Original Contribution

Epidemiologic Risk Factors for In Situ and Invasive Breast Cancers Among Postmenopausal Women in the National Institutes of Health-AARP Diet and Health Study

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Comparing risk factor associations between invasive breast cancers and possible precursors may further our understanding of factors related to initiation versus progression. Accordingly, among 190,325 postmenopausal participants in the National Institutes of Health-AARP Diet and Health Study (1995–2011), we compared the association between risk factors and incident ductal carcinoma in situ (DCIS; $n = 1,453$) with that of risk factors and invasive ductal carcinomas ($n = 7,525$); in addition, we compared the association between risk factors and lobular carcinoma in situ (LCIS; $n = 186$) with that of risk factors and invasive lobular carcinomas ($n = 1,191$). Hazard ratios and 95% confidence intervals were estimated from multivariable Cox proportional hazards regression models. We used case-only multivariable logistic regression to test for heterogeneity in associations. Younger age at menopause was associated with a higher risk of DCIS but lower risks of LCIS and invasive ductal carcinomas (P for heterogeneity < 0.01). Prior breast biopsy was more strongly associated with the risk of LCIS than the risk of DCIS (P for heterogeneity $= 0.04$). Increased risks associated with use of menopausal hormone therapy were stronger for LCIS than DCIS (P for heterogeneity $= 0.03$) and invasive lobular carcinomas (P for heterogeneity < 0.01). Associations were similar for race, age at menarche, age at first birth, family history, alcohol consumption, and smoking status, which suggests that most risk factor associations are similar for in situ and invasive cancers and may influence early stages of tumorigenesis. The differential associations observed for various factors may provide important clues for understanding the etiology of certain breast cancers.

breast cancer; DCIS; histology; LCIS; precursors; risk factors

Abbreviations: BMI, body mass index; CI, confidence interval; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy; NIH, National Institutes of Health.

Most invasive breast carcinomas arise from well-characterized precursors, such as ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). Statistics from the Surveillance, Epidemiology, and End Results Program show that between 2004 and 2008, DCIS accounted for 83.8% of all breast carcinomas in situ, with LCIS accounting for 11.4% (1). Invasive ductal carcinoma (IDC) and invasive lobular carcinoma (ILC) accounted for 70.6% and 8.3% of all invasive breast cancers, respectively (1).

Multiple studies suggest that DCIS is a nonobligate precursor lesion and that most invasive breast tumors arise and develop from this precursor lesion (2, 3). In contrast, LCIS is thought to be a more general marker of the risk of invasive breast cancer, because many of the cancers that occur after a diagnosis of LCIS are of ductal histological type (2). Results from molecular studies that suggested a clonal link of LCIS with ILC have renewed interest in LCIS as a nonobligate precursor lesion, as well as a risk indicator (4).

Comparative analyses of the associations of risk factors for breast cancer with in situ and with invasive carcinomas have not been definitively established. Studies of etiological heterogeneity

in which researchers compare risk factors for in situ versus those for invasive breast cancer, particularly with additional differentiation by ductal versus lobular histological type, are limited (5–7). Although breast cancer risk factors are likely to be important for tumor initiation, risk factors such as menopausal hormone therapy (MHT) (8) may also contribute to tumor progression and may show differential associations with invasive breast cancer compared with DCIS and LCIS (9). Identifying breast cancer risk factor differences and similarities between and within in situ and invasive carcinomas may help to further our understanding of disease etiology and progression.

The National Institutes of Health (NIH)-AARP Diet and Health Study is a large prospective cohort study that facilitates the analysis of risk relationships with specific tumor types, including in situ versus invasive carcinomas. We previously reported differences in risk factor associations by invasive histological types of breast carcinoma in this cohort (10, 11). In the present study, we aimed to expand these findings. First, we compared risk factor associations with DCIS to those with LCIS. We then compared risk factor associations for DCIS and LCIS with those observed for invasive breast tumors.

METHODS

Study population

We conducted this study using participants from the NIH-AARP Diet and Health Study, a longitudinal cohort established in 1995–1996 as previously described (12). Briefly, self-administered, baseline questionnaires regarding health and nutrition were mailed to 3.5 million members of the AARP (formerly, the American Association of Retired Persons) who resided in 6 states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia; and Detroit, Michigan). These regions were chosen for their large AARP populations and cancer registries with case ascertainment rates of 90% or more. Of this population, 566,398 satisfactorily completed and returned the questionnaire (12). We excluded participants with questionnaires completed by proxy (*n* = 15,760), men (*n* = 325,171), women who had a self-reported personal history of cancer other than nonmelanoma skin cancer (*n* = 23,998), premenopausal women (*n* = 9,418), women who reported extreme values for caloric intake (defined as >2 interquartile ranges above the 75th percentile or below the 25th percentile of log-transformed intake; *n* = 1,703), and women who had no follow-up time (*n* = 23). The final analytic population included 190,325 postmenopausal women who were cancer-free at baseline and who were followed up through December 31, 2011. A second questionnaire was administered to enrolled participants between 1996 and 1997, and additional risk factor data were collected (*n* = 120,780). The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute. All participants gave informed consent by virtue of completing and returning the questionnaire.

