DOI: 10.1093/jnci/djq526
Advance Access publication on December 29, 2010

ARTICLE

Associations of Breast Cancer Risk Factors With Tumor Subtypes: A Pooled Analysis From the Breast Cancer Association Consortium Studies

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Manuscript received May 13, 2010; revised November 22, 2010; accepted November 23, 2010.

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Background Previous studies have suggested that breast cancer risk factors are associated with estrogen receptor (ER) and progesterone receptor (PR) expression status of the tumors.

Methods We pooled tumor marker and epidemiological risk factor data from 35 568 invasive breast cancer case patients from 34 studies participating in the Breast Cancer Association Consortium. Logistic regression models were used in case–case analyses to estimate associations between epidemiological risk factors and tumor subtypes, and case–control analyses to estimate associations between epidemiological risk factors and the risk of developing specific tumor subtypes in 12 population-based studies. All statistical tests were two-sided.

Results In case–case analyses, of the epidemiological risk factors examined, early age at menarche (≤12 years) was less frequent in case patients with PR− than PR$^+$ tumors ($P = .001$). Nulliparity ($P = 3 \times 10^{-6}$) and increasing age at first birth ($P = 2 \times 10^{-9}$) were less frequent in ER− than in ER$^+$ tumors. Obesity (body mass index [BMI] ≥ 30 kg/m^2) in younger women (≤50 years) was more frequent in ER−/PR− than in ER$^+$/PR$^+$ tumors ($P = 1 \times 10^{-7}$), whereas obesity in older women (>50 years) was less frequent in PR− than in PR$^+$ tumors ($P = 6 \times 10^{-4}$). The triple-negative (ER−/PR−/HER2−) or core basal phenotype (CBP; triple-negative and cytokeratins [CK]5/6$^+$ and/or epidermal growth factor receptor [EGFR]$^+$) accounted for much of the heterogeneity in parity-related variables and BMI in younger women. Case–control analyses showed that nulliparity, increasing age at first birth, and obesity in younger women showed the expected associations with the risk of ER$^+$ or PR$^+$ tumors but not triple-negative (nulliparity vs parity, odds ratio [OR] = 0.94, 95% confidence interval [CI] = 0.75 to 1.19, $P = .61$; 5-year increase in age at first full-term birth, OR = 0.95, 95% CI = 0.86 to 1.05, $P = .34$; obesity in younger women, OR = 1.36, 95% CI = 0.95 to 1.94, $P = .09$) or CBP tumors.

Conclusions This study shows that reproductive factors and BMI are most clearly associated with hormone receptor–positive tumors and suggest that triple-negative or CBP tumors may have distinct etiology.

J Natl Cancer Inst 2011;103:250–263

Breast tumor subtypes with distinctive biology and treatment responses are defined by the immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR), and HER2. Furthermore, the ER-negative (ER^-), PR-negative (PR^-), and HER2-negative ($HER2^-$) tumors, also known as triple-negative phenotype ($ER^-/PR^-/HER2^-$), that express cytokeratin 5/6 (CK5/6) or cytokeratin 5 (CK5) proteins and/or the epidermal growth factor receptor (EGFR) may represent another distinctive breast tumor subtype, known as the core basal phenotype (CBP), characterized by $ER^-/PR^-/HER2^-$, CK5 or CK5/6 positive ([CK5 or CK5/6]$^+$), and/or EGFR positive ($EGFR^+$). CBP has been used to recapitulate the related "basal-like" breast cancers (1,2) and is associated with short- and long-term prognosis (3).

Epidemiological evidence suggests that associations between risk of breast cancer and both genetic and nongenetic risk factors vary by tumor pathology (4–6). In particular, reproductive risk factors such as parity-related factors and age at menarche seem more strongly associated with ER-positive (ER^+) or PR-positive (PR^+) tumors compared with those that are ER^- or PR^- (4,7). In addition, several breast cancer susceptibility loci in the genome also show differences in associations by hormone receptor expression (8). Although parity and premenopausal obesity are associated with reduced breast cancer risk overall, there is limited data on the association of these factors with reduced risk of CBP cancers (9). Tumors with CBP demonstrate unusual features that include over representation among *BRCA1* mutation carriers and African American women and are associated with specific histological patterns such as medullary or metaplastic carcinoma (10–12). Characterizing associations between breast cancer risk factors and tumor subtypes to which they are related may allow improved risk assessment; and predicting the risk for specific tumor subtypes may lead to targeted early detection of breast cancer and implementation of prevention strategies.

Despite amassing evidence that breast cancer is etiologically heterogeneous, results of individual studies have not been entirely consistent (4,13). Conclusions have been limited by insufficient statistical power in single investigations (4), and combining data from multiple studies has been restricted to systematic reviews or meta-analyses (4,7), which are susceptible to publication biases. In addition, recognition that finer tumor classification using expanded marker panels in addition to ER and PR may reveal greater heterogeneity (1), heightens the need for large datasets.

To address these limitations, we pooled individual data for 35 568 breast cancer case patients contributed by 34 studies participating in the Breast Cancer Association Consortium (BCAC), with risk factor information and ER and PR immunohistochemical expression data. We also performed extensive analyses of risk associations using five markers (ER, PR, HER2, CK5 or CK5/6, and EGFR) in a subset of case patients. Our goal was to definitively assess the evidence for heterogeneity in associations between nongenetic risk factors and breast cancer subtypes defined by marker expression in tumors.

CONTEXT AND CAVEATS

Prior knowledge

Breast cancer etiologic heterogeneity is attributed to genetic and nongenetic risk factors (eg, reproductive factors, body mass index, family history, etc.). The risk factors are known to vary by tumor subtypes, based on the expression of ER, PR, and HER2 receptors, as well as expression of core basal markers like CK5/6 and EGFR in the tumors.

Study design

To assess heterogeneity, associations between nongenetic risk factors and tumor subtypes were investigated. Data on risk factors and tumor subtypes were pooled from 34 studies participating in the Breast Cancer Association Consortium and risk associations were analyzed for ER, PR, HER2, CK5 or CK5/6, and EGFR on a large sample size.

Contribution

Reproductive risk factors (eg, age at menarche and parity-related variables) and increased body mass index were strongly associated with ER^+ or PR^+ tumors compared with ER^- and PR^- tumors. These factors were not associated with the risk of core basal phenotype ($ER^-/PR^-/HER2^-$/[CK5 or CK5/6]$^+$ or $EGFR^+$). Positive family history was associated with increased risk of breast cancer for all tumor subtypes; the association was slightly stronger for core basal phenotype.

Implications

Heterogeneity in breast cancer risk factors was defined by tumor subtypes. The etiology for core basal phenotype was different from that of hormone receptor positive tumors.

Limitations

Because data were pooled from different studies for analyses of risk associations, differences in collection and reporting of data may have introduced bias.

From the Editors

Materials and Methods

Study Population

This analysis includes data from 34 studies participating in the BCAC that provided information on breast cancer risk factors and data on ER and/or PR expression (14–46). These composed of 13 population-based studies that were defined as studies that included breast cancer case patients occurring in a geographically defined population during a specified period of time, and control subjects that were a random sample of the same source population as case patients and recruited during the same period of time (10 case–control and three prospective cohort studies); six hospital-based case–control studies that were defined as studies that included case patients diagnosed in a given hospital or hospitals during a specified period of time, and control subjects that were selected from the catchment area of case patients during the same period of time; and 15 studies of mixed design (all other studies) (Table 1 and Supplementary Table 1, available online). For case–case analyses, studies were classified on the basis of the source of case patients (population-based case series, hospital-based case series, and mixed sources of case patients), without taking into consideration the source of control subjects. Analyses were restricted to invasive breast carcinomas, based on the availability of samples. We excluded subjects with missing information on age. Approximately 92%

