Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

Research Article

Cancer Epidemiology, Biomarkers & Prevention

Risk Factors for Ductal, Lobular, and Mixed Ductal-Lobular Breast Cancer in a Screening Population

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Abstract

Background: Biological distinctions between histologic subtypes of breast cancer suggest etiologic differences, although few studies have been powered to examine such differences. We compared associations between several factors and risk of ductal, lobular, and mixed ductal-lobular breast cancers.

Methods: We used risk factor data from the Breast Cancer Surveillance Consortium for 3,331,744 mammograms on 1,211,238 women, including 19,119 women diagnosed with invasive breast cancer following mammography (n = 14,818 ductal, 1,602 lobular, and 1,601 mixed ductal-lobular). Histologic subtype–specific risk factor associations were evaluated using Cox regression.

Results: Significant positive associations with family history and breast density were similar across subtypes. Hormone therapy use was associated with increased risk of all subtypes, but was most strongly associated with lobular cancer [hazard ratio (HR) = 1.46; 95% confidence interval (CI), 1.25-1.70]. Relative to nulliparous women, parous women had lower risk of ductal and mixed but not lobular cancers (HR = 0.80; 95% CI, 0.76-0.84; HR = 0.79; 95% CI, 0.68-0.93; HR = 0.96; 95% CI, 0.81-1.15, respectively). Late age at first birth was associated with increased risk of all subtypes.

Conclusions: Similarities in risk factor associations with ductal, lobular, and mixed breast cancer subtypes were more pronounced than differences. Distinctions between subtype-specific associations were limited to analyses of hormone therapy use and reproductive history.

Impact: The results of this study indicate that the strongest risk factors for breast cancer overall (that is, family history and breast density) are not histologic subtype specific. Additional studies are needed to better characterize subtype-specific associations with genetic, hormonal, and nonhormonal factors. *Cancer Epidemiol Biomarkers Prev; 19(6); 1643–54. ©2010 AACR.*

Introduction

Increasing evidence indicates that the biological heterogeneity of breast cancers has clinical and epidemiologic implications. Classifying invasive breast cancers into distinct subtypes based on tumor histology is especially relevant in this regard: the distinct patterns of growth and cellular organization (1), chromosomal alterations (2-4), and tumor marker expression (5-8) associated with different histologic types of breast cancer suggest distinct etiologies. Consistent with these biological distinctions, some epidemiologic studies have reported that histologic subtypes of breast cancer differ in their associations with established breast cancer risk factors (9-21).

To date, studies comparing risk factor associations across histologic subtypes have focused primarily on hormonal exposures (9-17, 19-21). The most consistent observation is that the use of combined estrogen plus progestin hormone therapy (CHT) is more strongly associated with the risk of invasive lobular carcinoma (ILC) than with the risk of invasive ductal carcinoma (IDC; refs. 10, 13-15, 19-21); in a large meta-analysis, Reeves et al. (22) reported a 2.51-fold increased risk of ILC among current users of CHT compared with never users, but noted a less pronounced 1.76-fold increased risk of IDC among current CHT users. Also compatible with the fact that ILC is almost always estrogen receptor positive, several studies have reported stronger associations between age at first birth and risk of ILC than IDC (12, 14, 20, 23); studies have been less consistent in finding differences in associations with parity between histologic subtypes (9, 11, 12, 14-16, 20). Studies reporting on the differences between subtypes with respect to the role

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doi: 10.1158/1055-9965.EPI-10-0188

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

of family history (14, 15, 18) and body mass index (BMI; refs. 11, 14, 15) have been either inconsistent or null, and no prior studies have reported on associations between breast density and breast cancer risk by histologic subtype.

Since the distinctions between histologic subtypes of breast cancer are rooted in tumor biology, these distinctions may imply important differences in tumor etiology and heterogeneity in risk factor associations. Few studies have been adequately powered to assess differences in risk factor associations by tumor histology in the same population of women. Using data from the national Breast Cancer Surveillance Consortium (BCSC), we explored how associations with family history, parity, age at first birth, menopausal hormone therapy (HT) use, BMI, and breast density differed with histology. Because the vast majority of invasive breast cancers can be classified as having either a ductal histology (65-80%), a lobular histology (6-12%), or a mix of ductal and lobular histologic features (3-6%; refs. 9, 11, 20, 24, 25), we focus here on these three subtypes.

Materials and Methods

The BCSC is a collaborative effort between seven geographically dispersed mammography registries: the Carolina Mammography Registry, the Colorado Mammography Project, Group Health (western Washington State), the New Hampshire Mammography Network, the New Mexico Mammography Project, the San Francisco Mammography Registry, and the Vermont Breast Cancer Surveillance System. Details regarding the BCSC have been provided elsewhere (26). All registries collect risk factor information through self-administered risk factor questionnaires completed by women at the time of screening mammography (27). Information regarding age, race, Hispanic ethnicity, and family history of breast cancer in first-degree relatives is collected from all registries. Self-reported height and weight, current use of HT at the time of mammography, and radiologist-reported Breast Imaging–Reporting Data System (BI-RADS) breast density are also collected by all registries, although some registries began collecting these data elements later than others. Five of the seven registries also collect data on parity (yes/no) and age at first live birth.

