Hormonal Factors and the Risk of Breast Cancer According to Estrogen- and Progesterone-Receptor Subgroup[1]

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Abstract

Evidence suggests hormonal factors may be more strongly associated with estrogen receptor+progesterone receptor+ (ER+PR+) than ER−PR− breast cancer risk. This study evaluated risk factors according to ERPR tumor status among pre- and postmenopausal women participating in two recent population-based case-control studies. Breast cancer cases, ages 25–74 years, and diagnosed 1995–1998 were sampled from the Ontario Cancer Registry. Controls were a random sample of women identified using the Ontario Ministry of Finance rolls and were frequency-matched to cases within 5-year age groups. Epidemiological data were collected from breast cancer cases and controls using two self-administered questionnaires. ERPR data were obtained for 87% of the breast cancer cases (3276 of 3748). Multivariate polytomous logistic regression was used to obtain odds ratios estimates and 95% confidence intervals. The following significant differences were observed in the risk factor profiles for ER+PR+ and ER−PR− breast cancer: among premenopausal women, late age at menarche was only associated with a reduction in ER+PR+ breast cancer risk; obesity was associated with an increased ER−PR− and decreased ER+PR+ cancer risk; and the association between alcohol intake and breast cancer risk was heterogeneous across ERPR subgroups, although the direction varied across the levels of alcohol intake. Among postmenopausal women, there were no statistically significant differences observed in the risk factor profiles for ER+PR+ and ER−PR− breast cancer. Some heterogeneity exists in the risk factor profiles of ER+PR+ and ER−PR− premenopausal breast cancer; however, risk factor profiles did not differ markedly for postmenopausal breast cancer.

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Introduction

There is substantial scientific evidence that ovarian hormones, principally estrogens, play a major role in the etiology of breast cancer (1, 2). Ovarian hormones affect the rate of breast epithelial cell proliferation, perhaps via stimulation of the expression of genes encoding for growth factors (3). Cell proliferation is essential for carcinogenesis because cell division increases the risk of errors during DNA replication, which if not corrected, can lead to cancer (4, 5). Intracellular ERs[3] bind and transfer estrogen to the nucleus (estrogen/ER protein complex); this complex can then interact with estrogen response elements on DNA, thereby activating (transcribing) nearby target genes and resulting in the synthesis of proteins involved in cell division (6, 7). As the ability of estrogen and progesterone to influence breast cell proliferation is mediated by their respective receptors, expression of these receptors is important (8). Although ERs exist in normal breast epithelial cells to regulate breast development during puberty and pregnancy, they are usually present in extremely low quantities (9). In contrast, 30% of premenopausal and 60% of postmenopausal breast cancers have measurable ERs (10, 11).

Most established hormone-related risk factors (*e.g.*, age at menarche, parity, and postmenopausal obesity) are associated with only a modest to moderate increased breast cancer risk, whereas others (*e.g.*, oral contraceptives) show no consistent association with breast cancer risk (12–20). Although the modest and inconsistent associations may be attributable to variation in study design, it is also possible that they result from disease heterogeneity. There is evidence to suggest that hormonal factors may be associated with a stronger increased risk for ER+PR+ than for ER−PR− breast cancer risk (11, 21–25). Thus, associations reported in the many studies that treated breast cancer as a single entity may be modest, inconsistent, and attenuated because of the varying underlying ERPR distributions.

It has been hypothesized that risk factors most closely associated with ER+PR+ breast tumors may involve mechanisms related to estrogen and progesterone exposure, whereas the etiology of ER−PR− breast cancer may be independent of hormonal exposure (11, 21, 22, 25, 26). This may be the result of some mechanism such as alteration by risk factors of the ERPR status of the cells from which breast cancers ultimately develop (27). Most epidemiological studies able to classify breast cancer according to both ER and PR status found some differences in risk factor profiles according to ERPR status, although specific findings have not been consistent across studies (11, 21–23, 25, 26, 28).

[3] The abbreviations used are: ER, estrogen receptor; PR, progesterone receptor; WHS, Women's Health Study; ECSS, Enhanced Cancer Surveillance Study; OCR, Ontario Cancer Registry; MOF, Ministry of Finance; HRT, hormone replacement therapy; OR, odds ratio; CI, confidence interval; MVOR, multivariate-adjusted odds ratio; BMI, body mass index.

The present study evaluated the association between several hormonal and nonhormonal risk factors and breast cancer risk according to ERPR status among pre- and postmenopausal women participating in two recent population-based case-control studies in Ontario. The epidemiological data were previously collected from >7000 breast cancer cases and controls, and >85% of the cases were linked with ERPR data obtained from Ontario laboratories.

Materials and Methods

This study used epidemiological data from two recent population-based case-control studies in Ontario, Canada; the WHS (29) and the ECSS (30). ERPR data on the breast cancer cases, not previously available, was sought for the current study. Although the methods of the WHS and ECSS have been previously described, they are briefly summarized here.

