

## Hormone-related Factors and Risk of Breast Cancer in Relation to Estrogen Receptor and Progesterone Receptor Status

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Risk factors were examined for subgroups of breast cancer characterized by estrogen receptor (ER) and progesterone receptor (PR) status. Data from the Carolina Breast Cancer Study, a population-based, North Carolina case-control study of 862 breast cancer cases aged 20–74 years diagnosed during 1993–1996 and 790 controls frequency matched on race and age, were obtained by personal interview. ER and PR status was retrieved from medical records (80%) or was determined in the authors' laboratory (11%) but was missing for 9% of cases. The receptor status distribution was as follows: 53% ER+PR+, 11% ER+PR–, 8% ER–PR+, and 28% ER–PR–. Several hormone-related factors were associated with stronger increased risks for ER+PR+ than for ER–PR– breast cancer: the elevated odds ratios were strongest for ER+PR+ breast cancer among postmenopausal women who had an early age at menarche (odds ratio (OR) = 1.6, 95% confidence interval (CI): 1.0, 2.4), nulliparity/late age at first full-term pregnancy (OR = 1.7, 95% CI: 0.9, 3.2 and OR = 1.6, 95% CI: 1.0, 2.7, respectively), or a high body mass index (OR = 1.6, 95% CI: 0.9, 3.0) and among pre-/perimenopausal women who had a high waist-hip ratio (OR = 1.9, 95% CI: 1.2, 3.1). In contrast, family history of breast or ovarian cancer and medical radiation exposure to the chest produced higher odds ratios for ER–PR– than for ER+PR+ breast cancer, especially among pre-/perimenopausal women. *Am J Epidemiol* 2000;151:703–14.

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Estrogen and progesterone help regulate growth and differentiation of normal breast tissue, and they are considered important in the development and progression of breast cancer (1–4). Estrogen receptor (ER) and progesterone receptor (PR) are nuclear receptors; estrogen and progesterone bind specifically to these receptors and affect hormone-dependent organs (4–6). ER has both an estrogen-binding domain and a DNA-binding domain (7–9). The estrogen-ER complex binds directly to DNA and influences the expression of estrogen-responsive genes, including the gene for PR (10, 11). ER and PR levels in premalignant or malig-

nant lesions have been reported to be both higher (+) and lower (–) than in adjacent, normal breast tissues (4, 12, 13). Clinically, ER and PR levels in breast cancer tissue have been used as prognostic indicators to predict a patient's course of disease and response to adjuvant hormonal therapy. In general, women whose tumors are positive for both ER and PR (i.e., ER+PR+) survive longer and respond better to endocrine therapy compared with those whose tumors are negative for both receptors (i.e., ER–PR–); for women whose receptor status is discordant, survival and response are characterized as intermediate (14–18).

Epidemiologic studies that have examined breast cancer risk factors by either ER or PR status separately have shown inconsistent results (6, 19–27). Few studies have classified breast cancer by the joint status of ER and PR (28–31). By using data from a prospective cohort study, Potter et al. (30) found that several risk factors related to endogenous hormone exposure, including age at menarche, parity, age at first livebirth, body mass index, and waist-hip ratio, showed expected patterns of association with ER+PR+ but not with ER+PR– or ER–PR– breast cancers. Similarly, Giuffrida et al. (28) reported that breast cancer patients with a higher body mass index, in comparison to patients with a lower body mass index, were significantly more likely to have ER+PR+ tumors. By using

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Abbreviations: CI, confidence interval; ER, estrogen receptor; OR, odds ratio; PR, progesterone receptor.

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a hospital-based case-control study design, Yoo et al. (31) found positive associations with ER+PR+ compared with ER-PR- breast cancer for early age at menarche, menstrual irregularity at ages 20-29 years, and smoking but not for age at first full-term pregnancy or number of full-term pregnancies. The study by Kushi et al. (29) reported a positive association between dietary fat and ER+PR+ breast cancer.

Taken in aggregate, these results lead to the hypothesis that the risk factors most closely associated with ER+PR+ breast cancer may operate through exposure to estrogen and progesterone, whereas the risk factors most closely associated with ER-PR- breast cancer may involve mechanisms independent of hormonal exposure (30-32). Intermediate risk factor profiles may be found for tumors whose receptor status is discordant. Using data from a population-based case-control study, we examined risk factors for breast cancer after subdividing cases based on joint ER and PR status in tumor tissue to replicate analyses from previous studies and to evaluate these hypotheses.

## MATERIALS AND METHODS

### Data collection

Data were collected by the Carolina Breast Cancer Study, a population-based case-control study designed to investigate the etiology of breast cancer, including gene-environment interactions. Potential participants included women aged 20-74 years residing in 24 contiguous counties of central and eastern North Carolina. The geographic location and selection criteria for this study are described elsewhere (33).

Cases were identified by using a rapid case ascertainment system implemented through the North Carolina Central Cancer Registry (34). Fewer than 3 percent of the breast cancer patients living in the targeted area are diagnosed in hospitals outside these 24 counties (33). Women who met the residential and age criteria and were first diagnosed with invasive, primary breast cancer from May 1, 1993, to May 31, 1996, were eligible for recruitment. After eligibility was determined, sampling took place to ensure approximately equal frequencies of each of four subgroups categorized by age and race (i.e., we included 100 percent of Black women younger than 50 years of age, 75 percent of Black women aged 50 years or older, 67 percent of White women younger than 50 years of age, and 50 percent of White women aged 50 years or older). Races such as Native Americans, Asians, and other, which accounted for less than 2 percent of our underlying population, were included with Whites.

