobular carcinoma in situ (LCIS), and 84 women with nonepithelial tumors and rare or poorly defined tumors were excluded from analysis.

Age-adjusted RRs for HRT use and other breast cancer risk factors were computed for each tumor type (TABLE 2). Risk of invasive carcinoma with a favorable histology was positively associated with duration of ever use of HRT (P for trend = .009). There were no relationships with duration of ever use for DCIS or for invasive ductal or lobular carcinoma. Invasive carcinoma with a favorable histology and invasive ductal or lobular carcinoma were significantly and positively associated with increasing BMI (P for trend = .03 and $<.001$, respectively). Conversely, there were inverse dose-response relationships between each of the invasive tumor types and BMI at age 18 years. Increasing waist-to-hip ratio was associated with increased risks of the favorable histological tumors (P for trend = .02), and invasive ductal or lobular carcinoma (P for trend $\leq .001$). The incidence of DCIS was not related to BMI, BMI at age 18 years, or waist-to-hip ratio. Age at menarche, age at menopause, and type of menopause were not related to the age-adjusted incidence of any tumor type. For invasive carcinoma with a favorable histology, there was a nonsignificant inverse association with parity. A positive association between age at first birth and breast cancer risk was observed for all histological tumor types. For women with a family history of breast

Table 1. Distribution of Breast Cancer Cases According to Histologic Classification

Morphology	*International Classification of Diseases for Oncology* Codes	No. of Cases
Ductal Carcinoma In Situ (n = 175)		
Ductal carcinoma in situ	8500/2	121
Noninfiltrating comedocarcinoma	8501/2	35
Papillary carcinoma in situ	8050/2	1
Noninvasive cribriform carcinoma	8201/2	1
Noninfiltrating intraductal papillary	8503/2	6
Noninfiltrating intracystic carcinoma	8504/2	1
Mixed ductal carcinoma in situ and/or lobular carcinoma in situ	8522/2	3
Ductal carcinoma in situ and Paget disease	8543/3	7
Invasive—Favorable Histologic Subtypes (n = 82)		
Papillary carcinoma, NOS*	8050/3	3
Papillary adenocarcinoma	8260/3	2
Papillary ductal carcinoma in situ with invasion	8503/3	5
Intracystic papillary carcinoma	8504/3	1
Tubular adenocarcinoma	8211/3	18
Mucinous adenocarcinoma	8480/3	37
Medullary carcinoma	8510/3	16
Invasive—Ductal and/or Lobular Carcinoma (n = 1164)		
Infiltrating ductal carcinoma	8500/3, 8521/3	999
Comedocarcinoma, NOS*	8501/3	16
Infiltrating ductal and lobular carcinoma	8522/3	44
Paget disease and infiltrating ductal carcinoma	8541/3	4
Lobular carcinoma	8520/3	101
Excluded From Analysis (n = 99)		
Lobular carcinoma in situ	8520/2	15
Inflammatory carcinoma	8530/3	6
Malignant neoplasm	8000/3	4
Carcinoma, NOS*	8010/3	11
Adenocarcinoma, NOS*	8140/3	45
Scirrhous adenocarcinoma	8141/3	6
Other rare types	NA	12

*NOS indicates not otherwise specified; NA, not applicable.

cancer compared with women with no family history of breast cancer, there was a 2-fold increased risk of DCIS, and a 1.4-fold increased risk of invasive ductal or lobular carcinoma. There was a weak positive association between increasing alcohol intake and risk of invasive ductal or lobular carcinoma (P for trend = .04), but not with risks of DCIS or favorable histological breast cancer.

