Risk Factors for Hormone Receptor-Defined Breast Cancer in Postmenopausal Women

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Abstract

The effect of classic breast cancer risk factors on hormone receptor-defined breast cancer is not fully clarified. We explored these associations in a Swedish population-based study. Postmenopausal women ages 50 to 74 years, diagnosed with invasive breast cancer during 1993 to 1995, were compared with 3,065 age frequency-matched controls. We identified 332 estrogen receptor (ER^-) and progesterone receptor (PR^-) negative, 286 ER^+PR^-, 71 ER^-PR^+, 1,165 ER^+PR^+, and 789 tumors with unknown receptor status. Unconditional logistic regression was used to calculate odds ratios (OR) and 95% confidence intervals (95% CI). Women ages ≥30 years, compared with those ages 20 to 24 years at first birth, were at an increased risk of ER^+PR^+ tumors (OR, 1.5; 95% CI, 1.2-1.8) but not ER^-PR^- tumors (OR, 1.1; 95% CI, 0.8-1.6). Women who gained ≥30 kg in weight during adulthood had an ~3-fold increased relative risk of ER^+PR^+ tumors (OR, 2.7; 95% CI, 1.9-3.8), but no risk increase of ER^-PR^- tumors (OR, 1.0; 95% CI, 0.5-2.1), compared with women who gained <10 kg. Compared with never users, women who used menopausal estrogen-progestin therapy for at least 5 years were at increased risk of ER^+PR^+ tumors (OR, 3.0; 95% CI, 2.1-4.1) but not ER^-PR^- tumors (OR, 1.3; 95% CI, 0.7-2.5). In conclusion, other risk factors were similarly related to breast cancer regardless of receptor status, but high age at first birth, substantial weight gain in adult age, and use of menopausal estrogen-progestin therapy were more strongly related to receptor-positive breast cancer than receptor-negative breast cancer. (Cancer Epidemiol Biomarkers Prev 2006;15(12):2482–8)

Introduction

Exposure to ovarian hormones throughout life, probably even before birth, affects the risk of developing breast cancer (1). Early menarche and late menopause, as well as high endogenous levels of estrogens, increase the risk of breast cancer (1). Estrogen and progesterone most likely induce breast cancer by increasing cell proliferation as well as through genotoxicity (2). Both hormones act via nuclear receptors. More recently, estrogen receptors (ER) have been found also in the plasma membrane and in mitochondria, so the mechanisms of the receptors seem complex and are far from fully understood yet (2). It has been suggested that some breast cancer risk factors, especially reproductive factors and postmenopausal obesity, are associated mainly with ER^+ and progesterone receptor-positive (PR^+) tumors (3). Still, little is established about the etiology of receptor-defined breast cancer, and few reports exist where ER and PR status are considered jointly (3). Clarifying whether risk factors are associated with certain types of receptor-defined breast cancer will help us to understand the biological mechanisms behind breast carcinogenesis. We here report results on the relationships between reproductive, anthropometric, and various other breast cancer risk factors as well as menopausal hormone therapy and the risk of breast cancer according to joint receptor status, from a large population-based Swedish case-control study among postmenopausal women.

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Materials and Methods

Subjects. This study is an extension of a case-control study that we have reported on previously (4) The study base consisted of all native Swedish female residents ages 50 to 74 years, surveyed between October 1, 1993 and March 31, 1995 (5). The investigation was approved by the ethical review board at the Karolinska Institutet and by the five ethical review boards in other regions in Sweden. Women with incident primary invasive breast cancer were identified via the six Swedish Regional Cancer Registries and contacted via their doctors. Of the 3,979 case women identified, 3,345 (84%) participated in the study. Nonparticipation was mainly due to doctor's refusal because of the patient's poor health or the patient's refusal. The mean interval from diagnosis to data collection was 4.3 months (SD, 1.5 months). As controls, 4,188 age frequency-matched women were randomly selected from the Swedish National Population Register holding data on national registration number, name, address, and place of birth of all Swedish residents. The participation rate among controls was 82% (3,455 of 4,188). Women diagnosed previously with invasive cancer (other than nonmelanoma skin cancer) were excluded from the study (112 cases and 91 controls). Menopause was defined as the age at last menstrual period or age at bilateral oophorectomy, if 1 year or more before data collection. Premenopausal women (198 cases and 152 controls) as well as women below the age of 55 years with unknown age at menopause (202 cases and 101 controls) were excluded.

We retrieved information on hormone receptor status, various other tumor characteristics, and detection mode (mammography screening or other) from medical records of all participating cases. Following a decision of the Ethical Review Board of the University of Lund, written informed consent to retrieve this information was sought from cases in that region (n = 563), among whom 58 women did not provide informed consent.

Information from the medical records led us to further exclude 58 cases with noninvasive breast cancer, 35 cases with previous cancer, 1 case with a cancer diagnosis other than breast cancer, and 19 cases diagnosed before or after the study period. Women with missing information on body mass index (BMI; 14 cases and 45 controls) or age at first birth (5 cases and 1 control) were excluded from the study. Thus, the final analytic sample comprised 2,643 cases and 3,065 controls.

Data Collection. Data on sociodemographic, anthropometric, reproductive, and menstrual factors, use of oral contraceptives, medical history, lifetime physical activity, and smoking habits, as well as recent (1 year before data collection) dietary habits and alcohol use were collected by means of a postal questionnaire. Detailed information on use of menopausal hormone therapy, including timing and type for each treatment episode, was also requested. A color chart displaying all preparations ever marketed in Sweden was included with the questionnaire to aid recall. In addition, ~50% of both cases and controls were contacted by telephone to complete missing or ambiguous responses, mainly on the use of menopausal hormone therapy. Of all eligible controls, 14% did not return the questionnaire but agreed to a telephone interview covering the most important items, including use of menopausal hormone therapy.

