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ORIGINAL PAPER

Risk factors for contralateral breast cancer in postmenopausal breast cancer survivors in the NIH-AARP Diet and Health Study

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Abstract

Purpose The role of established breast cancer risk factors and clinical characteristics of the first breast cancer in the development of contralateral breast cancer (CBC) among postmenopausal women is unclear.

Methods We identified 10,934 postmenopausal women diagnosed with a first primary breast cancer between 1995 and 2011 in the NIH-AARP Diet and Health Study. CBC was defined as a second primary breast cancer diagnosed in the contralateral breast ≥ 3 months after the first breast cancer. Exposures included pre-diagnosis risk factors (lifestyle, reproductive, family history) and clinical characteristics of the first breast cancer. We used multivariable Cox proportional hazards regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs).

Results Over a median follow-up of 6.8 years, 436 women developed CBC. We observed an increasing trend in CBC risk by age (p-trend = 0.002) and decreasing trend by year of diagnosis (p-trend = 0.001) of the first breast cancer. Additional risk factor associations were most pronounced for endocrine therapy (HR 0.68, 95% CI 0.53–0.87) and family history of breast cancer (HR 1.38, 95% CI 1.06–1.80, restricted to invasive first breast cancer). No associations were found for lifestyle (body mass index, physical activity, smoking, alcohol) or reproductive factors (age at menarche, parity, age at first birth, age at menopause).

Conclusions This study suggests that clinical characteristics of the first breast cancer and family history of breast cancer, but not pre-diagnosis lifestyle and reproductive factors, are strongly associated with CBC risk among postmenopausal women. Future studies are needed to understand how these factors contribute to CBC etiology and to identify further opportunities for prevention.

Keywords Breast cancer survivors · Lifestyle factors · Reproductive factors · Breast cancer tumor characteristics · Breast cancer treatment · Contralateral breast cancer

Introduction

As breast cancer survival has improved over time due to early detection and advances in treatment, there are a growing number of breast cancer survivors at risk of developing contralateral breast cancer (CBC) [1]. Previous studies have found that breast cancer survivors have a two- to six-fold higher risk of developing cancer in the contralateral breast when compared to that expected in the general population [2, 3]. An elevated risk of CBC may be due to shared factors between the first and second primary breast cancer, including lifestyle and reproductive characteristics, as well as treatment-related factors from the first primary cancer [4].

Previous studies on the association between breast cancer risk factors, including lifestyle, reproductive, and family

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history, and the development of CBC, have been primarily conducted among premenopausal women (age < 55 years) [5–15]. Limited data are available on breast cancer risk factors and CBC risk among postmenopausal women [16–20]. Furthermore, although clinical characteristics of the first breast cancer have been studied in relation to CBC risk [21–28], whether these characteristics act independently of lifestyle and reproductive factors on CBC risk remains unclear.

The NIH-AARP Diet and Health study, a prospective cohort study among US adults aged 50 years and older, provides a unique opportunity to extend our knowledge on breast cancer risk factors and clinical characteristics and their impact on CBC risk among postmenopausal breast cancer survivors.

Methods

Study population

The NIH-AARP Diet and Health study started in 1995–1996 when 566,398 members of the AARP (formerly known as the American Association of Retired Persons) completed a self-administered baseline questionnaire to collect information on demographic and cancer risk factors including lifestyle, reproductive, and family history data [29]. Further details on the NIH-AARP Diet and Health study have been previously described [29]. Briefly, participants were aged 50 to 71 years and resided in 6 US states (California, Florida, Pennsylvania, New Jersey, North Carolina, and Louisiana) and two metropolitan areas (Atlanta, Georgia and Detroit, Michigan).

Analytic population

For the present analysis, we identified 14,317 participants without a breast cancer diagnosis prior to baseline and who developed an incident first primary breast cancer during follow-up (through 31st December 2011). Participants diagnosed with a first primary breast cancer with unknown laterality ($n = 65$) or first primary bilateral breast cancer ($n = 4$) were excluded. We further excluded participants who completed baseline questionnaires by proxy ($n = 59$), male breast cancer patients ($n = 262$), women who had a self-reported personal history of any cancer (except non-melanoma skin cancer) at baseline ($n = 698$), premenopausal women ($n = 875$), women diagnosed with a first distant stage breast cancer ($n = 307$) or unknown stage breast cancer ($n = 249$), women with contralateral prophylactic mastectomies as part of their initial treatment for first breast cancer ($n = 257$), and women with < 3 months of follow-up ($n = 607$). These exclusions resulted in a final analytic population of 10,934 postmenopausal women diagnosed with a first primary breast cancer.