The prevalence of postmenopausal hormone use was examined across strata of other breast cancer risk factors for never-users and for those who reported ever using hormones for 5 or fewer years or for more than 5 years (TABLE 3). Compared with never-users, women who reported long-term

Table 2. Age-Adjusted Relative Risk of Breast Cancer Stratified by Histologic Type*

	Ductal Carcinoma In Situ		Favorable Histologic Type		Invasive Ductal and/or Lobular Carcinoma	
Risk Factor	No. of Cases	Relative Risk (95% CI)	No. of Cases	Relative Risk (95% CI)	No. of Cases	Relative Risk (95% CI)
Duration of ever use of hormone replacement therapy						
Never	105	1.0	39	1.0	701	1.0
≤5 y	49	1.08 (0.77-1.52)	28	1.67 (1.02-2.71)	319	1.05 (0.92-1.20)
>5 y	20	1.10 (0.68-1.77)	15	2.22 (1.22-4.02)	130	1.07 (0.88-1.28)
Body mass index, kg/m^2						
<24.3	53	1.0	21	1.0	334	1.0
24.3-28.3	59	1.11 (0.77-1.61)	23	1.09 (0.60-1.97)	384	1.14 (0.98-1.32)
>28.3	63	1.18 (0.82-1.70)	38	1.80 (1.06-3.07)	446	1.32 (1.15-1.52)
Body mass index at age 18 y, kg/m^2						
<20.2	56	1.0	37	1.0	413	1.0
20.2-22.3	76	1.38 (0.98-1.95)	25	0.69 (0.42-1.15)	411	1.02 (0.89-1.17)
>22.3	41	0.73 (0.49-1.10)	20	0.54 (0.31-0.93)	333	0.81 (0.70-0.94)
Waist-to-hip ratio						
<0.79	55	1.0	21	1.0	342	1.0
0.79-0.87	60	1.09 (0.76-1.58)	23	1.11 (0.61-2.0)	361	1.04 (0.90-1.21)
>0.87	60	1.12 (0.77-1.62)	38	1.88 (1.10-3.22)	455	1.32 (1.15-1.52)
Age at menarche, y						
≤11	35	1.0	16	1.0	180	1.0
12-13	92	0.71 (0.48-1.05)	42	0.71 (0.40-1.27)	659	0.98 (0.83-1.15)
≥14	48	0.76 (0.49-1.17)	22	0.76 (0.40-1.45)	315	0.95 (0.79-1.14)
Age at menopause, y						
≤44	34	1.0	24	1.0	258	1.0
45-54	116	1.26 (0.86-1.85)	45	0.69 (0.42-1.14)	744	1.07 (0.93-1.23)
≥55	18	1.18 (0.67-2.10)	11	1.03 (0.50-2.12)	128	1.08 (0.88-1.34)
Type of menopause						
Natural	108	1.0	50	1.0	764	1.0
Surgical	61	1.19 (0.87-1.63)	31	1.30 (0.83-2.04)	355	0.99 (0.87-1.12)
Other	1	0.34 (0.47-2.40)	1	0.72 (0.10-5.22)	20	0.95 (0.61-1.49)
Parity						
0	17	1.0	10	1.0	106	1.0
1-2	60	0.98 (0.57-1.68)	31	0.86 (0.42-1.75)	385	1.02 (0.82-1.26)
≥3	98	0.87 (0.52-1.46)	39	0.58 (0.29-1.16)	663	0.97 (0.79-1.20)
Age at first birth (for parous women only), y						
≤20	39	1.0	24	1.0	305	1.0
21-29	102	1.25 (0.90-1.73)	36	0.73 (0.46-1.17)	652	1.07 (0.95-1.21)
≥30	16	1.92 (1.10-3.37)	9	1.82 (0.87-3.83)	83	1.29 (1.02-1.64)
Family history of breast cancer in a first-degree relative						
No	134	1.0	68	1.0	936	1.0
Yes	38	2.09 (1.46-3.00)	12	1.30 (0.71-2.41)	182	1.41 (1.20-1.65)
Alcohol intake, g/d						
0	98	1.0	54	1.0	645	1.0
<4	47	1.19 (0.84-1.69)	14	0.64 (0.36-1.16)	256	1.00 (0.87-1.16)
≥4	30	0.86 (0.57-1.29)	14	0.72 (0.40-1.30)	263	1.16 (1.01-1.34)

*For each tumor type, the total number of cases may vary for different risk factors because of missing data. Relative risks are adjusted for age as a continuous variable using Cox proportional hazards regression. CI indicates confidence interval.

use (>5 years) of HRT had a lower current BMI, BMI at age 18 years, and waist-to-hip ratio. Never-users reported a younger age at menopause and at first live birth. A higher proportion of never-users reported a natural menopause.