Controls were selected from two sources: records of the North Carolina Division of Motor Vehicles for

women younger than 65 years of age and records of the US Health Care Financing Administration for women aged 65 years or older. These sources covered approximately 96 percent of younger women and 93 percent of older women, respectively (33). Women in the same age range and residential area but without a history of breast cancer were eligible as controls. The same randomized recruitment method, applying a priori sampling fractions based on 5-year age group and race to the lists, was implemented to ensure that controls were frequency matched to cases on race and age (35, 36).

A 1-1.5-hour home interview was conducted by one of the trained female nurse-interviewers, who were matched with subjects on race for those aged 50 years or older. Interviewers administered a structured questionnaire, took body measurements, and, for cases, obtained consent for retrieving tumor tissue and medical documentation. Interviews were completed for 862 cases and 790 controls, corresponding to response rates of 77 percent (cases) and 68 percent (controls) among eligible and locatable women (37). Physician refusal (6 percent for cases) and participant refusal (17 percent of cases and 32 percent of controls) constituted the main categories of nonresponse. For interviewed cases, pathology reports and paraffin-embedded tissue blocks were retrieved and were reviewed by the study pathologist in a standardized way to confirm the diagnosis and to describe histologic characteristics of the breast cancer.

For 80 percent of the cases, ER and PR status was obtained from medical records. Although status was determined in various clinical laboratories, the vast majority used an immunohistochemical method with cutoffs for receptor positivity ranging from more than 0 to more than 20 percent for assays performed on paraffin-embedded tissues (about half) and of 10 or 15 fmol/mg for assays performed on frozen tissues (about half). For an additional 11 percent of the cases, for whom medical records data on ER and PR status were missing but paraffin-embedded tissues were available, receptor status was determined in our laboratory by using the same immunohistochemical method used by our institution for clinical purposes and a cutoff for positive assay at 5 percent. For the remaining 9 percent of the cases, ER and PR status was missing.

### Data analyses

Hormone-related risk factors for breast cancer that were available for analysis included the following: age at menarche less than 12 years (i.e., first quartile among controls), nulliparity/age at first full-term pregnancy more than 25 years (i.e., fourth quartile), history of breastfeeding, history of a spontaneous or induced

abortion, body mass index 1 year prior to interview of more than 31 kg/m<sup>2</sup> (i.e., fourth quartile), waist-hip ratio higher than 0.8 (i.e., median), use of oral contraceptives for more than 3 months, and hormone replacement therapy for more than 3 months. A pregnancy was classified as full-term if it resulted in a live-birth or lasted 7 or more months; otherwise, it was considered a spontaneous or induced abortion. To enable comparison with the hormone-related risk factors, we also tested a number of factors for which the relevance of hormones is less established, including a first-degree family history of breast or ovarian cancer, medical radiation exposure to the chest (including coronary catheterization or angioplasty or having the axilla, lung, or breast treated or monitored with radiation prior to the breast cancer diagnosis (cases) or to selection (controls)), lifetime smoking of more than five packs of cigarettes, alcohol drinking during the most recent age range (based on the woman's age at diagnosis or selection but categorized as less than 26, 26–49, or more than or equal to 50 years), and at least college graduation. In preliminary analyses, we evaluated various forms of these and related variables. Results reported here are for variables defined by using the fewest categories that captured relevant associations.

Women were classified as postmenopausal if their cycles ended naturally or from radiation therapy (prior to diagnosis for cases), from surgery in which both the uterus and ovaries were removed, or from surgery in which at least one ovary remained intact but age at diagnosis or selection was more than 55 years (i.e., the age beyond which 95 percent of the controls reported reaching menopause). Also considered postmenopausal were women who mentioned experiencing menopausal symptoms after surgery or receiving hormone replacement therapy although they had never stopped cycling and were older than 55 years of age. The remaining women who reported not having menstrual cycles were considered perimenopausal and were combined with premenopausal women for analysis.

Odds ratios and 95 percent confidence intervals comparing each case subgroup characterized by ER and PR status with controls were calculated for risk factors to estimate relative risks for each subtype of breast cancer. Odds ratios and 95 percent confidence intervals also were derived from case-case comparisons to quantify the presence as well as the degree of heterogeneity between the two disease subtypes (i.e., odds ratios deviating from 1.0 suggest possible heterogeneity between case subgroups) (38). The case-case odds ratio is a direct measure of heterogeneity of odds ratios and is useful for comparison of case subgroups. However, case-control odds ratios reveal the source of heterogeneity and are needed for etio-

logic inference, since only they provide estimates of effect.

To enable inferences to be made to the underlying population, all statistical analyses were weighted for the sampling fractions assigned to subgroups categorized by disease status, age, and race. Unconditional binary logistic regression models were run by using SAS PROC GENMOD (39–41). Using binary rather than polytomous logistic regression enabled us to incorporate an offset term (derived from the ratio of the sampling fractions for cases to controls) to control for the sampling design in case-control comparisons. All 13 primary exposure variables, as well as race (as a dichotomous variable) and age (as an 11-level ordinal variable for case-control odds ratios and as a 2-level variable for case-case odds ratios according to the sampling design), were included in the models to account for potential confounding effects. Hormone replacement therapy was additionally adjusted for menopausal status. Women for whom values for one or more of the variables in the models were missing were eliminated from the analyses.