Risk factors for breast cancer

All data on risk factors were self-reported at baseline except a history of mammography, which was self-reported in the sec-

ond questionnaire (i.e., at least 1 mammogram in the past 3 years; no or yes). Risk factors included age at study entry (<55, 55–59, 60–64, 65–69, or ≥70 years), race (white or nonwhite), age at menarche (≤12, 13–14, or ≥15 years), age at first birth (<20, 20–24, 25–29, or ≥30 years or nulliparous), and type of menopause (natural, which was further stratified into categories of <45, 45–49, 50–54, or ≥55 years; surgical, which was defined as cessation of menstrual cycle because of a surgical procedure; and medical or unknown, which was defined as cessation of menstrual cycle because of medical reasons or information not captured in the questionnaire). Use of MHT was defined as a combination of use of any MHT formulation and duration of use (never; former; current, <5 years; current, 5–9 years; or current, ≥10 years). Additional risk factors that were investigated included a family history of breast cancer in a first-degree female relative (no or yes), past breast biopsy (no or yes), alcohol consumption during the 12 months before completion of the questionnaire (0, 0.01–10.00, 10.01–20.00, or ≥20.01 g/day; estimated from the amount and frequency consumed, as previously described) (13), smoking status (never, former, or current), body mass index (BMI (calculated as weight (kg)/height (m)^2) <18.5, 18.5–24.9, 25–29.9, 30.0–34.9, or ≥35.0) (14), educational level (no college vs. some college or more), and frequency of vigorous physical activity (never or rarely, 1–3 times/month, 1–2 times/week, 3–4 times/week, or ≥5 times/week).

Ascertainment of breast cancer

Incident cases of in situ and invasive breast carcinomas were identified through probabilistic linkage to cancer registries in the 8 states in the cohort, as well as 3 in nearby states to which participants tended to move (Arizona, Nevada, and Texas). In a previous validation study of this cohort, Michaud et al. (15) estimated that 90% of all incident cancers were reported in states in which participants resided at baseline. Behavior and histology codes from the *International Classification of Diseases for Oncology, Third Edition*, were used to define invasive (behavior code 3), ductal (histology code 8500/3 or 8523/3), and lobular (histology code 8520/3 or 8524/3) histological types (16). To identify in situ disease that corresponded with the invasive codes included in this analysis, we defined DCIS and LCIS using the same histology codes and with the behavior code 2.

Statistical analysis

We estimated hazard ratios and 95% confidence intervals using Cox proportional hazards regression models with age as the time metric. Women were observed from the date on which the 1995–1996 study questionnaire was returned until the earliest of the following events occurred: movement out of the defined catchment area, death, diagnosis, or the end of follow-up (December 31, 2011). We used the Wald test to test for a linear trend between risk factors for breast cancer and risk of breast cancer. In multivariable models in which we evaluated histology-specific risk, women were censored at the date of diagnosis of other histological subtypes of breast cancer. Case-only logistic regression was used to test for statistical heterogeneity in the associations of risk factors with DCIS versus those with LCIS; associations with DCIS versus

those with IDC; and association with LCIS versus ILC. All multivariable models included adjustments for established risk factors for breast cancer that were determined in previous studies of postmenopausal breast cancer (10). Participants with missing data on covariates were retained in a designated "unknown" category in multivariable models. We repeated sensitivity analyses in a subset of women who completed the second questionnaire and who had a mammogram within 3 years of it (n = 120,780). In additional sensitivity analyses, we examined whether the relationship between BMI and risk of the histologic subtypes varied by MHT use. We conducted analyses using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina). Statistical tests were 2-sided. P values ≤ 0.05 were considered statistically significant.

RESULTS

Characteristics of study participants

A total of 1,453 DCIS, 186 LCIS, 7,525 IDC, and 1,191 ILC were diagnosed among these 190,325 postmenopausal women during an average of 13.3 (standard deviation, 4.3) years of follow-up. The distributions of breast cancer risk factors and patient characteristics stratified by cancer histological subtype are presented in Web Table 1 (available at https://academic.oup.com/aje).