Each mammography registry and the Statistical Coordinating Center of the BCSC have received Institutional Review Board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. All procedures are Health Insurance Portability and Accountability Act compliant, and all registries and the Statistical Coordinating Center have received a Federal Certificate of Confidentiality and other protection for the identities of women, physicians, and facilities who are subjects of this research.

Study population

We included women between the ages of 40 to 84 years with no prior invasive or *in situ* breast cancer at the time of mammography screening. Women meeting these criteria who received at least one screening mammogram at a facility associated with a BCSC registry during the study period were included in the study cohort. Mammograms were considered to be for screening purposes based on a standard definition used by the BCSC (28). The study period of eligibility varied across BCSC registries, reflecting differences in the date up to which cancer ascertainment was complete: across all registries, January 1, 1999 was treated as the earliest possible start of study follow-up, whereas registry-specific study period end dates ranged from December 31, 2003 (Colorado Mammography Project) to March 31, 2008 (New Hampshire Mammography Network). After excluding women not meeting the eligibility criteria, 3,331,744 screening mammograms from 1,211,238 women were eligible for inclusion in the present analysis. The average duration of follow-up contributed by women in the study population was 1,926 days from the time of the first eligible screening mammogram during the study period until either the end of the study period or breast cancer diagnosis, whichever came first.

Case population

Breast cancers were identified through linkage with state cancer registries and/or pathology databases. Information regarding tumor histology and other tumor characteristics was also obtained through linkage with these resources. Women in the study cohort were included as cases if they were diagnosed with an invasive breast cancer after a screening mammogram within the study period; the average time between breast cancer diagnosis and a case's most recent prior screening mammogram was 354 days (range, 0-3,011 d). Women diagnosed with *in situ* breast cancer during the study period were not included as cases and were instead censored at the time of *in situ* diagnosis. Among 19,119 eligible cases of invasive breast cancer, 14,818 (78%) were identified as having IDC, 1,602 (8%) had ILC, and 1,601 (8%) had invasive carcinoma with a mix of ductal and lobular histologic features (IDLC). The most prevalent histology among the remaining 1,098 cases was the mucinous subtype (n = 437). Classification of these subtypes was based on *International Classification of Diseases for Oncology* codes, collected by each BCSC registry. Specifically, cases with codes 8520 (n = 1,550) or 8524 (n = 52) were classified as ILC, cases with codes 8500-8503 (n = 13,422) or 8523 (n = 347) were classified as IDC, and cases with a code of 8522 were classified as IDLC.

Statistical analysis

We tabulated the distribution of demographic characteristics in the overall study population (allowing for multiple mammogram-level observations per person) and among women diagnosed with invasive breast cancer during the study period (tabulating only observations

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associated with the mammogram most closely preceding diagnosis). Among cases, we tabulated the distribution of tumor marker expression status, stage at diagnosis, tumor grade, and age at most recent screening mammogram for each case group; differences between case groups in these characteristics were evaluated by χ^2 tests.

We used Cox proportional hazards regression analysis to evaluate associations between family history of breast cancer, parity, age at first birth, current HT use, BMI, breast density, and breast cancer risk. Given our interest in assessing risk factor associations separately for different histologic types of breast cancer, we constructed three separate Cox models for each exposure of interest, specific to each of the three outcomes of interest (that is, IDC, ILC, and IDLC). In all models, the time axis was defined as the time (in days) since a woman's first eligible screening mammogram during the study period and women diagnosed with *in situ* breast cancer or with an invasive breast cancer of a histologic type other than the model-specific outcome were censored at the time of diagnosis. In all analyses, we compared hazard ratio (HR) estimates across case groups using competing risks partial likelihood methods (29). Because women could contribute risk factor information from multiple screening mammograms and questionnaires during study follow-up, most exposures and covariates were analyzed as time varying to allow for changes in exposure status with mammograms after the first qualifying mammogram. A few exceptions were made to this approach: all analyses were implicitly adjusted for age at the start of study follow-up and analyses of current HT use and BMI were based on exposure status at the start of follow-up rather than at the time of the most recent mammogram. We evaluated proportional hazard assumptions for all models by testing for a nonzero slope of the scaled Schoenfeld residuals on ranked failure times and on the log of analysis time. Violations of proportional hazard assumptions in analyses of current HT use and BMI were resolved by restricting the duration of follow-up to a maximum of 5 years for analyses of these two variables. Thus, cases diagnosed >5 years after their first eligible mammogram during the study period were censored before diagnosis; for this reason, analyses for BMI and HT use at the start of follow-up were based on a reduced case population of 11,589 IDC cases (78%), 1,209 ILC cases (75%), and 1,265 of IDLC cases (79%).

