Population and Prevention Science

Cancer Research

Pooled Analysis of Nine Cohorts Reveals Breast Cancer Risk Factors by Tumor Molecular Subtype

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Abstract

Various subtypes of breast cancer defined by estrogen receptor (ER), progesterone receptor (PR), and HER2 exhibit etiologic differences in reproductive factors, but associations with other risk factors are inconsistent. To clarify etiologic heterogeneity, we pooled data from nine cohort studies. Multivariable, joint Cox proportional hazards regression models were used to estimate HRs and 95% confidence intervals (CI) for molecular subtypes. Of 606,025 women, 11,741 invasive breast cancers with complete tissue markers developed during follow-up: 8,700 luminal A–like (ER^+ or $PR^+/HER2^-$), 1,368 luminal B–like (ER^+ or $PR^+/HER2^+$), 521 HER2-enriched ($ER^-/PR^-/HER2^+$), and 1,152 triple-negative ($ER^-/PR^-/HER2^-$) disease. Ever parous compared with never was associated with lower risk of luminal A–like (HR, 0.78; 95% CI, 0.73–0.83) and luminal B–like (HR, 0.74; 95% CI, 0.64–0.87) as well as a higher risk of triple-negative disease (HR, 1.23; 95% CI, 1.02–1.50; *P* value for overall tumor heterogeneity < 0.001). Direct associations with luminal-like, but not HER2-enriched or triple-negative, tumors were found for age at first birth, years between menarche and first birth, and age at menopause (*P* value for overall tumor heterogeneity < 0.001). Age-specific associations with baseline body mass index differed for risk of luminal A–like and triple-negative breast cancer (*P* value for tumor heterogeneity = 0.02). These results provide the strongest evidence for etiologic heterogeneity of breast cancer to date from prospective studies.

Significance: These findings comprise the largest study of prospective data to date and contribute to the accumulating evidence that etiological heterogeneity exists in breast carcinogenesis. *Cancer Res; 78(20); 6011–21. ©2018 AACR.*

Introduction

Despite advances in risk factor identification, screening, and treatment, breast cancer is still a leading cause of cancer incidence and death worldwide. Few breast cancer risk factors have been identified that are easily modifiable or strongly associated with incidence. Current risk prediction models incorporate multiple risk factors but have limited ability to predict fatal breast cancer (1). The heterogeneous nature of invasive breast cancer at the molecular level (2, 3) necessitates the need for subtype-specific models (1), including for triple-negative breast cancer [defined by the lack of expression of estrogen receptor-alpha (ER), progesterone receptor (PR), and HER2/*neu* status], that have a poor 5-year prognosis (4). Creating subtype-specific risk prediction models first requires clarification of the subtype associations with known risk factors and identification of novel subtype-specific risk factors (1).

Accumulating epidemiologic data support a dual effect of reproductive factors, including parity, age at first birth, and breastfeeding, on risk of ER-positive and ER-negative breast cancer (5–10). Other hormonal factors might also have different associations by molecular subgroups of breast cancer. A recent systematic review of 11 established breast cancer risk factors and their association with breast cancer risk by molecular subtype defined by ER, PR, and HER2 concluded there were insufficient data to draw conclusions about etiologic heterogeneity for other risk factors (11). Family history of breast cancer was the only risk

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factor consistently associated with increased risk of all breast cancer subtypes (11). Risk factors for luminal A–like breast cancer (ER^+ or $PR^+/HER2^-$), representing about 70% of all breast cancers, closely mirrored those for breast cancer overall. Limited knowledge has been gained regarding risk factors for luminal B–like (ER^+ or $PR^+/HER2^+$), HER2-enriched ($ER^-/PR^-/HER2^+$), or triple-negative breast cancers, due to their small numbers in any individual study (11), and regarding the value of HER2 to identify etiologic heterogeneity (12). More recently, a linkage analysis of the Danish Cancer Registry and a parity database found possible age interactions for reproductive risk factor-subtype associations (13).

To estimate risk factor associations with breast cancer molecular subtypes with more precision, we utilized a harmonized dataset of nine prospective cohort studies in the NCI Cohort Consortium with over 11,000 cases with molecular subtype based on ER, PR, and HER2 status data from 606,025 study participants. We also examined age interactions with parity and body mass index (BMI). In secondary analyses, we explored etiologic heterogeneity of HER2 status, including assessing risk factor associations by ER/PR status only.

Patients and Methods

Study population

Nine member studies of the NCI Cohort Consortium that had breast cancer cases with ER and PR, or HER2 data agreed to participate: the Cancer Prevention Study-II (CPS-II) Nutrition Cohort, the Melbourne Collaborative Cohort Study (MCCS), the National Institutes of Health-AARP (NIH-AARP) Diet and Health Study cohort study, the Nurses' Health Study (NHS), the Nurses' Health Study-II (NHS2), the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening cohort, the Swedish Mammographic Cohort (SMC), the Swedish Women's Lifestyle and Health Study (SWLH), and the Women's Health Initiative Observational Study (WHI-OS; Table 1). Individual-level data for 630,336 women (Fig. 1) were provided for each cohort after excluding males and those with a personal history of cancer (except non-melanoma skin cancer) at baseline, or with other cohort-specific exclusions. Further exclusions are described in the Statistical Analysis section as part of the calculation of person-time.

Written-informed consent was obtained from study participants at entry into each cohort or was implied by participants' return of the enrollment questionnaire. The present investigation was approved by the Institutional Review Board (IRB) at each participating institution or was considered within the scope of the original IRB protocol.

Exposure information

Deidentified data from the baseline questionnaire (i.e., exposures were not updated) were provided for known breast cancer risk factors using a common data dictionary. Data were harmonized, and variables were categorized *a priori*, including a category for missing or unknown values (see distribution of missing values in Supplementary Table S1 and categorizations in Supplementary Table S2). We calculated the years between menarche and first live birth using the ages of the respective life events. Age at menopause was reported based on age at natural or surgical menopause. Information on type of menopause, breastfeeding, or detailed postmenopausal hormone use was not requested from the individual cohorts.