Participant characteristics and risks of DCIS and LCIS

Relationships of participant characteristics with risks of DCIS and LCIS are shown in Table 1. We observed significant heterogeneity in risk factor associations of DCIS and of LCIS with age at menopause, MHT use, and a history of breast biopsy (Table 1). Specifically, compared with women whose age at natural menopause was 50–54 years, those who were younger natural menopause (<45 years) had a higher risk of DCIS (hazard ratio (HR) = 1.30; 95% confidence interval (CI): 1.06, 1.61) but not LCIS (HR = 0.71; 95% CI: 0.37, 1.34; P for heterogeneity < 0.01). Furthermore, the higher risk associated with MHT use was significantly stronger for LCIS than for DCIS (P for heterogeneity = 0.03). Current MHT use was associated with at least 2.5-fold higher risk of LCIS, irrespective of duration of use (for <5 years of use, HR = 2.59, 95% CI: 1.65, 4.05; for 5–9 years of use, HR = 3.63, 95% CI: 2.36, 5.59; and for ≥10 years of use, HR = 2.71, 95% CI: 1.70, 4.30). In contrast, the hazard ratios for the association between current MHT use and DCIS were 1.44 (95% CI: 1.22, 1.71), 1.76 (95% CI: 1.50, 2.07), and 1.57 (95% CI: 1.35, 1.82) for <5, 5–9, and ≥10 years of use, respectively. Women who had a history of a previous breast biopsy were more likely to be diagnosed with LCIS (HR = 2.21; 95% CI: 1.65, 2.96) than with DCIS (HR = 1.54, 95% CI: 1.38, 1.72; P for heterogeneity = 0.04) (Table 1). Differences between risk factor associations for DCIS and LCIS were not observed for age at entry, race, age at menarche, age at first birth, a family history of breast cancer, or alcohol or smoking (for DCIS vs. LCIS, P for heterogeneity > 0.05 for each risk factor). Furthermore, differences were not observed for educational level and frequency of vigorous physical activity (data not shown).

Participant characteristics and risk of in situ versus invasive breast cancers

Next, we examined the relationships of participant characteristics with risks of in situ breast cancers and invasive breast cancer. Similar patterns of association for the risks of DCIS and IDC were observed for most risk factors, including age, race, age at menarche, age at first birth, MHT use, a family history of breast cancer, and histories of alcohol and smoking (P for heterogeneity > 0.05) (Table 1). Similar patterns were also observed for educational level and frequency of vigorous physical activity (data not shown). Younger age at natural menopause was associated with a higher risk of DCIS, as noted before, but with a lower risk of IDC (P for heterogeneity < 0.01). A slightly stronger association with a history of breast biopsy was observed for the risk of DCIS (HR = 1.54, 95% CI: 1.38, 1.72) compared with the risk of IDC (HR = 1.38, 95% CI: 1.31, 1.45; P for heterogeneity = 0.05).

In a similar manner, when we compared risk relationships for LCIS and ILC, we observed few differences. Heterogeneity in the risk of LCIS versus ILC was suggested for age at entry (P for heterogeneity < 0.01). In addition, MHT use was more strongly associated with LCIS than with ILC (P for heterogeneity < 0.01). Whereas risk of LCIS increased more than 2.5-fold with current MHT use, the hazard ratios for the association between ILC and with current MHT use were 1.38 (95% CI: 1.15, 1.66), 1.42 (95% CI: 1.18, 1.71), and 1.35 (95% CI: 1.14, 1.59) for <5, 5–9, and ≥10 years of use, respectively (Table 1).

Sensitivity analyses

As has been previously shown in this study population (17) and in other study populations (18, 19), elevated BMI is associated with a higher risk of postmenopausal breast cancer that is particularly strong among those who have never used MHT (17, 20). Consistent with these studies, we also observed a significant interaction between BMI and MHT use with respect to risk (for current vs. noncurrent MHT users, P for interaction < 0.01). Therefore, we investigated the relationships between BMI and the risks of in situ and invasive breast cancers stratified by MHT use (Table 2). In general, risks of in situ and invasive ductal and lobular breast cancers were greatest among overweight and obese women compared with lean women (Table 2), particularly among women who had never used MHT (for all histological types, P for trend <0.01). Among never users of MHT, the magnitude of association was strongest for LCIS (for BMI ≥35 versus 18.5–24.9, HR = 3.08, 95% CI: 1.26, 7.54). The strength of this association was higher among former users of MHT, but no clear pattern of association was observed among current MHT users (Table 2).

To attempt to account for potential bias as a result of screening practices that may have influenced risk factor relationships within this population, we conducted analyses among the 120,780 women who had a mammogram in the 3 years before administration of the 1996–1997 questionnaire (Table 3). Overall, the findings within this population were consistent with those in the full cohort, although the P values for heterogeneity were somewhat attenuated by the reduced sample size. It is notable

Table 1. Associations of Participant Characteristics With Risks of In Situ and Invasive Breast Cancers, by Histological Type, Among Postmenopausal Women (n = 190,325), National Institutes of Health-AARP Diet and Health Study Cohort, 1995–2011[a]