Table 1. Characteristics of the studies included in the pooled analysis*

Study, first author, year (reference)	Control subjects† (N = 60273)	Case patients (N = 47184)	Breast cancer case patients with information on the expression of five markers in the tumors‡				
			ER (N = 35568)	PR (N = 31276)	HER2 (N = 14268)	CK5 or CK5/6 (6106)	EGFR (4311)
Prospective cohort							
MCCS, Giles, 2002 (31)	778	1234	878	876	462	464	445
MEC, Kolonel, 2000 (32)	829	873	790	786	0	0	0
NHS, Hankinson, 1998 (34)	1761	1029	904	883	0	0	0
Population-based case–control							
ABCFS, Dite, 2003 (14)	1077	1610	1358	1351	0	0	0
GENICA, Pesch, 2005 (20)	1015	1021	971	969	680	0	0
GESBC, Chang-Claude, 2000 (21)	1381	650	521	514	0	0	0
MARIE, Flesch-Janys, 2008 (28)	7341	3580	2547	2545	2310	0	0
NC-BCFR, John, 2004 (33)	337	1399	1226	1217	0	0	0
OFBCR, John, 2004 (33)	367	1407	1000	981	0	0	0
PBCS, Garcia-Closas, 2006 (37)	2378	2000	1804	1800	1291	1284	1283
POSH, Eccles, 2007 (38)	0	1001	987	745	617	0	0
SASBAC, Wedren, 2004 (40)	1524	1701	1056	1032	0	0	0
UCIBCS, Anton-Culver, 2000 (45)	633	933	753	743	0	0	0
Hospital-based case–control§							
BIGGS, Colleran, 2009 (17)	913	975	742	581	0	0	0
CGPS, Bojesen, 2005 (18)	12534	3306	2560	1969	0	0	0
KBCP, Hartikainen, 2005 (25)	532	492	438	436	389	327	328
RBCS, Easton, 2007 (39)	801	747	553	461	0	0	0
TBCS, Sangrajrang, 2008 (43)	390	474	243	233	220	0	0
TWBCS, Ding, 2009 (44)	1410	909	753	753	326	0	0
Mixed design§							
ABCS, Schmidt, 2007 (15)	1140	1481	953	948	902	774	0
BBCC, Fasching, 2008 (16)	1100	1374	1084	1081	950	0	0
CNIO-BCS, Milne, 2006 (19)	1249	1105	204	228	103	0	36
HABCS, Dork, 2001 (22)	1015	1108	748	670	0	0	0
HEBCS, Syrjakoski, 2000 (23)	1287	2247	2145	2144	1221	975	777
KARBAC, Lindblom, 1992 (24)	870	832	454	385	0	0	0
KConFab/AOCS, Beesley, 2007 (26)	1009	344	203	181	0	0	0
LMBC, De Maeyer, 2008 (27)	1142	1206	989	983	828	0	0
MBCSG, Catucci, 2009 (29)	1243	277	101	100	0	0	0
MCBCS, Olson, 2007 (30)	1574	1202	1049	1043	751	32	0
OBCS, Erkko, 2007 (35)	511	537	537	536	537	0	0
ORIGO, de Bock, 2004 (36)	1663	1326	989	818	0	0	0
SBCS, MacPherson, 2004 (41)	1271	1115	707	336	355	341	0
SEARCH, Lesueur, 2005 (42)	8096	6882	4568	2723	1949	1909	1442
SZBCS, Jakubowska, 2009 (46)	1032	807	753	225	377	0	0

* A total of 34 studies participating in the Breast Cancer Association Consortium were included in the pooled analysis. Breast cancer cases for each tumor subtype were pooled across all studies with available data. ABCFS = Australian Breast Cancer Family Study; ABCS = Amsterdam Breast Cancer Study; BBCC = Bavarian Breast Cancer Cases and Controls; BIGGS = Breast Cancer in Galway Genetic Study; CGPS = Copenhagen General Population Study; CNIO-BCS = Spanish National Cancer Centre Breast Cancer Study; GENICA = Gene Environment Interaction and Breast Cancer in Germany; GESBC = Genetic Epidemiology Study of Breast Cancer by Age 50; HABCS = Hannover Breast Cancer Study; HEBCS = Helsinki Breast Cancer Study; KARBAC = Karolinska Breast Cancer Study; KBCP = Kuopio Breast Cancer Project; KConFab/AOCS = Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer/Australian Ovarian Cancer Study; LMBC = Leuven Multidisciplinary Breast Centre; MARIE = Mammary Carcinoma Risk Factor Investigation; MBCSG = Milan Breast Cancer Study Group; MCBCS = Mayo Clinic Breast Cancer Study; MCCS = Melbourne Collaborative Cohort Study; MEC = Multiethnic Cohort; NC-BCFR = Northern California Breast Cancer Family Registry; NHS = Nurses Health Study; OBCS = Oulu Breast Cancer Study; OFBCR = Ontario Familial Breast Cancer Registry; ORIGO = Leiden University Medical Centre Breast Cancer Study; PBCS = NCI Polish Breast Cancer Study; POSH = Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer; RBCS = Rotterdam Breast Cancer Study; SASBAC = Singapore and Sweden Breast Cancer Study; SBCS = Sheffield Breast Cancer Study; SEARCH = Study of Epidemiology and Risk factors in Cancer Heredity; SZBCS = IHCC-Szczecin Breast Cancer Study; TBCS = IARC-Thai Breast Cancer Study; TWBCS = Taiwanese Breast Cancer Study; UCIBCS = UCI Breast Cancer Study. CK5 or CK5/6 = cytokeratins 5 or 5/6; ER = estrogen receptor; EGFR = epidermal growth factor receptor; PR = progesterone receptor.

† Control subjects in population-based studies were randomly selected from the same source population as the case patients and recruited during the same period of time.

‡ Only invasive cases with ER or PR and age at diagnosis data were included.

§ Studies within these design groups were only included in case–case analyses.

of case patients were of European ancestry, with a median age of 55.3 years at diagnosis (Table 1 and Supplementary Table 1, available online).

All investigations were approved by the institutional review boards of each study center. Written informed consent was obtained from all study subjects.

Breast Cancer Risk Factors

Participating studies provided information on one or more of the following factors—age at menarche (25 306 case patients from 27 studies), parity (28 869 case patients from 30 studies), age at first full-term birth (20 373 case patients from 25 studies), family history of breast cancer in first-degree relatives (32 868 case patients from 33 studies), and current (baseline for cohort studies) body mass index (BMI) (25 679 case patients from 23 studies) from study questionnaires, as detailed in Supplementary Table 2, available online.

Assessment of Tumor Markers

The source of tumor marker data (ie, data on expression of ER, PR, HER2, CK5 or CK5/6, and EGFR) and defining whether a tumor was positive for a specific marker varied across studies. ER, PR, and HER2 status of a breast tumor were primarily extracted from medical records (24 of 34 studies for ER and PR, and nine of 17 studies for HER2), whereas data for CK5 or CK5/6 and EGFR were obtained from immunohistochemical staining of tissue microarrays or whole sections. Details of numbers of case patients with marker information and methods of determination are presented in Table 1 and Supplementary Table 3, available online, respectively. Previous publications from participating groups in the current study have shown good concordances between marker status from medical records and standardized measurements from tissue microarray analyses (47–49), supporting our approach of combining data from different sources.

We classified breast tumors according to their expression of ER (35 568 case patients), PR (31 276 case patients), and joint status of both ER and PR expression (31 106 case patients). For studies with data available on ER, PR, and HER2 (14 141 case patients), we defined four tumor subtypes ($ER^+/HER2^-$ or $PR^+/HER2^-$, $ER^+/HER2^+$ or $PR^+/HER2^+$, $ER^-/PR^-/HER2^+$, and $ER^-/PR^-/HER2^-$ [triple negative]), shown in Figure 1. In seven studies with data available on CK5 or CK5/6 or EGFR, triple-negative tumors were subclassified into CBP ($ER^-/PR^-/HER2^-/[CK5$ or $CK5/6]^+$ and/or $EGFR^+$) and the 5-negative ($ER^-/PR^-/HER2^-/[CK5$ or $CK5/6]^-/EGFR^-$) phenotype. The 5-negative phenotype may represent biologically uncharacterized subtype(s) and a heterogeneous group that includes tissues with low immunoreactivity of all the five markers mentioned above. Therefore, the analyses presented in this article focused on the other tumor subtypes.