## RESULTS

Characteristics of study participants are presented in table 1. The high proportions of younger and of Black breast cancer patients reflect implementation of our sampling design. When all cases (receptor status known and unknown) were compared with controls, and after adjustment for potential confounding effects and for sampling fractions, an increased breast cancer risk was associated with older age, higher waist-hip ratio, oral contraceptive use, and first-degree family history of breast or ovarian cancer, whereas breastfeeding and hormone replacement therapy were associated with a decreased risk of breast cancer.

Distribution of the ER and PR status of breast tumors among cases is shown in table 2. The weighted distribution, which reflects the distribution in the underlying population, showed that slightly less than two-thirds of breast cancer patients were ER+ or PR+ (64 percent and 61 percent, respectively). The proportions by joint receptor status were 53 percent ER+PR+, 11 percent ER+PR–, 8 percent ER–PR+, and 28 percent ER–PR–.

Selected characteristics of patients subdivided by ER and PR status are presented in table 3. The ER+PR+ subgroup, in contrast to ER–PR– patients, included more older women (Mantel-Haenszel chi-square  $p = 0.001$ ) and White women ( $p = 0.001$ ) but fewer women with a family history of breast or ovarian cancer ( $p = 0.2$ ) or advanced-stage breast cancer ( $p = 0.001$ ). The profiles for the subgroups discordant

**TABLE 1. Characteristics of participants\* in the Carolina Breast Cancer Study, North Carolina, 1993–1996**

	Cases (n = 862)		Controls (n = 790)		OR† (95% CI)‡
	No.	%	No.	%	
Age at selection (years)					
≥50	356	41	383	48	2.7 (2.0, 3.5)§
<50	506	59	407	52	1.0
Race					
White	527	61	458	58	0.8 (0.7, 1.1)
Black	335	39	332	42	1.0
Menopausal status					
Postmenopausal	426	49	436	55	1.0 (0.7, 1.4)
Pre-/perimenopausal	436	51	354	45	1.0
Age at menarche (years)					
<12	203	24	164	21	1.2 (0.9, 1.6)
≥12	658	76	623	79	1.0
Nulliparity/age (years) at first full-term pregnancy					
Nulliparous	133	15	89	11	1.1 (0.8, 1.5)
>25	187	22	162	21	1.0 (0.8, 1.4)
≤25	538	62	537	68	1.0
Breastfeeding					
Ever	289	34	314	40	0.7 (0.5, 0.9)
Never	573	66	476	60	1.0
Abortion or miscarriage					
Ever	302	35	299	38	0.8 (0.7, 1.1)
Never	560	65	491	62	1.0
Body mass index (kg/m <sup>2</sup> )					
>31	216	25	194	25	1.0 (0.7, 1.3)
23–31	407	47	380	48	0.9 (0.7, 1.2)
<23	233	27	201	25	1.0
Waist-hip ratio					
>0.8	448	52	378	48	1.4 (1.1, 1.7)
≤0.8	403	47	405	51	1.0
Oral contraceptive use					
Ever (≥3 months)	552	64	470	59	1.3 (1.0, 1.7)
Never	307	36	319	40	1.0
Hormone replacement therapy					
Ever (≥3 months)	207	24	246	31	0.8 (0.6, 1.0)¶
Never	655	76	544	69	1.0
First-degree family history of breast or ovarian cancer					
Yes	140	16	96	12	1.5 (1.1, 2.0)
No	697	81	664	84	1.0
Medical radiation to the chest					
Ever	54	6	55	7	1.1 (0.7, 1.6)
Never	807	94	735	93	1.0
Cigarette smoking					
Ever (≥5 packs)	418	48	367	46	1.0 (0.8, 1.3)
Never	444	52	423	54	1.0
Alcohol drinking during most recent age range					
Yes	507	59	454	57	1.0 (0.8, 1.2)
No	355	41	335	42	1.0
Education					
≥College graduation	243	28	205	26	1.2 (0.8, 1.7)
≥High school graduation–college graduation	460	53	420	53	1.1 (0.8, 1.5)
<High school graduation	159	18	165	21	1.0

\* Because of missing data, the percentages for some of the variables do not sum to 100%; women for whom values were missing for one or more of the variables in the models were eliminated from the calculation of odds ratios.

† OR, odds ratio; CI, confidence interval.

‡ Adjusted for all 13 primary exposure variables assessed in the study as well as for race, age at diagnosis or selection (11 levels), and the offset term.

§ Not adjusted for 11 levels of age at diagnosis or selection.

¶ Additionally adjusted for menopausal status.

for receptor status were not always intermediate between those for ER+PR+ and ER–PR– tumors, nor

were they consistently similar to either of these subgroups; however, the ER+PR– group was more simi-

**TABLE 2. Distribution of estrogen receptor (ER) and progesterone receptor (PR) status among breast cancer patients in the study sample and in the underlying population of the Carolina Breast Cancer Study, North Carolina, 1993-1996**

	No.	%	Weighted %*
ER+PR+	381	49	53
ER+PR-	78	10	11
ER-PR+	64	8	8
ER-PR-	262	33	28
Unknown	77		

\* Weighted by the probabilities used in the sampling design.

lar to the ER+PR+ group regarding age and menopausal status. The profile for patients whose receptor status was unknown was similar to that for patients with ER-PR- breast cancer regarding race, menopausal status, and possibly family history, but this subgroup likely included a mixture of tumor types. Tumor stage was not statistically significantly different between receptor status known and unknown patients ( $p = 0.6$ ).