BMI was calculated from self-reported height and weight and was analyzed as a categorical variable according to cut-points for normal weight (<25 kg/m^2), overweight (25-29 kg/m^2), and obese status (≥30 kg/m^2). In light of prior evidence that the association between BMI and breast cancer risk differs according to age or menopausal status and HT use (30-32), we stratified analyses of BMI by age and HT use (that is, women age <50 y, women age ≥50 y who were not HT users at the start of follow-up, and women age ≥50 y who were HT users at the start of follow-up). Because BCSC registries collect current HT use data as a simple dichotomous variable (that is, current use versus no current use), we had no information on the duration of HT use, prior HT use, or specific preparation of HT used among women in the study population. However, because women with a prior hysterectomy are almost always given unopposed estrogen preparations of HT (ET) and most other women use combined estrogen plus progestin preparations (CHT), we conducted analyses of HT use at the start of follow-up both as a simple dichotomous variable and as a categorical variable distinguishing current HT users assumed to be using ET (that is, women known to have had a prior hysterectomy) and current HT users assumed to be using CHT (that is, all other HT users; ref. 33). Breast density was analyzed as a categorical variable, using BI-RADS categories recorded from radiology. BI-RADS categories include the following: 1, almost entirely fat (< 25% dense); 2, scattered fibroglandular densities (25-50% dense); 3, heterogeneously dense (51-75% dense); and 4, extremely dense (>75% dense; ref. 34). We performed separate analyses of breast density among women age <65 years and among women age ≥65 years in light of a prior BCSC analysis, which found breast density to be most predictive of breast cancer risk among women age <65 years (35).

Analyses were adjusted for a common set of confounders selected *a priori*, including age at the start follow-up (5-y categories), white race (yes/no), family history of breast cancer in first-degree relatives (yes/no), and prior history of a benign breast procedure (yes/no); analyses of breast density were further adjusted for BMI (<25, 25-29, ≥30 kg/m^2) and HT use (yes/no). We also evaluated possible confounding by education level and Hispanic ethnicity, as well as by other main effect variables; however, because some of these variables were associated with a greater degree of missingness than other adjustment variables and because further adjustment did not appreciably alter effect estimates, we did not include these variables in the final analytic models.

All exposures examined in this study were associated with some degree of missingness and some were associated with a rather substantial amount. For variables that were unlikely to change with great frequency over follow-up (that is, family history, parity, age at first birth, race, and history of benign breast procedure), we first used a filling process to resolve missing values: missing values of a variable were replaced with nonmissing data from the same woman provided at a prior mammogram or, if no prior nonmissing data were available, with nonmissing data provided by at a subsequent mammogram from the same woman. This approach was not used for exposures assumed to be more variable over study follow-up (that is, breast density, BMI, and HT use). To assess the effect of missingness in these variables (and missingness remaining in other variables after filling), we performed multiple imputation by chained equations (36) using imputation models that included all exposures of interest,

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

covariates included in the multivariate model, an outcome indicator variable, and a variable for the log of analysis time. However, the subtype-specific HRs we obtained from our analyses using multiple imputation by chained equations were nearly identical to those obtained using a complete-case approach, in which observations with data are excluded. Thus, only the results from complete-case analyses are presented here.

Results

Characteristics of the overall study population and of study cases are presented in Tables 1 and 2, respectively. The majority of the study population was of non-Hispanic white race/ethnicity (76%), had education beyond high school (64%), and was postmenopausal at the time of breast cancer screening (75%). Women diagnosed with breast cancer were, on average, older at the time of their most recent mammogram than the overall study population. Among cases, women diagnosed with ILC were, on average, older at their most recent prior mammogram than women diagnosed with IDC or IDLC. IDC cases were more likely to be estrogen receptor negative compared with ILC and IDLC cases (21% versus 5% and 6%, respectively) and more likely to be progesterone receptor negative (31% versus 18% and 15%, respectively). Consistent with these differences, IDC cases were also more likely to be human epidermal growth factor receptor 2/neu positive than ILC or IDLC cases (17% versus 7% and 7%, respectively). Significant differences across case groups were also observed in the distribution of tumor stage and grade at diagnosis (Table 2).

Having a family history of breast cancer in first-degree relatives was similarly associated with an increased risk of all three histologic types of breast cancer, with HRs ranging from 1.52 to 1.63 (Table 3). Associations with family history were strongest among women age 40 to 49 years at the start of study follow-up [HR_{IDC} = 1.80; 95% confidence interval (CI), 1.65-1.97; HR_{ILC} = 2.06; 95% CI, 1.56-2.72; HR_{IDLC} = 1.78; 95% CI, 1.36-2.32] and followed a similar pattern of decreasing magnitude with increasing age at the start of follow-up across all three subtypes. Analysis of partial likelihoods reinforced observed similarities across subtypes, indicating no significant departure from equality of the subtype-specific effect estimates overall and within age strata.

Similarities across subtype-specific associations were also noted with respect to breast density. A clear gradient of increasing risk with increasing breast density was observed for each of the three histologic subtypes: compared with women with a BI-RADS score of 2 (that is, scattered fibroglandular densities), women with a score of 1 (that is, almost entirely fat) had a significantly lower risk of IDC, ILC, and IDLC (HR_{IDC} = 0.59; 95% CI,

Table 1. Study population characteristics

	All study subjects		All breast cancer cases
	n (%)	Person-years (%)	*n* (%)
Age, y			
40-49	1,019,892 (31)	2,113,932 (33)	4,693 (25)
50-59	1,072,392 (32)	1,944,280 (31)	5,648 (30)
60-69	683,529 (21)	1,183,481 (19)	4,575 (24)
70-84	555,931 (17)	1,097,059 (17)	4,203 (22)
Race			
White non-Hispanic	2,386,452 (76)	4,397,206 (76)	14,148 (80)
Hispanic white	221,669 (7)	420,360 (7)	1,036 (6)
African-American	185,740 (6)	399,959 (7)	1,170 (7)
Other	325,792 (10)	595,055 (10)	1,401 (8)
Missing	212,091	526,172	1,364
Education			
≤High school graduate/General Education Development	883,554 (36)	1,717,431 (37)	5,339 (37)
>High school	1,596,254 (64)	2,907,384 (63)	9,170 (63)
Missing	851,936	1,713,937	4,610
Menopausal status			
Premenopausal	716,485 (24)	1,430,113 (25)	2,990 (17)
Perimenopausal	55,084 (2)	102,933 (2)	212 (1)
Postmenopausal	2,265,421 (75)	4,184,268 (73)	14,660 (82)
Missing	294,754	621,438	1,257

NOTE: Multiple observations possible per woman in total but only one case observation per woman.