Characteristic	DCIS (n = 1,453)		LCIS (n = 186)		DCIS vs. LCIS P for Heterogeneity	IDC (n = 7,525)		DCIS vs. IDC P for Heterogeneity	ILC (n = 1,191)		LCIS vs. ILC P for Heterogeneity
	HR	95% CI	HR	95% CI		HR	95% CI		HR	95% CI	
Age at entry, years					0.35			0.68			<0.01
<55	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
55–59	1.03	0.83, 1.27	0.86	0.53, 1.37		1.12	1.02, 1.23		0.92	0.72, 1.17	
60–64	1.09	0.87, 1.37	1.06	0.61, 1.85		1.16	1.05, 1.28		1.05	0.81, 1.36	
65–69	1.15	0.90, 1.47	1.04	0.54, 2.00		1.24	1.11, 1.39		1.24	0.95, 1.64	
≥70	1.08	0.73, 1.60	1.67	0.60, 4.71		1.29	1.10, 1.53		1.07	0.70, 1.62	
P for trend		0.24		0.54			<0.01			0.03	
Race					0.83			0.06			0.35
White	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Nonwhite	1.07	0.90, 1.28	1.03	0.62, 1.71		0.90	0.83, 0.97		0.79	0.64, 0.99	
Age at menarche, years					0.36			0.24			0.57
≤12	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
13–14	1.06	0.95, 1.18	0.85	0.62, 1.16		0.98	0.93, 1.02		1.04	0.92, 1.18	
≥15	0.83	0.68, 1.01	0.94	0.56, 1.58		0.91	0.84, 0.99		0.97	0.78, 1.19	
P for trend		0.42		0.46			0.03			0.89	
Age at first birth, years					0.80			0.06			0.62
<20	0.85	0.72, 1.00	0.91	0.57, 1.44		0.95	0.89, 1.02		0.78	0.64, 0.94	
20–24	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
25–29	1.18	1.03, 1.37	1.40	0.95, 2.06		1.05	0.99, 1.12		1.38	1.19, 1.60	
≥30 or nulliparous	1.39	1.22, 1.59	1.37	0.94, 2.00		1.21	1.14, 1.28		1.43	1.23, 1.65	
P for trend		<0.01		0.03			<0.01			<0.01	
Age at menopause, years					<0.01			<0.01			0.06
<45	1.30	1.06, 1.61	0.71	0.37, 1.34		0.77	0.69, 0.85		0.77	0.60, 0.99	
45–49	1.00	0.84, 1.18	0.61	0.39, 0.96		0.93	0.87, 1.00		0.83	0.70, 0.99	
50–54	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
≥55	1.23	0.99, 1.53	0.70	0.37, 1.33		1.20	1.10, 1.32		1.19	0.96, 1.48	
Surgical	0.93	0.81, 1.08	0.41	0.28, 0.59		0.74	0.70, 0.79		0.72	0.62, 0.84	
Unknown	1.71	1.31, 2.22	1.04	0.53, 2.05		0.91	0.79, 1.05		0.68	0.46, 1.02	
P for trend		0.63		<0.01			<0.01			<0.01	

Table continues

Table 1. Continued

Characteristic	DCIS (n = 1,453)		LCIS (n = 186)		DCIS vs. LCIS P for Heterogeneity	IDC (n = 7,525)		DCIS vs. IDC P for Heterogeneity	ILC (n = 1,191)		LCIS vs. ILC P for Heterogeneity
	HR	95% CI	HR	95% CI		HR	95% CI		HR	95% CI	
MHT use					0.03			0.13			<0.01
Never	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Former	1.14	0.93, 1.39	1.60	0.88, 2.92		1.05	0.96, 1.14		0.85	0.67, 1.07	
Current (<5 years)	1.44	1.22, 1.71	2.59	1.65, 4.05		1.22	1.13, 1.32		1.38	1.15, 1.66	
Current (5–9 years)	1.76	1.50, 2.07	3.63	2.36, 5.59		1.41	1.31, 1.52		1.42	1.18, 1.71	
Current (≥10 years)	1.57	1.35, 1.82	2.71	1.70, 4.30		1.35	1.26, 1.44		1.35	1.14, 1.59	
P for trend	<0.01		<0.01			<0.01			<0.01		
Family history of breast cancer					0.34			0.19			0.92
No	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	1.63	1.42, 1.86	1.15	0.76, 1.75		1.47	1.38, 1.56		1.28	1.09, 1.50	
Breast biopsy					0.04			0.05			0.08
No	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	1.54	1.38, 1.72	2.21	1.65, 2.96		1.38	1.31, 1.45		1.60	1.42, 1.80	
Alcohol consumption, g/day					0.46			0.39			0.60
0	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
0.01–10.00	1.05	0.93, 1.19	1.27	0.88, 1.83		1.03	0.97, 1.08		1.08	0.94, 1.24	
10.01–20.00	1.02	0.84, 1.25	1.55	0.92, 2.63		1.11	1.02, 1.21		1.13	0.91, 1.40	
≥20.01	1.08	0.87, 1.34	1.11	0.57, 2.14		1.26	1.15, 1.38		1.43	1.15, 1.79	
P for trend	0.50		0.33			<0.01			<0.01		
Smoking status					0.78			0.52			0.38
Never	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Former	1.03	0.92, 1.16	0.89	0.64, 1.23		1.11	1.05, 1.17		1.05	0.93, 1.20	
Current	1.02	0.87, 1.20	0.84	0.52, 1.35		1.13	1.05, 1.21		1.26	1.07, 1.50	
P for trend	0.62		0.41			<0.01			0.01		

Abbreviations: CI, confidence interval; DCIS, ductal carcinoma in situ; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy.