Each of the four subgroups of breast cancer cases according to receptor status was compared with controls regarding the established and suspected risk factors under study (table 4). No conclusive pattern of associations was found for ER+PR- and ER-PR+ breast cancer, perhaps partly because of small sample

sizes. We therefore focused our assessment on cases positive or negative for both receptors.

The case-case odds ratios helped to direct our attention to variables that differed according to ER and PR status, while the corresponding case-control odds ratios denoted the patterns of heterogeneity. When ER+PR+ cases and ER-PR- cases were compared, age at menarche, nulliparity/age at first full-term pregnancy, body mass index, waist-hip ratio, and first-degree family history of ovarian or breast cancer showed evidence of associations with ER and PR status (i.e., case-case odds ratios deviated from 1.0 by 30 percent or more, as shown in the last column of table 4). After adjustment for tumor stage, results were essentially the same (data not shown).

When we examined the corresponding case-control odds ratios, we found expected patterns of association. Positive associations were observed for ER+PR+ breast cancer regarding several hormone-related factors, including early age at menarche (odds ratio (OR) = 1.5), nulliparity/late age at first full-term pregnancy (OR = 1.4 and OR = 1.3, respectively), and high waist-hip ratio (OR = 1.4); for high body mass index, the odds ratio was less than 1.0 for ER-PR- breast cancer (OR = 0.7). Oral contraceptive use also was associated with ER+PR+ breast cancer (OR = 1.4), but it was associated with ER-PR- breast cancer as well (OR = 1.4). The odds ratios for recent use of oral contraceptives (within the

**TABLE 3. Basic characteristics of breast cancer patients by estrogen receptor (ER) and progesterone receptor (PR) status in the underlying population of the Carolina Breast Cancer Study, North Carolina, 1993-1996**

	Weighted %*				
	ER+PR+	ER+PR-	ER-PR+	ER-PR-	Receptor unknown
Age at selection (years)					
≥50	70	75	53	52	62
<50	30	25	47	48	38
Race					
White	84	80	83	71	72
Black	16	20	17	29	28
Menopausal status					
Postmenopausal	72	75	55	56	53
Pre-/perimenopausal	28	25	45	44	47
First-degree family history of breast or ovarian cancer					
Yes	15	19	11	22	30
No	85	81	89	78	70
Stage of breast cancer					
IV	1	2	1	4	8
III	5	12	6	7	4
II	42	36	46	48	23
I	52	50	47	41	65

\* Weighted by the probabilities used in the sampling design.

**TABLE 4.** Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association between hormone-related and other potential risk factors and breast cancer characterized by estrogen receptor (ER) and progesterone receptor (PR) status in the Carolina Breast Cancer Study, North Carolina, 1993–1996