Table 1. Description of nine cohort studies that contributed to the pooled analysis of risk factors by risk-invasive breast cancer subtypes in the National Cancer Institute Cohort Consortium

Study name (acronym)	Year of questionnaire	Age at questionnaire, mean (SD)	Follow-up years, mean (SD)	Total (*N*)	Case (*N*)	Parous, %	Age at first birth, mean (SD)	BMI, mean (SD)	1° family history, %	HR^+ cases, %	$HER2^+$ cases, %
Cancer Prevention Study-II (CPSII)	1992–1993	62.6 (6.5)	11.9 (4.0)	70,039	1,375	92.5	23.9 (4.0)	25.6 (4.8)	13.7	88.7	14.6
Melbourne Collaborative Cohort Study (MCCS)	1990–1994	54.8 (8.6)	15.2 (2.3)	22,569	577	86.3	25.0 (4.5)	26.7 (4.9)	N/A	81.6	16.3
NIH-AARP Diet and Health Study (NIH-AARP)	2004–2006	69.9 (5.4)	1.9 (0.4)	97,635	253	84.2	23.2 (4.2)	27.1 (5.9)	14.5	85.4	15.0
Nurses' Health Study (NHS)	1979	46.3 (7.2)	11.8 (2.7)	75,164	1,992	94.4	25.1 (3.3)	24.4 (4.4)	6.4	85.6	16.8
Nurses' Health Study II (NHS2)	1989	34.6 (4.7)	13.0 (2.5)	110,043	1,368	69.8	25.5 (4.0)	24.0 (4.7)	2.0	83.9	17.5
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO)	1993–2001	63.0 (5.4)	8.6 (2.5)	67,545	2,120	92.5	23.1 (4.3)	27.2 (5.6)	13.7	85.5	18.1
Swedish Mammography Cohort (SMC)	1997	61.8 (9.3)	13.0 (2.7)	35,581	552	90.5	24.0 (4.9)	25.0 (3.9)	8.8	88.8	12.0
Swedish Women's Lifestyle and Health Study (SWLH)	1991–1992	39.6 (5.8)	17.6 (0.9)	47,706	768	88.3	25.4 (4.7)	23.5 (3.7)	16.6	86.5	15.4
Women's Health Initiative Observational Study (WHI-OS)	1993–1997	63.7 (7.3)	9.7 (3.2)	79,743	2,736	86.9	24.4 (2.4)	27.2 (5.8)	17.8	85.6	15.1
Overall		54.3 (14.3)	10.6 (5.1)	606,025	11,741	85.9	24.3 (4.1)	25.6 (5.2)	10.8	85.8	16.1

Abbreviations: HR^+, hormone receptor–positive (estrogen receptor–positive or progesterone receptor–positive); N/A, not available.

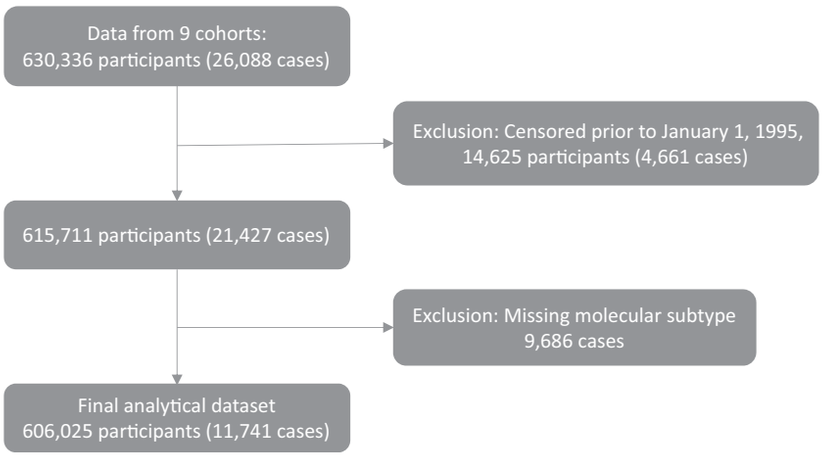

Figure 1.
Exclusion cascade resulting in an analytical dataset of 606,025 participants, of which 11,741 were breast cancer cases in a pooled analysis of nine prospective cohort studies.

Case definition

Cases were defined as incident, invasive breast cancers diagnosed after cohort enrollment and confirmed through cancer registry linkage or medical record/pathology report. For reported breast cancer deaths, breast cancer had to be listed as a primary or contributory cause of death (ICD-9: 174 or ICD-O, ICD-10: C50). ER, PR, and HER-2 status (positive or negative) was provided by the individual cohorts from the medical record/ pathology report or cancer registry data. For the main analyses, molecular subtype of the breast cancer was defined as luminal A–like (ER^+ or PR^+/$HER2^-$), luminal B–like (ER^+ or PR^+/$HER2^+$), HER2-enriched (ER^-/PR^-/$HER2^+$), or triple-negative (ER^-/PR^-/$HER2^-$). For the secondary analyses based only on ER and PR status, cases were defined as hormone receptor–positive (ER^+ or PR^+) or hormone receptor–negative (ER^- and PR^-).

Statistical model

The start of person-time was determined based on the date of the return of the baseline survey or January 1, 1995, whichever date was later. This entry date was selected because this was the year of diagnosis for the first case with HER-2 data in our dataset (14,625 women, 4,661 of whom were cases, were censored before entry; Fig. 1). For the main analyses, we further excluded cases with incomplete data on ER and PR, or HER2 ($n = 9,686$; Fig. 1). For the secondary analyses by hormone receptor status, we further excluded cases with incomplete data on hormone receptor status ($n = 2,760$) from the 615,711 eligible participants (Fig. 1), resulting in 612,951 participants. The end of person-time was the date of the first occurrence: invasive breast cancer diagnosis, diagnosis of carcinoma *in situ* of the breast, death, or end of follow-up of that cohort.