Cases and Controls

ECSS. Breast cancer cases, ages 25–74 years, and diagnosed between April 1995 and March 1996 were sampled from the population-based OCR pathology reports. Controls were an age-stratified random sample of women identified using the population-based assessment rolls of the Ontario MOF and were frequency matched, within 5-year age groups, to cases.

WHS. Breast cancer cases, ages 25–74 years, and diagnosed between July 1996 and September 1998 were identified using the OCR pathology reports. As in the ECSS, controls were a random sample of women identified from the assessment rolls of the MOF and were frequency-matched, within 5-year age groups, to the cases.

The OCR registers all cases of invasive cancer diagnosed among all residents of Ontario using computerized probabilistic record linkage to resolve four main sources of cancer information (pathology reports with any mention of cancer, hospital discharge summaries which include a diagnosis of cancer, reports from Ontario's regional cancer centers, and death certificates). It is estimated that >95% of pathology reports relating to breast cancer in Ontario are received by the OCR, nearly all within 3 months of biopsy (31). Greater than 95% of breast cancer cases were adenocarcinoma/carcinoma, with the two most common histologies being infiltrating ductal carcinoma and lobular carcinoma.

The Ontario MOF assessment database includes full name, age, sex, and address for all home owners and tenants in Ontario. A reabstraction study conducted several years ago was able to link >95% of people in the OCR to the MOF database, suggesting that the accuracy and completeness of the MOF database is high (32).

Epidemiological Data Collection and Response Rates

Physicians identified in the pathology reports were asked to give consent to contact their patients and to provide the patient's address, telephone number, and vital status. Cases and controls were mailed a self-administered epidemiological questionnaire. Within 2 weeks of questionnaire mailing, a follow-up postcard was sent to remind/thank all women and then nonresponders were telephoned several weeks later.

The ECSS response rate was 86% for breast cancer cases ($n = 728$) and 80% for controls ($n = 750$). The WHS response rate was 73% for cases ($n = 3125$) and 61% for controls ($n = 3062$). Reasons for nonparticipation included language, illness, too busy, and privacy concerns, although the majority of both case and control nonresponders provided no reason. It is possible that the subject response rate for the WHS was lower than that in the ECSS because of the sensitive nature of some questions included in this study's questionnaire (*e.g.*, mental illness history).

The current study stratified the data analysis on menopausal status, leading to the exclusion of 226 perimenopausal women (105 cases and 121 controls). Women reported on the questionnaire the age at which their periods stopped permanently, as well as HRT use; this information was then used to define menopausal status at diagnosis/referent date. Premenopausal status was defined as still menstruating, not taking HRT, and no bilateral oophorectomy. Perimenopausal status was defined as age < 55, still menstruating, and taking HRT. Postmenopausal status was defined as stopped menstruating, or age 55 and older, still menstruating, and taking HRT, or both ovaries removed.

ERPR Data Collection

The data on ERPR breast tumor status were obtained primarily from the four Ontario hospital laboratories that routinely conduct biochemical assays to determine the steroid receptor status of tumor tissue from breast cancer patients. These laboratories used the dextran-coated charcoal assay, with receptor levels reported in fmol/mg cytosol protein. Standardized methods, achieving reliable ERPR results, have long been established among these four Ontario laboratories (33). For breast cancer cases without biochemical assay results, pathology reports in the OCR were reviewed in an attempt to locate any immunohistochemical ERPR results issued by pathology laboratories. For the very few remaining cases lacking receptor data, their physicians were asked to provide the information.

Biochemical assay results were categorized as in previous ERPR breast cancer studies: a concentration of estrogen and progesterone binding protein ≤10 fmol/mg was considered negative and >10 fmol/mg was considered positive (11, 22, 23, 28). Immunohistochemical assays were interpreted as positive (presence of antibody nuclear staining) or negative by pathologists who recorded this result directly onto the pathology report. Concordance between the two assay methods (biochemical *versus* immunohistochemical) is ~90% (34).

ERPR status was obtained for 87% of the breast cancer cases ($n = 3276$ of 3748); of the remaining cases, no result was available ($n = 113$), or no assay was performed ($n = 359$; *e.g.*, tissue sample too small for testing). Sixty-six percent of the ERPR data came from the four hospital laboratories (biochemical assay) and 34% from pathology laboratory reports (immunohistochemical assay). One-hundred eleven of the cases were missing either ER or PR data, 187 were ER−PR+, and 340 were ER+PR−. This left 2638 breast cancer cases included in the ER+PR+ and ER−PR− subsets for data analyses.

Data Analysis

Cases were stratified into six risk sets based on ERPR receptor status, within each menopausal stratum (pre/post): ER+PR+; ER−PR−; PR+; PR−; ER+; and ER−. All controls within each menopausal stratum were included for each of the analyses. Only the main ER+PR+ and ER−PR− subgroup analyses are presented because findings did not differ between ER+, PR+, and ER+PR+, nor between ER−, PR−, and ER−PR−. Any exposures occurring in the year before the breast cancer diagnosis date (or referent date for controls) were excluded from the analysis. Variables were categorized based on categorizations previously demonstrated to be associated with breast cancer risk in the literature or defined as tertiles/quartiles based on the distribution in the controls.