ER and PR. ER and PR content of breast tumors were routinely measured in Sweden at the time of the study but was often not done on tumors ≤1 cm in size due to lack of tumor tissue. Receptor analyses were usually done at one particular laboratory within each region. All seven laboratories in Sweden analyzing ER and PR content used an enzyme immunoassay (Abbott Laboratories) on cytosol samples. The method used for assessing ER content was ERα specific (6). Three laboratories reported amount of receptor per microgram DNA, three laboratories reported amount of receptor per milligram protein, and one laboratory reported both. Quantitative receptor content was available for 67% of the tumors for both ER and PR. Solely qualitative receptor status (strongly positive, positive, weakly positive, or negative) was obtained in 4% and 3% of the tumors, for ER and PR, respectively. We defined receptor-positive tumors as ≥0.05 fmol receptor/μg DNA or ≥10 fmol receptor/mg protein. For the laboratory reporting both analyses, the proportion of receptor-positive tumors was most similar to the proportion among the other laboratories when measured as amount of receptor per microgram DNA. Hence, we used these values. Tumors with qualitative information were defined as receptor negative if they were classified as negative, otherwise as receptor positive.

Statistical Analyses. We used χ^2 tests to evaluate the statistical significance of associations between missing receptor status information, or receptor status category, and categorical variables, such as age group and various tumor characteristics.

We used unconditional logistic regression to estimate odds ratios (OR) with associated 95% confidence intervals (95% CI) separately for each receptor-defined group and for undefined tumors compared with controls. To formally test heterogeneity, whether effect estimates were similar between ER^+PR^+ and ER^-PR^- tumors, we fitted adjusted case-case models and estimated the tests for association. As missing receptor status was associated with tumor size, tumor size was included as a covariate in the heterogeneity models. We report *P* values from Wald statistics for the heterogeneity. To test whether the observed heterogeneities in the associations between risk factors and ER^-PR^- or ER^+PR^+ tumors could be due to earlier detection of ER^+PR^+ tumors compared with ER^-PR^- tumors, we did models additionally, including detection mode and lymph node involvement, but these covariates did not influence the estimates and were not included in the final heterogeneity models.

We adjusted all estimates for age and assessed the potential confounding effects of a variety of other risk factors, including number of births, age at first birth, age at menopause, bilateral oophorectomy, menopausal symptoms, recent BMI, height, socioeconomic status, recent smoking, recent alcohol intake, and ever use of estrogen-progestin therapy. Factors were defined as confounders and included in the final models when adjustment introduced a change of age-adjusted point estimates >10%.

To assure accurate classification of age at menopause and avoid confounding, we restricted the analyses of age at menopause to women with known age at menopause that had not used menopausal hormone therapy before menopause. The influence of recent BMI (kg/m^2) as well as weight gain from age 18 to 1 year before data collection was evaluated among never users of menopausal hormone therapy as the association between body fatness and breast cancer risk seems to be confined to this group (4). Alcohol has been reported to interact with menopausal hormone therapy to increase the risk of certain groups of receptor-defined breast cancer (7, 8), so we stratified the analyses of alcohol use according to ever or never use of estrogen ± progestin. We included alcohol use, menopausal hormone therapy use, and an interaction term in a model for each receptor-defined group compared with controls to test for interaction. Tumors detected through the national mammography screening program or through other health check-ups (mostly due to menopausal hormone therapy or employment related) were defined as screening detected and other tumors as nonscreening detected.

We categorized menopausal hormone therapy into four types: estrogen alone (mainly estradiol and to a lesser extent conjugated estrogens), use of estrogen-progestin (mainly estradiol combined sequentially or continuously with levonorgestrel or norethisterone acetate), use of orally administered estriol, or local estrogen treatment. Use of only one type of therapy was defined as exclusive use. We explored the influence of all use as well as exclusive use of each type of therapy. Exclusive use was evaluated as ever use, as well as by duration (<5 or ≥5 years) and recency of use (current use defined as last use <6 months before reference date and past use as last use >6 months before reference date). All use of each type was only assessed as ever and current use, as the estimates for past use and duration of use could be severely influenced by the other therapies. Exposure to hormone therapy after a reference date (defined in cases as date of diagnosis minus 3 months; in controls as the date of questionnaire arrival minus mean time from diagnosis to questionnaire arrival in cases, minus an additional 3 months), was censored.

Results

Overall, we had information on joint ERPR status for 1,854 (70%) of all cases. The cases with missing information on receptor status had smaller tumors, less lymph node involvement, a higher proportion of low-grade tumors, higher proportion of histologies other than ductal or lobular, more screening-detected tumors, and lower socioeconomic status (Table 1). However, all differences, except for socioeconomic status, were explained by tumor size (data not shown).