A joint Cox proportional hazards regression model was used to calculate HRs and 95% confidence intervals (CI; ref. 14). The joint Cox proportional model is based on a competing risk model and utilizes time-to-event data, different baseline hazard functions for each tumor subtype, and direct comparison of associations with tumor subtypes (14). Calendar time was used as the underlying time scale to accommodate studies that began after 1995 and to more efficiently control for secular trends (15). All Cox models were stratified on cohort study and single year of age at the start of follow-up, and adjusted for race.

Because ER, PR, and HER2 statuses were not available for all cases ($n = 9,686$; Fig. 1) in the main analyses, we compared the magnitude of risk factor associations using cases with and without tumor markers using the joint Cox proportional hazard model as a Supplementary analysis. An interaction variable for cases with and without complete subtype information was modeled and compared with a model without the interaction variable using the difference in the −2 log likelihood.

Multivariable-adjusted models included the variables under study: menopausal status, age at menopause, age at menarche, parity, age at first birth, first-degree family history of breast cancer, personal history of benign breast disease, ever oral contraceptive use, ever menopausal hormone use, BMI, alcohol consumption, and smoking status. Variables were coded as in Table 2. Missing values were treated differently based on whether modeling the variable as the main exposure of interest (subjects dropped from analysis) or as a covariate (subjects retained as separate missing category). To minimize the number of covariates with subtype-interaction variables, we only include interaction terms for covariates in the multivariate models that showed evidence of tumor heterogeneity in initial joint Cox models (14), including the following variables: age at menopause, parity, age at first birth, benign breast disease, and alcohol intake. Effect modification by attained age (dichotomized using 55 years of age as the cut-point because 99% of women aged $\geq$55 were postmenopausal at baseline) was evaluated for BMI and parity. Associations with BMI by age were also examined among never users of menopausal hormones.

Between-study heterogeneity was evaluated using a likelihood ratio test comprising models with and without interaction terms for exposure and cohort.

Estimates based on fewer than 10 cases were not reported. Reported *P* values were two-sided and considered statistically significant if <0.05. Interpretations of tumor heterogeneity results were based on *P* values for the continuous variables, where applicable. Analyses were performed using R (version 3.3.1).

Results

During follow-up (median of 10.4 years) of 606,025 study participants in this analysis, 11,741 invasive breast cancer cases were diagnosed and had complete information on tumor

Table 2. Multivariate[a]-adjusted associations of known and suspected breast cancer risk factors with invasive breast cancer risk by status of the ER, PR, and HER-2/*neu* in a pooled analysis of nine prospective cohort studies