Table 1 Distribution (*n*, %) of study and sociodemographic variables for controls and for cases stratified on availability of ERPR results status

Variable	Controls		Cases		Cases		χ^2 (obtained *versus* missing)
			ERPR results obtained		ERPR results missing		
	n	(%)	*n*	(%)	*n*	%	
Study							
ECSS (1995–1996)	721	(20)	649	(20)	65	(14)	0.01
WHS (1996–1998)	2970	(80)	2617	(80)	415	(86)	
Household income							
Low	406	(11)	359	(11)	51	(11)	0.99
Middle	1189	(34)	1064	(34)	159	(35)	
High	1200	(34)	1134	(36)	165	(36)	
No answer	749	(21)	567	(18)	81	(18)	
Marital status							
Married	2756	(75)	2408	(74)	357	(75)	0.85
Single	180	(5)	166	(5)	27	(6)	
Divorced/separated	309	(8)	303	(9)	44	(9)	
Widowed	423	(12)	372	(11)	49	(10)	
Education							
≤Grade 8	470	(13)	366	(11)	67	(14)	0.20
Grades 9–13	1615	(45)	1500	(47)	209	(44)	
College/university	1542	(43)	1340	(42)	201	(42)	

Multivariate polytomous logistic regression was performed, using Stata (35), to obtain simultaneous OR estimates for each case group for variables of interest while simultaneously adjusting for age, all other variables in the model, and additional identified confounders. Confounders were evaluated for each variable of interest using the 10% change-in-estimate method (36). Strenuous physical activity met the criteria for confounding in the premenopausal model and bilateral oophorectomy in the postmenopausal model (and were included in the final models). Using polytomous logistic regression, the likelihood ratio statistic *P* was calculated to assess heterogeneity between the two case group OR estimates (ER+PR+ and ER−PR−).

Results

Table 1 shows the frequency distribution of the study variable and several sociodemographic variables for controls, cases with ERPR data available, and cases with ERPR data missing. The distribution of income, marital status, and education was similar for cases with and without ERPR data available, however, cases missing receptor data were more likely to be in the WHS. The WHS period of diagnosis (1996–1998) was several years after the ECSS (1995–1996); therefore, the higher proportion of cases without ERPR data in the WHS is likely because of the shift from biochemical assay to immunohistochemical assay over the last few years (and biochemical assays results are more readily obtained in Ontario).

There were 1239 premenopausal controls, 500 premenopausal ER+PR+ cases, and 271 premenopausal ER−PR− cases. There were 2452 postmenopausal controls, 1401 postmenopausal ER+PR+ cases, and 466 postmenopausal ER−PR− cases.

Table 2 shows the frequency distribution, MVOR estimates, and 95% CI for many risk factors by ER+PR+ and ER−PR− breast cancer subgroup, among premenopausal women. Late age at menarche was associated with a halving of ER+PR+ breast cancer risk (MVOR, 0.49; 95% CI, 0.31–0.76) and was not associated with the risk of ER−PR− tumors. The difference between the MVOR estimates for the two receptor subgroups was statistically significant ($P = 0.04$). Parity was associated with ER+PR+ breast cancer risk: having more than two pregnancies was associated with a statistically significant halving of ER+PR+ breast cancer risk (MVOR, 0.44; 95% CI, 0.26–0.75), whereas parity was not associated with ER−PR− breast cancer risk. Age at first birth was not associated with either ER+PR+ or ER−PR− breast cancer risk. Use of oral contraceptives was not significantly associated with either ER+PR+ or ER−PR− breast cancer risk.

Obesity (BMI > 27 kg/m^2) was not significantly associated with ER−PR− breast cancer; however, a reduction in risk of borderline significance was observed for ER+PR+ breast cancer (MVOR, 1.35; 95% CI, 0.89–2.05 and MVOR, 0.71; 95% CI, 0.50–1.00, respectively). The difference between the obesity MVOR estimates for the two receptor subgroups was statistically significant ($P = 0.03$). Compared with nondrinkers, heavy consumption of alcohol (>3.5 alcoholic beverages/week) was associated with a nonstatistically significant increased risk of ER+PR+ breast cancer but was not associated with ER−PR− breast cancer. Consuming moderate amounts of alcohol (1–2.5 drinks/week) was associated with an increased risk of ER−PR− tumors (not statistically significant) but was not associated with ER+PR+ tumors. The heterogeneity between these MVORs was statistically significant ($P = 0.03$).

There was no statistically significant association observed between smoking and either ER+PR+ or ER−PR− breast cancer risk. Breast feeding for >6 months was associated with a nonstatistically significant 40% increase in ER+PR+ breast cancer risk and was not associated with ER−PR− breast cancer risk. Benign breast disease was associated with a 3-fold increased risk of both ER+PR+ and ER−PR− breast cancer (MVOR, 3.73; 95% CI, 2.72–5.11 and MVOR, 3.13; 95% CI, 2.09–4.71, respectively). Having a first-degree relative with breast cancer was associated with an increased risk of both ER+PR+ and ER−PR− breast cancer (MVOR, 1.73; 95% CI, 1.08–2.76 and MVOR, 2.35; 95% CI, 1.35–4.10, respectively).