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

Table 2. Tumor characteristics by histologic subtype

	Ductal cases	Lobular cases	Mixed cases	χ^2 *P**
	n (%)	*n* (%)	*n* (%)	
Age at most recent mammogram, y				
40-49	3,019 (20)	261 (16)	324 (20)	<0.01
50-59	4,322 (29)	428 (27)	470 (29)	
60-69	3,675 (25)	403 (25)	405 (25)	
70-84	3,802 (26)	510 (32)	402 (25)	
Estrogen receptor status				
Positive	9,975 (79)	1,321 (95)	1,307 (94)	<0.01
Negative	2,620 (21)	63 (5)	86 (6)	
Missing	2,223	218	208	
Progesterone receptor status				
Positive	8,531 (69)	1,106 (82)	1,155 (85)	<0.01
Negative	3,797 (31)	247 (18)	208 (15)	
Missing	2,490	249	228	
HER2/neu status				
Positive	661 (17)	30 (7)	35 (7)	<0.01
Negative	3,299 (83)	427 (93)	437 (93)	
Missing	10,858	1,175	1,129	
Stage at diagnosis				
I	8,343 (60)	690 (45)	782 (51)	<0.01
IIA	3,000 (21)	368 (24)	379 (25)	
IIB	1,133 (8)	198 (13)	149 (10)	
III	1,264 (9)	232 (15)	200 (13)	
IV	226 (2)	38 (2)	28 (2)	
Missing	852	76	63	
Grade at diagnosis				
1	3,317 (24)	372 (30)	360 (24)	<0.01
2	5,690 (41)	671 (54)	771 (52)	
3	4,593 (33)	180 (15)	320 (22)	
4	259 (2)	14 (1)	21 (1)	
Missing	959	365	129	

Abbreviation: HER2, human epidermal growth factor receptor.

* *P* values presented are from χ^2 tests comparing the distribution of characteristics across the three tumor subtypes.

0.52-0.67; HR_{ILC} = 0.48; 95% CI, 0.31-0.74; HR_{IDLC} = 0.41; 95% CI, 0.26-0.66) and women with a score of 4 (that is, extremely dense) had a significantly higher risk of all three subtypes (HR_{IDC} = 1.62; 95% CI, 1.45-1.81; HR_{ILC} = 1.62; 95% CI, 1.15-2.26; HR_{IDLC} = 1.76; 95% CI, 1.27-2.42). After stratifying on age, associations with breast density were most pronounced among women age <65 years at the start of study follow-up. However, within each age strata, there was no significant difference between histologic subtypes in the magnitude of the association with breast density.

Less consistency in subtype-specific associations was noted with respect to BMI, although no statistically significant departures from equality of the subtype-specific HRs were noted, regardless of age group or HT use status. Although the risk of all three histologic subtypes was similarly decreased with elevated BMI among women age 40 to 49 years at the start of study follow-up, there was no clear trend of decreasing risk with increasing BMI with the exception of HR estimates for the IDC subtype, and CIs were wide. Although BMI was not associated with risk of ILC among women age 50 to 84 years who were not HT users at the start of study follow-up, a positive association with BMI was noted with respect to IDC and IDLC within this subset of the study population: compared with normal-weight women (that is, BMI of <25 kg/m^2), obese women had a 1.22-fold increased risk of IDC (95% CI, 1.11-1.35) and a 1.21-fold increased risk of IDLC (95% CI, 0.89-1.64). Associations with BMI were similar and null across subtypes when confined to women age 50 to 84 years who were HT users at the start of study follow-up.

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

Table 3. Breast cancer risk factor associations by histologic subtype within relevant strata of age at start of follow-up and HT use