	Luminal A–like		Luminal B–like			HER2-enriched			Triple-negative			
Risk factor categorization	**Case (*N*)**	**HR (95% CI)**	**Case (*N*)**	**HR (95% CI)**	***P* value[b]**	**Case (*N*)**	**HR (95% CI)**	***P* value[b]**	**Case (*N*)**	**HR (95% CI)**	***P* value[b]**	***P* value[c]**
Parity												
Nulliparous	1,163	1.00	192	1.00		57	1.00		109	1.00		
Parous	7,523	0.78 (0.73–0.83)	1,174	0.74 (0.63–0.87)	0.61	427	1.00 (0.76–1.32)	0.07	954	1.23 (1.02–1.50)	<0.001	<0.001
Number of live births among parous women												
1 births	891	1.00	135	1.00		50	1.00		120	1.00		
2 births	2,646	1.04 (0.96–1.12)	398	0.99 (0.81–1.21)		155	1.05 (0.75–1.46)		350	0.97 (0.78–1.20)		
3 births	2,117	1.01 (0.93–1.09)	351	1.05 (0.85–1.29)		124	1.03 (0.72–1.46)		290	0.96 (0.77–1.20)		
4+ births	1,849	0.91 (0.83–0.99)	284	0.85 (0.68–1.06)		127	1.09 (0.76–1.57)		274	0.92 (0.73–1.16)		
Continuous		0.96 (0.94–0.98)		0.95 (0.89–1.01)	0.76		1.02 (0.92–1.14)	0.24		0.97 (0.91–1.04)	0.66	0.64
Age at first live birth among parous women												
<20	488	1.00	75	1.00		42	1.00		73	1.00		
20–24	3,882	1.09 (0.98–1.20)	624	1.16 (0.91–1.49)		253	0.90 (0.63–1.26)		578	1.08 (0.84–1.40)		
25–29	1,978	1.30 (1.17–1.44)	317	1.38 (1.06–1.78)		103	0.78 (0.54–1.13)		247	1.09 (0.83–1.43)		
30+	994	1.58 (1.41–1.77)	132	1.38 (1.03–1.84)		50	0.90 (0.59–1.38)		100	1.03 (0.76–1.40)		
Continuous		1.04 (1.03–1.04)		1.02 (1.01–1.04)	0.17		0.99 (0.96–1.02)	0.001		1.00 (0.98–1.02)	0.001	<0.001
Age at menarche												
<12	1,860	1.00	276	1.00		114	1.00		256	1.00		
12	2,655	0.99 (0.93–1.05)	441	1.08 (0.93–1.26)		147	0.89 (0.69–1.14)		355	0.97 (0.83–1.15)		
13	2,136	0.96 (0.90–1.03)	333	1.07 (0.91–1.26)		123	1.00 (0.77–1.29)		267	0.90 (0.76–1.07)		
14+	1,998	0.93 (0.87–0.99)	309	1.00 (0.85–1.18)		131	1.05 (0.81–1.35)		270	0.95 (0.80–1.13)		
Continuous age		0.97 (0.95–0.99)		1.00 (0.95–1.05)	0.44		1.03 (0.95–1.12)	0.20		0.98 (0.92–1.03)	0.91	0.56
Years between menarche and first birth among parous women												
0–7.9	1,185	1.00	197	1.00		103	1.00		203	1.00		
8–9.9	1,289	1.11 (1.02–1.20)	207	1.05 (0.86–1.27)		77	0.75 (0.55–1.01)		173	0.86 (0.70–1.06)		
10–11.9	1,545	1.15 (1.06–1.24)	239	1.09 (0.90–1.32)		105	0.92 (0.69–1.22)		206	0.87 (0.71–1.07)		
12–14.4	1,563	1.22 (1.13–1.32)	263	1.24 (1.03–1.51)		66	0.57 (0.42–0.79)		220	0.97 (0.80–1.19)		
14.5–79	1,721	1.53 (1.42–1.65)	236	1.25 (1.03–1.52)		95	0.91 (0.68–1.21)		194	0.97 (0.79–1.19)		
Continuous		1.03 (1.03–1.04)		1.02 (1.01–1.03)	0.11		0.99 (0.97–1.01)	<0.001		1.00 (0.99–1.02)	0.001	<0.001
Age at menopause												
<50	2,338	1.00	379	1.00		120	1.00		267	1.00		
50–54	2,309	0.81 (0.76–0.86)	343	0.73 (0.62–0.85)		135	0.92 (0.71–1.19)		357	1.07 (0.90–1.26)		
55+	689	1.13 (1.04–1.24)	98	1.00 (0.80–1.26)		31	1.04 (0.69–1.55)		66	0.95 (0.72–1.24)		
Continuous		1.03 (1.02–1.04)		1.04 (1.02–1.05)	0.43		1.01 (0.98–1.04)	0.22		0.99 (0.97–1.01)	<0.001	<0.001
Ever use of menopausal hormones												
Never	4,650	1.00	727	1.00		300	1.00		652	1.00		
Ever	3,854	1.21 (1.15–1.28)	624	1.32 (1.15–1.51)	0.24	210	1.04 (0.83–1.31)	0.20	483	1.09 (0.94–1.27)	0.20	0.17
Ever use of oral contraceptives												
Never	4,274	1.00	654	1.00		251	1.00		537	1.00		
Ever	4,402	1.01 (0.96–1.06)	710	1.04 (0.93–1.18)	0.59	268	0.95 (0.78–1.16)	0.60	613	1.03 (0.90–1.18)	0.72	0.87
First-degree family history of breast cancer												
No	5,709	1.00	882	1.00		346	1.00		721	1.00		
Yes	1,299	1.35 (1.26–1.44)	230	1.68 (1.44–1.96)	0.01	78	1.39 (1.07–1.80)	0.83	183	1.59 (1.34–1.89)	0.08	0.04
Personal history of benign breast disease												
No	3,873	1.00	578	1.00		230	1.00		486	1.00		
Yes	1,757	1.28 (1.21–1.36)	333	1.55 (1.34–1.78)	0.01	110	1.36 (1.08–1.72)	0.60	231	1.33 (1.13–1.56)	0.66	0.10

(Continued on the following page)

Table 2. Multivariate[a]-adjusted associations of known and suspected breast cancer risk factors with invasive breast cancer risk by status of the ER, PR, and HER-2/*neu* in a pooled analysis of nine prospective cohort studies (Cont'd)

	Luminal A–like		Luminal B–like			HER2-enriched			Triple-negative		
Risk factor categorization	**Case (*N*)**	**HR (95% CI)**	**Case (*N*)**	**HR (95% CI)**	***P* value[b]**	**Case (*N*)**	**HR (95% CI)**	***P* value[b]**	**Case (*N*)**	**HR (95% CI)**	***P* value[b]**	***P* value[c]**
Alcohol intake at baseline												
Not current	2,188	1.00	373	1.00		151	1.00		362	1.00		
<1 drink/day	4,635	1.12 (1.06–1.18)	713	1.03 (0.90–1.17)		275	0.94 (0.76–1.15)		584	0.87 (0.76–1.00)		
1–2 drinks/day	843	1.34 (1.23–1.46)	137	1.31 (1.07–1.59)		37	0.87 (0.61–1.24)		88	0.86 (0.68–1.09)		
2+ drinks/day	295	1.55 (1.37–1.76)	45	1.33 (0.98–1.82)		13	0.98 (0.55–1.73)		30	0.98 (0.67–1.43)		
Continuous		1.15 (1.11–1.20)		1.16 (1.04–1.29)	0.97		0.98 (0.79–1.21)	0.11		1.03 (0.90–1.18)	0.10	0.17
Cigarette smoking status												
Never	4,477	1.00	731	1.00		271	1.00		589	1.00		
Former	3,115	1.07 (1.02–1.13)	469	1.00 (0.88–1.12)		187	1.14 (0.94–1.37)		403	1.14 (1.00–1.30)		
Current	1,108	1.04 (0.97–1.12)	168	0.95 (0.80–1.14)	0.43	63	0.97 (0.73–1.29)	0.68	160	1.19 (0.99–1.42)	0.38	0.55

[a]Multivariable-adjusted models were stratified on age at enrollment (continuous) and cohort study and adjusted for race, education, age at menopause (categorical), age at menarche (continuous), parity, age at first birth, family history of breast cancer, benign breast disease, ever oral contraceptive use, ever menopausal hormone use, BMI (per 2 kg/m^2), alcohol (categorical), and smoking status as well as subtype interactions with age at menopause, parity, age at first birth, benign breast disease, and alcohol intake.

[b]*P* value for heterogeneity of that subtype compared with luminal A.