Assessment of breast cancer risk factors

Lifestyle and reproductive factors were self-reported on the baseline questionnaire prior to the first breast cancer diagnosis (i.e., pre-diagnosis). Lifestyle factors included body mass index (BMI) (< 25 kg/m^2, 25–< 30 kg/m^2, and ≥ 30 kg/m^2, missing), frequency of vigorous physical activity defined as exercise for ≥ 20 min that caused an increase in breathing or heart rate, or worked up a sweat (< 1 time/week, 1–2 times/week, 3–4 times/week ≥ 5 times/week, missing), smoking status (never, former, current, missing), and alcohol consumption (none, ≤ 10 g/day, > 10–< 20 g/day, ≥ 20 g/day, missing). Reproductive factors were age at menarche (≤ 12 years, 13–14 years, ≥ 15 years, missing), parity (nulliparous, 1 child, 2 children, ≥ 3 children, missing), age at first birth (nulliparous, < 20 years, 20–24 years, 25–29 years, ≥ 30 years, missing), and age at menopause (< 45 years, 45–49 years, 50–54 years, ≥ 55 years, missing). We also assessed self-reported family history of cancer (except basal-cell skin cancer) in a first-degree relative (yes, no, missing) and family history of breast cancer in a first-degree female relative (yes, no, missing).

Ascertainment of incident cancer and clinical cancer characteristics

Incident in situ and invasive breast cancer diagnoses were identified via linkage to the cancer registries in the study areas and several adjacent states (Texas, Arizona, and Nevada) through 31st December 2011 [30]. Contralateral breast cancer was defined as a second primary breast cancer (in situ or invasive) diagnosed in the contralateral breast at least 3 months after the first primary breast cancer diagnosis. The first 3 months of follow-up was excluded to reduce potential misclassification of CBC as metastases that occurred after diagnosis or undetected synchronous bilateral breast cancer [4]. Information on clinical characteristics was captured from cancer registries and included calendar year of diagnosis (1995–1999, 2000–2004, 2005–2011), age at diagnosis (50–< 60, 60–< 65, 65–< 70, 70–< 75, ≥ 75 years), tumor histology (ductal, lobular, mixed, other, unknown), tumor grade (well differentiated, moderately differentiated, poorly differentiated/undifferentiated, unknown), disease stage (in situ, localized, regional), and estrogen receptor (ER) status (positive, negative, unknown). ER status was examined among invasive tumors only and restricted to a subgroup that excluded registry data from the Florida, Pennsylvania, and Texas cancer registries due to under-ascertainment of ER status in those registries. Information on human epidermal growth factor receptor 2 (HER2) was not

routinely collected during the study period. First course of treatment including radiotherapy (yes, no, unknown), chemotherapy (yes, no, unknown), and endocrine therapy (yes, no, unknown) was ascertained from cancer registry records. Surgery conducted as part of the first course of treatment was categorized as none, breast conserving, unilateral mastectomy, or unknown.

Statistical analysis

We used Cox proportional hazards regression to calculate age- and multivariable-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for CBC risk by breast cancer risk factors and clinical characteristics of the first breast cancer. Time since diagnosis was the underlying time metric. Follow-up started 3 months after the date of first primary breast cancer diagnosis until the date of second primary cancer diagnosis, date of death, lost to follow-up, or end of study (31st December 2011), whichever came first.

In initial multivariable models, we mutually adjusted for clinical characteristics of the first breast cancer, including age at diagnosis, calendar year of diagnosis, tumor stage, histology, ER status, first course of treatment, and family history of breast cancer. In the main multivariable models, we additionally adjusted for lifestyle and reproductive breast cancer risk factors, including BMI, physical activity, smoking status, alcohol consumption, age at menarche, parity, age at first birth, age at menopause, and menopausal hormone therapy. We present the main multivariable models in the text. We used Schoenfeld residuals to assess the proportional hazards assumption and did not find any violations of this assumption. *p* for trends were estimated from the Wald test using an ordinal variable.

In sensitivity analyses, we conducted analyses among subgroups of women diagnosed with (1) a first invasive breast cancer ($n = 8{,}776$) and (2) a first invasive ER-positive breast cancer ($n = 4{,}124$) as risk factors may differ among these subgroups. For lifestyle exposures, we further restricted analyses to women diagnosed with a first primary breast cancer within 5 years of the baseline questionnaire ($n = 3{,}851$) since these factors may change over time and updated questionnaire data at the time of first breast cancer diagnosis were not available. We also restricted analyses within 5 years of the first breast cancer diagnosis so that follow-up time was the same across calendar periods when examining year of diagnosis and CBC risk. Given that age is such a strong confounder, we conducted analyses using attained age as the underlying time scale; however, results were largely similar, and therefore, we present results using time since diagnosis as it is a more clinically meaningful metric. Since contralateral prophylactic mastectomies may have been misclassified as unknown for surgery type, we also conducted sensitivity analyses excluding women with unknown surgery (type or laterality) ($n = 882$). However, we did not exclude these women from our analytic population as rates of contralateral prophylactic mastectomy were relatively low among older postmenopausal women during this time period (1.9–4.7%) [31] and results were unchanged in sensitivity analyses. Finally, we estimated subdistribution hazard ratios with Fine and Gray regression to account for the competing risk of death [32].

p-values were based on 2-sided tests and a p-value < 0.05 was considered statistically significant. Analyses were conducted using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and Stata version 16 (StataCorp LP, College Station, TX, USA).