[a] All analyses were adjusted for age at entry, race, body mass index, smoking status, alcohol consumption, age at menarche, age at first birth, age at menopause, MHT use and duration of use, past breast biopsy, family history of breast cancer in a first-degree female relative, educational level, and frequency of vigorous physical activity.

Table 2. Associations of Body Mass Index With Risks of In Situ and Invasive Breast Cancers, by Menopausal Hormone Therapy Use and Histological Type, Among Postmenopausal Women, National Institutes of Health-AARP Diet and Health Study Cohort, 1995–2011[a]

MHT Use Category and BMI[b]	Total	DCIS			LCIS			DCIS vs. LCIS P for Heterogeneity	IDC			DCIS vs. IDC P for Heterogeneity	ILC			LCIS vs. ILC P for Heterogeneity
		No.	HR	95% CI	No.	HR	95% CI		No.	HR	95% CI		No.	HR	95% CI	
Overall[c]	190,325	1,453			186			0.28	7,525			0.65	1,191			0.45
<18.5			0.78	0.46, 1.32		—[d]				0.80	0.63, 1.01			0.58	0.30, 1.12	
18.5–24.9			1.00	Referent		1.00	Referent			1.00	Referent			1.00	Referent	
25.0–29.9			1.07	0.95, 1.21		0.85	0.60, 1.22			1.12	1.06, 1.18			1.08	0.94, 1.23	
30.0–34.9			1.09	0.93, 1.29		1.41	0.92, 2.15			1.24	1.16, 1.33			1.12	0.93, 1.34	
≥35.0			1.25	1.02, 1.54		1.20	0.67, 2.16			1.44	1.32, 1.57			1.25	0.99, 1.57	
P for trend			0.02			0.12				<0.01				0.02		
Never users	87,271	530			47			0.21	3,145			0.97	503			0.42
<18.5			0.74	0.27, 1.99		—[d]				0.95	0.66, 1.35			0.68	0.25, 1.84	
18.5–24.9			1.00	Referent		1.00	Referent			1.00	Referent			1.00	Referent	
25.0–29.9			1.26	1.02, 1.56		1.01	0.45, 2.23			1.27	1.16, 1.39			1.25	1.00, 1.55	
30.0–34.9			1.37	1.06, 1.77		2.00	0.87, 4.65			1.41	1.27, 1.57			1.26	0.96, 1.66	
≥35.0			1.48	1.10, 2.00		3.08	1.26, 7.54			1.62	1.43, 1.83			1.64	1.21, 2.23	
P for trend			<0.01			<0.01				<0.01				<0.01		
Former users	17,690	121			14			0.28	646			0.67	83			0.27
<18.5						—[d]				0.44	0.14, 1.38			1.05	0.14, 7.74	
18.5–24.9			1.00	Referent		1.00	Referent			1.00	Referent			1.00	Referent	
25.0–29.9			1.40	0.89, 2.22		1.44	0.41, 5.12			0.99	0.82, 1.19			1.13	0.66, 1.94	
30.0–34.9			1.91	1.13, 3.23		1.82	0.41, 8.01			1.18	0.94, 1.48			1.62	0.86, 3.08	
≥35.0			1.83	0.93, 3.62						1.50	1.13, 1.99			1.78	0.75, 4.21	
P for trend			0.01			0.92				<0.01				0.06		
Current users	84,820	798			125			0.31	3,723			0.17	604			0.58
<18.5			0.87	0.47, 1.64		—[d]				0.73	0.53, 1.02			0.47	0.17, 1.26	
18.5–24.9			1.00	Referent		1.00	Referent			1.00	Referent			1.00	Referent	
25.0–29.9			0.96	0.82, 1.13		0.79	0.51, 1.21			1.05	0.97, 1.13			0.98	0.81, 1.18	
30.0–34.9			0.83	0.65, 1.07		1.27	0.75, 2.15			1.12	1.01, 1.24			0.96	0.73, 1.26	
≥35.0			0.99	0.71, 1.38		0.70	0.28, 1.76			1.24	1.08, 1.44			0.76	0.49, 1.18	
P for trend			0.40			0.97				<0.01				0.57		

Abbreviations: BMI, body mass index; CI, confidence interval; DCIS, ductal carcinoma in situ; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy.

[a] All analyses were adjusted for age at entry, race, smoking status, alcohol consumption, age at menarche, age at first birth, age at menopause, past breast biopsy, family history of breast cancer in a first-degree female relative, educational level, and frequency of vigorous physical activity.