	OR (95% CI)				
	ER+PR+ cases/controls* (n = 381/790)	ER+PR- cases/controls* (n = 78/790)	ER-PR+ cases/controls* (n = 64/790)	ER-PR- cases/controls* (n = 262/790)	ER+PR+ cases/ ER-PR- cases† (n = 381/262)
Age at menarche (years)					
<12	1.5 (1.1, 2.0)	0.8 (0.4, 1.7)	1.0 (0.5, 1.9)	1.1 (0.7, 1.5)	1.4 (0.9, 2.0)
≥12	1.0	1.0	1.0	1.0	1.0
Nulliparity/age (years) at first full-term pregnancy					
Nulliparous	1.4 (0.9, 2.2)	0.6 (0.3, 1.5)	0.7 (0.3, 1.5)	0.9 (0.6, 1.5)	1.3 (0.8, 2.3)
>25	1.3 (0.9, 1.8)	1.3 (0.7, 2.5)	0.6 (0.3, 1.3)	0.8 (0.5, 1.3)	1.3 (0.8, 2.0)
≤25	1.0	1.0	1.0	1.0	1.0
Breastfeeding					
Ever	0.7 (0.5, 1.0)	0.5 (0.3, 0.8)	0.4 (0.2, 0.8)	0.8 (0.5, 1.1)	0.9 (0.6, 1.3)
Never	1.0	1.0	1.0	1.0	1.0
Abortion or miscarriage					
Ever	1.0 (0.7, 1.3)	0.8 (0.5, 1.4)	0.5 (0.3, 0.9)	0.8 (0.6, 1.2)	1.2 (0.8, 1.7)
Never	1.0	1.0	1.0	1.0	1.0
Body mass index (kg/m <sup>2</sup> )					
>31	1.1 (0.7, 1.7)	1.0 (0.5, 2.3)	1.0 (0.4, 2.4)	0.7 (0.4, 1.2)	1.5 (0.8, 2.7)
23–31	0.9 (0.6, 1.2)	1.0 (0.5, 1.9)	1.3 (0.6, 2.6)	1.0 (0.7, 1.5)	0.9 (0.6, 1.3)
<23	1.0	1.0	1.0	1.0	1.0
Waist-hip ratio					
>0.8	1.4 (1.0, 1.9)	1.2 (0.6, 2.1)	1.5 (0.8, 2.8)	1.2 (0.8, 1.6)	1.4 (0.9, 2.0)
≤0.8	1.0	1.0	1.0	1.0	1.0
Oral contraceptive use					
Ever (≥3 months)	1.4 (1.0, 2.0)	0.9 (0.5, 1.7)	1.4 (0.7, 2.8)	1.4 (1.0, 2.0)	0.9 (0.6, 1.4)
Never	1.0	1.0	1.0	1.0	1.0
Hormone replacement therapy‡					
Ever (≥3 months)	0.9 (0.7, 1.3)	0.3 (0.2, 0.7)	1.2 (0.6, 2.5)	0.7 (0.5, 1.1)	1.2 (0.8, 2.0)
Never	1.0	1.0	1.0	1.0	1.0
First-degree family history of breast or ovarian cancer					
Yes	1.2 (0.8, 1.7)	1.5 (0.8, 3.0)	1.6 (0.7, 3.2)	1.8 (1.2, 2.7)	0.6 (0.4, 1.0)
No	1.0	1.0	1.0	1.0	1.0
Medical radiation to the chest					
Ever	1.1 (0.7, 1.9)	1.0 (0.4, 2.9)	0.7 (0.2, 3.2)	1.2 (0.6, 2.2)	0.9 (0.4, 1.8)
Never	1.0	1.0	1.0	1.0	1.0
Cigarette smoking					
Ever (≥5 packs)	1.1 (0.8, 1.5)	1.1 (0.6, 1.8)	0.6 (0.3, 1.0)	1.1 (0.8, 1.5)	1.2 (0.9, 1.8)
Never	1.0	1.0	1.0	1.0	1.0
Alcohol drinking during most recent age range					
Yes	0.8 (0.6, 1.1)	1.5 (0.9, 2.8)	1.5 (0.8, 2.8)	0.9 (0.6, 1.2)	0.8 (0.6, 1.3)
No	1.0	1.0	1.0	1.0	1.0
Education					
≥College graduation	1.2 (0.7, 1.9)	0.6 (0.2, 1.3)	1.0 (0.4, 2.5)	1.3 (0.8, 2.3)	0.9 (0.5, 1.7)
≥High school graduation– college graduation	1.1 (0.7, 1.6)	0.6 (0.3, 1.2)	0.8 (0.3, 1.8)	1.2 (0.8, 1.9)	0.9 (0.5, 1.5)
<High school graduation	1.0	1.0	1.0	1.0	1.0

\* Adjusted for all 13 exposure variables simultaneously as well as for race, age at diagnosis or selection (11 levels), and the offset term.

† Case-case odds ratios adjusted for all 13 exposure variables simultaneously as well as for race and age at diagnosis or selection (2 levels).

‡ Additionally adjusted for menopausal status.

past 4 years) again failed to distinguish between ER+PR+ and ER-PR- breast cancers (data not shown). In contrast, a first-degree family history of breast or ovarian cancer was associated with a stronger increased risk for ER-PR- breast cancer (OR = 1.8). The effect of each factor was independent of all other factors under study.

When women were further stratified by menopausal status, we again observed elevated odds ratios for ER+PR+ breast cancer and some hormone-related factors as well as elevated odds ratios for ER-PR- breast cancer and some potentially hormone-unrelated factors (table 5). The positive associations with early age at menarche were stronger for ER+PR+ breast cancer among both postmenopausal and pre-/perimenopausal women (OR = 1.6 and OR = 1.5, respectively, compared with OR = 1.3 and OR = 0.9, respectively, for ER-PR- breast cancer). Although the odds ratios for nulliparity were higher for postmenopausal women, the odds ratios for ER+PR+ and ER-PR- breast cancers did not particularly differ in either menopausal group. Late age at first full-term pregnancy (OR = 1.6) and high body mass index (OR = 1.6) were associated with elevated odds ratios for ER+PR+ breast cancer only among postmenopausal women. On the other hand, high waist-hip ratio (OR = 1.9) showed a positive association with ER+PR+ breast cancer exclusively among pre-/perimenopausal women.

Ever use of oral contraceptives was associated with a higher odds ratio for ER+PR+ (OR = 1.5) than for ER-PR- (OR = 1.1) breast cancer in pre-/perimenopausal women, whereas the reverse was found for postmenopausal women (OR = 1.6 for ER-PR- and OR = 1.3 for ER+PR+ breast cancer). In contrast, when recent oral contraceptive use (within the past 4 years) was analyzed, the odds ratios were more elevated for ER+PR+ breast cancer among both menopausal groups (OR = 2.0, 95 percent confidence interval (CI): 0.4, 11.8 for ER+PR+ and OR = 1.1, 95 percent CI: 0.1, 7.5 for ER-PR- breast cancer among postmenopausal women; OR = 1.6, 95 percent CI: 0.7, 3.4 for ER+PR+ and OR = 1.3, 95 percent CI: 0.6, 2.6 for ER-PR- breast cancer among pre-/perimenopausal women). However, the confidence intervals were very wide and overlapped. After perimenopausal women were included with postmenopausal women (since hormone replacement therapy is not prescribed for premenopausal women), hormone replacement therapy was found to be associated with a decreased risk for ER-PR- breast cancer only; similar results were observed for recent use of hormone replacement therapy (data not shown).