[c]*P* value for overall subtype heterogeneity.

markers, including 8,700 luminal A–like (ER$^+$ or PR$^+$/HER2$^-$), 1,368 luminal B–like (ER$^+$ or PR$^+$/HER2$^+$), 521 HER2-enriched (ER$^-$/PR$^-$/HER2$^+$), and 1,152 triple-negative (ER$^-$/PR$^-$/HER2$^-$) subtypes. For participants included in the analysis, the mean age at baseline was 54.7 years, the mean BMI was 25.6, 85.9% were parous, and the mean age at first birth was 24.3 years (Table 1; Supplementary Table S1).

As shown in Supplementary Table S2, associations among women in the analytical cohort (first column of HRs) were similar to those among women excluded from analyses due to a lack of ER, PR, and HER2 data (second column of HRs).

Considering cases only with complete data for ER, PR, and HER2, associations of reproductive factors with risk differed by molecular subtypes of breast cancer (Table 2). Being parous was associated with 22% to 26% lower risk of luminal-like subtypes, but a 23% higher risk of triple-negative breast cancer (*P* value for heterogeneity compared with luminal A < 0.001; Table 2). The difference between associations for risk HER2-enriched and triple-negative breast cancer was not statistically significant (*P* value for tumor heterogeneity = 0.23; data not in tables). The association between being parous and risk of triple-negative breast cancer differed by attained age, such that the association was stronger with parity for women ages 55 years or older (HR, 1.56; 95% CI, 1.21–2.01) than for younger women (HR, 0.81; 95% CI, 0.58–1.14; *P* value for age interaction = 0.002; Table 3).

For parous women, the association for each additional live birth did not differ by molecular subtype of the tumor (*P* value for overall tumor heterogeneity = 0.64). However, the association for age at first birth did (*P* value for overall tumor heterogeneity < 0.001). An older age at first live birth was associated with higher risk of luminal A–like. Similar associations were found for risk of luminal B–like subtypes (*P* value for heterogeneity = 0.06), but not with HER2-enriched (*P* values for heterogeneity = 0.001) or triple-negative breast cancers (*P* values for heterogeneity < 0.001; Table 2). We found evidence of study-specific differences for subtype-specific associations with number of live births (*P* = 0.007; Supplementary Table S3).

Age at menarche associations did not vary by molecular subtype (*P* value for overall heterogeneity = 0.56; Table 2). However, for parous women, greater number of years between menarche and first birth was associated with higher risk of luminal A–like (per year HR, 1.03; 95% CI, 1.03–1.04) and luminal B–like breast cancer (per year HR, 1.02; 95% CI, 1.01–1.03), but not with the other subtypes (*P* value for heterogeneity < 0.0001).

Age at menopause was differentially associated with breast cancer molecular subtypes (*P* value for overall heterogeneity = 0.007). A 1-year increase in age at menopause was associated with a 3% to 4% increase in risk for luminal-like cancers, whereas associations were null for HER2-enriched or triple-negative breast cancers.

Although there was no evidence of between-subtype variation (*P* value for overall heterogeneity = 0.17; Table 2), the direct association with use of menopausal hormones was statistically significant only for luminal-like tumors. No significant associations were observed between ever use of oral contraceptives and breast cancer risk, overall or by molecular subtype.

Family history of breast cancer and a personal history of benign breast disease were associated with increased risk of all molecular subtypes; however, the strength of the association between both risk factors and risk of luminal B–like breast cancer was slightly stronger than for risk of luminal A–like breast cancer (*P* value for

Table 3. Multivariate[a]-adjusted associations of parity and BMI with invasive breast cancer risk by status of the ER, PR, and HER-2/*neu* and attained age in a pooled analysis of nine prospective cohort studies

	Parity				BMI (kg/m^2)								
	Nulliparous		Parous		18.5–22.4		22.5–24.9		25–24.9		30+		Per 5
Categories of subtype and attained age	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**Cases**	**HR (95% CI)**	**HR (95% CI)**
Luminal A–like													
Age < 55	291	1.00	745	0.87 (0.76–1.00)	498	1.02 (0.87–1.19)	246	1.00	192	1.02 (0.85–1.24)	82	0.89 (0.69–1.15)	0.95 (0.89–1.02)
Age 55+	872	1.00	6778	0.81 (0.75–0.87)	1,801	0.87 (0.82–0.93)	1,864	1.00	2,388	1.05 (0.99–1.12)	1,492	1.20 (1.12–1.28)	1.10 (1.08–1.12)
P value for age interaction				0.39								0.06	7.06E–05
Luminal B–like													
Age < 55	64	1.00	131	0.68 (0.50–0.92)	103	1.35 (0.94–1.96)	39	1.00	37	1.20 (0.77–1.89)	13	0.83 (0.44–1.55)	0.91 (0.77–1.08)
Age 55+	128	1.00	1,043	0.84 (0.70–1.01)	290	0.98 (0.83–1.16)	267	1.00	361	1.10 (0.94–1.29)	237	1.28 (1.07–1.53)	1.09 (1.03–1.14)
P value for age interaction				0.24								0.12	0.06
P value for tumor heterogeneity[b]				0.24								0.46	0.47
HER2-enriched													
Age < 55	16	1.00	64	1.41 (0.80–2.46)	43	1.02 (0.61–1.70)	22	1.00	11	0.64 (0.31–1.31)	4	N/C	0.79 (0.61–1.01)
Age 55+	46	1.00	394	0.90 (0.67–1.23)	116	0.98 (0.76–1.28)	109	1.00	135	0.97 (0.76–1.25)	78	0.95 (0.71–1.28)	1.01 (0.92–1.11)
P value for age interaction				0.17								0.91	0.07
P value for tumor heterogeneity[b]				0.15								0.13	0.07
Triple-negative													
Age < 55	51	1.00	117	0.81 (0.58–1.14)	73	0.81 (0.56–1.17)	47	1.00	25	0.66 (0.41–1.08)	22	1.14 (0.68–1.89)	1.09 (0.94–1.26)
Age 55+	64	1.00	919	1.56 (1.21–2.01)	223	0.90 (0.75–1.08)	230	1.00	340	1.16 (0.98–1.38)	175	1.02 (0.84–1.24)	1.04 (0.98–1.10)
p-value for age interaction				0.002								0.63	0.58
P value for tumor heterogeneity[b]				<0.001								0.02	0.02
P value for overall tumor heterogeneity[c]				<0.001								0.63	0.04

Abbreviation: N/C, not calculated.