Among tumors with known receptor status, 332 (18%) were ER^-PR^-, 286 (15%) were ER^+PR^-, 71 (4%) were ER^-PR^+, and 1,165 (63%) were ER^+PR^+ (Table 1). Receptor status varied significantly with age, tumor characteristics, and mode of detection but not with socioeconomic status. Tumors in women ages 50 to 54 years at diagnosis were less often ER^+PR^+ than those in older women. The fraction of ER^+PR^+ tumors decreased, and ER^-PR^- increased, with increasing tumor size, lymph node involvement, and grade. Lobular

Table 1. Characteristics of breast cancer cases by joint ER and PR status

	Unknown receptor status		Known receptor status	ER^-PR^-	ER^+PR^-	ER^-PR^+	ER^+PR^+
	n (%)*		*n* (%) *	*n* (%) †	*n* (%) †	*n* (%) †	*n* (%) †
	789 (30)		1,854 (70)	332 (18)	286 (15)	71 (4)	1165 (63)
Age at diagnosis (y)							
50-54	64 (24)		199 (76)	50 (25)	22 (11)	16 (8)	111 (56)
55-59	182 (30)		416 (70)	80 (19)	59 (14)	15 (4)	262 (63)
60-64	160 (29)		388 (71)	68 (18)	53 (14)	13 (3)	254 (65)
65-69	204 (31)		463 (69)	74 (16)	76 (16)	15 (3)	298 (64)
70-74	179 (32)		388 (68)	60 (15)	76 (20)	12 (3)	240 (62)
P values, χ^2		0.29			0.0033		
Tumor size (mm)							
≤10	387 (54)		334 (46)	52 (16)	43 (13)	10 (3)	229 (69)
11-20	264 (23)		881 (77)	129 (15)	143 (16)	37 (4)	572 (65)
21-50	109 (15)		577 (84)	129 (22)	89 (15)	20 (3)	339 (59)
>50	13 (19)		55 (81)	22 (40)	7 (13)	3 (5)	23 (42)
Missing	16		7	0	4	1	2
P values, χ^2		<0.0001			<0.0001		
Involved lymph nodes							
0	588 (34)		1,149 (66)	189 (16)	170 (15)	42 (4)	748 (65)
1-3	118 (22)		425 (78)	75 (18)	68 (16)	15 (4)	267 (63)
>3	38 (14)		231 (86)	61 (26)	33 (14)	14 (6)	123 (53)
Missing	45		49	7	15	0	27
P values, χ^2		<0.0001			0.0054		
Grade, differentiation							
Well	100 (37)		170 (63)	13 (8)	20 (12)	7 (4)	130 (76)
Moderate	171 (23)		565 (77)	67 (12)	80 (14)	15 (3)	403 (71)
Poor	164 (22)		596 (78)	166 (28)	95 (16)	22 (4)	313 (53)
Missing	354		523	86	91	27	319
P values, χ^2		<0.0001			<0.0001		
Histology							
Ductal	548 (29)		1,340 (71)	256 (19)	202 (15)	46 (3)	836 (62)
Lobular	77 (25)		231 (75)	19 (8)	41 (18)	10 (4)	161 (70)
Other	140 (34)		271 (66)	53 (20)	41 (15)	14 (5)	163 (60)
Missing	24		12	4	2	1	5
P values, χ^2		0.026			0.0048		
Screening detection							
Yes	496 (33)		990 (67)	135 (14)	152 (15)	41 (4)	662 (67)
No	268 (24)		854 (76)	194 (23)	131 (15)	30 (4)	499 (58)
Missing	25		10	3	3	0	4
P values, χ^2		<0.0001			<0.0001		
Socioeconomic status ‡							
Low	421 (32)		907 (68)	158 (17)	135 (15)	38 (4)	576 (64)
High	362 (28)		936 (72)	172 (18)	148 (16)	33 (4)	583 (62)
Missing	6		11	2	3	0	6
P values, χ^2		0.033			0.77		

*Denominator includes all cases.
†Denominator includes only receptor-defined cases.
‡Low level includes blue-collar workers and low-level white-collar workers, whereas high level includes all other categories.

tumors were more likely to be ER^+PR^+ than tumors of other histologic types. ER^+PR^+ tumors were more common among screening detected tumors than among those clinically detected.

Risk of Receptor-Defined Breast Cancer according to Endogenous Factors. Age at first birth seemed more strongly associated with the two ER^+ groups (P = 0.059 for heterogeneity between ER^+PR^+ and ER^-PR^-; Table 2). Women who were at least 170 cm tall were at a significantly increased risk of ER^+, but not ER^-, tumors compared with women who were shorter than 160 cm, but with no signs of significant heterogeneity. Women in the highest quintile of BMI (≥28.3 kg/m^2) were at increased risk for all tumor types, except ER^+PR^- tumors. Women who gained ≥30 kg in weight during adulthood had an ~3-fold increased relative risk of ER^+PR^+ tumors (OR, 2.7; 95% CI, 1.9-3.8) compared with women who gained <10 kg. This difference was, however, only apparent in the highest weight gain category (P overall heterogeneity, 0.064), and tumors with unknown receptor status were not associated with the largest weight gain. Weight gain in adult age seemed more strongly associated with the two PR^+ groups compared with the two PR^- groups. The other endogenous risk factors seemed similarly associated with the different receptor-defined tumor groups (Table 2).

Risk of Receptor-Defined Breast Cancer according to Exogenous Factors. We found no associations between either oral estriol or local estrogen treatment and any of the receptor-defined groups (data not shown). Therefore, use of these regimens was not defined as hormone therapy in the following analyses. Users of oral estriol or local estrogen were thus included among never as well as exclusive users of other regimens.