Statistically significant ERPR subgroup differences were observed for age at menarche, alcohol, and BMI.

Table 3 shows the frequency distribution, MVOR estimates and 95% CI for many risk factors and for the ER+PR+ and ER−PR− breast cancer subgroups among postmenopausal women. As expected, the proportion of ER+PR+ (*versus*

Table 2 Distribution (*n*, %) and MVOR estimates and 95% CIs for several hormone-related and nonhormone-related risk factors and breast cancer characterized by ER+PR+ and ER−PR− subgroups among premenopausal women

Note: the control group is the same for both ERPR subgroup analyses.

Risk factor	Controls		ER+PR+ premenopausal cases				ER−PR− premenopausal cases				P^b
	n	(%)	*n*	(%)	MVOR[a]	(95% CI)	*n*	(%)	MVOR[a]	(95% CI)	
Age at menarche (yrs)											
≤11	204	(17)	122	(25)	1.00		44	(17)	1.00		0.04
12	336	(28)	124	(25)	0.59	(0.39–0.89)	85	(32)	1.08	(0.62–1.88)	
13	402	(33)	137	(28)	0.50	(0.33–0.75)	83	(31)	1.02	(0.60–1.76)	
≥14	270	(22)	112	(23)	0.49	(0.31–0.76)	55	(21)	1.12	(0.62–2.03)	
Parity											
Nulliparous[c]	207	(17)	82	(17)	1.00		48	(18)			0.32
1	178	(15)	75	(15)	0.61	(0.35–1.06)	48	(18)	0.99	(0.50–1.95)	
2	530	(43)	224	(45)	0.65	(0.41–1.04)	122	(45)	1.09	(0.61–1.95)	
≥3	313	(26)	115	(23)	0.44	(0.26–0.75)	52	(19)	0.90	(0.46–1.76)	
Age at first live birth (yrs)											
13–23	382	(31)	141	(29)	1.00		84	(31)	1.00		0.24
24–27	320	(26)	130	(26)	1.19	(0.81–1.77)	61	(23)	0.88	(0.54–1.46)	
≥28	315	(26)	141	(29)	1.08	(0.73–1.60)	77	(29)	1.00	(0.60–1.65)	
Nulliparous	206	(17)	82	(17)	1.79	(1.10–2.91)	48	(18)	0.93	(0.51–1.68)	
Duration of OC[d] (yr)											
Never or <1	329	(29)	145	(33)	1.00		55	(23)	1.00		0.41
≤4	247	(22)	91	(21)	0.79	(0.53–1.19)	50	(21)	1.27	(0.75–2.17)	
5–9	250	(22)	93	(21)	0.90	(0.60–1.35)	54	(23)	1.08	(0.62–1.87)	
≥10	292	(26)	110	(25)	0.92	(0.61–1.37)	81	(34)	1.33	(0.79–2.25)	
BMI (kg/m^2)[e]											
≤25	721	(59)	295	(60)	1.00		155	(59)	1.00		0.03
25.1–27	165	(14)	68	(14)	1.14	(0.76–1.72)	38	(14)	1.36	(0.80–2.31)	
>27	335	(27)	126	(26)	0.71	(0.50–1.00)	72	(27)	1.35	(0.89–2.05)	
Alcohol (drinks/wk)[f]											
0	309	(26)	129	(27)	1.00		50	(20)	1.00		0.03
≤1	319	(27)	122	(26)	1.08	(0.72–1.60)	75	(29)	1.31	(0.78–2.19)	
1.5–3	324	(27)	112	(23)	0.84	(0.55–1.28)	75	(29)	1.36	(0.81–2.28)	
≥3.5	248	(21)	116	(24)	1.38	(0.91–2.10)	56	(22)	0.92	(0.51–1.68)	
Cigarette smoking (pack-years)											
0	651	(56)	257	(54)	1.00		124	(49)	1.00		0.75
0.1–10	241	(21)	93	(20)	0.91	(0.62–1.34)	64	(25)	1.05	(0.66–1.68)	
>10	278	(24)	124	(26)	1.10	(0.77–1.57)	66	(26)	1.31	(0.83–2.06)	
Breast feeding (mos)											
Never or nulliparous	557	(47)	209	(44)	1.00		140	(53)	1.00		0.12
1–6	274	(23)	112	(23)	1.17	(0.77–1.78)	56	(21)	0.70	(0.41–1.19)	
>6	367	(31)	160	(33)	1.41	(0.96–2.08)	70	(26)	0.86	(0.53–1.39)	
Benign breast disease											
No	998	(83)	238	(53)	1.00		154	(63)	1.00		0.44
Yes	200	(17)	212	(47)	3.73	(2.73–5.09)	92	(37)	3.15	(2.10–4.72)	
Family history breast cancer[g]											
No	1102	(93)	400	(84)	1.00		221	(85)	1.00		0.32
Yes	78	(7)	77	(16)	1.73	(1.08–2.76)	38	(15)	2.35	(1.35–4.10)	
Age group (yrs)											
25–34	124	(10)	27	(5)	n/a[h]		40	(15)	n/a		
35–39	212	(17)	64	(13)			54	(20)			
40–44	324	(26)	129	(26)			75	(28)			
45–49	381	(31)	177	(35)			79	(29)			
50–64	198	(16)	103	(21)			23	(9)			