Independent effects of HRT use for all types of breast cancer combined and for each tumor type were assessed in multivariate Cox proportional hazards regression after adjusting for age, BMI, BMI at age 18 years, waist-to-hip ratio, age at menarche, age at menopause, type of menopause, parity, age at first birth, family history of breast cancer, and alcohol intake. The multivariate-adjusted RRs of all breast cancer combined among women who ever used HRT for 5 or fewer years or for more than 5 years were 1.07 (95% CI, 0.94-1.22) and 1.11 (95% CI, 0.92-1.35), respectively.

The FIGURE shows associations between duration of ever use of HRT for each tumor type. Similar to the age-adjusted associations, ever use of HRT appeared to be related only to an increased incidence of invasive carcinoma with a favorable histology. The RRs for this tumor type among women who reported ever using HRT for 5 or fewer years or for more than 5 years compared with never-users were 1.81 (95% CI, 1.07-3.07), and 2.65 (95% CI, 1.34-5.23), respectively (*P* for trend = .005). For both short-term (≤5 years) and long-term (>5 years) HRT users, the RRs of invasive carcinoma with a favorable histology were statistically significantly greater than the RRs for DCIS (*P* for difference = .03 and .02, respectively) and for invasive ductal/lobular carcinoma (*P* for difference = .05 and .01, respectively).

Among the 37 105 women at risk for breast cancer, data on mammography screening were self-reported by 31 809 women who responded to the second follow-up survey. Women who reported ever using HRT for 5 or fewer years and for more than 5 years were more likely to report that they had undergone mammography within 1 year before the survey (41% and 48%, respectively) than women who never used HRT (33%). Despite the apparent increased surveillance for women who reported ever HRT use, adjustment for mammography in the multivariate model had no marked effect on the associations of hormone use with any histological type of breast cancer. Among women who reported ever using HRT for 5 or fewer years, the RRs of DCIS, invasive carcinoma with a favorable histology, and invasive ductal or lobular carcinoma were 0.83 (95% CI, 0.46-1.48), 2.54 (95% CI, 1.20-5.40), and 0.96 (95% CI, 0.76-1.21), respectively.

Associations of past vs current hormone use with risk of each tumor type are shown in TABLE 4. Duration of past HRT use appeared to be associated with a reduced risk of DCIS. There was no association between duration of current HRT use and risk of DCIS. For women

Table 3. Prevalence of Postmenopausal Hormone Use at Baseline According to Selected Breast Cancer Risk Factors*

Risk Factor	Duration of Postmenopausal Hormone Use		
	Never Use	≤5 Years	>5 Years
Age, y			
≤59	37	33	34
60-64	34	37	37
≥65	29	30	29
Body mass index, kg/m^2			
<24.3	32	34	39
24.3-28.3	33	34	34
>28.3	35	32	27
Body mass index at age 18 y, kg/m^2			
<20.2	32	35	39
20.2-22.3	33	33	33
>22.3	35	32	28
Waist-to-hip ratio			
<0.79	32	34	40
0.79-0.87	33	34	33
>0.87	35	32	27
Age at menarche, y			
≤11	15	16	17
12-13	57	57	57
≥14	28	27	26
Age at menopause, y			
≤44	19	28	46
45-54	69	63	49
≥55	12	9	5
Type of menopause			
Natural	79	56	24
Surgical	19	42	75
Other	2	2	1
Parity (No. of live births)			
0	9	8	11
1-2	31	34	37
3-4	60	58	52
Age at first birth (for parous women only), y			
≤20	31	33	36
21-29	62	61	60
≥30	7	6	4
Family history of breast cancer in a first-degree relative			
No	88	88	88
Yes	12	12	12
Alcohol intake, g/d			
0	58	55	52
<4	22	23	24
≥4	20	22	24