	TOTAL		Ductal cases		Lobular cases		Mixed cases	
	n (%)*	Person-years (%)	*n* (%)*	HR (95% CI)†	*n* (%)*	HR (95% CI)†	*n* (%)*	HR (95% CI)†
Family history of breast cancer (first degree female relatives)								
Overall								
No	2,709,038 (86)	5,136,569 (88)	10,830 (81)	1.0 (Reference)	1,150 (80)	1.0 (Reference)	1,170 (81)	1.0 (Reference)
Yes	434,781 (14)	729,282 (12)	2,539 (19)	1.55 (1.48-1.62)	294 (20)	1.63 (1.43-1.86)	279 (19)	1.52 (1.33-1.74)
Missing	187,925	456,709	1,449		158		152	
Age 40-49 y								
No	1,058,329 (88)	2,039,322 (89)	2,744 (82)	1.0 (Reference)	238 (78)	1.0 (Reference)	302 (81)	1.0 (Reference)
Yes	150,074 (12)	244,264 (11)	621 (18)	1.80 (1.65-1.97)	66 (22)	2.06 (1.56-2.72)	71 (19)	1.78 (1.36-2.32)
Missing	67,084	163,084	319		25		38	
Age 50-69 y								
No	1,322,073 (86)	2,389,958 (87)	5,841 (82)	1.0 (Reference)	613 (80)	1.0 (Reference)	618 (80)	1.0 (Reference)
Yes	218,679 (14)	355,422 (13)	1,323 (18)	1.50 (1.41-1.59)	153 (20)	1.61 (1.34-1.93)	151 (20)	1.53 (1.28-1.84)
Missing	90,005	206,991	787		75		82	
Age 70-84								
No	328,636 (83)	707,289 (85)	2,245 (79)	1.0 (Reference)	299 (80)	1.0 (Reference)	250 (81)	1.0 (Reference)
Yes	66,028 (17)	129,596 (15)	595 (21)	1.42 (1.29-1.56)	75 (20)	1.38 (1.06-1.79)	57 (19)	1.23 (0.91-1.66)
Missing	30,836	86,634	343		58		32	
Breast density (BI-RADS)‡ §								
Overall								
1	205,527 (9)	396,096 (8)	511 (5)	0.59 (0.52-0.67)	43 (4)	0.48 (0.31-0.74)	40 (4)	0.41 (0.26-0.66)
2	1,073,985 (45)	2,114,668 (45)	4,536 (43)	1.0 (Reference)	467 (41)	1.0 (Reference)	442 (39)	1.0 (Reference)
3	921,472 (39)	1,808,306 (39)	4,625 (44)	1.35 (1.27-1.44)	534 (47)	1.56 (1.29-1.89)	551 (49)	1.56 (1.30-1.89)
4	173,158 (7)	341,732 (7)	837 (8)	1.62 (1.45-1.81)	95 (8)	1.62 (1.15-2.26)	94 (8)	1.76 (1.27-2.42)
Missing	957,602	1,673,617	4,309		463		474	

(*Continued on the following page*)

Table 3. Breast cancer risk factor associations by histologic subtype within relevant strata of age at start of follow-up and HT use (Cont'd)

	TOTAL		Ductal cases		Lobular cases		Mixed cases	
	n (%)*	Person-years (%)	*n* (%)*	HR (95% CI)†	*n* (%)*	HR (95% CI)†	*n* (%)*	HR (95% CI)†
Age 40-64 y								
1	140,467 (8)	260,805 (7)	235 (4)	0.50 (0.42-0.61)	18 (3)	0.47 (0.24-0.89)	20 (3)	0.41 (0.22-0.77)
2	795,852 (43)	1,537,220 (42)	2,667 (40)	1.0 (Reference)	239 (34)	1.0 (Reference)	275 (36)	1.0 (Reference)
3	767,001 (41)	1,492,912 (41)	3,363 (50)	1.41 (1.31-1.53)	367 (52)	1.83 (1.44-2.33)	384 (50)	1.53 (1.22-1.92)
4	157,284 (8)	308,960 (9)	731 (11)	1.79 (1.58-2.03)	79 (11)	1.80 (1.22-2.66)	82 (11)	1.83 (1.28-2.61)
Missing	756,161	1,295,561	2,934		266		310	
Age 65-84 y								
1	65,060 (13)	135,291 (13)	276 (8)	0.69 (0.57-0.83)	25 (6)	0.47 (0.26-0.85)	20 (5)	0.41 (0.20-0.86)
2	278,133 (54)	577,448 (54)	1,869 (53)	1.0 (Reference)	228 (52)	1.0 (Reference)	167 (46)	1.0 (Reference)
3	154,471 (30)	315,393 (30)	1,262 (36)	1.24 (1.10-1.39)	167 (38)	1.19 (0.87-1.64)	167 (46)	1.65 (1.18-2.29)
4	15,874 (3)	32,771 (3)	106 (3)	0.97 (0.71-1.33)	16 (4)	1.35 (0.65-2.80)	12 (3)	1.25 (0.54-2.89)
Missing	201,441	378,056	1,375		197		164	
BMI at start of follow-up (kg/m^2)‖								
Age 40-49 y								
<25	333,751 (53)	562,453 (52)	835 (55)	1.0 (Reference)	88 (60)	1.0 (Reference)	114 (59)	1.0 (Reference)
25-29	166,357 (26)	290,447 (27)	366 (24)	0.86 (0.76-0.98)	30 (20)	0.69 (0.45-1.06)	44 (23)	0.62 (0.42-0.92)
30+	130,414 (21)	235,615 (22)	309 (20)	0.85 (0.74-0.98)	29 (20)	0.77 (0.50-1.21)	35 (18)	0.78 (0.53-1.14)
Missing	480,479	899,392	1,448		107		144	
Age 50-84 y								
Not HT user at start								
<25	212,402 (43)	355,965 (42)	942 (38)	1.0 (Reference)	104 (44)	1.0 (Reference)	102 (38)	1.0 (Reference)
25-29	160,914 (32)	274,512 (32)	811 (33)	1.08 (0.98-1.20)	76 (32)	0.96 (0.70-1.30)	89 (33)	1.12 (0.84-1.50)
30+	125,967 (25)	221,986 (26)	716 (29)	1.22 (1.11-1.35)	55 (23)	0.94 (0.67-1.33)	78 (29)	1.21 (0.89-1.64)
Missing	429,211	790,414	2,393		252		228	