[a]Multivariable-adjusted models were stratified on age at enrollment (continuous) and cohort study and adjusted for race, education, age at menopause (categorical), age at menarche (continuous), parity (1 = nulliparous, 0 = parous), age at first birth (continuous variable centered on median value among parous with the nulliparous and missing coded as that median value), family history of breast cancer, benign breast disease, ever oral contraceptive use, ever menopausal hormone use, BMI (per 2 kg/m^2), alcohol (categorical), age at smoking initiation (continuous) as well as subtype interactions with age at menopause, parity, age at first birth, benign breast disease, and alcohol intake.

[b]*P* value for heterogeneity of that subtype compared with luminal A.

[c]*P* value for overall subtype heterogeneity.

Table 4. Multivariate[a]-adjusted associations of known and suspected breast cancer risk factors with invasive breast cancer risk by joint ER and PR in a pooled analysis of nine prospective cohort studies

	ER^+ or PR^+		ER^-/PR^-		
	Cases	**HR (95% CI)**	**Cases**	**HR (95% CI)**	***P* value[b]**
Parity					
No	2,065	1.00	298	1.00	
Yes	13,905	0.78 (0.75–0.82)	2,378	1.04 (0.92–1.17)	<0.001
Number of live births among parous women					
1 births	1,631	1.00	287	1.00	
2 births	4,879	1.04 (0.98–1.10)	798	0.93 (0.81–1.06)	
3 births	4,009	1.04 (0.98–1.10)	681	0.95 (0.82–1.10)	
4+ births	3,334	0.92 (0.86–0.98)	603	0.90 (0.77–1.05)	
Continuous		0.96 (0.95–0.98)		0.98 (0.93–1.02)	0.61
Age at first birth among parous women					
<20	942	1.00	187	1.00	
20–24	6,979	1.11 (1.04–1.19)	1,253	1.01 (0.86–1.18)	
25–29	3,892	1.32 (1.22–1.42)	631	1.03 (0.87–1.22)	
30+	1,790	1.54 (1.42–1.67)	248	1.03 (0.85–1.25)	
Continuous		1.03 (1.03–1.04)		1.00 (0.99–1.01)	<0.001
Age at menarche					
<12	3,378	1.00	595	1.00	
12	4,571	0.98 (0.93–1.02)	739	0.93 (0.83–1.04)	
13	4,140	0.98 (0.94–1.03)	679	0.94 (0.84–1.06)	
14+	3,790	0.95 (0.90–1.00)	645	0.97 (0.86–1.09)	
Continuous		0.98 (0.97–1.00)		0.99 (0.96–1.03)	0.66
Years between menarche and first birth among parous women					
0–7.9	2,304	1.00	476	1.00	
8–9.9	2,418	1.09 (1.03–1.15)	430	0.92 (0.80–1.05)	
10–11.9	2,890	1.17 (1.10–1.23)	474	0.89 (0.78–1.02)	
12–14.4	2,717	1.21 (1.14–1.28)	429	0.89 (0.78–1.02)	
14.5–79	3,185	1.46 (1.38–1.54)	498	1.03 (0.91–1.18)	
Continuous		1.03 (1.03–1.03)		1.00 (0.99–1.01)	<0.001
Age at menopause					
<50	4,477	1.00	635	1.00	
50–54	4,256	0.80 (0.77–0.84)	754	0.96 (0.86–1.08)	
55+	1,260	1.13 (1.06–1.20)	166	1.05 (0.89–1.25)	
Continuous		1.03 (1.02–1.03)		1.01 (0.99–1.02)	<0.001
Ever use of menopausal hormones					
Never	8,494	1.00	1,548	1.00	
Ever	7,086	1.25 (1.20–1.30)	1,056	1.06 (0.96–1.17)	0.003
Ever use of oral contraceptives					
Never	8,052	1.00	1,292	1.00	
Ever	7,869	1.03 (0.99–1.07)	1,377	1.05 (0.97–1.15)	0.60
First-degree family history of breast cancer					
No	10,720	1.00	1,764	1.00	
Yes	2,488	1.42 (1.36–1.49)	409	1.50 (1.34–1.68)	0.37
Personal history of benign breast disease					
No	7,637	1.00	1,220	1.00	
Yes	3,374	1.31 (1.25–1.36)	583	1.39 (1.25–1.53)	0.29
Alcohol intake at baseline					
Not current	4,078	1.00	793	1.00	
<1 drink/day	8,272	1.10 (1.06–1.14)	1,336	0.93 (0.85–1.02)	
1–2 drinks/day	1,432	1.31 (1.23–1.40)	193	0.92 (0.79–1.08)	
2+ drinks/day	545	1.45 (1.32–1.59)	71	0.95 (0.74–1.21)	
Continuous		1.14 (1.10–1.17)		1.00 (0.91–1.09)	0.005
Cigarette smoking status					
Never	8,227	1.00	1,406	1.00	
Former	5,639	1.07 (1.03–1.11)	915	1.08 (0.99–1.17)	
Current	2,123	1.04 (0.99–1.09)	357	1.01 (0.89–1.14)	0.88
BMI (kg/m^2) among women <55 years of age at baseline					
18.5–22.4	1,073	1.01 (0.91–1.12)	208	0.87 (0.70–1.09)	
22.5–24.9	571	1.00	131	1.00	
25.0–29.9	431	0.98 (0.86–1.11)	88	0.85 (0.65–1.11)	
≥30	182	0.89 (0.75–1.05)	47	0.95 (0.68–1.32)	
Per 5 kg/m^2		0.96 (0.91–1.00)		1.05 (0.95–1.16)	0.09
BMI (kg/m^2) among women ≥55 years of age at baseline					
18.5–22.4	3,247	0.91 (0.87–0.95)	540	0.96 (0.85–1.08)	
22.5–24.9	3,278	1.00	523	1.00	