Results

Patient characteristics

Among 10,934 postmenopausal women diagnosed with a first primary breast cancer (20% in situ, 80% invasive), the mean age at first breast cancer diagnosis was 69.4 years, and women were primarily diagnosed with invasive and ER-positive breast cancer (Table 1). Approximately, 44% of women had known receipt of radiotherapy, 17% received chemotherapy, and 32% were reported to receive endocrine therapy for the first breast cancer. The distribution for prediagnosis lifestyle, reproductive, and family history factors are presented in Supplementary Table 1.

A total of 436 women developed CBC during 6.8 median years of follow-up (range 0.3–16.1 years). The mean age at CBC diagnosis was 72.8 years and women primarily developed invasive and ER-positive CBC (Supplementary Table 2). The median time from the first breast cancer to the development of CBC was 4.2 years (range 0.3–14.3 years). A total of 1,344 women were censored due to death and 36% of these deaths were due to breast cancer ($n = 484$).

Lifestyle and reproductive factors and CBC risk

Overall, lifestyle and reproductive risk factors captured prior to the first breast cancer were not statistically significantly associated with CBC risk (Tables 2, 3). HRs were slightly elevated for higher BMI (overweight vs. normal: HR 1.15, 95% CI 0.92–1.44; obese vs. normal: HR 1.20, 95% CI 0.92–1.55; p-trend = 0.12) and among current and former smokers compared with non-smokers (current smokers: HR 1.19, 95% CI 0.87–1.61; former smokers: HR 1.16, 95% CI 0.94–1.43). Higher levels of physical activity were associated with a lower risk of CBC (physical activity ≥ 5 times/week vs. < 1 time/week: HR 0.93, 95% CI 0.69–1.23; p-trend = 0.35). No association was observed between alcohol intake and CBC risk. Results for lifestyle factors were

Table 1 Clinical characteristics of 10,934 postmenopausal women diagnosed with a first breast cancer in the NIH-AARP Diet and Health Study

First breast cancer characteristic	*n*	% or mean (SD)
Age at diagnosis, years		
50–< 60	946	8.7
60–< 65	1,776	16.2
65–< 70	3,049	27.9
70–< 75	2,914	26.7
≥ 75	2,249	20.6
Age at diagnosis, years[a]	–	69.4 (6.5)
Calendar year of diagnosis		
1995–1999	3,045	27.9
2000–2004	3,849	35.2
2005–2011	4,040	37.0
Calendar year of diagnosis[b]	–	2003 (4.4)
Stage		
In situ	2,158	19.7
Localized	6,573	60.1
Regional	2,203	20.2
Histology		
Ductal	8,177	74.8
Lobular	1,110	10.2
Mixed	716	6.6
Other	911	8.3
Unknown	20	0.2
Grade		
Well differentiated	2,283	20.9
Moderately differentiated	4,127	37.7
Poorly differentiated, undifferentiated	2,783	25.5
Unknown	1,741	15.9
Estrogen receptor status[c]		
Positive	4,124	71.7
Negative	789	13.7
Unknown	843	14.7
Surgery		
None	1,145	10.5
Breast conserving	6,729	61.5
Unilateral mastectomy	2,178	19.9
Unknown	882	8.1
Radiation therapy		
None	5,102	46.7
Yes	4,853	44.4
Unknown	979	9.0
Chemotherapy		
None	8,224	75.2
Yes	1,857	17.0
Unknown	853	7.8
Endocrine therapy		
None	6,416	58.7
Yes	3,511	32.1
Unknown	1,007	9.2

Table 1 (continued)

Values are means (SD) for continuous variables; percentages for categorical variables

The median time from enrollment to first breast cancer was 6.6 years (25–75th percentile: 3.3–10.5 years)

[a]The median age at first breast cancer diagnosis was 69.5 years (range 51.5–85.7 years)

[b]The median year of first breast cancer diagnosis was 2002 (range 1995–2011)

[c]Restricted to invasive breast cancer and excludes women diagnosed in TX, FL, and PA since state registries did not systematically collect estrogen receptor status ($n = 5{,}756$)

similar, but attenuated for some associations, among women whose first breast cancer was diagnosed within 5 years of the baseline questionnaire (Supplementary Table 3). Reproductive factors, including age at menarche, parity, and age at menopause, were not associated with CBC risk (Table 3). Similar findings for lifestyle and reproductive factors were observed when restricted to women diagnosed with a first invasive breast cancer or invasive ER-positive breast cancer, although some risk factors showed stronger associations with CBC risk (Supplementary Table 4). Results accounting for the competing risk of death were similar (Supplementary Table 5).