In contrast, a family history of breast or ovarian cancer showed stronger positive associations for ER-PR-

than for ER+PR+ breast cancer, especially among pre-/perimenopausal women (OR = 2.1 and OR = 1.3, respectively). Similarly, the odds ratio for medical radiation to the chest was elevated for ER-PR- breast cancer (OR = 1.8) but was reduced for ER+PR+ breast cancer (OR = 0.6) among pre-/perimenopausal women.

Before we included the 11 percent of the ER and PR data generated by our laboratory, odds ratio estimates were further from the null value by 6-21 percent. This led to an overall pattern of stronger distinctions between ER+PR+ and ER-PR- breast cancers (data not shown).

## DISCUSSION

Our results from this population-based case-control study of breast cancer in North Carolina women aged 20-74 years showed that several hormone-related risk factors were associated with an increased risk of developing breast cancer positive for ER and PR, including early age at menarche, nulliparity, late age at first full-term pregnancy, high body mass index, high waist-hip ratio, and possibly oral contraceptive use (summarized in table 6). The elevated odds ratios for ER+PR+ breast cancer were stronger for postmenopausal women with a late age at first full-term pregnancy or a high body mass index and for pre-/perimenopausal women with a high waist-hip ratio. Late age at menarche and recent use of oral contraceptives were more strongly and positively associated with ER+PR+ breast cancer among women in both menopausal groups. In contrast, women with a family history of breast or ovarian cancer in parents or siblings, especially pre-/perimenopausal women, were at increased risk of developing breast tumors negative for ER and PR. Likewise, women reporting radiation exposure to the chest from medical procedures, although few in number, had an increased risk of ER-PR- but a decreased risk of ER+PR+ breast cancer before reaching menopause. Despite the wide confidence intervals, which frequently overlapped and contained a value of 1.0, this pattern of results is provocative and deserves further attention in large studies.

These results support the hypothesis that risk factors most closely associated with an increased risk for ER+PR+ breast cancer may operate through exposure to estrogen and progesterone, whereas risk factors most closely associated with an increased risk for ER-PR- breast cancer may involve mechanisms independent of hormonal exposure (30-32). Breast cancer is hypothesized to evolve through a series of genetic changes from normal epithelium to invasive carcinoma and subsequent metastases (4, 42). The manifestations of ER and PR in breast tumor cells may be

**TABLE 5. Adjusted\* odds ratios (OR) and 95% confidence intervals (CI) for the association between hormone-related and other potential risk factors and ER+PR+† and ER-PR- breast cancer among postmenopausal and pre-/perimenopausal women in the Carolina Breast Cancer Study, North Carolina, 1993-1996**

	OR (95% CI)			
	Postmenopausal		Pre-/perimenopausal	
	ER+PR+ cases/controls (n = 213/436)	ER-PR- cases/controls (n = 111/436)	ER+PR+ cases/controls (n = 168/354)	ER-PR- cases/controls (n = 151/354)
Age at menarche (years)				
<12	1.6 (1.0, 2.4)	1.3 (0.7, 2.2)	1.5 (1.0, 2.5)	0.9 (0.6, 1.5)
≥12	1.0	1.0	1.0	1.0
Nulliparity/age (years) at first full-term pregnancy				
Nulliparous	1.7 (0.9, 3.2)	1.5 (0.7, 3.3)	1.2 (0.7, 2.3)	0.8 (0.4, 1.5)
>25	1.6 (1.0, 2.7)	0.9 (0.4, 1.7)	1.0 (0.6, 1.7)	0.9 (0.5, 1.5)
≤25	1.0	1.0	1.0	1.0
Breastfeeding				
Ever	0.8 (0.5, 1.2)	1.1 (0.6, 1.8)	0.7 (0.4, 1.1)	0.7 (0.4, 1.1)
Never	1.0	1.0	1.0	1.0
Abortion or miscarriage				
Ever	1.0 (0.7, 1.4)	1.0 (0.6, 1.6)	1.1 (0.7, 1.6)	0.8 (0.5, 1.2)
Never	1.0	1.0	1.0	1.0
Body mass index (kg/m <sup>2</sup> )				
>31	1.6 (0.9, 3.0)	0.8 (0.4, 1.7)	0.6 (0.3, 1.2)	0.6 (0.3, 1.2)
23-31	1.1 (0.7, 1.8)	1.0 (0.6, 1.9)	0.7 (0.4, 1.1)	0.9 (0.6, 1.6)
<23	1.0	1.0	1.0	1.0
Waist-hip ratio				
>0.8	1.1 (0.7, 1.7)	1.1 (0.6, 1.8)	1.9 (1.2, 3.1)	1.2 (0.8, 2.0)
≤0.8	1.0	1.0	1.0	1.0
Oral contraceptive use				
Ever (≥3 months)	1.3 (0.8, 2.0)	1.6 (0.9, 2.7)	1.5 (0.8, 2.7)	1.1 (0.6, 1.9)
Never	1.0	1.0	1.0	1.0
Hormone replacement therapy				
Ever (≥3 months)	0.9 (0.6, 1.2)‡	0.6 (0.4, 0.9)‡		
Never	1.0	1.0		
First-degree family history of breast or ovarian cancer				
Yes	1.1 (0.7, 1.8)	1.6 (0.9, 2.8)	1.3 (0.7, 2.4)	2.1 (1.2, 3.8)
No	1.0	1.0	1.0	1.0
Medical radiation to the chest				
Ever	1.2 (0.7, 2.1)	1.1 (0.5, 2.2)	0.6 (0.1, 3.4)	1.8 (0.5, 5.9)
Never	1.0	1.0	1.0	1.0
Cigarette smoking				
Ever (≥5 packs)	1.2 (0.8, 1.7)	0.9 (0.6, 1.5)	1.1 (0.7, 1.7)	1.1 (0.7, 1.7)
Never	1.0	1.0	1.0	1.0
Alcohol drinking during most recent age range				
Yes	0.9 (0.6, 1.3)	0.8 (0.5, 1.4)	0.7 (0.4, 1.1)	0.9 (0.5, 1.4)
No	1.0	1.0	1.0	1.0
Education				
≥College graduation	1.2 (0.6, 2.2)	1.1 (0.5, 2.5)	1.3 (0.6, 2.8)	1.5 (0.7, 3.5)
≥High school graduation- college graduation	1.0 (0.6, 1.7)	1.1 (0.6, 2.0)	1.1 (0.5, 2.4)	1.3 (0.6, 2.8)
<High school graduation	1.0	1.0	1.0	1.0