(*Continued on the following page*)

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

Table 3. Breast cancer risk factor associations by histologic subtype within relevant strata of age at start of follow-up and HT use (Cont'd)

	TOTAL		Ductal cases		Lobular cases		Mixed cases	
	n (%)*	Person-years (%)	*n* (%)*	HR (95% CI)†	*n* (%)*	HR (95% CI)†	*n* (%)*	HR (95% CI)†
HT user at start								
<25	157,442 (48)	246,415 (47)	787 (49)	1.0 (Reference)	105 (50)	1.0 (Reference)	105 (48)	1.0 (Reference)
25-29	104,714 (32)	169,000 (32)	511 (32)	0.94 (0.84-1.06)	60 (29)	0.86 (0.62-1.19)	71 (33)	0.97 (0.71-1.31)
30+	65,538 (20)	111,546 (21)	320 (20)	0.94 (0.83-1.08)	45 (21)	0.97 (0.67-1.39)	41 (19)	0.91 (0.63-1.32)
Missing	243,357	394,258	1,291		153		128	
Parity								
Nulliparous	395,541 (18)	692,804 (18)	1,744 (19)	1.0 (Reference)	172 (16)	1.0 (Reference)	218 (20)	1.0 (Reference)
Parous	1,802,553 (82)	3,214,852 (82)	7,250 (81)	0.80 (0.76-0.84)	878 (84)	0.96 (0.81-1.15)	867 (80)	0.79 (0.68-0.93)
Missing	1,133,650	2,431,096	5,824		552		516	
Age at first birth (parous women)								
<30	1,461,227 (83)	2,627,722 (83)	5,894 (83)	1.0 (Reference)	686 (79)	1.0 (Reference)	660 (78)	1.0 (Reference)
≥30	308,778 (17)	526,043 (17)	1,197 (17)	1.24 (1.16-1.33)	179 (21)	1.72 (1.44-2.06)	183 (22)	1.74 (1.45-2.07)
Missing	32,548	61,087	159		13		24	
Current HT use at start of follow-up‖								
No	1,797,148 (72)	3,201,220 (74)	7,183 (69)	1.0 (Reference)	683 (64)	1.0 (Reference)	767 (67)	1.0 (Reference)
Yes								
No known hysterectomy	455,417 (18)	744,216 (17)	2,223 (21)	1.17 (1.11-1.23)	265 (25)	1.46 (1.25-1.70)	287 (25)	1.29 (1.11-1.50)
Reported hysterectomy	231,739 (9)	383,729 (9)	974 (9)	0.98 (0.91-1.05)	121 (11)	1.26 (1.03-1.54)	84 (7)	0.74 (0.58-0.93)
Missing	383,762	664,622	1,732		205		191	

*Multiple observations per woman possible in the total population but only one case observation per woman.

†Adjusted for age at start of follow-up (5-y categories), white race, family history of breast cancer, and history of prior breast procedure (that is, surgery, aspirate, or nonaspirate biopsy).

‡Additionally adjusted for BMI and current HT use at the time of the most recent mammogram.

§BI-RADS scale: 1, almost entirely fat; 2, scattered fibroglandular densities; 3, heterogeneously dense; 4, extremely dense.

‖Time axis truncated at 5 y (maximum) after the first eligible mammogram during the study period due to violations of proportional hazards assumptions at later time points.

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

Greater differences between histologic subtypes were noted in associations with parity and age at first birth. Compared with nulliparous women, women who reported at least one prior full-term birth had a significantly reduced risk of IDC (HR = 0.80; 95% CI, 0.76-0.84) and IDLC (HR = 0.79; 95% CI, 0.68-0.93). No association was observed between parity and risk of ILC; however, among parous women, those who had their first birth at or after age 30 years experienced a significantly increased risk of ILC (HR = 1.72; 95% CI, 1.44-2.06). Having a later age at first birth was similarly associated with an increased risk of IDLC (HR = 1.74; 95% CI, 1.45-2.07) but was less strongly associated with risk of IDC (HR = 1.24; 95% CI, 1.16-1.33). Analysis of partial likelihoods indicated that observed differences in HRs across subtypes were statistically significant with respect to age at first birth ($P < 0.01$) but not parity ($P = 0.11$).

Differences between subtypes were also noted in associations with HT use. Overall, HT use was associated with an increased risk of all three histologic subtypes; however, significant differences in subtype-specific associations with HT use were noted when stratifying HT users according to hysterectomy status ($P_{heterogeneity} < 0.01$). HT users who reported having had a prior hysterectomy (that is, those HT users likely to be using ET formulations) had an increased risk of ILC (HR = 1.26; 95% CI, 1.03-1.54) but not other subtypes. Although HT users who did not report a prior hysterectomy had a significantly increased risk of all three subtypes compared women who were not HT users at the start of study follow-up, this association was strongest with respect to risk of ILC (HR = 1.46; 95% CI, 1.25-1.70) and was less pronounced with respect to risk of IDC (HR = 1.17; 95% CI, 1.11-1.23). This increased risk among HT users who did not report a prior hysterectomy was slightly stronger with respect to all three subtypes when limited to women with a BMI of <25 kg/m^2 (HR_{IDC} = 1.27; 95% CI, 1.16-1.40; HR_{ILC} = 1.67; 95% CI, 1.27-2.19; HR_{IDLC} = 1.45; 95% CI, 1.12-1.89); however, interaction by BMI was not statistically significant for any histologic subtype regardless of prior hysterectomy status (data not shown).