Clinical factors of the first breast cancer and CBC risk

Associations for clinical characteristics of the first primary breast cancer and CBC risk are shown in Table 4. We observed a significant increasing trend in CBC risk with older age at first breast cancer diagnosis (p-trend = 0.002). CBC risk was highest in women aged ≥ 75 years at first breast cancer diagnosis relative to those aged 50–< 60 years (HR 2.28, 95% CI 1.40–3.71). Additionally, CBC risk declined by calendar year of first breast cancer diagnosis (2000–2004 vs. 1995–1999: HR 0.81, 95% CI 0.64–1.02; 2005–2011 vs. 1995–1999: HR 0.55, 95% CI 0.38–0.78; p-trend = 0.001). Results were similar when restricted to ≤ 5 years since first breast cancer diagnosis (2000–2004: HR 0.76, 95% CI 0.56–1.02; 2005–2011: HR 0.46, 95% CI 0.30–0.69; p-trend < 0.001). Compared to women diagnosed with a first in situ breast cancer, those diagnosed with localized or regional tumors had a significantly lower risk of developing CBC (HR 0.72, 95% CI 0.56–0.91; HR 0.65, 95% CI 0.46–0.92, respectively). Associations between stage and CBC risk did not differ when stratified by receipt of initial treatment (Supplementary Table 6). Women who received endocrine therapy had a 32% significantly lower risk of CBC compared to women without endocrine therapy (HR 0.68, 95% CI 0.53–0.87). Risk of CBC was higher in women diagnosed with a first ER-negative tumor compared to ER-positive tumor (HR 1.50, 95% CI 1.02–2.20). We

Table 2 Hazard Ratios (95% CI) for lifestyle factors and contralateral breast cancer risk among 10,934 postmenopausal women diagnosed with a first breast cancer in the NIH-AARP Diet and Health Study

Lifestyle factors	No. of cases	Model 1[a]		Model 2[b]		Model 3[c]	
		HR	95% CI	HR	95% CI	HR	95% CI
Body mass index, kg/m^2							
< 25	167	1.00	(ref)	1.00	(ref)	1.00	(ref)
25– < 30	147	1.16	(0.93, 1.45)	1.15	(0.92, 1.44)	1.15	(0.92, 1.44)
≥ 30	108	1.20	(0.95, 1.53)	1.22	(0.95, 1.55)	1.20	(0.92, 1.55)
p-trend			0.11	0.10		0.12	
Physical activity, ≥ 20 min							
< 1 time/week	175	1.00	(ref)	1.00	(ref)	1.00	(ref)
1–2 times/week	85	0.85	(0.65, 1.10)	0.86	(0.66, 1.11)	0.86	(0.66, 1.11)
3–4 times/week	102	0.82	(0.64, 1.05)	0.82	(0.64, 1.05)	0.84	(0.66, 1.08)
≥ 5 times/week	68	0.89	(0.67, 1.18)	0.90	(0.68, 1.19)	0.93	(0.69, 1.23)
p-trend		0.21		0.22		0.35	
Smoking status							
Never	179	1.00	(ref)	1.00	(ref)	1.00	(ref)
Former	182	1.17	(0.95, 1.44)	1.17	(0.96, 1.44)	1.16	(0.94, 1.43)
Current	57	1.15	(0.85, 1.54)	1.18	(0.87, 1.59)	1.19	(0.87, 1.61)
Alcohol consumption (g/day)							
Non-drinker	116	1.00	(ref)	1.00	(ref)	1.00	(ref)
≤ 10	236	0.98	(0.79, 1.23)	1.00	(0.80, 1.25)	0.99	(0.79, 1.24)
> 10–≤ 20	44	0.99	(0.70, 1.41)	1.00	(0.71, 1.42)	1.00	(0.70, 1.44)
> 20	40	1.07	(0.74, 1.53)	1.08	(0.75, 1.55)	1.06	(0.73, 1.54)
p-trend		0.79		0.73		0.79	

[a]Model adjusted for age at first breast cancer diagnosis (years)

[b]Model adjusted for covariates in model 1 plus year of diagnosis (1995–1999, 2000–2004, 2005–2011), stage (in situ, localized, regional), estrogen receptor status (positive, negative, unknown), histology (ductal, lobular, other, unknown), radiation therapy (yes, no, unknown), chemotherapy (yes, no, unknown), endocrine therapy (yes, no, unknown), and family history of breast cancer (yes, no, missing)

[c]Model adjusted for covariates in model 2 plus body mass index (< 25 kg/m^2, 25– < 30 kg/m^2, ≥ 30 kg/m^2, missing), physical activity (< 1 time/week, 1–2 times/week, 3–4 times/week, ≥ 5 times/week, missing), smoking status (never, ever, missing), alcohol consumption (non-drinker, < 5 g/day, ≥ 5 g/day, missing), age at menarche (≤ 12, > 12 years, missing), parity and age at first birth (nulliparous, < 25 years at first birth and ≤ 2 children, < 25 years at first birth and ≥ 3 children, ≥ 25 years at first birth, missing), age at menopause (< 45 years, 45–49 years, 50–54 years, ≥ 55 years, missing), and menopausal hormone therapy duration (never, < 5 years, 5– < 10 years, ≥ 10 years, missing)

found no statistically significant associations for first breast cancer grade, histology, radiotherapy, and chemotherapy. Results were generally similar, but also slightly stronger, when models were restricted to women diagnosed with a first invasive breast cancer or invasive ER-positive breast cancer (Supplementary Table 7). Subdistribution HRs for associations between first breast cancer characteristics and CBC risk were slightly attenuated (Supplementary Table 8).