Statistical Analysis

Our primary goal was to assess heterogeneity in associations between epidemiological risk factors and breast tumor subtypes that are defined by immunohistochemical staining patterns. The number of case patients for each tumor subtype was pooled across all studies with data on the particular subtype; heterogeneity in breast cancer risk was determined by comparing the associations between different tumor subtypes and risk factors using case–case odds ratios (ORs). We then performed case–control analyses by comparing case patients in each tumor subtype to a common set of control subjects to assess how associations between risk factors and tumor subtypes in case patients, measured by the case–case odds ratios, translated into differences in relative risks by tumor subtype, measured by the tumor subtype–specific case–control odds ratios. It should be noted that a case–case odds ratio for a dichotomous tumor characteristic (eg, ER status) is the ratio of case–control odds ratios for the association of the risk factor for each of the two subtypes defined by the tumor marker (eg, ER^+ and ER^- tumors).

Case–Case Analyses for the Assessment of Associations Between Risk Factors and Tumor Characteristics. Case–case comparisons were performed using a standard and polychotomous unconditional logistic regression model to estimate odds ratios, 95% confidence intervals (CIs), and *P* values for associations between risk factors and breast tumor subtypes. Outcome (dependent) variables were breast tumor subtypes defined by specific

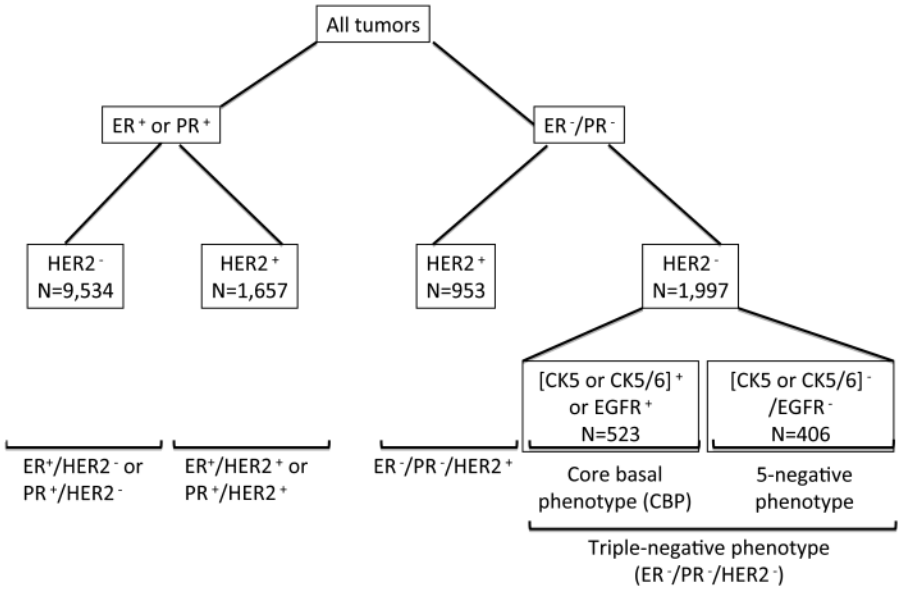

Figure 1. Breast tumor subtypes defined by expression of estrogen receptor (ER), progesterone receptor (PR), HER2, cytokeratins 5 or 5/6 (CK5 or CK5/6), and epidermal growth factor receptor (EGFR) in 34 studies participating in the Breast Cancer Association Consortium. The number of case patients for each tumor subtype was pooled across all studies with data on the particular subtype.

tumor markers, and explanatory variables comprised risk factors of interest, as well as age at diagnosis (<40, 40–49, 50–59, 60–69, ≥70 years) and study. Risk factors were specified as: age at menarche (≤12, 13, 14, ≥15 years), parity (nulliparous vs parous), age at first full-term birth (<20, 20–24, 25–29, 30–34, ≥35 years, and as a continuous variable), family history of breast cancer among first-degree relatives (present vs absent), and BMI (<25, 25–30, ≥30 kg/m^2). Because it is known that BMI is associated with breast cancer risk differently in pre- and postmenopausal women, we stratified these analyses by age (≤50 and >50 years) as a surrogate for menopausal status. Results from analyses using more extreme age cut points (≤45 and >55 years) as surrogates for menopausal status were similar and, therefore, not shown. A multivariable-adjusted logistic regression model that included all risk factors produced similar risk estimates as those adjusted for age at diagnosis and study only; for simplicity, we present the latter. To evaluate which of the several related tumor features (histological type, grade, nodal status, marker expression) were most important in driving associations with exposures, we also fitted regression models with the risk exposure of interest as the outcome variable and tumor characteristics as the explanatory variables.

Forest plots were used to present study-specific case–case odds ratios and 95% confidence intervals for associations between risk factors and tumor markers. We also performed meta-analyses using the random-effects model of DerSimonian and Laird (50) to estimate summary case–case odds ratios from study-specific estimates, weighted by the inverse of the variance. The I^2 statistic was used to test the null hypothesis that associations were homogeneous across studies (51). I^2 value less than 0.25 indicates low heterogeneity, 0.5 indicates moderate heterogeneity, and greater than 0.75 indicates high heterogeneity (51).

Case–Control Analyses for the Estimation of Relative Risks Associated With Risk Factors. Table 1 shows the design of all studies included in this report. Hospital-based case–control studies or studies of mixed designs are more prone to selection biases for the estimation of relative risks than population-based or cohort studies. Thus, to minimize selection bias, estimation of relative risks was restricted to three case–control studies nested in cohorts and nine population-based case–control studies (one population-based study, Prospective Study of Outcomes in Sporadic versus Hereditary Breast Cancer [POSH], did not have control subjects and therefore was excluded from case–control analyses). Two of the 12 studies (Ontario Familial Breast Cancer Registry [OFBCR] and Northern California Breast Cancer Family Registry [NC-BCFR]) were excluded from analysis of family history because recruitment was based on family history of breast cancer (Supplementary Table 1, available online). Odds ratios, 95% confidence intervals, and *P* values were estimated using an unconditional logistic regression model with case–control status (each tumor subtype vs control) as outcome variables, and age, study, and each risk factor as explanatory variables.

All statistical tests were two-sided and performed using SAS (version 9.1; SAS Institute, Inc, Cary, NC), except for forest plots that were obtained using STATA (version 9; StataCorp, College Station, TX). All *P* values less than .05 were considered statistically significant.

Table 2. Characteristics of breast cancer case patients included in the participating studies*

Characteristic	No. of studies	Case patients, No. (%)
Clinical risk factors		
Age at diagnosis, y	34	
<40		3940 (11)
40–49		7657 (21)
50–59		10746 (30)
60–69		8959 (25)
≥70		4436 (12)
Ethnicity	34	
Caucasian		32321 (92)
Asian		1829 (5)
Other		1061 (3)
Age at menarche, y	27	
≤12		8697 (35)
13		6405 (25)
14		5265 (21)
≥15		4801 (19)
Parity	30	
Parous		24558 (85)
Nulliparous		4311 (15)
No. of full-term births in parous women	30	
1		5676 (23)
2		10737 (44)
≥3		8145 (33)
Age at first full-term birth, y	25	
<20		2418 (12)
20–24		10547 (40)
25–29		16980 (32)
30–34		19505 (12)
≥35		20373 (4)
BMI, kg/m^2		
Among women ≤50 y	23	
<25		5172 (58)
25–30		2528 (28)
≥30		1299 (14)
Among women >50 y	23	
<25		7214 (43)
25–30		6069 (36)
≥30		3397 (21)
Family history of breast cancer in first-degree relatives	33	
Absent		26175 (80)
Present		6693 (20)
Expression of tumor markers		
ER status	34	
ER$^-$		8519 (24)
ER$^+$		27049 (76)
PR status	34	
PR$^-$		10976 (35)
PR$^+$		20300 (65)
ER and PR status	34	
ER$^+$/PR$^+$		18907 (61)
ER$^+$/PR$^-$		4324 (14)
ER$^-$/PR$^+$		1310 (4)
ER$^-$/PR$^-$		6565 (21)
HER2 status	18	
HER2$^-$		11619 (81)
HER2$^+$		2649 (19)
ER, PR, and HER2 status	18	
ER$^+$/HER2$^-$ or PR$^+$/HER2$^-$		9534 (67)
ER$^+$/HER2$^+$ or PR$^+$/HER2$^+$		1657 (12)

(Table continues)

Table 2 (Continued).