Use of estrogen alone (other than oral estriol or local estrogen) hormone therapy was associated with an increased risk for all receptor-defined tumors, both among all users and exclusive users (Table 3). Risks were generally higher after ≥5 years than <5 years of use. For ER^-PR^- and ER^+PR^-, risks were higher with past, but not current use, compared with never use. The highest point estimate was found for the ER^-PR^+ group (OR, for ≥5 years of use 10.2; 95% CI, 4.2-24.6). The risks were very similar for the ER^+PR^+ and ER^-PR^- groups (Table 3).

Use of estrogen-progestin hormone therapy, either all use or exclusive use, was not associated with the risk of ER^-PR^-

Table 2. Endogenous factors and risk for breast cancer defined by joint ER and PR status

	Control group	ER^-PR^-		ER^+PR^-		ER^-PR^+		ER^+PR^+		Unknown ERPR		*P*, Wald (df)*
	n	*n*	OR† (95% CI)	*n*	OR† (95% CI)	*n*	OR† (95% CI)	*n*	OR† (95% CI)	*n*	OR† (95% CI)	
Parous‡												
No	348	42	1.0 (Ref)	47	1.0 (Ref)	6	1.0 (Ref)	173	1.0 (Ref)	140	1.0 (Ref)	0.31 (1)
Yes	2,717	290	0.8 (0.6-1.2)	239	0.7 (0.5-0.9)	65	1.4 (0.6-3.2)	992	0.7 (0.6-0.9)	649	0.6 (0.5-0.7)	
Age at first birth (y)§												
<20	311	24	0.7 (0.4-1.1)	13	0.5 (0.3-1.0)	8	1.0 (0.5-2.3)	93	0.9 (0.7-1.2)	69	1.1 (0.8-1.5)	
20-24	1,164	129	1.0 (Ref)	98	1.0 (Ref)	29	1.0 (Ref)	369	1.0 (Ref)	239	1.0 (Ref)	0.059 (3)
25-29	858	83	0.8 (0.6-1.1)	80	1.0 (0.8-1.4)	20	0.9 (0.5-1.6)	340	1.2 (1.0-1.4)	218	1.2 (0.9-1.4)	
≥30	384	54	1.1 (0.8-1.6)	48	1.2 (0.8-1.8)	8	1.0 (0.4-2.2)	190	1.5 (1.2-1.8)	123	1.4 (1.1-1.8)	
No. births												
1	573	81	1.0 (Ref)	70	1.0 (Ref)	9	1.0 (Ref)	247	1.0 (Ref)	161	1.0 (Ref)	0.37 (3)
2	1,099	129	0.8 (0.6-1.1)	98	0.8 (0.6-1.1)	30	1.6 (0.8-3.6)	435	0.9 (0.8-1.1)	302	1.0 (0.8-1.3)	
3	653	56	0.6 (0.4-0.9)	55	0.8 (0.5-1.1)	21	1.9 (0.8-4.4)*	213	0.8 (0.7-1.0)	125	0.7 (0.5-0.9)	
≥4	392	24	0.5 (0.3-0.8)	16	0.4 (0.2-0.7)	5	0.8 (0.3-2.5)	97	0.7 (0.5-0.9)	61	0.6 (0.4-0.9)	
Age at menarche (y)												
<12	166	27	1.5 (1.0-2.4)	14	0.9 (0.5-1.7)	10	2.3 (1.1-5.0)	83	1.2 (0.9-1.7)	52	1.2 (0.8-1.7)	
12-13	1,187	120	1.0 (Ref)	113	1.0 (Ref)	28	1.0 (Ref)	454	1.0 (Ref)	305	1.0 (Ref)	0.56 (3)
14-15	1,200	129	1.1 (0.9-1.5)	123	1.1 (0.8-1.4)	24	0.9 (0.5-1.6)	429	1.0 (0.9-1.2)	315	1.1 (0.9-1.3)	
≥16	241	23	1.0 (0.6-1.7)	15	0.6 (0.4-1.1)	4	0.8 (0.3-2.3)	80	0.9 (0.7-1.2)	51	0.9 (0.6-1.2)	
Age at menopause (y)‖												
<45	332	31	0.9 (0.6-1.3)	18	0.5 (0.3-0.8)	5	0.6 (0.2-1.7)	79	0.6 (0.5-0.8)	61	0.6 (0.5-0.9)	
45-49	670	77	1.1 (0.8-1.5)	50	0.7 (0.5-0.9)	15	0.9 (0.5-1.8)	228	0.9 (0.7-1.1)	164	0.9 (0.7-1.1)	0.34 (3)
50-54	1,261	132	1.0 (Ref)	139	1.0 (Ref)	28	1.0 (Ref)	480	1.0 (Ref)	342	1.0 (Ref)	
≥55	283	31	1.1 (0.8-1.7)	28	0.9 (0.6-1.4)	7	1.3 (0.6-3.1)	110	1.0 (0.8-1.3)	65	0.8 (0.6-1.2)	
Height (cm)												
<160	675	67	1.0 (Ref)	55	1.0 (Ref)	13	1.0 (Ref)	224	1.0 (Ref)	140	1.0 (Ref)	0.18 (3)
160-164	1,035	104	1.0 (0.7-1.4)	99	1.2 (0.8-1.7)	28	1.4 (0.7-2.7)	356	1.0 (0.9-1.3)	266	1.3 (1.0-1.6)	
165-169	900	108	1.1 (0.8-1.6)	78	1.0 (0.7-1.5)	16	0.8 (0.4-1.8)	347	1.2 (1.0-1.4)	239	1.3 (1.0-1.6)	
≥170	455	53	1.1 (0.7-1.6)	54	1.4 (1.0-2.1)	14	1.5 (0.7-3.2)	238	1.5 (1.2-1.9)	144	1.5 (1.1-1.9)	
Recent BMI (kg/m^2)¶												
<22.2	477	35	1.0 (Ref)	45	1.0 (Ref)	7	1.0 (Ref)	105	1.0 (Ref)	79	1.0 (Ref)	0.48 (4)
22.2-24.0	463	41	1.3 (0.8-2.0)	35	0.8 (0.5-1.3)	2	0.3 (0.1-1.5)	128	1.3 (1.0-1.7)	104	1.4 (1.0-2.0)	
24.1-25.8	480	45	1.4 (0.9-2.2)	40	0.9 (0.6-1.5)	11	1.7 (0.7-4.5)	135	1.3 (1.0-1.8)	98	1.3 (0.9-1.8)	
25.9-28.2	489	50	1.5 (0.9-2.3)	37	0.9 (0.5-1.3)	7	1.1 (0.4-3.1)	176	1.7 (1.3-2.3)	113	1.5 (1.1-2.1)	
≥28.3	501	55	1.6 (1.0-2.5)	45	1.0 (0.7-1.6)	14	2.2 (0.9-5.6)	228	2.2 (1.7-2.8)	151	2.0 (1.4-2.7)	
Adult weight gain (kg)¶**												
<0	185	13	0.7 (0.4-1.3)	15	0.6 (0.3-1.1)	1	0.3 (0.0-2.2)	39	0.7 (0.5-1.1)	36	0.8 (0.5-1.2)	
0-9.5	518	51	1.0 (Ref)	63	1.0 (Ref)	10	1.0 (Ref)	146	1.0 (Ref)	119	1.0 (Ref)	0.064 (4)
10-19.5	611	78	1.3 (0.9-1.8)	39	0.5 (0.3-0.8)	12	1.0 (0.4-2.4)	242	1.4 (1.1-1.8)	172	1.3 (1.0-1.7)	
20-29.5	264	36	1.4 (0.9-2.2)	28	0.9 (0.6-1.4)	7	1.4 (0.5-3.8)	114	1.6 (1.2-2.1)	82	1.4 (1.0-1.9)	
≥30	111	11	1.0 (0.5-2.1)	11	0.8 (0.4-1.7)	4	2.1 (0.6-6.8)	81	2.7 (1.9-3.8)	25	1.1 (0.7-1.7)	
Mother or sister with breast cancer												
No	2,348	279	1.0 (Ref)	237	1.0 (Ref)	54	1.0 (Ref)	945	1.0 (Ref)	648	1.0 (Ref)	0.33 (1)
Yes	236	46	1.7 (1.2-2.3)	39	1.7 (1.2-2.4)	15	2.7 (1.5-4.9)	193	2.0 (1.7-2.5)	119	1.8 (1.4-2.3)	
Operated due to benign breast disease												
No	2,369	289	1.0 (Ref)	241	1.0 (Ref)	60	1.0 (Ref)	1,012	1.0 (Ref)	671	1.0 (Ref)	0.92 (1)
Yes	249	43	1.5 (1.1-2.1)	44	1.8 (1.2-2.5)	11	1.9 (1.0-3.7)	145	1.4 (1.1-1.8)	115	1.7 (1.3-2.1)	