Family history of cancer and CBC risk

Family history of breast cancer in a first-degree female relative was associated with a statistically significant higher risk of CBC, particularly among women diagnosed with a first invasive breast cancer (HR 1.38, 95% CI 1.06–1.80) (Table 5). Results were similar but slightly attenuated when restricted to first invasive ER-positive cancer (data not shown). A history of any cancer in a first-degree relative was not associated with CBC risk. Results for family history of cancer or breast cancer and CBC risk were unchanged after accounting for the competing risk of death (Supplementary Table 9).

Discussion

In this prospective study of postmenopausal breast cancer survivors in the NIH-AARP Diet and Health Study, we found that clinical characteristics of the first breast cancer, including earlier calendar year of diagnosis, older age, lower stage, negative ER status, and absence of endocrine therapy, were associated with an increased risk of CBC. Whereas most pre-diagnosis lifestyle and reproductive factors were not associated with CBC risk, a family history of

Table 3 Hazard Ratios (95% CI) for reproductive factors and contralateral breast cancer risk among 10,934 postmenopausal women diagnosed with a first breast cancer in the NIH-AARP Diet and Health Study

Reproductive factors	No. of cases	Model 1[a]		Model 2[b]		Model 3[c]	
		HR	95% CI	HR	95% CI	HR	95% CI
Age at menarche							
≤ 12 years	221	1.00	(ref)	1.00	(ref)	1.00	(ref)
13–14 years	188	1.01	(0.83, 1.23)	1.02	(0.84, 1.23)	1.02	(0.84, 1.25)
≥ 15 years	25	0.67	(0.45, 1.02)	0.67	(0.45, 1.02)	0.68	(0.45, 1.03)
p-trend		0.23		0.24		0.26	
Parity							
Nulliparous	85	1.00	(ref)	1.00	(ref)	1.00	(ref)
1 child	48	0.95	(0.67, 1.36)	0.95	(0.66, 1.35)	0.93	(0.65, 1.32)
2 children	98	0.77	(0.58, 1.04)	0.76	(0.57, 1.02)	0.76	(0.57, 1.02)
≥ 3 children	203	0.92	(0.71, 1.18)	0.88	(0.69, 1.14)	0.88	(0.68, 1.13)
p-trend		0.49		0.33		0.31	
Age at first birth							
Nulliparous	85	1.28	(0.91, 1.81)	1.30	(0.92, 1.83)	1.35	(0.95, 1.91)
< 20 years	53	1.00	(ref)	1.00	(ref)	1.00	(ref)
20–24 years	178	1.14	(0.84, 1.54)	1.11	(0.82, 1.52)	1.16	(0.85, 1.58)
25–29 years	96	1.29	(0.92, 1.81)	1.27	(0.91, 1.78)	1.32	(0.94, 1.86)
≥ 30 years	24	0.91	(0.56, 1.47)	0.89	(0.55, 1.44)	0.91	(0.56, 1.49)
p-trend[d]		0.68		0.76		0.74	
Age at menopause							
< 45 years	128	1.03	(0.81, 1.30)	1.03	(0.81, 1.30)	1.08	(0.85, 1.38)
45–49 years	109	1.02	(0.79, 1.30)	1.02	(0.80, 1.30)	1.03	(0.81, 1.33)
50–54 years	148	1.00	(ref)	1.00	(ref)	1.00	(ref)
≥ 55 years	49	1.22	(0.88, 1.69)	1.22	(0.88, 1.69)	1.21	(0.87, 1.67)
p-trend		0.60		0.63		0.97	

[a]Model adjusted for age at first breast cancer diagnosis (years)

[b]Model adjusted for covariates in model 1 plus year of diagnosis (1995–1999, 2000–2004, 2005–2011), stage (in situ, localized, regional), estrogen receptor status (positive, negative, unknown), histology (ductal, lobular, other, unknown), radiation therapy (yes, no, unknown), chemotherapy (yes, no, unknown), endocrine therapy (yes, no, unknown), and family history of breast cancer (yes, no, missing)

[c]Model adjusted for covariates in model 2 plus body mass index (< 25 kg/m^2, 25–< 30 kg/m^2, ≥ 30 kg/m^2, missing), physical activity (< 1 time/week, 1–2 times/week, 3–4 times/week, ≥ 5 times/week, missing), smoking status (never, ever, missing), alcohol consumption (non-drinker, < 5 g/day, ≥ 5 g/day, missing), age at menarche (≤ 12, > 12 years, missing), parity and age at first birth (nulliparous, < 25 years at first birth and ≤ 2 children, < 25 years at first birth and ≥ 3 children, ≥ 25 years at first birth, missing), age at menopause (< 45 years, 45–49 years, 50–54 years, ≥ 55 years, missing), and menopausal hormone therapy duration (never, < 5 years, 5–< 10 years, ≥ 10 years, missing)

[d]*p*-trends for age at first birth were estimated without nulliparous women

breast cancer in a first-degree female relative was associated with an increased risk of CBC, particularly for those whose first breast cancer was invasive. These findings suggest that clinical characteristics of the first breast cancer and family history of breast cancer may play a larger role than pre-diagnosis lifestyle and reproductive factors in the development of CBC among postmenopausal women.