*All data are presented as percentage of subjects.

who reported past HRT use for more than 5 years compared with never-users, there was a 2.7-fold increased incidence of invasive carcinoma with a favorable histology. Among current hormone users, the RRs of invasive carcinoma with a favorable histology were 4.42 and 2.63 for 5 or fewer years and more than 5 years of use, respectively. The incidence of invasive ductal or lobular carcinoma was not associated with past HRT use, but there was a marginally statistically significantly increased risk associated with current use (RR, 1.38; 95% CI, 1.03-1.85).

COMMENT

A priori breast tumors were classified according to their histological and prognostic characteristics.[13] This classification allowed us to investigate differences in associations of breast cancer risk with HRT use across tumor types more fully than previous studies that compared in situ carcinomas with all invasive carcinomas combined.[8-10] In this study, we observed a positive, dose-response relationship between duration of postmenopausal hormone use and the incidence of breast cancer with a favorable prognosis; this relationship appeared to be stronger for current users compared with past users. Conversely, the incidence of DCIS and invasive ductal or lobular carcinoma were not related to ever use of hormones in this cohort. The data, however, are suggestive of a modest increased risk of invasive ductal or lobular carcinoma among women who, at baseline, reported current HRT use for 5 or fewer years.

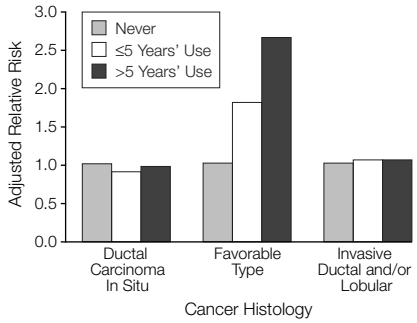
Few studies have examined the effect of HRT use on risk of histologically defined breast cancer.[8-10] At least 2 studies reported a higher risk of in situ carcinoma compared with invasive carcinoma associated with postmenopausal hormone use.[8,9] For example, in the Breast Cancer Detection and Demonstration Project, there was a 1.9-fold increased risk of in situ breast cancer among long-term hormone users (>10 years) compared with never-users, whereas duration of use was not associated with risk of invasive carcinoma.[8] Conversely, in a population-based case-control study of middle-aged women, Stanford et al[10] found no association with postmenopausal hormone use for in situ or invasive breast cancer.

A significant increase in risk of invasive breast cancer with a favorable histology or with DCIS among HRT users provides a plausible explanation for the lower breast cancer mortality rates (or improved survival) among hormone users observed in some,[21-24] but not all[25,26] epidemiological studies. Unfortunately, we could not evaluate differences in breast cancer mortality between hormone users and nonusers for each tumor type because only 11 women with DCIS, 7 women with a favorable histological type of breast cancer, and 179 women with invasive ductal or lobular carcinoma died during follow-up. Further stratification of these deaths by HRT use would result in too few deaths in any strata, and comparisons of mortality rates by HRT use across tumor type would yield inconclusive estimates.

There are several possible reasons for a specific risk association of HRT with breast cancer with a favorable histology. For example, an increased risk of in situ carcinoma and a reduced breast cancer mortality rate for women using postmenopausal hormones may be attributed to increased medical surveillance among hormone users compared with nonusers. The frequency of medical surveillance does not explain the increased incidence of tumors with a favorable histology, as observed in this study, since these tumors are not precursor lesions for the more common infiltrating ductal or lobular carcinomas. Adjustment for mammography use had no effect on the observed associations.