NOTE: Recent, 1 year before data collection.
Abbreviation: df, degrees of freedom.
*P value for association from case-case analysis for ER^+PR^+ compared with ER^-PR^- cancer, in a model adjusted for age, BMI, age at first birth, and tumor size.
†Adjusted for age, BMI, and age at first birth where applicable.
‡Not adjusted for age at first birth.
§Adjusted for number of births, age, and BMI.
‖Women with unknown age at menopause and women using menopausal hormone therapy before menopause excluded.
¶Women ever using menopausal hormone therapy excluded.
**Weight gain from 18 years to 1 year before data collection.

tumors. In contrast, such treatment was related to the risk of all other tumor groups, especially for current users (Table 3). The heterogeneities between the relative risks for ER^+PR^+ and ER^-PR^- tumors in women who used combined estrogen-progestin treatment were all borderline statistically significant. At least 5-year use of estrogen-progestin was associated with a 3-fold increased risk of ER^+PR^+ tumors (OR, 3.0; 95% CI, 2.1-4.1) compared with OR of 1.3 (95% CI, 0.7-2.5) for ER^-PR^- tumors.

Recent alcohol intake of >10 g/d was associated with a seemingly higher risk of ER^-PR^- tumors (OR, 1.6; 95% CI, 0.9-2.7) than for ER^+PR^+ tumors (OR, 1.0; 95% CI, 0.6-1.6) compared with no recent alcohol intake, but the heterogeneity was nonsignificant. We found no interaction between menopausal hormone therapy and recent alcohol intake for any of the receptor-defined groups (Table 4).

Oral contraceptive use, which consisted mainly of past use in these postmenopausal women, and recent smoking were not associated with risk of any receptor-defined tumor group (Table 3).

The heterogeneities found were not attenuated by introducing screening or nonscreening detection and lymph node involvement in the models (data not shown).

Discussion

Our results indicate that a few established breast cancer risk factors are differently associated with breast cancers of different receptor-defined subtypes. Older age at first birth seemed to be a risk factor only for ER^+ tumors. Adult weight gain was associated primarily with PR^+ tumors, and users of

combined estrogen-progestin menopausal hormone therapy were at clearly increased risk of receptor-positive tumors but not receptor-negative tumors.