Although we found no clear associations for pre-diagnosis lifestyle and reproductive factors with CBC risk in this study, previous research has been inconsistent and primarily conducted among case–control studies of younger and premenopausal breast cancer patients. Prior studies have found that obesity [14, 16, 17], weight gain [7], alcohol use [6, 12, 17], and current smoking [6, 17] were associated with increased CBC risk while other studies have found no overall association for these lifestyle factors [10, 15, 20]. For reproductive factors, older age at menarche [8, 11, 13] and higher parity [8, 11, 13, 18, 19] have been associated with a decreased risk of CBC. A potential modest association has also been reported for age at first birth [8, 18]. Supporting some of these findings, a recent meta-analysis [33] found that higher BMI (≥ 25 vs. < 25 kg/m^2: HR 1.22, 95% CI 1.01–1.47), alcohol use (ever vs. never: HR 1.15, 95% CI 1.02–1.31), and older age at first birth (age ≥ 25

Table 4 Hazard Ratios (95% CI) for clinical characteristics of the first breast cancer and contralateral breast cancer risk among 10,934 postmenopausal women diagnosed with a first breast cancer in the NIH-AARP Diet and Health Study

First breast cancer characteristics	No. of cases	Model 1[a]		Model 2[b]		Model 3[c]	
		HR	95% CI	HR	95% CI	HR	95% CI
Age at diagnosis, years							
50–< 60	43	1.00	(ref)	1.00	(ref)	1.00	(ref)
60–< 65	93	1.38	(0.96, 1.98)	1.49	(1.04, 2.15)	1.58	(1.09, 2.29)
65–< 70	147	1.47	(1.05, 2.07)	1.63	(1.16, 2.31)	1.79	(1.25, 2.55)
70–< 75	106	1.36	(0.95, 1.94)	1.57	(1.09, 2.28)	1.77	(1.21, 2.60)
≥ 75	47	1.42	(0.93, 2.17)	1.98	(1.24, 3.17)	2.28	(1.40, 3.71)
p-trend		0.19		0.01		0.002	
Year of diagnosis							
1995–1999	206	1.00	(ref)	1.00	(ref)	1.00	(ref)
2000–2004	169	0.82	(0.66, 1.03)	0.83	(0.66, 1.04)	0.81	(0.64, 1.02)
2005–2011	61	0.58	(0.41, 0.82)	0.57	(0.40, 0.82)	0.55	(0.38, 0.78)
p-trend		0.002		0.003		0.001	
Stage							
In situ	113	1.00	(ref)	1.00	(ref)	1.00	(ref)
Localized	250	0.73	(0.59, 0.91)	0.71	(0.56, 0.91)	0.72	(0.56, 0.91)
Regional	73	0.68	(0.51, 0.91)	0.65	(0.46, 0.91)	0.65	(0.46, 0.92)
Grade							
Well differentiated	83	1.00	(ref)	1.00	(ref)	1.00	(ref)
Moderately differentiated	132	0.88	(0.67, 1.16)	0.89	(0.67, 1.17)	0.90	(0.68, 1.18)
Poorly differentiated, undifferentiated	122	1.22	(0.92, 1.61)	1.13	(0.84, 1.52)	1.13	(0.84, 1.52)
Histology							
Ductal	307	1.00	(ref)	1.00	(ref)	1.00	(ref)
Lobular	48	1.15	(0.85, 1.56)	1.24	(0.91, 1.69)	1.24	(0.91, 1.69)
Mixed	35	1.25	(0.88, 1.77)	1.38	(0.97, 1.97)	1.38	(0.97, 1.97)
Other	46	1.32	(0.96, 1.79)	1.31	(0.95, 1.79)	1.33	(0.97, 1.82)
Estrogen receptor status[d]							
Negative	41	1.69	(1.20, 2.40)	1.43	(0.98, 2.09)	1.50	(1.02, 2.20)
Positive	139	1.00	(ref)	1.00	(ref)	1.00	(ref)
Endocrine therapy							
No	297	1.00	(ref)	1.00	(ref)	1.00	(ref)
Yes	95	0.62	(0.50, 0.79)	0.67	(0.52, 0.87)	0.68	(0.53, 0.87)
Radiotherapy							
No	211	1.00	(ref)	1.00	(ref)	1.00	(ref)
Yes	181	0.91	(0.75, 1.11)	1.06	(0.86, 1.31)	1.06	(0.86, 1.31)
Chemotherapy							
No	324	1.00	(ref)	1.00	(ref)	1.00	(ref)
Yes	67	0.92	(0.71, 1.21)	1.04	(0.76, 1.41)	1.03	(0.76, 1.40)