[b] BMI was calculated as weight (kg)/height (m)^2.

[c] Additionally adjusted for MHT use and duration.

[d] There were an insufficient number of cases to estimate the HR.

Table 3. Associations of Participant Characteristics With Risks of In Situ and Invasive Breast Cancers, by Histological Type, Among Postmenopausal Women Who Have Had a Mammogram (*n* = 120,780)[a], National Institutes of Health-AARP Diet and Health Study Cohort, 1995–2011[b]

Characteristic	DCIS (*n* = 865)		LCIS (*n* = 113)		DCIS vs. LCIS P for Heterogeneity	IDC (*n* = 4,592)		DCIS vs. IDC P for Heterogeneity	ILC (*n* = 734)		LCIS vs. ILC P for Heterogeneity
	HR	95% CI	HR	95% CI		HR	95% CI		HR	95% CI	
Age at entry, years					0.72			0.22			0.94
<55	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
55–59	0.97	0.72, 1.32	1.44	0.68, 3.06		1.09	0.96, 1.25		1.20	0.85, 1.70	
60–64	1.28	0.92, 1.76	1.57	0.68, 3.65		1.14	0.99, 1.31		1.36	0.93, 1.97	
≥65	1.26	0.89, 1.78	1.44	0.57, 3.65		1.24	1.06, 1.44		1.52	1.02, 2.27	
P for trend		0.07		0.58			<0.01			0.03	
Race					0.41			0.29			0.90
White	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Nonwhite	1.08	0.85, 1.38	0.83	0.38, 1.80		0.94	0.84, 1.05		0.86	0.64, 1.14	
Age at menarche, years					0.55			0.24			0.98
≤12	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
13–14	1.11	0.97, 1.28	1.02	0.69, 1.51		0.99	0.94, 1.06		1.02	0.86, 1.17	
≥15	0.83	0.63, 1.08	1.04	0.53, 2.05		0.89	0.80, 0.99		0.96	0.73, 1.25	
P for trend		0.87		0.91			0.12			0.84	
Age at first birth, years					0.29			0.04			0.32
<20	0.79	0.63, 0.98	1.15	0.63, 2.09		0.97	0.89, 1.06		0.76	0.59, 0.98	
20–24	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
25–29	1.21	1.01, 1.45	1.75	1.07, 2.86		1.07	0.98, 1.16		1.42	1.17, 1.71	
≥30 or nulliparous	1.44	1.21, 1.71	1.74	1.08, 2.82		1.24	1.15, 1.34		1.32	1.09, 1.60	
P for trend		<0.01		0.03			<0.01			<0.01	
Age at menopause, years					0.03			<0.01			0.36
<45	1.51	1.15, 1.97	0.77	0.35, 1.73		0.81	0.71, 0.93		0.74	0.53, 1.04	
45–49	1.08	0.87, 1.34	0.62	0.35, 1.12		0.92	0.84, 1.00		0.97	0.78, 1.21	
50–54	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
≥55	1.33	1.00, 1.75	0.59	0.25, 1.39		1.22	1.09, 1.36		1.34	1.03, 1.75	
Surgical	1.01	0.84, 1.21	0.41	0.25, 0.67		0.71	0.66, 0.77		0.75	0.62, 0.91	
Unknown	1.55	1.07, 2.23	0.78	0.30, 1.99		0.93	0.77, 1.12		0.60	0.34, 1.03	
P for trend		0.28		0.03			<0.01			0.08	
MHT use					0.06			0.23			0.01
Never	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Former	1.17	0.90, 1.52	1.70	0.76, 3.79		1.08	0.97, 1.21		0.95	0.71, 1.28	
Current (<5 years)	1.56	1.26, 1.95	2.72	1.47, 5.02		1.23	1.12, 1.35		1.42	1.13, 1.80	
Current (5–9 years)	1.89	1.53, 2.32	4.62	2.66, 8.05		1.49	1.36, 1.64		1.50	1.19, 1.89	