[a] MVOR, model is adjusted for all other variables plus age (continuous) and current strenuous activity.
[b] *P* (likelihood ratio test) for heterogeneity in MVORs between ER−PR− and ER+PR+; calculated using polytomous logistic regression.
[c] Includes both never pregnant and no live births.
[d] OC, oral contraceptives.
[e] BMI was calculated using "weight 2 years ago" (prediagnosis).
[f] Includes beer, wine and liquor.
[g] First degree relative.
[h] n/a, not available.

ER−PR−) cases increased with age. Late age at menarche was not significantly associated with either ER+PR+ or ER−PR− breast cancer risk. Parity was associated with a reduced risk of both ER+PR+ and ER−PR− breast cancer, although this association only reached statistical significance for ER+PR+ breast cancer. Late age at first birth significantly increased ER+PR+ breast cancer risk (MVOR, 1.64; 95% CI, 1.28–2.10) and showed no statistically significant association with ER−PR− breast cancer risk. Use of oral contraceptives for >9 years was not associated with ER+PR+ breast cancer risk and

Table 3 Distribution (*n*, %) and MVOR estimates and 95% CIs for several hormone-related and nonhormone related risk factors and breast cancer characterized by ER+PR+ and ER−PR− subgroups among postmenopausal women

Note: the control group is the same for both ERPR subgroup analyses.

Risk factor	Controls		ER+PR+ premenopausal cases				ER−PR− premenopausal cases				P^b
	n	(%)	*n*	(%)	MVOR[a]	(95% CI)	*n*	(%)	MVOR[a]	(95% CI)	
Age at menarche (yrs)											
≤11	431	(18)	255	(19)	1.00		102	(23)	1.00		0.24
12	541	(23)	344	(25)	1.27	(0.97–1.67)	110	(24)	1.03	(0.70–1.52)	
13	651	(27)	392	(29)	1.18	(0.90–1.54)	109	(24)	0.96	(0.65–1.42)	
≥14	778	(32)	376	(28)	0.84	(0.64–1.10)	133	(29)	0.94	(0.64–1.37)	
Parity											
Nulliparous[c]	275	(11)	195	(14)	1.00		63	(13)	1.00		0.84
1	251	(10)	168	(12)	0.95	(0.66–1.36)	56	(12)	0.93	(0.55–1.55)	
2	716	(29)	436	(31)	0.84	(0.61–1.15)	137	(30)	0.73	(0.46–1.15)	
≥3	1196	(49)	594	(43)	0.71	(0.53–0.97)	206	(45)	0.72	(0.46–1.12)	
Age at first live birth (yr)											
13–23	1216	(50)	590	(43)	1.00		207	(45)	1.00		0.50
24–27	560	(23)	323	(23)	1.21	(0.97–1.52)	113	(25)	1.31	(0.95–1.81)	
≥28	367	(15)	275	(20)	1.64	(1.28–2.10)	77	(17)	1.30	(0.89–1.89)	
Nulliparous	273	(11)	195	(14)	1.46	(1.08–1.97)	63	(12)	1.46	(0.95–2.26)	
Duration of OC[d] (yr)											
Never or <1	1373	(62)	834	(64)	1.00		225	(52)	1.00		0.27
≤4	313	(14)	174	(13)	0.85	(0.65–1.11)	72	(17)	1.04	(0.71–1.53)	
5–9	283	(13)	153	(12)	0.86	(0.64–1.15)	60	(14)	1.06	(0.70–1.59)	
≥10	259	(12)	149	(11)	0.95	(0.71–1.27)	72	(17)	1.41	(0.96–2.08)	
Age at menopause (yr)											
<45	812	(35)	389	(29)	1.00		141	(32)	1.00		0.32
45–49	622	(27)	351	(26)	1.17	(0.92–1.49)	122	(28)	1.52	(1.08–2.16)	
≥50	890	(38)	601	(45)	1.50	(1.19–1.88)	174	(40)	1.63	(1.15–2.30)	
Duration of HRT[e] use (yr)											
Never or <1	1498	(66)	920	(69)	1.00		297	(68)	1.00		0.40
≤2	280	(12)	130	(10)	0.77	(0.57–1.03)	56	(13)	0.89	(0.60–1.32)	
2–11	243	(11)	144	(11)	0.97	(0.72–1.30)	42	(10)	0.80	(0.52–1.24)	
≥12	247	(11)	131	(10)	0.94	(0.67–1.31)	42	(10)	1.26	(0.79–2.01)	
BMI (kg/m^2)[f]											
20–25	1008	(42)	489	(36)	1.00		172	(38)	1.00		0.29
<20	119	(5)	45	(3)	0.72	(0.43–1.21)	25	(5)	1.34	(0.72–2.49)	
25.1–27	392	(16)	208	(15)	1.10	(0.84–1.43)	72	(16)	1.09	(0.74–1.61)	
>27	881	(37)	631	(46)	1.61	(1.32–1.98)	190	(41)	1.48	(1.09–1.99)	
Alcohol (drinks/week)[g]											
0	766	(33)	435	(33)	1.00		144	(33)	1.00		0.89
≤1	591	(26)	330	(25)	1.03	(0.23–1.30)	112	(25)	1.06	(0.75–1.50)	
1.5–3	483	(21)	256	(19)	0.90	(0.69–1.15)	93	(21)	0.90	(0.62–1.32)	
≥3.5	471	(20)	311	(23)	1.27	(1.00–1.64)	93	(21)	1.13	(0.79–1.64)	
Cigarette smoking (pack-years)											
0	1287	(56)	693	(52)	1.00		210	(48)	1.00		0.07
0.1–10	310	(13)	174	(13)	1.04	(0.79–1.37)	56	(13)	0.89	(0.58–1.37)	
>10	714	(31)	459	(35)	1.16	(0.94–1.42)	175	(40)	1.53	(1.15–2.04)	
Breast feeding (mos)											
Never or nulliparous	1178	(50)	705	(52)	1.00		237	(52)	1.00		0.64
1–6	606	(26)	332	(24)	0.99	(0.78–1.25)	114	(25)	1.00	(0.72–1.40)	
>6	595	(25)	332	(24)	0.92	(0.73–1.16)	107	(23)	1.09	(0.77–1.52)	
Benign breast disease											
No	1784	(77)	598	(48)	1.00		215	(52)	1.00		0.06
Yes	524	(23)	660	(53)	3.83	(3.17–4.61)	199	(48)	2.95	(2.25–3.86)	
Family history breast cancer[h]											
No	1990	(87)	1089	(81)	1.00		374	(85)	1.00		0.64
Yes	291	(13)	255	(19)	1.30	(1.01–1.66)	68	(15)	1.19	(0.83–1.71)	
Age group (yr)											
25–49	222	(9)	140	(10)			77	(17)			
50–54	360	(15)	167	(12)			78	(17)			
55–59	459	(19)	270	(19)			90	(19)			
60–64	458	(19)	270	(19)			83	(18)			
65–69	522	(21)	305	(22)			80	(17)			
70–74	431	(18)	249	(18)			58	(12)			