Discussion

In this large cohort analysis, we observed several similarities in risk factor associations for breast cancers with ductal, lobular, and a mix of ductal and lobular histologic features. In particular, we found that family history and increasing breast density were similarly positively associated with breast cancer risk across histologic subtypes, even after stratifying by age group. Although still similar in directionality, associations with age at first birth, BMI, and HT use exhibited greater differences in magnitude across subtypes.

The limitations of this analysis should be considered before interpreting these findings. Because the BCSC is not a true prospective cohort with complete follow-up, incomplete case ascertainment could result if women in the study population were diagnosed with breast cancer after moving outside the area covered by the BCSC. We expect the effect of bias due to out-migration to be small; in an exploratory analysis, we restricted follow-up to the 24-month interval following a screening mammogram (thereby reducing the opportunity for out-migration) and found almost no change in effect estimates. Because classification of tumor histology by the BCSC is taken from pathology reports submitted by cancer registries and hospitals to each BCSC site, without centralized review, misclassification of case subtypes is also possible; such misclassification, however, is likely nondifferential with respect to the exposures examined here. Potential biases and shortcomings in exposure information present additional limitations. Misclassification of BI-RADS categories could lead to an overestimation or underestimation of the association between breast density and the risk of histologic types of breast cancer. A continuous measure of breast density might have made these associations more precise. With the exception of breast density data, risk factor information are collected by the BCSC from questionnaires self-administered at the time of screening mammography. For this reason, the scope of ascertained exposures is limited and data are subject to errors in recall; however, any bias attributable to errors in recall is likely nondifferential because questionnaires are administered before the mammogram is conducted. The substantial degree of missing data for some of the collected exposure variables could also be a source of bias. In particular, BMI is missing on 43% of mammograms included in the study population, primarily because this information was not collected by all BCSC sites for the full duration of the study period. To assess the potential effect of such missingness on study findings, we constructed multiple imputation models for each analysis and found that the results based on multiple imputation were not appreciably different from primary analyses (data not shown).

The results of this analysis are consistent with the limited existing literature on risk factor associations by histologic subtype of breast cancer. Risk factors for IDC observed here are similar to those reported in studies of breast cancer overall. Specifically, family history of breast cancer, especially in women age <50 years, and high breast density were strongly associated with risk of IDC, whereas less pronounced but still significant associations were observed with respect to parity, age at first birth, and HT use. Also consistent with prior studies of breast cancer overall, associations between BMI and the risk of IDC were modified by age and HT use, such that BMI was weakly inversely associated with risk in women age <50 years and positively associated with risk among women age ≥50 years who were not HT users. Similar associations with family history (14, 15, 18), parity (9, 12, 14-16, 20), age at first birth (9, 15, 16, 20), and HT use (14, 21) have been reported by prior studies looking specifically at IDC. Stronger associations between current HT use and risk of IDC have been reported by studies

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

able to distinguish former HT users from never users (15, 17, 19).

Relatively few studies have characterized risk factor relationships for the less predominant ILC subtype, and most such studies have focused on hormonal exposures and reproductive history. Most consistently, prior studies have reported a 1.8- to 3.9-fold increased risk of ILC among current users of CHT (10, 14, 15, 17, 19, 21, 37-39), with most studies noting a stronger association between HT use and risk of ILC than IDC (10, 14, 15, 19, 21, 37-39). In a large case-control study, Li et al. (10) reported a 3.1-fold (95% CI, 1.9-5.2) increased risk of ILC among women who were current users of CHT, compared with a 1.7-fold (95% CI, 1.2-2.4) increased risk of IDC. In line with this literature, we found a significantly increased risk of ILC among current users of HT that was stronger than that for other subtypes. Although information on duration of use, past use, and specific preparation of HT were not available in the present analysis, the fact that this association was less pronounced among women who reported having had a prior hysterectomy is consistent with findings that use of CHT, not ET, is most strongly associated with risk (40-42). Most, although not all, studies not stratified by histologic type suggest there is, if anything, a reduced risk of breast cancer associated with use of ET (41, 42), which is consistent with what we observed with the IDC and IDLC subtypes. The few studies that have looked specifically at current use of ET in relation to histologic subtype–specific breast cancer risk have been inconclusive but, on the whole, suggest a very modest positive association with risk of ILC comparable with that observed here (10, 15, 17, 19). In a recent meta-analysis, Reeves et al. (22) reported a very modest increased risk of IDC among current users of ET (RR = 1.10; 95% CI, 1.05-1.15) and a more pronounced association with respect to the risk of ILC [Relative risk (RR) = 1.42; 95% CI, 1.27-1.57]; associations with both subtypes were considerably weaker than associations between use of CHT and subtype-specific risk. With respect to reproductive history, we found that late age at first birth was more strongly associated with the risk of ILC than with the risk of IDC, which is consistent with several (9, 12, 14, 20, 23), but not all (11, 15, 16), prior studies. Given that ILC is almost always hormone receptor positive, the fact that HT use and age at first birth were most strongly associated with the risk of this subtype may reflect a greater hormone sensitivity of ILC. Differences between subtypes in the role of reproductive and hormonal risk factors may also stem from the fact that certain hormonal exposures tend to have greater effects in promoting lobular differentiation than in promoting differentiation in ductal breast tissue (43).