Table 3. Continued

Characteristic	DCIS (n = 865)		LCIS (n = 113)		DCIS vs. LCIS P for Heterogeneity	IDC (n = 4,592)		DCIS vs. IDC P for Heterogeneity	ILC (n = 734)		LCIS vs. ILC P for Heterogeneity
	HR	95% CI	HR	95% CI		HR	95% CI		HR	95% CI	
Current (≥10 years)	1.59	1.30, 1.93	3.32	1.83, 6.01		1.43	1.32, 1.56		1.42	1.15, 1.75	
P for trend		<0.01		<0.01			<0.01			<0.01	
Family history of breast cancer					0.90			0.58			0.47
No	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	1.57	1.32, 1.87	1.43	0.87, 2.35		1.48	1.37, 1.60		1.26	1.03, 1.54	
Breast biopsy					0.22			0.10			0.16
No	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Yes	1.51	1.31, 1.74	2.08	1.42, 3.03		1.34	1.26, 1.43		1.54	1.32, 1.80	
Alcohol consumption, g/day					0.96			0.64			0.95
0	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
0.01–10.00	1.16	0.99, 1.37	1.15	0.73, 1.83		1.05	0.98, 1.13		1.01	0.85, 1.21	
10.01–20.00	1.29	1.00, 1.65	1.40	0.71, 2.73		1.13	1.01, 1.26		1.12	0.86, 1.47	
≥20.01	1.20	0.91, 1.59	1.11	0.49, 2.50		1.22	1.09, 1.37		1.28	0.96, 1.69	
P for trend		0.06		0.53			<0.01			0.09	
Smoking status					0.29			0.71			0.30
Never	1.00	Referent	1.00	Referent		1.00	Referent		1.00	Referent	
Former	1.06	0.91, 1.22	0.74	0.49, 1.13		1.11	1.04, 1.18		1.10	0.93, 1.29	
Current	1.03	0.83, 1.28	0.81	0.43, 1.50		1.14	1.04, 1.25		1.27	1.01, 1.58	
P for trend		0.57		0.27			<0.01			0.04	

Abbreviations: BMI, body mass index; CI, confidence interval; DCIS, ductal carcinoma in situ; HR, hazard ratio; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma in situ; MHT, menopausal hormone therapy.

[a] All analyses were adjusted for age at entry, race, body mass index, smoking status, alcohol consumption, age at menarche, age at first birth, age at menopause, MHT use and duration of use, past breast biopsy, family history of breast cancer in a first-degree female relative, educational level, and frequency of vigorous physical activity.

[b] The women had a mammogram within the 3 years before completion of the second study follow-up questionnaire. Follow-up for this analysis involved mammographic screening data captured on the second study questionnaire, and follow-up for this analysis began on the date on which that questionnaire was returned.

that among this population, early age at natural menopause was still associated with a higher risk of DCIS but not LCIS (for DCIS, HR = 1.51, 95% CI: 1.15, 1.97; *P* for heterogeneity = 0.03) or IDC (HR = 0.81, 95% CI: 0.71, 0.93; *P* for heterogeneity < 0.01). In addition, current MHT use was still most strongly associated with a higher risk of LCIS than of ILC (*P* for heterogeneity = 0.01).

DISCUSSION

Within the NIH-AARP Diet and Health Study, we identified many similarities in and a few differences between associations of breast cancer risk factors with incident in situ and invasive breast cancers among postmenopausal women. Although associations were similar for race, age at menarche, age at first birth, a family history of breast cancer, and lifestyle factors (BMI, alcohol use, cigarette smoking status, and level of physical activity), we observed significant heterogeneity in risk associated with age at natural menopause, MHT use, and a history of breast biopsy. In particular, higher risks associated with MHT use and previous breast biopsy were stronger for LCIS than for ILC and DCIS, respectively. These findings suggest that most risk factors for breast cancer act at the precursor stage, but there may be a few with differential associations for in situ versus invasive breast cancers.

There have been few longitudinal studies in which investigators have examined associations between risk factors and LCIS. Our findings, which demonstrated similar risk patterns in the associations of race, age at menarche, age at first birth, family history, alcohol use, and smoking status with both DCIS and LCIS, suggest that these noninvasive lesions may share at least some common etiology. Given that cases of LCIS and low-grade DCIS are nearly uniformly estrogen receptor (ER)–positive, comparisons might have been tighter had grade information been available. Our findings also suggest some possible etiological differences: Differences in patterns of association were observed for age at natural menopause and risk of DCIS versus LCIS. Our findings are consistent with those from a previous analysis by Claus et al. (21) but were not in agreement with results from a case-control study that showed a lower risk of DCIS associated with younger age at menopause (22). Among women who experienced menopause at a younger age, we observed a significantly higher risk of DCIS but not LCIS. One possible biological hypothesis for this finding may be accounted for by the relationship between decreased mammographic breast density and menopause (23). Higher mammographic breast density is associated with lower mammographic sensitivity (24). A possible implication of younger menopausal age is that mammographic density will have also declined at a younger age, which potentially renders DCIS more visible on a mammogram during screening. Because LCIS are less frequently detected with mammography, it is not necessarily surprising that this association was not observed for LCIS. This is supported by the findings in our sensitivity analysis, which showed even higher hazard ratios for the association of DCIS with a younger age at menopause compared with the association with LCIS when the population was restricted to women who reported a previous mammogram in the 3 years prior to the second study follow-up questionnaire. However, because measurements of mammographic

breast density were not available for analysis among this study population, we cannot directly investigate this hypothesis. Because multiple statistical tests were carried out, we also acknowledge that this finding may be spurious.