That older age at first birth seems to be a risk factor mainly for ER^+ tumors, and to be less strongly correlated to PR status was concluded in the review by Althuis et al. (3). This association is also supported by another recent study (9) in addition to ours.

A few studies, including postmenopausal women comparing parous with nulliparous women, have found, as we did, similarly reduced risks for ER^+ and ER^- tumors (10) or ER^+PR^+ and ER^-PR^- tumors (11, 12), now supported by our finding. However, three studies found a reduced risk only of ER^+ or ER^+PR^+ tumors (9, 13, 14) among parous women, whereas two other studies reported nonsignificantly doubled risks of ER^- or ER^-PR^- tumors among parous women (15, 16). For increasing number of children compared with uniparous women, all studies but one (9) have given evidence of a protective effect regardless of ER (14) or ERPR status (11, 12, 16, 17). In conclusion, increasing number of births seems to similarly reduce the risk of all receptor-defined groups of breast cancer.

Our finding of comparable influences of age at menarche and age at menopause on postmenopausal breast cancer risk regardless of receptor status agrees with previous publications (3, 11, 12, 16).

To our knowledge, only one study has explored the association between height and receptor-defined breast cancer and reported no difference in association between different subtypes (18). We found no significant differences but a tendency toward a stronger association with tumors expressing at least one receptor in taller women.

Four (16, 19-21) of five (12) previous studies on postmenopausal BMI and joint receptor status found high postmenopausal BMI to be a stronger risk factor for ER^+PR^+ tumors than ER^-PR^- tumors. Potter et al. (16) assessed the risks for all combinations of ER and PR and found high BMI to be associated with the two PR^+ groups. Three studies reported ER and PR separately (18, 22, 23) and found postmenopausal BMI to be more strongly associated with PR than ER expression. When we assessed adult weight gain, perhaps a better proxy for body fat than BMI, we found no association with ER^-PR^- tumors but a strong association with ER^+PR^+ tumors and a high point estimate also for ER^-PR^+ tumors. The absence of an association in the highest weight gain category for the unknown receptor group is however intriguing, as those tumors are small and thus probably receptor positive to a high

Table 3. Exogenous factors and risk for breast cancer defined by joint ER and PR status

	Control group	ER^-PR^-		ER^+PR^-		ER^-PR^+		ER^+PR^+		Unknown ERPR		*P*, Wald (df)*
	n	n	OR† (95% CI)	*n*	OR† (95% CI)	*n*	OR† (95% CI)	*n*	OR† (95% CI)	*n*	OR† (95% CI)	
Menopausal hormone therapy												
Estrogen alone												
No use‡	2,384	225	1.0 (Ref)	200	1.0 (Ref)	41	1.0 (Ref)	771	1.0 (Ref)	542	1.0 (Ref)	
All use												
Ever	222	41	1.9 (1.3-2.7)	30	1.6 (1.1-2.5)	13	3.2 (1.7-6.2)	135	1.9 (1.5-2.5)	87	1.7 (1.3-2.3)	0.88 (1)
Current	130	23	1.9 (1.2-3.0)	18	1.8 (1.0-3.0)	8	3.5 (1.6-7.6)	69	1.7 (1.2-2.3)	50	1.8 (1.2-2.5)	0.59 (1)
Exclusive use§												
Ever	141	26	2.0 (1.3-3.1)	18	1.6 (1.0-2.7)	8	3.3 (1.5-7.2)	79	1.8 (1.3-2.4)	52	1.7 (1.2-2.4)	0.70 (1)
Duration (y)												
<5	85	13	1.6 (0.9-3.0)	14	2.0 (1.1-3.7)	1	0.6 (0.1-4.5)	36	1.3 (0.9-2.0)	31	1.7 (1.1-2.5)	0.86 (2)
≥5	45	10	2.4 (1.2-4.8)	4	1.2 (0.4-3.3)	7	10.2 (4.2-24.6)	33	2.4 (1.5-3.8)	19	2.0 (1.1-3.4)	
Recency												
Current	58	6	1.0 (0.4-2.4)	4	0.9 (0.3-2.6)	4	3.5 (1.2-10.3)	31	1.7 (1.1-2.6)	24	1.9 (1.2-3.1)	0.25 (2)
Past	72	17	2.7 (1.5-4.6)	14	2.4 (1.3-4.4)	4	3.5 (1.2-10.1)	38	1.7 (1.1-2.5)	26	1.7 (1.0-2.7)	
Estrogen-progestin												
No use‡	2,384	225	1.0 (Ref)	200	1.0 (Ref)	41	1.0 (Ref)	771	1.0 (Ref)	542	1.0 (Ref)	
All use												
Ever	409	66	1.4 (1.0-1.9)	55	1.7 (1.2-2.4)	22	2.4 (1.4-4.3)	261	2.0 (1.6-2.4)	163	1.7 (1.4-2.2)	0.068 (1)
Current	289	41	1.2 (0.8-1.8)	41	1.8 (1.3-2.7)	16	2.5 (1.3-4.7)	177	1.9 (1.5-2.4)	121	1.9 (1.5-2.4)	0.036 (1)
Exclusive use§												
Ever	306	44	1.3 (0.9-1.8)	42	1.8 (1.2-2.6)	16	2.4 (1.3-4.4)	182	1.8 (1.5-2.3)	122	1.8 (1.4-2.3)	0.067 (1)
Duration (y)												
<5	201	29	1.2 (0.8-1.8)	26	1.6 (1.0-2.6)	12	2.5 (1.2-5.1)	98	1.4 (1.1-1.9)	59	1.3 (0.9-1.7)	0.051 (2)
≥5	88	12	1.3 (0.7-2.5)	15	2.3 (1.3-4.1)	4	2.6 (0.9-7.5)	78	3.0 (2.1-4.1)	62	3.4 (2.4-4.9)	
Recency												
Current	191	26	1.1 (0.7-1.8)	27	1.8 (1.2-2.9)	14	3.2 (1.6-6.4)§	131	2.2 (1.7-2.8)	98	2.4 (1.8-3.2)	0.037 (2)
Past	98	15	1.4 (0.8-2.5)	14	1.9 (1.0-3.4)	2	1.1 (0.2-4.5)	45	1.4 (1.0-2.0)	23	1.7 (1.0-2.7)	
Oral contraceptives												
No use	2,093	204	1.0 (Ref)	198	1.0 (Ref)	45	1.0 (Ref)	763	1.0 (Ref)	550	1.0 (Ref)	0.29 (2)
<5 y	477	52	0.9 (0.6-1.2)	34	0.8 (0.5-1.1)	13	0.8 (0.4-1.6)	196	1.0 (0.8-1.3)	138	1.1 (0.8-1.3)	
≥5 y	341	53	1.3 (0.9-1.8)	35	1.2 (0.8-1.8)	10	0.9 (0.4-1.8)	142	1.1 (0.9-1.4)	76	0.8 (0.6-1.1)	
Recent alcohol use (g/d)												
No alcohol	1,139	129	1.0 (Ref)	114	1.0 (Ref)	38	1.0 (Ref)	459	1.0 (Ref)	321	1.0 (Ref)	0.52 (3)
<5	925	128	1.2 (0.9-1.5)	110	1.3 (0.9-1.7)	22	0.6 (0.3-1.0)	401	1.0 (0.8-1.2)	277	1.1 (0.9-1.3)	
≥5 to 10	216	32	1.2 (0.8-1.9)	22	1.1 (0.7-1.8)	3	0.3 (0.1-1.1)	130	1.2 (0.9-1.6)	67	1.1 (0.8-1.5)	
>10	100	19	1.6 (0.9-2.7)	14	1.4 (0.8-2.6)	1	0.2 (0.0-1.8)	50	1.0 (0.6-1.6)	42	1.5 (1.0-2.3)	
Recent smoking												
No	2,275	263	1.0 (Ref)	213	1.0 (Ref)	55	1.0 (Ref)	902	1.0 (Ref)	597	1.0 (Ref)	0.23 (1)
Yes	712	69	0.8 (0.6-1.0)	73	1.2 (0.9-1.6)	16	0.8 (0.4-1.4)	261	1.0 (0.8-1.1)	189	1.1 (0.9-1.3)	