[a] MVOR, model is adjusted for all other variables plus continuous age and oophorectomy.
[b] *P* (likelihood ratio test) for heterogeneity in MVORs between ER−PR− and ER+PR+; calculated using polytomous logistic regression.
[c] Includes both never pregnant and no live births.
[d] OC, oral contraceptives.
[e] HRT, includes both estrogen and estrogen/progestin regimens.
[f] BMI was calculated using "weight 2 years ago" (prediagnosis).
[g] Includes beer, wine, and liquor.
[h] First degree relative.

was associated with a nonstatistically significant increased risk of ER−PR− breast cancer compared with never users (MVOR, 1.41; 95% CI, 0.96–2.08). Late age at menopause was associated with a statistically significant increased risk of both ER+PR+ and ER−PR− breast cancer. HRT use was not associated with either ER−PR− or ER+PR+ breast cancer.

Obesity (BMI > 27 *versus* normal) was associated with an increased risk of both ER+PR+ and ER-PR-breast cancer (MVOR, 1.61; 95% CI, 1.32–1.98 and MVOR, 1.48; 95% CI, 1.09–1.99, respectively). Compared with nondrinkers, heavy consumption of alcohol (>3.5 alcoholic beverages/week) was associated with an increased risk of ER+PR+ breast cancer (MVOR, 1.27; 95% CI, 1.00–1.64), and the association with ER−PR− breast cancer approached unity.

Compared with nonsmokers, smoking >10 pack-years was significantly associated with an increase in ER−PR− breast cancer risk (MVOR, 1.53; 95% CI, 1.15–2.04), and smoking was not significantly associated with ER+PR+ breast cancer risk. Breastfeeding for >6 months was not associated with either ER+PR+ or ER−PR− breast cancer risk. Benign breast disease was associated with a significant 3- and 4-fold increased risk of ER−PR− and ER+PR+ breast cancer, respectively. A first-degree relative with breast cancer was associated with an increased risk of both ER+PR+ and ER−PR− breast cancer, although this association was only statistically significant for ER+PR+ tumors.

There were no statistically significant ERPR subgroup risk factor profile differences observed among postmenopausal women.