Characteristic	No. of studies	Case patients, No. (%)
$ER^-/PR^-/HER2^+$		953 (7)
$ER^-/PR^-/HER2^-$†		1997 (14)
CK5/6 or CK5 status	8	
$CK5/6^-$ or $CK5^-$		5311 (87)
$CK5/6^+$ or $CK5^+$		795 (13)
EGFR status	6	
$EGFR^-$		3756 (87)
$EGFR^+$		555 (13)

* A total of 34 studies participating in the Breast Cancer Association Consortium were included in the pooled analysis. Risk factor and marker expression data were pooled from case patients across all studies. BMI = body mass index; CK5 or CK5/6 = cytokeratins 5 or 5/6; EGFR = epidermal growth factor receptor; ER = estrogen receptor; PR = progesterone receptor .

† Also known as triple-negative phenotype.

Results

Distribution of Breast Cancer Risk Factors and Tumor Subtypes

The distribution of risk factors and tumor subtypes included in this pooled analysis of 34 BCAC studies are shown in Table 2. The associations between tumor subtypes and patient and tumor characteristics, including age at diagnosis, tumor size, histology, and grade, were consistent with those established in the literature (Supplementary Table 4, available online).

Case–Case Analyses of Risk Factor Associations With Tumor Subtypes

Age at Menarche. Early menarche (≤12 years) was less frequent in case patients with PR^- tumors compared with case patients with PR^+ tumors (OR = 0.88, 95% CI = 0.81 to 0.95, P = .001) (Table 3), a finding that was consistent across studies (Supplementary Figure 1, A, available online). For tumor subtypes defined by combined ER and PR status, the lowest frequency of early menarche in women was associated with ER^+/PR^- tumors (P = .001). When the analysis was extended to include HER2 expression, compared with $ER^+/HER2^-$ or $PR^+/HER2^-$ tumors, there were no statistically significant differences in age at menarche in the other three subtypes—$ER^+/HER2^+$ or $PR^+/HER2^+$ (P = .89), $ER^-/PR^-/HER2^+$ (P = .16), and $ER^-/PR^-/HER2^-$ (triple negative; P = .35). However, early menarche was less frequent in case patients with $ER^-/PR^-/HER2^+$ tumors compared with case patients with $ER^+/HER2^-$ or $PR^+/HER2^-$ tumors (OR = 0.85, 95% CI = 0.67 to 1.07, P = .16) (Table 3).

Parity. Nulliparity was consistently less frequent in case patients with ER^- tumors compared with case patients with ER^+ tumors (OR = 0.82, 95% CI = 0.76 to 0.89, $P = 3 \times 10^{-6}$) (Table 4 and Supplementary Figure 1, B, available online) and showed a weaker association with PR status (PR^- vs PR^+ tumors: OR = 0.91, 95% CI = 0.84 to 0.98, P = .01). Similarly, nulliparity was less frequent in case patients with ER^-/PR^- tumors compared with case patients with ER^+/PR^+ tumors (OR = 0.80, 95% CI = 0.73 to 0.88, $P = 5 \times 10^{-6}$). This finding was strengthened when analyses were extended to additional markers, such that the frequency of nulliparity was lowest among triple-negative tumors (13%) compared with other subtypes—$ER^+/HER2^-$ or $PR^+/HER2^-$ tumors (17%), $ER^+/HER2^+$ or $PR^+/HER2^+$ tumors (18%), and $ER^-/PR^-/HER2^+$ tumors (18%) (Table 4). Among parous women, increasing age at first full-term birth was less frequent in case patients with ER^- tumors compared with case patients with ER^+ tumors (per 5-year increase, OR = 0.90, 95% CI = 0.87 to 0.93, $P = 2 \times 10^{-9}$). Similar to parity, this difference was confined to triple-negative tumors and

Table 3. Associations between age at menarche and tumor subtypes in case–case analyses*

		Age at menarche, y					
		≥15	14	13	≤12	≤12 vs ≥15	
Tumor subtypes†	No. of studies	No. (%)	No. (%)	No. (%)	No. (%)	OR (95% CI)	P‡
ER^+	27	3622 (19.0)	4036 (21)	4835 (25)	6571 (34)	1.00 (referent)	
ER^-	27	1154 (19.3)	1213 (20)	1539 (26)	2082 (35)	0.92 (0.85 to 1.01)	.06
PR^+	27	2743 (18.8)	3048 (21)	3703 (25)	5069 (35)	1.00 (referent)	
PR^-	27	1615 (20.6)	1656 (21)	2006 (25)	2556 (32)	0.88 (0.81 to 0.95)	.001
ER^+/PR^+	27	2554 (18.8)	2858 (21)	3439 (25)	4701 (35)	1.00 (referent)	
ER^+/PR^-	27	694 (22.2)	696 (22)	783 (25)	955 (30)	0.83 (0.74 to 0.93)	.001
ER^-/PR^+	27	174 (18.3)	184 (19)	252 (26)	342 (36)	0.90 (0.74 to 1.10)	.3
ER^-/PR^-	27	911 (19.6)	947 (20)	1204 (26)	1583 (34)	0.90 (0.81 to 0.99)	.03
$ER^+/HER2^-$ or $PR^+/HER2^-$	14	1605 (21.5)	1619 (22)	1834 (25)	2422 (32)	1.00 (referent)	
$ER^+/HER2^+$ or $PR^+/HER2^+$	14	227 (20.8)	238 (22)	275 (25)	350 (32)	1.01 (0.84 to 1.22)	.89
$ER^-/PR^-/HER2^+$	14	153 (22.7)	155 (23)	179 (27)	187 (28)	0.85 (0.67 to 1.07)	.16
$ER^-/PR^-/HER2^-$	14	280 (19.1)	337 (23)	360 (25)	490 (33)	1.08 (0.92 to 1.28)	.35

* Unconditional logistic regression models were used to estimate associations between tumor subtypes and age at menarche (comparing case patients who were aged ≤12 years at menarche to case patients who were aged ≥15 years at menarche) using tumor subtypes as the outcome variable and age at menarche, age at diagnosis, and study as independent variables. CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor .

† Defined by expression status of ER, PR, and HER2 in tumors. Expression data were based on immunohistochemical staining and pathologist readings and/or imaging analysis.

‡ P values were calculated using a two-sided Wald test.

Table 4. Associations between parity and tumor subtypes in case–case analyses*

		Parity			
		Parous	Nulliparous	Nulliparous vs parous	
Tumor subtypes†	No. of studies	No. (%)	No. (%)	OR (95% CI)	*P*‡
ER^+	30	18640 (85)	3378 (15)	1.00 (referent)	
ER^-	30	5826 (86)	917 (14)	0.82 (0.76 to 0.89)	3×10^{-6}
PR^+	30	14202 (85)	2610 (16)	1.00 (referent)	
PR^-	30	7571 (86)	1287 (15)	0.91 (0.84 to 0.98)	.01
ER^+/PR^+	30	13248 (84)	2441 (16)	1.00 (referent)	
ER^+/PR^-	30	2988 (84)	572 (16)	1.06 (0.96 to 1.18)	.25
ER^-/PR^+	30	904 (85)	161 (15)	0.99 (0.83 to 1.18)	.88
ER^-/PR^-	30	4541 (87)	707 (14)	0.80 (0.73 to 0.88)	5×10^{-6}
$ER^+/HER2^-$ or $PR^+/HER2^-$	15	6661 (83)	1331 (17)	1.00 (referent)	
$ER^+/HER2^+$ or $PR^+/HER2^+$	15	1001 (82)	216 (18)	1.00 (0.85 to 1.18)	.98
$ER^-/PR^-/HER2^+$	15	622 (82)	135 (18)	0.98 (0.81 to 1.20)	.87
$ER^-/PR^-/HER2^-$	15	1374 (87)	204 (13)	0.69 (0.59 to 0.81)	7×10^{-6}

* Unconditional logistic regression models were used to estimate associations between tumor subtypes and parity (comparing nulliparous case patients to parous case patients) using tumor subtypes as the outcome variable and parity, age at diagnosis, and study as independent variables. CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor .

† Defined by expression status of ER, PR, and HER2 in tumors. Expression data were based on immunohistochemical staining and pathologist readings and/or imaging analysis.

‡ *P* values were calculated using a two-sided Wald test.

consistent across studies (Table 5 and Supplementary Figure 1, C, available online). Compared with having one child, having greater than or equal to three children was slightly more frequent in case patients with ER^- particularly triple-negative tumors compared with case patients with hormone receptor–positive tumors (Supplementary Table 5, available online).

BMI Among Younger Women (≤50 years). Obesity (BMI ≥ 30 kg/m^2) was more frequent in case patients with ER^-/PR^- tumors compared with case patients with other combinations of hormone receptor expression (ER^-/PR^- vs ER^+/PR^+ tumors: OR = 1.49, 95% CI = 1.29 to 1.73, $P = 1 \times 10^{-7}$) (Table 6). However, there was some evidence of heterogeneity for this relationship by study (for hospital-based and population-based case patients, ER^- vs ER^+ tumors: OR = 1.67, 95% CI = 1.28 to 2.17 and OR = 1.39, 95% CI = 1.14 to 1.69, respectively, *P* for heterogeneity = .03) (Supplementary Figure 2, A, available online). When tumors were further classified according to HER2, the association in younger women between obesity and ER and PR status appeared to be confined to case patients with triple-negative tumors (triple-negative vs $ER^+/HER2^-$ or $PR^+/HER2^-$ tumors: OR = 1.80, 95% CI = 1.42 to 2.29, $P = 2 \times 10^{-6}$) (Table 6).

Table 5. Associations between age at first full-term birth among parous women and tumor subtypes in case–case analyses*

		Age at first full-term birth, y						
		<20	20–24	25–29	30–34	≥35	5-year increase	
Tumor subtypes†	No. of studies	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	OR (95% CI)	*P*‡
ER^+	25	1711 (11)	6060 (40)	4853 (32)	1925 (13)	681 (5)	1.00 (referent)	
ER^-	25	692 (14)	2050 (40)	1563 (31)	589 (12)	185 (4)	0.90 (0.87 to 0.93)	2×10^{-9}
PR^+	25	1322 (11)	4576 (39)	3736 (32)	1505 (13)	512 (4)	1.00 (referent)	
PR^-	25	793 (12)	2602 (40)	2019 (31)	787 (12)	288 (4)	0.97 (0.94 to 1.01)	.11
ER^+/PR^+	25	1204 (11)	4250 (39)	3454 (32)	1412 (13)	484 (5)	1.00 (referent)	
ER^+/PR^-	25	256 (10)	1006 (40)	830 (33)	313 (12)	134 (5)	1.05 (1.01 to 1.10)	.02
ER^-/PR^+	25	110 (13)	317 (39)	275 (34)	90 (11)	27 (3)	0.91 (0.84 to 0.98)	.02
ER^-/PR^-	25	530 (14)	1586 (41)	1179 (30)	466 (12)	153 (4)	0.91 (0.88 to 0.95)	6×10^{-6}
$ER^+/HER2^-$ or $PR^+/HER2^-$	13	659 (11)	2490 (42)	1841 (31)	735 (12)	240 (4)	1.00 (referent)	
$ER^+/HER2^+$ or $PR^+/HER2^+$	13	101 (11)	379 (42)	269 (30)	113 (12)	46 (5)	0.99 (0.92 to 1.07)	.7
$ER^-/PR^-/HER2^+$	13	56 (10)	242 (43)	180 (32)	64 (11)	25 (4)	1.01 (0.92 to 1.10)	.91
$ER^-/PR^-/HER2^-$	13	178 (14)	552 (44)	333 (26)	153 (12)	44 (4)	0.89 (0.83 to 0.95)	.0007

* Unconditional logistic regression models were used to estimate associations between tumor subtypes and age at first full-term birth (per 5-year increase) using tumor subtypes as the outcome variable and age at first full-term birth (continuous, per 5-year increase), age at diagnosis, and study as independent variables. CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor .

† Defined by expression status of ER, PR, and HER2 in tumors. Expression data were based on immunohistochemical staining and pathologist readings and/or imaging analysis.

‡ *P* values were calculated using a two-sided Wald test.

Table 6. Associations between body mass index (BMI) among women aged 50 years or younger and tumor subtypes in case–case analyses*

		BMI in younger women, kg/m²				
		<25	25–30	≥30	≥30 vs <25	
Tumor subtypes†	No. of studies	No. (%)	No. (%)	No. (%)	OR (95% CI)	P‡
ER+	23	3557 (58)	1719 (28)	830 (14)	1.00 (referent)	
ER−	23	1594 (56)	798 (28)	461 (16)	1.41 (1.24 to 1.61)	1×10^{-7}
PR+	23	3029 (59)	1467 (28)	678 (13)	1.00 (referent)	
PR−	23	1614 (57)	773 (27)	456 (16)	1.32 (1.16 to 1.51)	4×10^{-5}
ER+/PR+	23	2692 (58)	1308 (28)	607 (13)	1.00 (referent)	
ER+/PR−	23	430 (60)	190 (27)	96 (13)	0.96 (0.76 to 1.22)	.76
ER−/PR+	23	331 (60)	156 (28)	66 (12)	1.03 (0.78 to 1.37)	.82
ER−/PR−	23	1169 (56)	575 (27)	357 (17)	1.49 (1.29 to 1.73)	1×10^{-7}
ER+/HER2− or PR+/HER2−	13	1188 (57)	625 (30)	287 (14)	1.00 (referent)	
ER+/HER2+ or PR+/HER2+	13	333 (58)	165 (29)	80 (14)	0.95 (0.71 to 1.28)	.75
ER−/PR−/HER2+	13	168 (55)	93 (31)	43 (14)	1.25 (0.87 to 1.80)	.22
ER−/PR−/HER2−	13	319 (52)	173 (28)	128 (21)	1.80 (1.42 to 2.29)	2×10^{-6}

* Unconditional logistic regression models were used to estimate associations between tumor subtypes and BMI among women aged 50 years or younger (comparing case patients who had BMI ≥30 kg/m² to case patients who had BMI <25 kg/m²) using tumor subtypes as the outcome variable and BMI among women aged 50 years or younger, age at diagnosis, and study as independent variables. BMI = body mass index; CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor .

† Defined by expression status of ER, PR, and HER2 in tumors. Expression data were based on immunohistochemical staining and pathologist readings and/or imaging analysis.

‡ *P* values were calculated using a two-sided Wald test.

BMI Among Older Women (age >50 years). Obesity (BMI ≥ 30 kg/m²) among older women was consistently less frequent in case patients with PR− tumors compared with case patients with PR+ tumors (OR = 0.85, 95% CI = 0.78 to 0.93, $P = 6 \times 10^{-4}$), particularly for smaller tumors (Table 7 and Supplementary Table 6, available online). This association was driven by a lower frequency of obesity among ER+/PR− tumors, which occurred in both smaller and larger tumors. No statistically significant differences were observed upon further classification of tumors by HER2, CK5/6 or CK5, and EGFR (Supplementary Table 6, available online).

Family History of Breast Cancer. The frequency of family history of breast cancer did not vary statistically significantly by tumor subtypes defined by hormone receptors and HER2, although having a positive family history of breast cancer was more frequent in case patients with CBP tumors compared with case patients with ER+/HER2− or PR+/HER2− tumors (OR = 1.38, 95% CI = 1.08 to 1.75, $P = .01$) (Supplementary Table 7, available online).