(Continued on the following page)

Table 4. Multivariate[a]-adjusted associations of known and suspected breast cancer risk factors with invasive breast cancer risk by joint ER and PR in a pooled analysis of nine prospective cohort studies (Cont'd)

	ER^+ or PR^+		ER^-/PR^-		
	Cases	HR (95% CI)	Cases	HR (95% CI)	*P* value[b]
25.0–29.9	4,315	1.07 (1.02–1.12)	713	1.08 (0.97–1.21)	
≥30	2,585	1.19 (1.13–1.26)	388	1.04 (0.91–1.19)	
Per 5 kg/m^2		1.09 (1.07–1.10)		1.04 (1.00–1.09)	0.08

[a]Multivariable-adjusted models were stratified on age at enrollment (continuous) and cohort study and adjusted for race, education, age at menopause (categorical), age at menarche (continuous), parity (1 = nulliparous; 0 = parous), age at first birth (continuous variable centered on median value among parous with the nulliparous and missing coded as that median value), family history of breast cancer, benign breast disease, ever oral contraceptive use, ever menopausal hormone use, BMI (per 2 kg/m^2), alcohol (categorical), age at smoking initiation (continuous) as well as subtype interactions with age at menopause, parity, age at first birth, benign breast disease, and alcohol intake.

[b]*P* value for heterogeneity of ER^-/PR^- compared with ER^+ or PR^+.

tumor heterogeneity = 0.01). No statistically significant differences in the magnitude of the association for these risk factors were found comparing risk of HER2-enriched and triple-negative breast cancer (*P* value for tumor heterogeneity > 0.4; Supplementary Table S4).

Alcohol consumption (per drink per day) was associated with 16% higher risk of luminal cancers but not with other subtypes, although the differences by subtype were not statistically significant (*P* value for overall tumor heterogeneity = 0.17). Associations with smoking status were null for all subtypes (overall *P* value for heterogeneity = 0.55).

BMI was associated with increased risk of luminal A–like and luminal B–like tumors in women ages 55 and older but not in younger women (Table 3). BMI was not associated with risk of triple-negative (*P* value for tumor heterogeneity compared with risk of luminal A–like tumors = 0.02) in either age group. Associations of BMI with breast cancer subtypes in women who never took menopausal hormones (Supplementary Table S5) were similar to those in Table 3. By hormone receptor status (Table 4), associations with BMI among women < 55 years of age were not statistically different (*P* value for tumor heterogeneity = 0.09). In the older women, the direct association with BMI was slightly stronger for hormone receptor–positive breast cancer, but not statistically significant than that for ER^-/PR^- breast cancer.

Secondary analyses by hormone receptor status (not accounting for HER2) included 15,989 hormone receptor–positive cases and 2,678 hormone receptor–negative cases (Table 4). Parity, age at first birth, years between menarche and first birth among parous women, age at menopause, and alcohol intake were differentially associated by hormone receptor status (Table 4) as well as molecular subtype based on ER, PR, and HER2 status (Table 2). Associations with ever use of menopausal hormones and alcohol varied by hormone receptor status (*P* value for tumor heterogeneity = 0.003 and <0.001, respectively; Table 4), but not molecular subtype (Table 2). For family history of breast cancer, associations differed by molecular subtype (Table 2) but not hormone receptor status (Table 4).

Discussion

In our pooled analysis of nine cohort studies with prospective data on 606,025 study participants including 11,741 invasive breast cancer cases with ER, PR, and HER2 status, we found evidence of etiologic heterogeneity across tumor molecular subtypes. In general, the patterns of etiologic heterogeneity were similar whether stratified by hormone receptor (ER/PR) status or molecular subtype approximated by ER, PR, and HER2 status. Established breast cancer risk factors were associated with luminal A–like breast cancer risk in the direction established for overall breast cancer risk. Risk factors' associations with luminal B–like tumors, with the exception of family history of breast cancer and personal history of benign breast disease, were in the same direction as, and of similar magnitude to, those for luminal A–like tumors. To the contrary, the pattern of association with parity-related factors, age at menopause, and BMI differed for risk of triple-negative cancers.

The well-documented protection of parity-related factors with respect to breast cancer risk overall was limited to luminal-like/hormone receptor–positive breast cancer, whereas ever parous was associated with an increased risk of triple-negative breast cancer in our pooled analysis. The duality of the parity association has been consistently reported in the largest previous studies (6, 9, 13, 16, 17). However, a recent meta-analysis of 14 cohort or case–control studies reported no association between ever parous and risk of triple-negative breast cancer (pooled OR, 1.01; 95% CI, 0.87–1.17; ref. 10). Between-study heterogeneity was observed in the meta-analysis (I^2 = 30%). Some of the between-study heterogeneity might be due to effect modification by attained age and different distributions of age among study participants. However, the direction of potential age interaction has been inconsistent across our pooled analysis, the Danish study (13), and a pooled analysis of data from African-American study participants (9). In the largest study of reproductive factors by age to date, the Danish registry study with 9,123 $ER^-/HER2^-$ cases found that parity was directly associated with risk of ER^- breast cancer (HR, 1.36; 95% CI, 1.04–1.77), but not with risk of ER^+ breast cancer (HR, 1.03; 95% CI, 0.84–1.26) among women <50 years of age (13). With 1,083 ER^- cases, the African American Breast Cancer Epidemiology and Risk (AMBER) Consortium reported direct associations between parity and ER^- disease of similar magnitude across four age strata (*P* value for interaction = 0.68). Both of these reported findings are inconsistent with the 56% higher risk of triple-negative breast cancer (n = 1,151) associated with parity among women ≥55 years of age in our study. Furthermore, other studies have found that breastfeeding might ameliorate the higher risk of triple-negative breast cancer associated with parity (7, 10), and differences in breastfeeding rates among studies might also contribute to between-study heterogeneity. The biological underpinnings of associations between parity and breast cancer subtypes might provide important understandings of early breast carcinogenesis.