Shairer et al[8] proposed that the observed risk differences across tumor types could be due to a selective biological effect of hormone use on the growth of less aggressive breast tumors. In a recent study of 477 women with breast cancer, Holli et al[27] reported that breast tumors among HRT users were smaller, better differentiated, and had lower mean tumor proliferation rate as measured by the S-phase fraction. The results of that study are similar to other studies showing that breast tumors among estrogen users ap-

Figure. Relative Risk of Breast Cancer and Hormone Replacement Therapy Use



Relative risks have been adjusted, using Cox proportional hazards regression, for age, body mass index, body mass index at age 18 years, waist-to-hip ratio, age at menarche, age at menopause, type of menopause, parity, age at first birth, family history of breast cancer in a first-degree relative, and alcohol intake.

Table 4. Duration of Past and Current Postmenopausal Hormone Use and Multivariate-Adjusted Relative Risk of Breast Cancer Stratified by Histologic Type*

Hormone Use	Ductal Carcinoma In Situ, Relative Risk (95% CI)	Favorable Histologic Type, Relative Risk (95% CI)	Invasive Ductal and/or Lobular, Relative Risk (95% CI)
Never	1.0	1.0	1.0
Past user			
≤5 y	0.91 (0.61-1.34)	1.44 (0.80-2.58)	1.01 (0.87-1.18)
>5 y	0.29 (0.07-1.18)	2.68 (1.08-6.69)	0.92 (0.65-1.28)
Current user			
≤5 y	0.94 (0.41-2.16)	4.42 (2.00-9.76)	1.38 (1.03-1.85)
>5 y	1.35 (0.77-2.36)	2.63 (1.18-5.89)	1.16 (0.90-1.49)

*Adjusted for age (continuous variable), body mass index, body mass index at age 18 years, waist-to-hip ratio, age at menarche, age at menopause, age at first birth, parity, family history of breast cancer in a first-degree relative, type of menopause, and alcohol intake using Cox proportional hazards regression. CI indicates confidence interval.

pear to be well-differentiated,[28] with fewer cells in mitosis.[29] Similarly, endometrial tumors that develop in estrogen users also appear to be more highly differentiated and rarely invade deeply in the myometrium.[30]

It is important to recognize the potential limitations of this study. First, breast cancer histology was recorded by Surveillance, Epidemiology and End Results personnel from pathology reports, and was not determined by a single reference laboratory. Although the assessment of tumor histology may vary among pathologists, these variations would probably not result in spuriously elevated associations because HRT exposure was assessed prior to diagnosis. Second, it is unlikely that the pathologist would know exposure status. Third, it is improbable that women who developed invasive breast cancer with a favorable histology during follow-up were more likely to overestimate their hormone use at baseline than women who developed DCIS or invasive ductal or lobular carcinoma. In this study, we could not determine the effect of type of HRT because data regarding the type of postmenopausal hormones used (ie, combined estrogen-progesterone vs estrogen alone) were not available from the 1986 baseline questionnaire. Based on results of other studies,[31,32] it is estimated that in this cohort approximately 20% of current hormone users and a smaller proportion of former users were prescribed combination HRT in 1986.

In conclusion, the results of this study provide important new data suggesting that postmenopausal hormone use is associated with an increased incidence of invasive breast cancer with a favorable histology, and there is little evidence of associations with DCIS or invasive ductal or lobular carcinoma. If confirmed by other studies, this information could have important public health implications given the widespread use of HRT among postmenopausal women in the United States.[33] Moreover, although breast cancer is the most commonly diagnosed cancer among women in the United States,[34] only a small proportion (<15%) of invasive cancer cases are of a favorable histological type.[13] If HRT use selectively increases the risk of the less commonly occurring tumors with a good prognosis, then the overall risks and benefits of hormone use in the population should be reexamined. Furthermore, this information would be particularly useful to clinicians assisting patients in making informed decisions regarding postmenopausal hormone use. Further research is needed to corroborate the results of this study and should include a large series of breast cancer cases with information available on type of HRT to explore differences in association between hormone use and invasive breast cancer risk across tumor types more fully.

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