For both pre- and postmenopausal women, findings for PR+, ER+, PR−, and ER− breast cancer risk did not differ appreciably from the findings for ER+PR+ and ER−PR− tumors, respectively (data not shown).

Discussion

Our findings are somewhat consistent with the growing body of evidence suggesting that some hormonal factors may increase the risk of ER+PR+ breast cancer, as opposed to ER-PR- breast cancer, and that certain nonhormonal factors may be more strongly associated with ER-PR- than ER+PR+ breast cancer risk.

Among the premenopausal women in our study, main significant differences observed in the risk factor profiles between ER+PR+ and ER−PR− breast cancer were: (*a*) late age at menarche was associated with a significant reduction in ER+PR+ breast cancer risk, although no association was seen with ER−PR− cancer risk; (*b*) obesity was not associated with ER−PR− cancer risk but was associated with a decreased ER+PR+ breast cancer risk; and (*c*) the association between alcohol intake and breast cancer risk was heterogeneous across ERPR subgroups, although the direction varied across the levels of alcohol intake. In addition, two factors thought not to be directly related to hormones, benign breast disease, and family history of breast cancer were associated with a statistically significant increased risk of both ER+PR+ and ER−PR− premenopausal breast cancer.

Among the postmenopausal women, no statistically significant differences were observed in risk factor profiles between ER+PR+ and ER−PR− breast cancer; however, smoking almost reached statistical significance. In addition, obesity, late age at menopause, and benign breast disease were significantly associated with an increased risk of both ER+PR+ and ER−PR− postmenopausal breast cancer.

It is not possible to compare our findings directly with previous studies that did not assess pre- and postmenopausal women separately. One such Japanese case-control study conducted in the early 1990s reported that early age at menarche was associated with a reduced risk of ER+PR+ breast cancer and was not associated with ER−PR− breast cancer, although no differences were seen for parity or age at first pregnancy, which may be considered hormone-related variables (23). Because receptor status was known for only 40% of breast cases in that study, the validity may have been compromised; in addition, wide CIs make interpretation difficult. Inconsistent with our findings, The Iowa WHS (postmenopausal) found that parity, late age at first birth, early age at menarche, and BMI—markers of endogenous hormone exposure—were positively associated with ER+PR+ tumors, but no association was seen with ER−PR− tumors (21). Unfortunately, ERPR status was available for only 65% of cases, and premenopausal breast cancer could not be evaluated in the Iowa study. Inconsistent with our findings among premenopausal women, a recent case-control study conducted among women ages 20–44 years found only modest differences in the risk factor profiles for ER+PR+ and ER−PR− breast cancer, and the standard hormone-related risk factors (*e.g.,* age at menarche) were not differentially associated with either ER+PR+ or ER−PR− breast cancer risk (24).

The population-based Carolina Breast Cancer Study was the first ERPR study to stratify women based on menopausal status; in addition, ERPR data were available for 90% of cases (11). In this study, several hormone-related factors were associated with stronger increased risks for ER+PR+ than for ER−PR− breast cancer. ORs were strongest for the ER+PR+ subgroup of breast cancer among postmenopausal women with an early age at menarche, nulliparity/late age at first pregnancy, and BMI and among premenopausal women with a high waist-to-hip ratio; however, the heterogeneity between ER−PR− and ER+PR+ subgroups for each of these risk factors was not statistically significant.

Interpretation of the findings regarding parity and age at first pregnancy is complicated because it is not known whether these risk factors act through hormone-related or nonhormone-related mechanisms. Explanations for the decreased breast cancer risk associated with younger age at first pregnancy and increased parity include: (*a*) the possibility that differentiation of mammary tissue during the third trimester may lower the susceptibility of these breast cells to malignant transformation; and (*b*) the potential for long-lasting hormonal changes such as decreased prolactin and estrogen levels, which may decrease breast cancer risk (38–41). Categorizing these risk factors as hormone related may be deceptive.

It has been suggested that among postmenopausal women the conversion of androgens to estrogens in adipose tissue may increase breast cancer risk and may preferentially lead to ER+PR+ breast cancer risk (22, 42). This is consistent with our finding among premenopausal women only. Previous studies that evaluated obesity and postmenopausal breast cancer risk by ERPR subgroups are not consistent with our finding that obesity (BMI < 25 *versus* > 27) was associated with both ER+PR+ and ER−PR− breast cancer risk; this may, however, be attributable to inconsistent definitions of the referent group. A case-control study by Enger *et al.* (22) in the 1980s reported that among postmenopausal women, increased BMI (>27 *versus* <22) doubled the risk of ER+PR+ breast cancer, whereas obesity was not associated with ER−PR− tumors. As ERPR data were unavailable for 40% of cases, it is important to consider the possibility that risk factor profiles may differ between women with and without available ERPR data. A

recent reanalysis of the Yoo *et al.* (23) dataset reported that among postmenopausal women, increased BMI was most strongly associated with PR+ breast cancer risk and ER+ breast cancer risk (*versus* PR− and ER−); no joint ERPR analyses were presented, probably because of sample size limitations (25). Huang *et al.* (11) reported that among postmenopausal women, increased BMI (>31 *versus* <23) was significantly associated with ER+PR+ breast cancer risk, and no association was seen with the ER−PR− breast cancer.