[a]Model adjusted for age at first breast cancer diagnosis (years)

[b]Model adjusted for covariates in model 1 plus year of diagnosis (1995–1999, 2000–2004, 2005–2011), stage (in situ, localized, regional), estrogen receptor status (positive, negative, unknown), histology (ductal, lobular, other, unknown), radiation therapy (yes, no, unknown), chemotherapy (yes, no, unknown), endocrine therapy (yes, no, unknown), and family history of breast cancer (yes, no, missing)

[c]Model adjusted for covariates in model 2 plus body mass index (< 25 kg/m^2, 25–< 30 kg/m^2, ≥ 30 kg/m^2, missing), physical activity (< 1 time/week, 1–2 times/week, 3–4 times/week, ≥ 5 times/week, missing), smoking status (never, ever, missing), alcohol consumption (nondrinker, < 5 g/day, ≥ 5 g/day, missing), age at menarche (≤ 12, > 12 years, missing), parity and age at first birth (nulliparous, < 25 years at first birth and ≤ 2 children, < 25 years at first birth and ≥ 3 children, ≥ 25 years at first birth, missing), age at menopause (< 45 years, 45–49 years, 50–54 years, ≥ 55 years, missing), and menopausal hormone therapy duration (never, < 5 years, 5–< 10 years, ≥ 10 years, missing)

[d]Restricted to invasive tumors and excludes women diagnosed in TX, FL, and PA since state registries did not systematically collect estrogen receptor status (n = 5,756)

Table 5 Hazard Ratios (95% CI) for family history of cancer and contralateral breast cancer risk among postmenopausal women diagnosed with a first breast cancer in the NIH-AARP Diet and Health Study

	All first breast cancer ($n=10,934$)							Invasive first breast cancer ($n=8,776$)						
	No. of cases	Model 1[a]		Model 2[b]		Model 3[c]		No. of cases	Model 1[a]		Model 2[b]		Model 3[c]	
		HR	95% CI	HR	95% CI	HR	95% CI		HR	95% CI	HR	95% CI	HR	95% CI
Family history of cancer[d]														
No	183	1.00	(ref)	1.00	(ref)	1.00	(ref)	140	1.00	(ref)	1.00	(ref)	1.00	(ref)
Yes	234	0.93	(0.77, 1.13)	0.93	(0.77, 1.13)	0.93	(0.76, 1.13)	168	0.86	(0.69, 1.08)	0.86	(0.69, 1.07)	0.86	(0.69, 1.08)
Family history of breast cancer[e]														
No	327	1.00	(ref)	1.00	(ref)	1.00	(ref)	234	1.00	(ref)	1.00	(ref)	1.00	(ref)
Yes	90	1.22	(0.97, 1.54)	1.21	(0.96, 1.53)	1.21	(0.96, 1.53)	74	1.40	(1.08, 1.82)	1.39	(1.07, 1.80)	1.38	(1.06, 1.80)

[a]Model adjusted for age at first breast cancer diagnosis (years)

[b]Model adjusted for covariates in model 1 plus year of diagnosis (1995–1999, 2000–2004, 2005–2011), stage (in situ, localized, regional), estrogen receptor status (positive, negative, unknown), histology (ductal, lobular, other, unknown), radiation therapy (yes, no, unknown), chemotherapy (yes, no, unknown), and endocrine therapy (yes, no, unknown)

[c]Model adjusted for covariates in model 2 plus body mass index (<25 kg/m^2, 25–<30 kg/m^2, ≥ 30 kg/m^2, missing), physical activity (<1 time/week, 1–2 times/week, 3–4 times/week, ≥ 5 times/week, missing), smoking status (never, ever, missing), alcohol consumption (non-drinker, <5 g/day, ≥ 5 g/day, missing), age at menarche (≤ 12, >12 years, missing), parity and age at first birth (nulliparous, <25 years at first birth and ≤ 2 children, <25 years at first birth and ≥ 3 children, ≥ 25 years at first birth, missing), age at menopause (<45 years, 45–49 years, 50–54 years, ≥ 55 years, missing), and menopausal hormone therapy duration (never, <5 years, 5–<10 years, ≥ 10 years, missing)

[d]Family history is defined as family history of cancer in a first-degree relative

[e]Family history is defined as family history of breast cancer in a first-degree female relative

vs. < 25 years: HR 1.06, 95% CI 1.02–1.10) were suggestive of increased CBC risk, while higher parity was associated with a lower risk of CBC (≥ 4 full-term births vs. nulliparous: HR 0.56, 95% CI 0.42–0.76). However, results from this meta-analysis were limited in scope with only 2–5 studies per risk factors and conducted primarily among younger and premenopausal women. In our study, it is possible that any associations between lifestyle or reproductive factors and CBC risk in postmenopausal breast cancer survivors may be modest and we therefore may have been underpowered to detect these smaller effects. Although we observed no statistically significant associations between lifestyle and reproductive factors and CBC risk, the direction of associations in our study, particularly for BMI, were largely consistent with prior studies. Future larger studies among postmenopausal breast cancer survivors are needed to confirm our findings and to further examine whether associations between lifestyle and reproductive factors may vary by characteristics of CBC (e.g., ER status).