Analyses Restricted to Case Patients With CBP Marker (CK5/6 or CK5 or EGFR) Data. When triple-negative tumors were further

Table 7. Associations between body mass index (BMI) among women older than 50 years and tumor subtypes in case–case analyses*

		BMI in women older than 50 years, kg/m²				
		<25	25-30	≥30	≥30 vs <25	
Tumor subtypes†	No. of studies	No. (%)	No. (%)	No. (%)	OR (95% CI)	P‡
ER+	23	5712 (43)	4818 (37)	2637 (20)	1.00 (referent)	
ER−	23	1477 (43)	1240 (36)	753 (22)	1.06 (0.96 to 1.17)	.22
PR+	23	4113 (43)	3504 (36)	2012 (21)	1.00 (referent)	
PR−	23	2403 (45)	1870 (35)	1018 (19)	0.85 (0.78 to 0.93)	.0006
ER+/PR+	23	3905 (43)	3323 (36)	1906 (21)	1.00 (referent)	
ER+/PR−	23	1192 (48)	889 (36)	417 (17)	0.70 (0.62 to 0.79)	3×10^{-8}
ER−/PR+	23	194 (41)	174 (37)	101 (22)	0.94 (0.74 to 1.20)	.62
ER−/PR−	23	1200 (43)	977 (35)	599 (22)	0.99 (0.89 to 1.11)	.92
ER+/HER2− or PR+/HER2−	13	2208 (40)	2099 (38)	1198 (22)	1.00 (referent)	
ER+/HER2+ or PR+/HER2+	13	349 (44)	301 (38)	147 (18)	0.93 (0.76 to 1.14)	.48
ER−/PR−/HER2+	13	224 (47)	165 (34)	92 (19)	0.84 (0.65 to 1.08)	.18
ER−/PR−/HER2−	13	397 (41)	336 (35)	238 (25)	1.09 (0.91 to 1.29)	.36

* Unconditional logistic regression models were used to estimate associations between tumor subtypes and BMI among women older than 50 years (comparing case patients who had BMI ≥30 kg/m² to case patients who had BMI <25 kg/m²) using tumor subtypes as the outcome variable and BMI among women older than 50 years, age at diagnosis, and study as independent variables. BMI = body mass index; CI = confidence interval; ER = estrogen receptor; OR = odds ratio; PR = progesterone receptor.

† Defined by expression status of ER, PR, and HER2 in tumors. Expression data were based on immunohistochemical staining and pathologist readings and/or imaging analysis.

‡ *P* values were calculated using a two-sided Wald test.

classified according to the expression of CBP markers from seven studies (15,23,25,31,37,41,42), CBP tumors were found to be statistically significantly associated with lower frequency of nulliparity (OR = 0.56, 95% CI = 0.41 to 0.76, $P = .0002$), lower frequency of older age (>30 years) at first birth (per 5-year increase: OR = 0.81, 95% CI = 0.71 to 0.92, $P = .001$), higher frequency of obesity among younger women (OR = 2.15, 95% CI = 1.44 to 3.19, $P = .0002$), and family history of breast cancer (OR = 1.38, 95% CI = 1.08 to 1.75, $P = .01$) compared with $ER^+/HER2^-$ or $PR^+/HER2^-$ tumors.

Differences by Age and Study Design. The associations between risk factors and tumor subtypes defined by marker expressions remained statistically significant after adjustment for clinical tumor characteristics (stage, histology, size, and nodal status) and showed similar patterns in analyses stratified by tumor characteristics. Associations were also similar in analyses restricted to white case patients, population-based case series, and younger (≤40 years) or older (>50 years) case patients (data not shown), with the exception of the association between ER and BMI in younger women that varied in population- and hospital-based case series.

Case–Control Analyses of Risk Factor Associations by Tumor Subtypes

Case–control comparisons in a subset of 12 cohort or population-based case–control studies (14,20,21,28,31–34,37,40,45) showed relative risk estimates for risk factors generally consistent with expected associations based on the literature. The only exception was elevated BMI among older women (>50 years) that was associated with increased risk of large (>2 cm) tumors (OR = 1.29, 95% CI = 1.12 to 1.50, $P = .0005$) but not with breast cancer overall (OR = 0.92, 95% CI = 0.86 to 1.00, $P = .04$). Relative risk estimates for specific tumor subtypes based on case–control analyses of cohort/population-based studies were consistent with the risk factor–tumor marker associations observed in case–case analyses including all studies in this report. Figure 2 shows the case–control comparisons stratified by mutually exclusive categories of ER status. The analysis included up to 14795 case patients (10900 for ER^+ and 3895 for ER^-) and 17399 control subjects. This figure shows the expected relationships for ER^+ tumors. However, reproductive history and BMI in younger women were not associated with the risk of ER^- tumors, and the risk association for early age at menarche was only seen in the extreme categories. A similar pattern was found when stratifying tumors by PR status (data not shown). Further tumor stratification with HER2 suggested that age at menarche was associated with the risk of all tumor subtypes, except for $ER^-/PR^-/HER2^+$, although this interpretation was limited by the precision of the estimates because analyses were only based on four studies (20,28,31,37) with data for the three markers (data not shown). Based on these four studies, nulliparity and increasing age at first full-term birth were not associated with increased risk for triple-negative tumors (nulliparity vs parity, OR = 0.94, 95% CI = 0.75 to 1.19, $P = .61$; 5-year increase in age at first full-term birth, OR = 0.95, 95% CI = 0.86 to 1.05, $P = .34$). This observation was unique to triple-negative tumors and was not observed in other tumor subtypes (data not shown). Information on CBP markers was only available in two population-based studies (31,37) that also showed no increase in risk for CBP for nulliparity (OR = 0.97, 95% CI = 0.63 to 1.51, $P = .90$) and increasing age at first birth (OR = 0.92, 95% CI = 0.76 to 1.10, $P = .48$). Similarly, obesity among younger women was protective for all tumor subtypes except triple-negative tumors (BMI ≥ 30 vs <25, OR = 1.36, 95% CI = 0.95 to 1.94, $P = .09$).

The risk association for BMI among women older than 50 years was not statistically significantly modified by ER status and thus is not shown in Figure 2. However, in case–control analyses, higher

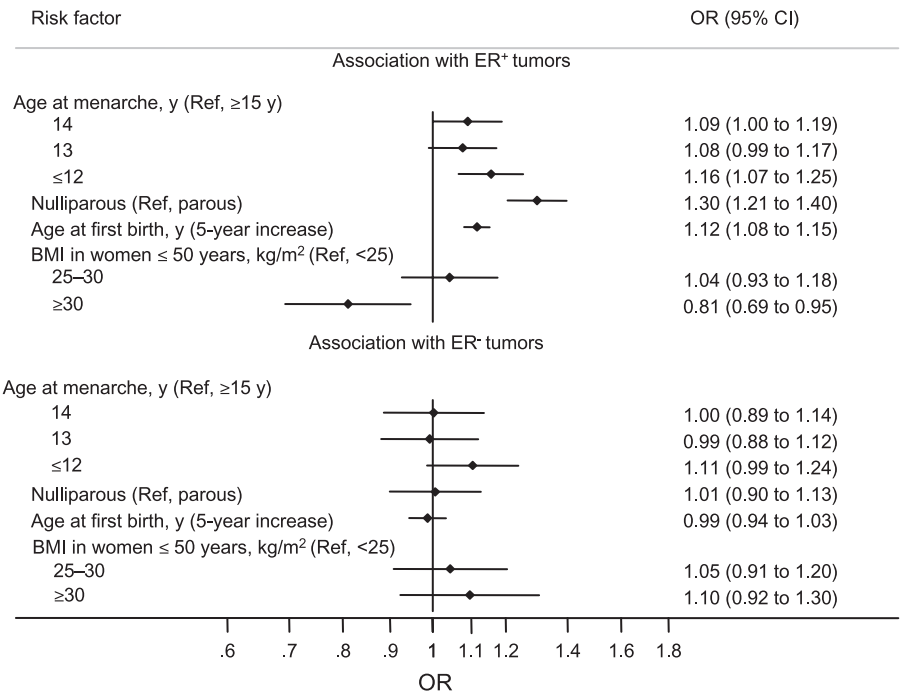

Figure 2. Risk factors and differential associations with the risk of estrogen receptor (ER)–positive and ER-negative tumor subtypes based on case–control comparisons in 12 population-based studies. Case–control comparisons were stratified by mutually exclusive categories of ER status. The analysis included 14795 case patients (10900 for ER^+ and 3895 for $ER-$) and 17399 control subjects pooled across 12 studies. The **black diamonds** and the **horizontal lines** represent odds ratios (ORs) and corresponding 95% confidence intervals (CIs), respectively. Odds ratios were obtained from unconditional logistic regression models with case–control status (case patients were stratified by ER status) as outcome variables and age, study, and each risk factor separately as independent variables. The associations between body mass index (BMI) in women older than 50 years and family history in first-degree relatives are not shown because they were not statistically significantly modified by ER status in case–case comparisons. Ref = referent category. Odds ratio are presented on the log scale.