Although recent pooled and meta-analyses and systematic reviews have found consistent support for alcohol as a risk factor for breast cancer, many individual studies have shown no effect (43–45). Our study found an increased risk with heavy alcohol intake for premenopausal and postmenopausal women with ER+PR+ tumors. Of two other published analyses of alcohol intake according to both menopausal and ERPR status, one reported a similar result (22) and the other found nonsignificant reductions in risk with alcohol consumption across all groups (11). Our finding is inconsistent with the association of alcohol and ER−PR− tumor risk in the postmenopausal women in the Iowa cohort (21). A recent report on women ages 20–44 years (24) found a nonsignificant increased risk associated with alcohol intake for both ER+PR+ and ER−PR− breast cancer. Proposed biological mechanisms for alcohol include effects both hormonal and nonhormonal and at both early and late stages: increased circulating estrogens and androgens; enhancement of mammary gland susceptibility to carcinogenesis; increased mammary carcinogen DNA damage (possibly through effects on protective dietary factors); and greater potential for invasiveness of breast cancer cells (45).

Evidence regarding breast feeding and breast cancer risk is inconclusive, although suggestive of a reduced risk after several years of breastfeeding (13, 46). Breastfeeding may be protective for breast cancer because of nonhormonal factors such as differentiation of breast epithelial cells induced by lactation or because of possible estrogen reduction as a result of lactation (46). Yoo *et al.* (23) found that breastfeeding was not associated with either ER−PR− or ER+PR+ breast cancer risk, and Huang *et al.* (11) reported that among premenopausal women, breast feeding was slightly protective for both ER+PR+ and ER−PR− breast cancer risk.

Somewhat consistent with our finding among postmenopausal women, a Swedish cohort study among women of all ages (and receptor status available for 90% of the cases) reported that smoking was associated with a significant doubling of ER− breast cancer risk (and to a lesser degree PR− tumors also), whereas smoking was not associated with ER+ breast cancers (26). We found smoking >10 years was associated with a statistically significant increased ER−PR− postmenopausal breast cancer risk but was not associated with ER+PR+ risk; however, this heterogeneity did not reach statistical significance ($P = 0.07$). In contrast, Yoo *et al.* (23) reported that smoking was strongly associated with ER+PR+ breast cancer risk and modestly associated with ER-PR- breast cancer risk. However, as discussed above, this case-control study had several methodological flaws, the most important the availability of ERPR data for only 40% of cases.

The recent Carolina Breast Cancer Study found that among premenopausal women, a family history of breast cancer was more strongly associated with ER−PR− than ER+PR+ breast cancer risk (11). Although our study did not find that the difference between the two case groups achieved statistical significance, it is interesting that we found premenopausal women with a family history of breast cancer were slightly more likely to have ER−PR− than ER+PR+ breast cancer. Consistent with our finding among postmenopausal women, the Iowa WHS's (postmenopausal women) found no significant differences between ER−PR− and ER+PR+ breast cancer risk and family history of breast cancer (21).

A limitation of our study is that information on stage is not available, so it is possible that differential associations across receptor status may be because of stage-related differences across receptor status subgroups. The preponderance of evidence from previous studies, however, has shown that stage/tumor size does not differ across ERPR subgroups and adjustment for disease stage makes no difference in the pattern of results, suggesting that ERPR subtypes do not simply represent different stages along the same disease pathway (11, 21, 47). Although recall bias and selection bias must be considered in all case-control studies, it is unlikely to account for any differences observed between the risk factor profiles of breast tumor subgroups. Each ERPR case group was compared with the same control group, therefore, any biases would equally affect estimates among the tumor subgroups.

Another possible concern is that two assay methods were used to determine ERPR status (biochemical and immunohistochemical); however, concordance between the two assay measures is ~90% (34), suggesting that the use of these two assays should not substantially affect our study findings. It is important to note that breast cancer studies to date have only evaluated ER-β status; a second ER isoform, ER-α, has recently been discovered and may complicate the ER− breast cancer story (48). There are currently no routine ER-α assays performed on breast tissue, and studies of ER-α's role in breast cancer are still at the animal model level. In future, breast cancer studies may need to incorporate ER-α information.

Previous studies that evaluated the association between hormonal factors and ERPR subgroups of breast cancer were limited by small sample size, less than optimal receptor data availability (coverage was usually <60% of cases), insufficient joint ERPR data, and lack of consistent risk factor exposure data (11, 21–28). As well, most previous studies did not evaluate both pre- and postmenopausal women. An important advantage of the current study is the large sample size that permitted analysis of both pre- and postmenopausal women. Finally, because ERPR data were available for >85% of breast cancer cases, the potential for selection bias was minimal.

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Hormonal Factors and the Risk of Breast Cancer According to Estrogen- and Progesterone-Receptor Subgroup

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