In addition, we found that current MHT use was more strongly associated with the risk of LCIS than with the risk of DCIS, findings that are of a similar magnitude to a previous analysis within the prospective cohort from the Million Women Study (MWS), although a larger number of LCIS cases were included in this present analysis than in the previous report (5). Further within the Million Women Study, Reeves et al. (5) showed strong relationships between MHT use and increased risks of both DCIS (*n* = 1,443) and LCIS (*n* = 86). In addition, in our prospective analysis we showed a stronger association of previous benign breast biopsy with LCIS risk than with DCIS, which is in agreement with results from 3 population-based case-control studies (6, 7, 21). The observed associations between a history of benign breast biopsy and an elevated risk of in situ lesions are complex and likely due to the influence of multiple factors. For example, these findings may be driven by biological mechanisms relating benign lesions to the risk of subsequent development of in situ lesions. Furthermore, these associations may be the result of higher surveillance among women who would have had a prior biopsy than among women who did not.

DCIS is widely accepted as a nonobligate precursor of IDC, and both are thought to share common etiologies, as reviewed by Virnig et al. (25). In a second analysis conducted with the prospective cohort from the Million Women Study, Reeves et al. (26) compared risk factors for DCIS and IDC among that cohort of 1.1 million postmenopausal women from the United Kingdom, which included 3,715 women with DCIS and 21,137 with IDC. Similar to our findings, significant heterogeneity was not observed between the risks of DCIS and IDC for most breast cancer risk factors, including age at menarche, age at first birth, MHT use, and a family history of breast cancer (26). However, in that prior study, investigators observed stronger associations of higher BMI and alcohol consumption with an increased risk of IDC than with DCIS (26). Although we observed somewhat stronger positive associations of BMI and alcohol consumption with the risk of IDC versus the risk of DCIS, the test for statistical heterogeneity was null in our study population.

The role of LCIS as a precursor lesion of ILC is less well understood (27). It is a less common histological type, it is often not recognized radiologically, and its classification is often surrounded by inconsistency (28). However, multiple studies have shown that LCIS is associated with an increased risk of invasive breast cancer (29–32). The most notable differences between LCIS and ILC risks in our analyses were observed for MHT use, with significantly stronger associations with the risk of LCIS than with ILC, findings that were also observed in our sensitivity analysis restricted to women who had undergone a mammogram. Several lines of evidence support a hormonal influence on the development of LCIS. First, incidence trends for LCIS in the United States declined sharply between 2001 and 2004 (27, 33), which is likely the result of decreased use of MHT after the publication of results from the Women's Health Initiative (8). In addition, findings from the National Surgical Adjuvant Breast and Bowel Project

P-1 chemoprevention trial highlighted the potential for the selective ER modulator tamoxifen to reduce the development of LCIS (34), and the American Society for Clinical Oncology guidelines include recommendations for antiestrogen therapy as chemoprevention for future breast cancer risk among women with LCIS (35).

A strength of the present study was the large number of cases and extended follow-up period (through 2011). Although the NIH-AARP Diet and Health Study is population-based, it was geographically restricted. Most participants were older, with the largest proportion of women 65 years of age or older, which may limit the generalizability of these findings among younger postmenopausal women. In addition, compared with the other histological types assessed, the number of LCIS cases was somewhat limited. Despite this limitation, our study highlighted higher risks associated with current MHT use, particularly for LCIS. Because prior work has demonstrated differential associations of breast cancer risk by MHT formulation (e.g., estrogen alone vs. combined estrogen plus progestin) (5, 17, 36), future efforts in larger diverse populations are needed to examine these relationships in order to further understand the risks of in situ and invasive breast cancers associated with specific MHT formulations. Furthermore, although the majority of breast cancers diagnosed in older women are ER-positive, we were unable to directly examine associations of risk factors specifically for pathologically confirmed ER-positive breast cancers. ER status was not systematically reported in Florida, Texas, and Pennsylvania registries. In addition, ER classification of in situ breast cancer was not routinely recorded in registries until recently, with ER status for DCIS in the data captured by the Surveillance, Epidemiology, and End Results Program only reaching 72% completeness in 2005 (37, 38). Furthermore, within our analysis, a large number of statistical tests for heterogeneity were carried out; therefore, we cannot eliminate the possibility that findings may be the result of chance.

In conclusion, we found that associations of many breast cancer risk factors with in situ and invasive carcinomas were similar, which suggest that most risk factors act during the early stages of breast tumorigenesis. However, certain associations differed between in situ and invasive breast cancers, which may suggest that some factors act differentially during the in situ stage or that there are possibly unaccounted for effects, such as detectability by mammography. These similarities and differences are important in order to increase our understanding of the etiology of histological tumor types and may help to inform prevention strategies. Future ongoing work will determine the importance of these risk factors among women who are diagnosed with an in situ lesion and subsequently develop an invasive breast cancer at a later time point. Additional studies that include distinct molecular subtypes are required to expand these findings to further understand the role of MHT use, menopausal age, and benign breast disease in breast carcinogenesis.

Data System or the Florida Department of Health. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

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