Clinical characteristics for the first breast cancer, including age, stage and year of diagnosis, ER status, and receipt of endocrine therapy, were the strongest factors for developing CBC in this study. These associations remained after accounting for pre-diagnosis lifestyle and reproductive factors, and family history of breast cancer. Interestingly, we reported an increased risk of CBC associated with older age at first breast cancer diagnosis, and this association remained when we used attained age as the time scale and when we accounted for the competing risk of death. Previous studies on age at first diagnosis [2, 14, 15, 18, 20] have been inconsistent, although several have found that younger age is associated with a higher risk of developing CBC [2, 14, 18]. Our study, however, is the first to examine age at diagnosis among postmenopausal women aged 50 years and older, and further studies are needed to confirm this finding. We also observed a significant decreased risk of CBC after an invasive tumor relative to an in situ tumor. Although this finding is surprising, it is possible that women diagnosed with invasive tumors may have been more likely to receive treatment that significantly reduced the risk of CBC compared to those with a first in situ tumor. However, we were unable to confirm this hypothesis and further studies with more detailed treatment are needed to evaluate and characterize these findings.

In our study, a decline in CBC risk among women treated in more recent calendar periods is consistent with advances in treatment for the first breast cancer, such as the widespread uptake of tamoxifen therapy and the introduction and uptake of aromatase inhibitors for postmenopausal women. However, it is possible that there is residual confounding as we still observed a significant decline in risk after adjustment for receipt of initial treatment, including endocrine therapy. Both clinical trials [34, 35] and observational studies [36, 37] have shown that endocrine therapy significantly reduces the risk of CBC via estrogen suppression. Supporting these findings, we also observed that women treated with endocrine therapy had a significantly lower risk of developing CBC relative to those without endocrine therapy and that women with a first invasive ER-negative tumor had a significantly higher risk of CBC compared to those diagnosed with an invasive ER-positive tumor.

Consistent with previous literature [2, 5, 18–20, 38, 39] our study found that family history of breast cancer in a first-degree relative was a significant risk factor for CBC, particularly among those diagnosed with a first invasive breast cancer. Interestingly, prior studies have found that breast cancer family history remained a significant risk factor even after excluding women with known deleterious mutations (e.g., BRCA1/2) [5, 39]. This suggests that other genetic susceptibility loci and/or gene–environment interactions may play a role in CBC risk [5].

Our findings should be considered within the context of the strengths and limitations of this study. The NIH-AARP Diet and Health Study represents a distinctive opportunity to prospectively examine pre-diagnosis breast cancer risk factors for CBC among a large cohort of postmenopausal breast cancer survivors. Furthermore, although lifestyle and reproductive factors were self-reported, they were ascertained prior to the first breast cancer and therefore not susceptible to recall bias. Our study examined pre-diagnosis lifestyle factors at enrollment into the NIH-AARP cohort, and it is possible that these factors may change over time. However, we observed similar yet attenuated patterns of association for lifestyle factors when restricted to women who were diagnosed with a first breast cancer within 5 years of enrollment into the NIH-AARP cohort. Attenuation of these results is likely due to the smaller sample size. Finally, our study utilized cancer registry data for first breast cancer treatment and therefore was limited to the first course of treatment and susceptible to under-ascertainment. Additionally, data on recurrences and subsequent treatment were not available. Future studies on CBC risk among postmenopausal breast cancer patients with comprehensive and detailed treatment are needed.

In summary, our findings suggest that clinical characteristics of the first breast cancer and family history of breast cancer, but not pre-diagnosis lifestyle and reproductive factors, were significantly associated with CBC risk among postmenopausal breast cancer survivors in the NIH-AARP Diet and Health Study. These findings provide potential insight on the etiology of CBC in postmenopausal women and underlie the importance of treatment, particularly endocrine therapy, to reduce the risk of CBC. Further analyses are warranted to improve understanding of how these clinical characteristics and breast cancer family history contribute to the etiology of CBC and to identify possible prevention opportunities for

CBC, which remains the most common cancer diagnosis in breast cancer survivors.

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Author contributions CR, ABdG conceived and designed the study and conducted and reviewed statistical analysis. All authors substantially contributed to the preparation and critical review of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets analyzed during the current study were obtained from the NIH-AARP Diet and Health Study at the National Cancer Institute. The data used in this study are available with the submission of a proposal and approval from the NIH-AARP Steering Committee (https://dietandhealth.cancer.gov/).

Code availability Code is available upon request.

Declarations

Conflict of interest All authors declare that they have no conflicts of interest.

Ethical approval The NIH-AARP Diet and Health Study (Protocol Number: OH95CN025) was approved by the Special Studies Institutional Review Board (SSIRB) of the US National Cancer Institute. This study was conducted in accordance with the ethical standards of the institutional review board and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication All participants provided informed consent by completing and returning the self-administered baseline questionnaire.

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