\* Adjusted for all 13 exposure variables simultaneously as well as for race, age at diagnosis or selection (11 levels), and the offset term.

† ER, estrogen receptor; PR, progesterone receptor.

‡ Including perimenopausal with postmenopausal women.

either inappropriate expression of wild-type ER and PR or expression of ER and PR variants; these events are thought to occur early in breast cancer evolution, providing an environment for subsequent genetic errors (4). Some researchers speculate that breast tumors progress from ER+ to ER- (and PR+ to PR-)

over time (43). However, in our study, adjustment for disease stage in the case-case comparisons made essentially no difference in the pattern of results, suggesting that classification by ER and PR status defines subsets of breast cancer with separate etiologies rather than different stages along the same disease pathway.

**TABLE 6. Summary of the associations\* between hormone-related and other potential risk factors and ER+PR+† and ER-PR- breast cancer among all, postmenopausal, and pre-/perimenopausal women in the Carolina Breast Cancer Study, North Carolina, 1993-1996**

	All		Postmenopausal		Pre-/perimenopausal	
	ER+PR+ cases/ controls (n = 381/790)	ER-PR- cases/ controls (n = 262/790)	ER+PR+ cases/ controls (n = 213/436)	ER-PR- cases/ controls (n = 111/436)	ER+PR+ cases/ controls (n = 168/354)	ER-PR- cases/ controls (n = 151/354)
<i>Hormone-related risk factors‡</i>						
Early age at menarche	++	+	++	+	++	-
Nulliparity/ Late age at first full-term pregnancy	+	-	++	++	+	-
Breastfeeding	-	-	-	+	-	-
Abortion or miscarriage	0	-	0	0	+	-
High body mass index	+	-	++	-	--	--
High waist-hip ratio	+	+	+	+	++	+
Oral contraceptive use	+	+	+	++	++	+
Hormone replacement therapy	-§	-§	-¶	--¶		
<i>Other risk factors‡</i>						
First-degree family history of breast or ovarian cancer	+	++	+	++	+	+++
Medical radiation to the chest	+	+	+	+	--	++
Cigarette smoking	+	+	+	-	+	+
Alcohol drinking during most recent age range	-	-	-	-	-	-
High level of education	+	+	+	+	+	++

\* 0, odds ratio (OR) = 1; +, OR > 1.0-1.4, ++, OR = 1.5-2.0; +++, OR > 2.0; -, OR = 0.7-1.0; --, OR = 0.5-0.6. Bold type, 95% confidence interval excludes 1.0 or is bordered by 1.0. Adjusted for all 13 exposure variables simultaneously as well as for race, age at diagnosis or selection (11 levels), and the offset term.

† ER, estrogen receptor; PR, progesterone receptor.

‡ Variables are defined the same as in tables 1, 4, and 5.

§ Additionally adjusted for menopausal status.

¶ Including perimenopausal with postmenopausal women.

The upregulated ER and PR expression for ER+PR+ breast cancer and the downregulated expression for ER-PR- breast cancer may involve distinct mechanisms, with only the former related to hormonal exposures (30, 31).

Early age at menarche, nulliparity, and late age at first full-term pregnancy may contribute to the development of ER+PR+ breast cancer as a result of increased exposure to estrogen and progesterone from the ovaries. In addition, obesity may increase the risk for ER+PR+ breast cancer because of peripheral conversion of adrenal-derived androgens to estrogen in adipose tissue after women reach menopause (32, 44, 45). Body fat distribution may be more important to the development of ER+PR+ breast cancer during a woman's reproductive years, when ovarian hormones predominate, since central fat distribution may reflect a greater concentration of more metabolically active

fat (46, 47). Oral contraceptives and hormone replacement therapy, composed of synthetic steroids and natural hormones, respectively, are the major sources of exogenous hormone exposure (48-50). Oral contraceptives may modestly increase the risk for ER+PR+ breast cancer prior to menopause, and recent use may affect postmenopausal women the same, although these latter results were based on small numbers. Hormone replacement therapy apparently had no adverse effect on this study population, a finding that contradicts the slightly positive association reported in a recent meta-analysis that did not assess breast cancer cases by receptor status (51).