BMI was associated with increased risk of larger breast tumors only; data suggested a decreased risk of smaller tumors (data not shown). Among larger tumors (>2 cm), risk associated with BMI was not statistically significantly modified by PR status. However, consistent with the case–case analysis, the reduced risk for smaller tumors (≤2 cm) was stronger for PR^- tumors (data not shown).

Family history of breast cancer was associated with increased risk of all tumor subtypes, with some suggestion of a stronger association for tumors with CBP (data not shown).

Discussion

In this large pooled analysis of 35 568 invasive breast cancer case patients, we pooled tumor marker and epidemiological risk factor data from 34 studies participating in the BCAC and demonstrated that reproductive factors, such as early age at menarche, nulliparity, increasing age at first full-term birth in parous women, and elevated BMI in younger women, were more strongly associated with hormone receptor–positive tumors as compared with hormone receptor–negative tumors in case–case analyses. Our findings also suggested that the triple-negative or CBP tumors account for much of the risk factor heterogeneity between hormone receptor–positive and hormone receptor–negative tumors. We also conducted case–control analyses in 12 population-based studies and observed that nulliparity, increasing age at first birth, and BMI in younger women were associated with the risk of ER^+ or PR^+ tumors but not with ER^-/PR^- tumors, particularly, triple-negative or CBP tumors.

These findings strengthen and quantify conclusions of previous reviews and meta-analyses (4,7), in addition to suggesting further etiological differences among subtypes of ER^- tumors. These results complement emerging evidence that associations between common genetic variants and breast cancer risk varied by breast tumor subtypes (8) and data showing that breast cancer incidence rates varied markedly by histological type, grade, and molecular subtype (52).

In the case–control analyses, we observed that nulliparity and increasing age at first full-term birth were mainly associated with elevated risk of ER^+ and/or PR^+ breast cancers, but not with ER^-/PR^- cancers, as suggested previously. A meta-analysis estimated that each birth was associated with an 11% decrease in the risk of ER^+/PR^+ breast cancers but was unrelated to the risk of ER^-/PR^- cancers (7). The Hawaii–Los Angeles Multiethnic Cohort study showed similar results (53). Furthermore, we extended this work to suggest that nulliparity and increasing age at first birth do not increase risk for triple-negative tumors, and perhaps more specifically, for CBP tumors. Similarly, Millikan et al. (9) reported that parity and early age at first full-term birth were not protective for CBP and suggested that these factors may actually increase the risk for CBP. Estimates of association from our case–control analyses are consistent with these findings but are based on limited data.

A meta-analysis (7) and subsequent studies (53,54) suggested that early age at menarche might be more strongly associated with the risk of ER^+/PR^+ tumors. Our data support these findings, although associations with ER and PR were weaker than for parity-related variables, perhaps reflecting larger measurement error for this variable. Data suggested strongest differences in age at menarche for ER^+/PR^- cancers, which might differ biologically from ER^+/PR^+ cancers (55,56); however, further studies are needed to confirm this finding. Hypotheses suggested to account for the stronger associations between menstrual and reproductive risk factors and receptor positive tumors include relationships of menstrual period with levels of circulating hormones, total number of menstrual cycles, and induction of cell differentiation (57). The differences in associations that we found between menarche and parity-related variables and tumor subtypes might point to differences in mechanisms underlying these factors.

Epidemiological studies have shown that premenopausal obesity is overall protective for breast cancer (58), whereas postmenopausal obesity is associated with increased risk (59). Our case–control analysis showed that among younger women, obesity was inversely associated with risk for receptor positive tumors only, which seems to reflect a lack of protection for ER^-/PR^- cancers. However, this question deserves further study since there were inconsistencies among population-based studies, which might reflect differences in the definition of this variable. Further analysis suggested that differences by hormone receptor status were driven by a lack of protection for triple-negative/CBP tumors. Millikan et al. (9) previously found that increased waist to hip ratio, a measure of central adiposity, was related to elevated risk for CBP, irrespective of menopausal status. It has been postulated that a high prevalence of central obesity among African American women may contribute to the particularly strong risk for CBP tumors (60); however, we could not assess this finding in our dataset. Proposed mechanisms underlying the protective effect for premenopausal obesity include increased anovulatory cycles, which would reduce cumulative exposure to cyclic sex hormones and might reduce risk for hormone responsive tumors (61,62). However, obesity (particularly central adiposity) may be associated with increased levels of insulin and related growth factors, which could increase risk specifically for some breast tumor subtypes, possibly including the triple-negative/CBP group (63,64). A recent study found that women with triple-negative tumors had a high prevalence of metabolic syndrome, characterized by obesity and insulin resistance (63). Insulin resistance may increase risk of premenopausal breast cancer by reducing sex hormone–binding globulin levels, resulting in an increase in free estrogen and androgen levels, and increasing proliferation of breast epithelial cells (64).

Among older case patients, obesity was less frequent in women with PR^- tumors, particularly those that were ER^+/PR^-. A meta-analysis found that a consistent result across studies was that postmenopausal obesity women were not associated with increased risk of ER^+/PR^- breast cancer (65). These data suggest a possible link between postmenopausal obesity, elevated circulating estrogens, and cancers with intact ER-induced transcription, resulting in PR coexpression (66). A previous publication using data from the Polish Breast Cancer Study (PBCS, included in this report) suggested that the risk association with obesity in postmenopausal women was limited to large tumors (37). Case–case and case–control analyses of our data further support these findings, independent of ER or PR status. Interpreting relationships for obesity in older women is complicated by several factors, including the positive relationship with tumor size, screening history, and possible interactions with use of hormone replacement (67,68).

Finally, we found that a positive family history increased risk similarly for all subtypes of breast cancer, though possibly somewhat more for CBP. However, completeness and methods for evaluating family history varied among studies, and our dataset undoubtedly includes unidentified *BRCA1* carriers, who are particularly prone to develop CBP.

Strengths of this analysis compared with previous reports include a large sample size from a large set of studies unselected by prior publication. However, differences in study populations, designs and methods of collecting risk factors, and marker data are potential limitations. However, these factors are unlikely to be related to risk factors of interests and thus would tend to underestimate rather than overestimate the case–case comparisons that support our main conclusions. The average age at diagnosis was younger, and percentage of case patients having a positive family history of breast cancer was higher in this analysis than in most populations because some studies were enriched for younger and familial case patients. Nonetheless, most of our findings were consistent across studies (Supplementary Figures 1 and 2, available online), thus supporting our interpretations. We also restricted our case–control analyses to prospective cohorts and population-based case–control studies to minimize selection bias derived from the inclusion of nonrepresentative control subjects in analyses to estimate relative risks. Although misclassification of markers may have weakened the strength of associations observed, previous studies have found good concordances between marker status from pathology reports from different sources and standardized measurements (47–49). In addition, the relationships between marker data with age and pathological variables were as expected. Furthermore, associations between tumor subtypes and all risk factors were similar in analyses restricted to eight studies in which marker data were based on immunohistochemical staining of tissue microarrays or whole sections (data not shown). Another limitation is the large amount of missing data for HER2 and CBP markers, which may have limited power and generalizability of our findings. Ongoing efforts in BCAC to standardize and quantify marker analyses from tissue microarrays aided by automated image analyses may address the above limitations in future studies.