In our study, onset of menopause at older ages was associated with a higher risk of luminal-like breast cancers but not HER2-enriched or triple-negative breast cancers. Although prior results varied across studies (18), our results are consistent with the incidence patterns by ER expression (19, 20), in which the

incidence of ER^- tumors flattens out after menopause (21), whereas the incidence of ER^+ tumors continues to increase after menopause (22). Type of menopause (surgical or natural) should be considered in future analyses.

Reports of associations between BMI and breast cancer subtypes for older/postmenopausal women have been inconsistent (11, 23), perhaps due in part to recall bias, small sample size, as well as differences in age distributions, BMI cut-points and reference group selection, and screening patterns across studies. Our results support a direct association between BMI and risk of luminal tumors for women $\geq$55 years, and no association with risk of triple-negative breast cancer. We selected 55 years as the age cut-point to minimize women in the menopausal transition among the older women at the expense of a more heterogeneous group of younger women (<55 years of age). Despite this limitation, we still observed inverse associations between BMI and risk of luminal and HER2-enriched tumors for women <55 years of age, and a direct association with risk of triple-negative breast cancer. Our results are consistent with reviews of associations by ER, PR, and HER2 (24) and by ER/PR status (25–27). However, the Breast Cancer Surveillance Consortium (BCSC) investigators found direct associations for ER^- (as well as ER^+) breast cancers with BMI (23). It is unclear how the large proportion of missing data (43%) influenced results from the BCSC. Disentangling the biological pathways perturbed with obesity (25), driving these associations will require pooled analyses of studies with prospectively-collected biospecimens and well-characterized tumor characteristics.

First-degree family history of breast cancer varied by molecular subtype with the strongest association found for risk of luminal B cancers, but no difference was found by ER/PR status alone in our study. Our results might have been biased by the large percentage of missing values for this exposure, or the large percentage range across studies for first-degree family history (2.0%–17.8%). However, the magnitude of our results is consistent with a synopsis of prior studies reporting that risk estimates associated with a positive family history range between 1.5 and 2.0 for each of the molecular subtypes (11), and we found no evidence of between-study heterogeneity for the associations between family history and molecular subtypes. We were not able to examine the association of number, year of onset, and bilaterality of affected relatives, or by *BRCA1/2* mutation status, which might refine a possible relationship between family history of breast cancer and molecular subtypes. In the future, pooled analyses should include detailed family history and risk of breast cancer subtypes, which might improve risk assessment models that incorporate tumor pathology.

Personal history of benign breast disease is an indicator of higher risk of subsequent breast cancer overall (28) and is an integral part of some risk assessment models [refs. 29 (#4174), 30 (#4175); and Tice, 2015 (#4723)]. In our study, benign breast disease was a risk factor for all breast cancer subtypes with stronger magnitude of association with risk of luminal B–like breast cancer. In smaller studies, benign breast disease was associated consistently with risk of luminal A tumors, but not for other subtypes (16, 31). A better understanding of the clinical characteristics of breast cancers after a benign biopsy could inform risk assessment models to identify women who might benefit from risk-reducing strategies.

Our results suggest that ER status explains much of the etiologic heterogeneity of breast cancer, consistent with trends in national incidence rates (12, 19, 22, 32). The minor differences in associations of family history of breast cancer or benign breast disease between luminal A and luminal B are likely not clinically relevant enough to warrant distinction.

Furthermore, reliance primarily on immunohistochemical stains for ER, PR, and HER2 to classify breast cancer molecular subtypes likely led to misclassification of outcomes. Historic changes in immunohistochemical thresholds for positivity and interpretation criteria over the time of case diagnoses (2, 3) likely led to misclassification of up to 20% of cases (33, 34). In addition, use of these surrogate markers to assign intrinsic subtypes also introduces misclassification, particularly for luminal B–like and HER2-enriched subtypes (35). The St. Gallen International Breast Cancer Conference expert panel (36) recommends using grade or ki67 status to improve classification using surrogate markers, but we implemented commonly used definitions based solely on ER, PR, and HER-2/*neu* status to compare our results with those from other epidemiologic studies. Misclassification of subtype is likely to be unrelated to risk factors, and the bias would tend to minimize true differences in association, for at least dichotomous variables, by subtype, as shown in a recent analysis of etiologic heterogeneity (17). Despite this potential bias, we did observe differences in associations of benign breast disease and family history of breast cancer between luminal A–like and B–like disease.

Our study benefitted from the existing pooled data with ten exposures by subtype. However, examination of more detailed risk factor information and other risk factors not available here (e.g., physical inactivity, breastfeeding) might reveal further evidence of etiologic heterogeneity. Furthermore, we did not harmonize updated information on exposure; this limitation may have led to misclassification of exposure and attenuated associations. We did use statistical methods that allowed us to carefully control for risk factor–subtype interactions and assess between-subtype heterogeneity overall and relative to the most common subtype (14).

In summary, our results are based on the largest study of prospective data to date and contribute to the accumulating evidence that etiologic heterogeneity exists in breast carcinogenesis. Pooled analyses of studies with more detailed exposure and tumor classification are likely to be increasingly informative about etiology and risk factor identification (37). More precise estimates of risk factor associations will be required to improve risk assessment models with clinicopathologic data.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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