NOTE: All use, use of other types of hormone therapy allowed; exclusive use, only use of one type of hormone therapy. Recency: current, last use ≤6 months before reference date; past, last use >6 months before reference date. Recent, 1 year before data collection.

*P value for association from case-case analysis for ER^+PR^+ compared with ER^-PR^- cancer, in a model adjusted for age, BMI, age at first birth, and tumor size.

†All ORs adjusted for age, BMI, and age at first birth.

‡No use: no use of any kind of menopausal hormone therapy (apart from oral estriol or local estrogen).

§Users of more than one kind of therapy excluded.

Table 4. Alcohol consumption and the risk for receptor-defined breast cancer among users and nonusers of menopausal hormone therapy

	Control group	ER^-PR^-		ER^+PR^-		ER^-PR^+		ER^+PR^+		Unknown ER/PR	
	n	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)	*n*	OR* (95% CI)
Never users of menopausal hormone therapy†											
Recent alcohol use (g/d)											
No alcohol	960	99	1.0 (Ref)	90	1.0 (Ref)	28	1.0 (Ref)	367	1.0 (Ref)	250	1.0 (Ref)
<5	681	87	1.2 (0.9-1.7)	75	1.3 (0.9-1.8)	10	0.4 (0.2-0.9)	244	1.0 (0.8-1.2)	189	1.2 (0.9-1.4)
≥5 to 10	146	17	1.1 (0.6-1.9)	13	1.1 (0.6-2.0)	1	0.2 (0.0-1.6)	65	1.2 (0.9-1.7)	37	1.0 (0.7-1.5)
>10	68	12	1.8 (0.9-3.5)	7	1.2 (0.5-2.8)	0	-	26	1.1 (0.7-1.8)	22	1.4 (0.9-2.4)
Ever users of menopausal hormone therapy†											
Recent alcohol use (g/d)											
No alcohol	171	30	1.0 (Ref)	23	1.0 (Ref)	10	1.0 (Ref)	92	1.0 (Ref)	70	1.0 (Ref)
<5	237	41	0.9 (0.6-1.6)	35	1.2 (0.6-2.1)	12	0.9 (0.3-2.1)	156	1.2 (0.9-1.7)	86	0.8 (0.5-1.2)
≥5 to 10	68	14	1.1 (0.5-2.2)	8	0.9 (0.4-2.2)	2	0.5 (0.1-2.3)	65	1.8 (1.2-2.8)	30	1.0 (0.6-1.7)
>10	32	7	1.0 (0.4-2.6)	7	1.5 (0.6-3.9)	1	0.4 (0.0-3.2)	24	1.4 (0.8-2.5)	20	1.3 (0.7-2.4)
$P_{interaction}$			0.78		0.97		0.70		0.30		0.57

*Adjusted for age, BMI (kg/m^2), and age at first birth.
†Estrogen alone (apart from oral estriol or local estrogen) or estrogen-progestin.

extent. In line with our findings, a recent cohort study reported higher point estimates for the association between weight gain and ER^+PR^+ than ER^-PR^- tumors (24).