On the other hand, relations of family history and radiation exposure with hormone use are less clear, and their associations with ER-PR- breast cancer support the likelihood that they operate through other mechanisms. Women from families with a history of

breast or ovarian cancer may have a mutation in a breast cancer susceptibility gene or share adverse environmental factors with family members (52, 53). Radiation is known to induce DNA damage (54, 55). The effects of these risk factors may be more pronounced for breast cancer occurring at younger ages.

Other exposures that showed weak differentiation in effects between ER+PR+ and ER-PR- breast cancers, such as breastfeeding, spontaneous or induced abortion, smoking, and alcohol drinking, may influence ER+PR- and/or ER-PR+ breast cancer, as suggested by the data in table 4, but these results were based on rather small sample sizes. A consensus has not been established on the mechanisms underlying the phenotypes discordant for ER and PR. Fuqua (4) hypothesized that ER+PR- breast cancer may be incapable of binding DNA and stimulating the expression of genes such as the one for PR, and ER-PR+ breast cancer may be incapable of binding estrogen and thus be functionally similar to ER- or hormone-independent breast cancer. However, other evidence suggests that ER-PR+ tumors may represent a subset of ER+PR+ tumors or result from false-negative tests for ER status (31, 56).

Our findings generally agreed with those reported by Potter et al. (30) and Giuffrida et al. (28) but differed from those of Yoo et al. (31); stratification by menopausal status was not assessed in previous studies. The usually minor variations in findings across studies could have resulted from differences in study populations and/or study designs. Potter et al. used data from a cohort study of breast cancer in Iowa women aged 55-69 years, almost all of whom were postmenopausal and White. A variety of clinical laboratories determined the ER and PR status of 610 breast tumors (65 percent of all cases); 69 percent were ER+PR+, 15 percent were ER+PR-, 3 percent were ER-PR+, and 13 percent were ER-PR-. Yoo et al. (31) reported results from a hospital-based case-control study of women aged 25 years or older in Japan. Data on both ER and PR status, determined by using different methods, were available for 455 women (39 percent of all cases); the distribution was 39 percent ER+PR+, 25 percent ER+PR-, 5 percent ER-PR+, and 31 percent ER-PR-.

In our study, women who were White and older were more likely to have ER+PR+ than ER-PR- breast cancer (table 3), a finding consistent with the higher proportion of ER+PR+ and lower proportion of ER-PR- breast cancer patients in Potter et al.'s study (30). The risk factor profiles we observed also were more similar to those reported by Potter et al., especially for postmenopausal women, than to the results from Yoo et al.'s study on Asian women (31). The hypothesis that ER and PR status may determine etiologically dis-

tinct subtypes of breast cancer and potentially explain international variations in breast cancer profiles is also suggested by a recent study that examined age-specific incidence rates of breast cancer among women in the United States, Denmark, and Japan (57).

We are not sure why the pattern of associations became less pronounced after we included ER and PR data on the 95 cases whose medical records information was missing. Our laboratory determined ER and PR status for these cases 2-5 years after that for the other cases. The subgroup analyzed in our laboratory contained fewer ER+PR+ and more ER-PR- breast cancers than the larger group with data from medical records ( $p = 0.02$ ). This difference was not expected based on the characteristics of cases (e.g., age at diagnosis, family history, and tumor stage; data not shown). In addition, the methodology for examining these hormone receptors has become relatively routine and standardized (30, 58); the assay used in our laboratory is compatible with methods currently used in clinical practice; and, when previously tested tumors have been retested in our clinical laboratory, similar results regarding ER and PR status have almost always been obtained. Degradation of the receptor proteins in the archived samples was possible although unlikely; moreover, lowering the cutpoint for receptor positivity in the additional 95 samples and repeating statistical analyses did not restore the patterns of results (data not shown). The most likely explanation is that the difference arose from sampling variability, given the relatively small number of samples by hormone-receptor status in the subgroup tested in our laboratory, and the results from analyses of the pooled data were more conservative because of regression toward the mean.

Other general issues concerning the Carolina Breast Cancer Study did not undermine confidence in our results because we used a population-based case-control study with a relatively large sample size compared with previous studies that used similar biomarkers. Although refusal rates differed by disease status, and nonparticipation may have been related to risk factor status, substantial selection bias is not expected because of our relatively high response rates (70-80 percent for most subgroups) and our assessment of a minisurvey conducted on a portion of the nonparticipants (37). Another potential source of bias could have resulted from excluding cases whose receptor status was unknown (9 percent); however, data availability was not statistically significantly associated with tumor stage ( $p = 0.6$ ) or with other characteristics listed in table 3 ( $p = 0.08$  for race,  $p = 0.2-1.0$  for the others).

The addition of these findings to the literature supports the notion that breast cancer is likely a heterogeneous disease. ER and PR status, in combination with

menopausal status, has been shown to be potentially useful in discriminating risks between subgroups of breast cancer, especially for hormone-related factors. This finding suggests that ER and PR alterations at the genetic or protein level may be crucial to how hormone-related factors influence breast cancer risk. Future efforts aimed at elucidating biologic mechanisms of breast carcinogenesis according to the ER and PR status of tumor tissues should help enhance epidemiologic efforts to identify causal factors for breast cancer.

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