In conclusion, this large pooled analysis demonstrates that associations for menstrual and reproductive risk factors and BMI vary by breast cancer tumor subtypes defined by ER, PR, HER2, and CBP markers. Our results support the view that, from an etiological perspective, there is more than one type of breast cancer and specifically supports the hypothesis that CBP tumors have different etiology from hormone receptor–positive tumors. This evidence suggests that developing risk models for specific types of breast cancer may improve prediction and allow targeted screening and prevention in the future. This approach would align the efforts of prevention research with those of clinical research where delineating the molecular pathogenesis of specific types of breast cancers has enabled the development of targeted treatments.

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Funding

This study was supported in part by the European Community's Seventh Framework Programme under grant agreement number 223175 (HEALTH-F2-2009-223175). The individual Breast Cancer Association Consortium (BCAC) studies were funded by the following sources: Australian

Breast Cancer Family Study (ABCFS) and Ontario Familial Breast Cancer Registry (OBCFR): National Cancer Institute (NCI), National Institutes of Health (NIH) under RFA CA-06-503 and through cooperative agreements with members of the Breast Cancer Family Registry (BCFR) and Principal Investigators, including Cancer Care Ontario (U01 CA69467), Northern California Cancer Center (U01 CA69417), and University of Melbourne (U01 CA69638).

Amsterdam Breast Cancer Study (ABCS): The Dutch Cancer Society (NKI 2001-2423; 2007-3839) and the Dutch National Genomics Initiative.

Breast Cancer in Galway Genetic Study (BIGGS): E.J.S. is funded by the National Institute for Health Research (NIHR) comprehensive Biomedical Research Centre award to Guy's and St Thomas' NHS Foundation Trust in partnership with King's College London.

Copenhagen General Population Study (CGPS): The Chief Physician Johan Boserup and Lise Boserup Fund, the Danish Medical Research Council, and Copenhagen University Hospital, Herlev Hospital.

Spanish National Cancer Centre Breast Cancer Study (CNIO-BCS): The Red Temática de Investigación Cooperativa en Cáncer and grants from the Asociación Española Contra Cáncer and the Fondo de Investigación Sanitario (PI081120 to J.B. and PI081583 to R.L.M.).

Gene Environment Interaction and Breast Cancer in Germany (GENICA): Federal Ministry of Education and Research (BMBF) Germany (01KW9975/5, 01KW9976/8, 01KW9977/0, and 01KW0114), the Robert Bosch Foundation of Medical Research, Stuttgart, Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Institute for Prevention and Occupational Medicine of the German Social Accident Insurance (IPA), Bochum, as well as the Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany.

Genetic Epidemiology Study of Breast Cancer by Age 50 (GESBC): Deutsche Krebshilfe (70492) and the state of Baden-Württemberg through the Medical Faculty of the University of Ulm (P.685).

Helsinki Breast Cancer Study (HEBCS): The Helsinki University Central Hospital Research Fund, Academy of Finland (110663), the Finnish Cancer Society, and the Sigrid Juselius Foundation.

Leuven Multidisciplinary Breast Centre (LMBC): European Union Framework Programme 6 Project LSHC-CT-2003-503297 (the Cancerdegradome) and by the 'Stichting tegen Kanker' (232-2008).

Karolinska Breast Cancer Study (KARBAC): The Swedish Cancer Society, the Gustav V Jubilee Foundation, the Cancer Society in Stockholm, and the Bert von Kantzow Foundation.

Kuopio Breast Cancer Project (KBCP): The Kuopio University Central EVO Research Fund, Academy of Finland, the Finnish Cancer Society, the University of Kuopio and EVO research funding of Vaasa Hospital District.

Kathleen Cuningham Foundation Consortium for research into Familial Breast Cancer (kConFab): NHMRC (145684, 288704 and 454508), the National Breast Cancer Foundation, the National Health and Medical Research Council (NHMRC), the Queensland Cancer Fund, the Cancer Councils of New South Wales, Victoria, Tasmania and South Australia, and the Cancer Foundation of Western Australia. A.B.S. is supported by an NHMRC Senior Research Fellowship, and G.C.-T. by an NHMRC Senior Principal Research Fellowship.

Mammary Carcinoma Risk Factor Investigation (MARIE): Deutsche Krebshilfe e.V. (70-2892-BR I), the Hamburg Cancer Society, and the German Cancer Research Center.

Mayo Clinic Breast Cancer Study (MCBCS): NIH (CA122340), NIH recovery act (ARRA CA122340Z), and an NCI-sponsored Specialized Program Of Research Excellence (SPORE) in Breast Cancer to the Mayo Clinic (CA116201).

Melbourne Collaborative Cohort Study (MCCS): The Cancer Council Victoria, VicHealth, and NHMRC (209057, 251533, 396414, 504711).

Multiethnic Cohort (MEC): NIH (R01-CA63464 and R37-CA54281).

Nurses Health Study (NHS): NIH (CA87969).

Oulu Breast Cancer Study (OBCS): Finnish Cancer Foundation, the Sigrid Juselius Foundation, the Academy of Finland, the University of Finland, and Oulu University Hospital.

Leiden University Medical Centre Breast Cancer Study (ORIGO): The Dutch Cancer Society.

Polish Breast Cancer Study (PBCS): Intramural Research Program of US NIH, NCI, Division of Cancer Epidemiology and Genetics (DCEG).

Prospective Study of Outcomes in Sporadic Versus Hereditary Breast Cancer (POSH): Wessex Cancer Trust, Cancer Research UK and the National Cancer Research Network.

Rotterdam Breast Cancer Study (RBCS): The Dutch Cancer Society (DDHK 2004-3124).

Sheffield Breast Cancer Study (SBCS): The Breast Cancer Campaign (2004Nov 49) and Yorkshire Cancer Research.

Study of Epidemiology and Risk factors in Cancer Heredity (SEARCH): Cancer Research UK.

IHCC-Szczecin Breast Cancer Study (SZBCS): Polish Ministry of Science (PBZ-KBN-122/PO5/2004).

Taiwanese Breast Cancer Study (TWBCS): The Institute of Biomedical Sciences, Academia Sinica, National Sciences Council and Taiwan Biobank.

UCI Breast Cancer Study (UCIBCS): The NIH , NCI (CA-58860) and the Lon V Smith Foundation (LVS-39420).

Notes

X. R. Yang and J. Chang-Claude contributed equally to this work; P. Pharoah, M. E. Sherman, and M. Garcia-Closas are senior authors of this work.

The content of this article does not necessarily reflect the views or policies of the NCI or any of the collaborating centers in the BCAC, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government or the BCAC. The study sponsors had no role in the design of the study, analysis or interpretation of the data, the writing of the article, or the decision to submit the article for publication.

We thank all the participants in these studies and all the many individuals who helped in their recruitment and provided technical support. In particular we thank: Hans Peterse, Renate de Groot, Renate Udo (ABCS); Anna González-Neira, Charo Alonso, Tais Moreno, and Guillermo Pita (CNIO-BCS); U. Eilber and T Koehler (GESBEC); Kirsimari Aaltonen, R. N. Hanna Jäntti, Ari Ristimäki, Mira Heinonen, Laura Hautala, and the Finnish Cancer Registry (HEBCS); Eija Myöhänen and Aija Parkkinen (KBCP); Heather Thorne and Eveline Niedermayr (kConFab); T. Slanger, E. Mutschelknauss, S. Behrens, R. Birr, W. Busch, U. Eilber, B. Kaspereit, N. Knese, and K. Smit (MARIE); Natacha Lays and Gilian Peuteman (LMBCS); Elaine Maloney and members of the Ontario Cancer Genetics Network (OFBCR); E. Krol-Warmerdam and J. Blom (ORIGO); Petra Bos, Jannet Blom, Ellen Crepin, Elisabeth Huijskens, and Annette Heemskerk (RBCS); Sue Higham (SBCS); the SEARCH team.

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