Postmenopausal obese women, compared with slim, have higher levels of bioavailable estrogens (25), and estrogen upregulates the PR expression via the ER in normal breast tissue (26). This could be part of the explanation why most epidemiologic researches, including our study, link postmenopausal obesity to tumors expressing receptors and possibly PR more than ER (3). In line with this is the finding that the proportion of PR^+ breast cancer is higher among premenopausal women than postmenopausal women of the same age (27). The proportion of tumors expressing ER, on the other hand, does not vary with menopausal status after accounting for age (27).

Two recent studies from the United States reported use of estrogen alone to be unrelated to breast cancer risk regardless of receptor status (28, 29). However, investigators reporting on two other U.S. studies found increased relative risks for ER^+PR^+ tumors (30, 31). We found similarly increased risks for both ER^+PR^+ and ER^-PR^- tumors among estrogen alone users.

There is accumulating data consistently linking use of estrogen-progestin therapy solely to receptor-positive tumors (28-30, 32, 33). All studies have found an increased risk for ER^+PR^+ tumors, and all but one (29) have found an increased risk for the relatively rare ER^-PR^+ group. In contrast to the findings from the observational studies, Women's Health Initiative investigators found no differences in ER or PR expression in tumors when comparing women treated with estrogen-progestin therapy or placebo (34).

Our findings of similar risks of receptor-negative and receptor-positive tumors for family history of breast cancer, alcohol, smoking, and operation due to benign breast disease are in line with most previous studies and the conclusion from the review by Althuis et al. (3, 12, 13, 18). An interaction between menopausal hormone therapy and alcohol intake was reported from the Iowa Women's Health Study, with increased risks for ER^+PR^+ and ER^-PR^- tumors but not ER^+PR^- among hormone therapy users compared with nonusers (7). A recent Swedish study on alcohol and menopausal hormone therapy found a strong interaction between these two factors and risk for ER^+ but not ER^- tumors (8). However, similar to another study (18), we found no signs of interactions between alcohol and hormone therapy for any receptor-defined group. Generally, recent but not past use of oral contraceptives is believed to be a risk factor for breast cancer (3). Among our postmenopausal women, very few women were recent oral contraceptive users, and as expected, we observed no associations with any receptor-defined group for this treatment.

Our study was population based and the response rate was high (84% among cases and 82% among controls). Yet, nonparticipants had larger tumors on average, which thus were more likely to be receptor negative. To what extent nonresponders differed in exposure status is not known. Recall bias is theoretically of concern in this retrospective study. Recall differences according to receptor status are, however, unlikely, rendering such bias of case-case comparison less of a problem.

We lacked information on receptor status for 30% of the cases, with a larger proportion of missing information among women with smaller tumors. Small tumors are more often receptor positive, and the ORs for tumors with missing receptor status were similar to those for the ER^+PR^+ group, except for adult weight gain ≥30 kg. Within categories of tumor size, apart from the slight association with socioeconomic status, there was no suspicion that missingness was related to the outcome (receptor status), so we assumed that missingness was covariate dependent (tumor size) missing completely at random (35) or ''missing at random''; thus, missingness did not bias our results. Tumor size is only available for cases, so we could only adjust our case-case analyses for this covariate. A methodologic problem is that tumor size could theoretically be an effect of both exposure and outcome and in that case, adjusting for it might introduce a bias (36). However, because the exposures were at most only slightly correlated with tumor size, this should not be a major concern (data not shown). Studying ER and adjusting for PR could similarly introduce a bias if ER causally affects expression of PR. Therefore, we chose to study the receptors jointly. In an attempt to see if heterogeneity could be explained by earlier detection of receptor-positive tumors, we additionally included screening or nonscreening detection and lymph node involvement as covariates in the case-case models, but our findings of heterogeneity remained.

There is no evident cutoff value discriminating receptor-positive tumors from receptor-negative tumors, and other studies have used cutoffs from 3 to ≥10 fmol receptor/mg protein (3). Interlaboratory and intralaboratory reproducibility for six of the seven laboratories used in our study was evaluated in a study in 1996, showing that the concordance in receptor status was 98.4% (37). Despite this, we found that the fraction of ER^-PR^- tumors ranged from 13% to 24% between different laboratories. Receptor status may thus have been misclassified to an extent that was likely to affect our estimates. Because such misclassification is not likely to be associated with breast cancer risk factors, it cannot explain our positive findings but may rather have resulted in attenuated risk estimates. Tumors in the two groups with mixed receptor

status (ER^+PR^- and ER^-PR^+) were more likely to be misclassified, as the quantitative values of ER and PR were closer to the cutoff value than for the other two groups (data not shown).

We believe it is more relevant to discuss our results in relation to previous results and biological credibility than to adjust for multiple comparisons in the statistical analyses (38). As the power to study subtypes that make up a small proportion of all breast cancers is low in most single studies, a pooled analysis on this topic is warranted.

In conclusion, our findings, seen in the light of results from previous work, seem to indicate that most breast cancer risk factors are similarly related to breast cancer regardless of receptor status. However, age at first birth, postmenopausal obesity, and use of estrogen-progestin menopausal hormone therapy are stronger risk factors for receptor-positive breast cancer than receptor-negative breast cancer.

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