The literature characterizing risk factors for IDLC is even sparser than that for ILC. An inverse association between parity and risk of IDLC similar to that found here has been reported by five prior studies (12-14, 16, 20), and two prior studies have reported an increased risk of IDLC among current users of CHT more pronounced than for ILC (14, 17). No other risk factor relationships have been consistently reported for IDLC. The lack of consistency in the limited literature on this subtype may be a reflection of small numbers but may also reflect heterogeneity within this subtype. Specifically, under the *International Classification of Diseases for Oncology* classification system, a tumor may be considered IDLC if it contains both a ductal and a lobular component, but only one of these two components must be invasive (44). In a recent analysis, Beaber et al. (16) assessed the risk factors for IDLC using a more restrictive case definition such that all IDLC cases were deemed to have invasive ductal and invasive lobular components after a centralized review of pathology reports and/or tumor tissue; results from that study indicated a reduced risk of IDLC associated with parity that was similar in magnitude to associations with IDC and ILC, a 2.1-fold (95% CI, 1.0-4.3) increased risk of IDLC in women with a first birth at age 30 years or greater versus age 20 years or younger that was stronger than for other subtypes, and differences in associations with age at menarche and breastfeeding. In the present analysis, we found that risk factor associations with the IDLC subtype resembled those with the IDC subtype for some variables (e.g., parity, BMI, and HT use) but more closely resembled those with respect to the ILC subtype for other variables (e.g., age at first birth).

In contrast to the differences noted between subtypes in association with HT use, reproductive history, and BMI, associations with family history and breast density were markedly similar across histologic subtypes. Consistent with results presented here, three additional recent studies have reported similar associations between family history of breast cancer and risk of IDC, ILC, and IDLC (14, 15, 18). One prior study reported no significant difference in breast density among women subsequently diagnosed with breast tumors of ductal, lobular, or mixed histology (measured by mean percent density, mean dense area, or mean nondense area; ref. 45). In line with this report, we observed a consistent pattern of increasing risk with increasing breast density across all subtypes. These associations were largely confined to women age <65 years, although, relative to women with a BI-RADS score of 2 (that is, scattered fibroglandular densities), women with a BI-RADS score of 1 (that is, almost entirely fat) experienced a significantly reduced breast cancer risk that was similar in magnitude across age strata and across subtypes. Although the mechanisms through which breast density affects breast cancer risk are not fully understood, it is plausible that associations with breast density could vary across histologic subtypes. Given that clinical trials of HT use have documented a significant increase in breast density associated with the use of CHT (46, 47), and given the association between HT use and risk of ILC in particular, it might be expected that women with ILC would have more elevated breast density than noncases or cases of IDC or IDLC. Given also that detection of ILC on mammography is more difficult because tumors of this type

Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

exhibit a growth pattern characterized by single rows or sheets of malignant cells rather than a discrete mass, it is plausible that extensive breast density could have a more profound adverse effect on the detection of ILC than on the detection of IDC or IDLC; thus, masking bias could be of particular concern in analyses looking at ILC. However plausible, our findings suggest that the mechanisms responsible for the association between breast density and breast cancer risk do not have a strong influence on tumor histology.

The pronounced biological and clinical distinctions between breast cancers with ductal, lobular, and mixed histologies suggest distinct etiologies and, therefore, support the need to separately assess risk factors for disease by histologic subtype. The findings of this study further reinforce the notion that breast cancer is a heterogeneous disease. However, although the present analysis supports previously reported differences between histologic subtypes with respect to such HT use and reproductive history, it also suggests that the mechanisms of action behind associations between family history, breast density, and breast cancer risk may have less bearing on tumor histology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank the participating women, mammography facilities, and radiologists for the data they have provided for this study. A list of the BCSC investigators and procedures for requesting BCSC data for research purposes are provided at: http://breastscreening.cancer.gov/.

Grant Support

National Cancer Institute–funded BCSC cooperative agreement (U01CA63740, U01CA86076, U01CA86082, U01CA63736, U01CA70013, U01CA69976, U01CA63731, U01CA70040). The collection of cancer data used in this study was supported in part by several state public health departments and cancer registries throughout the United States. For a full description of these sources, please see: http://breastscreening.cancer.gov/work/acknowledgement.html. This publication was supported by grant number T32 CA09168 from the National Cancer Institute, NIH. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute, NIH.

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Received 02/23/2010; revised 03/30/2010; accepted 04/05/2010; published OnlineFirst 05/25/2010.

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Published OnlineFirst May 25, 2010; DOI: 10.1158/1055-9965.EPI-10-0188

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Risk Factors for Ductal, Lobular, and Mixed Ductal-Lobular Breast Cancer in a Screening Population

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Cancer Epidemiol Biomarkers Prev 2010;19:1643-1654. Published OnlineFirst May 25, 2010.