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Age-Specific Indicators of a Healthy Lifestyle and Postmenopausal Breast Cancer

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Abstract

Introduction: Modifiable lifestyle factors have been consistently associated with breast cancer, and risk may vary by menopausal status. However, whether these associations vary according to age among postmenopausal women remains unresolved.

Methods: Using postmenopausal women from a population-based case–control study (990 cases and 1006 frequency-matched controls), we conducted multivariable-adjusted unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for lifestyle factors (lifetime alcohol intake, body mass index [BMI] in the year before diagnosis, lifetime recreational physical activity [RPA], and nonsteroidal anti-inflammatory drug use) in association with breast cancer stratified by age (<65 vs. 65+). We examined estrogen-related subgroups by (1) further stratifying by hormone replacement therapy (HRT) use and (2) restricting cases to estrogen receptor (ER)+/progesterone receptor (PR)+ cancers.

Results: Postmenopausal breast cancer incidence in women 65 years and older was positively associated with alcohol intake (OR = 1.79 for 15–30 g/day vs. nondrinkers, 95% CI: 1.03–3.12) and BMI (OR = 1.83 for BMI ≥30 vs. <25, 95% CI: 1.29–2.60), and inversely with RPA (OR = 0.69 for fourth quartile vs. inactive, 95% CI: 0.47–1.03). For postmenopausal women younger than 65, ORs were closer to the null. Tests for heterogeneity by age were significant at the $p < 0.10$ level for BMI and RPA, but not alcohol. Among older women, associations were stronger among never users of HRT and for those with ER+/PR+ cancers. The inverse associations with aspirin use did not differ by age.

Conclusions: Interventions targeting modifiable lifestyle factors may reduce the burden of postmenopausal breast cancer among older women.

Keywords: breast cancer, risk factors, alcohol, obesity, physical activity, aspirin

Introduction

Breast cancer remains a great public health concern in the United States, with an estimated 230,000 new cases and more than 40,000 deaths in 2015.[1] The median age at diagnosis is 61 years, and age-adjusted incidence rates for women 65 and older are almost six times as high as the rates for women younger than 65 (242.6 vs. 41.8/100,000, respectively).[1] While breast cancer is frequently diagnosed in older women (65+ years) and older women comprise about 40% of all newly diagnosed cases,[2] these women are underrepresented in most studies of breast cancer. As the demographics of the United States begin to change and with the increase in life expectancy,[3,4] the burden of older women with breast cancer will also increase.

There is some evidence of modification of breast cancer risk factors by age, but this research has been limited primarily to reproductive and hormonal factors.[5–9] Modifiable lifestyle factors have been shown to play a role in the development of breast cancer, some with different patterns of association

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according to menopausal status.[10–14] However, few studies have addressed these modifiable lifestyle factors specifically among this subpopulation of older women and whether they differ from postmenopausal women of younger ages.[7–9,15]

Hormone receptor-positive cancers (defined as any estrogen receptor [ER] or progesterone receptor [PR] positive) are the most frequently diagnosed types of breast cancer among older women in the United States,[16] and the rates of ER+ cases have been rising in the United States and other Western countries.[17,18] Although hormone replacement therapy (HRT) use has declined over the past two decades, non-Hispanic white women and women of higher socioeconomic status are more likely to use HRT.[19] The risk factors evaluated in the study reported here have each been postulated to be associated with breast cancer through an estrogenic pathway.[10,20–23] We therefore hypothesized that the associations with lifestyle risk factors among postmenopausal women may differ by HRT use or by ER/PR case status.

The objective of our study was to investigate whether alcohol intake, body mass index (BMI), recreational physical activity (RPA), and nonsteroidal anti-inflammatory drug (NSAID) use exhibit age-specific associations (<65 years vs. 65+ years) with postmenopausal breast cancer. Secondary aims were to examine these associations stratified by ever HRT use and when restricted to ER+/PR+ cases.

Methods

To address our study objectives, we used case–control resources from the Long Island Breast Cancer Study Project (LIBCSP), a population-based study conducted in Nassau and Suffolk counties on Long Island, New York. Details of the case–control design have been previously published[24] and are summarized below.

Study population

Cases were English-speaking women who were newly diagnosed with a first primary *in situ* or invasive breast cancer, between August 1, 1996, and July 31, 1997. Cases were identified by rapid case ascertainment techniques, which involved daily or weekly contact with pathology departments of 28 hospitals on Long Island and three hospitals in New York City. Physicians of the cases were contacted to confirm the diagnosis and for permission to contact the subjects.

Control women were English-speaking residents of Nassau and Suffolk counties who did not have a personal history of breast cancer. The controls were frequency matched to the expected age distribution of the cases by 5-year age groups. Controls younger than the age of 65 were identified by Waksberg's method of random digit dialing, and controls 65 years and older were randomly identified using Healthcare Finance Administration rosters.

The LIBCSP did not have any age or race restrictions on subject eligibility, resulting in a range of ages from 20 to 98 years, and a sample of women who were predominantly postmenopausal (66.7% of cases and 63.6% of controls) and white (93.8% of cases and 91.8% of controls), which is consistent with the United States Census of these two counties at the time of data collection. The ancillary study reported here includes only the women who were postmenopausal (*e.g.*, only premenopausal were excluded).

Data collection

Information on known and suspected risk factors for breast cancer, including menopausal and reproductive factors, family and personal medical history (such as family history of breast cancer and personal history of benign breast disease and use of mammography), exogenous hormone use, and factors associated with a healthy lifestyle (such as body size, participation in RPA, alcohol use, use of aspirin and other NSAIDs, cigarette smoking) was collected through an interviewer-administered structured questionnaire conducted by trained interviewers in the respondent's home shortly after date of diagnosis/identification. On average, this length of time was about 3 months for cases and 5–6 months for controls.

The main questionnaire was completed by 1508 (82.1%) eligible cases (235 with *in situ* and 1273 with invasive breast cancer) and 1556 (62.7%) eligible controls.

Exposure assessment

Alcohol intake was ascertained during the in-person interview. Women were asked about the type, quantity, and frequency of alcohol intake in each decade of life. Women who answered ''no'' to ever consuming alcoholic beverages at least once a month for 6 months or more were classified as nondrinkers. Women who answered ''yes'' to the same question were asked to report consumption separately for beer, wine, and liquor for six time periods: younger than 20 years, 20–29 years old, 30–39 years old, 40–49 years old, 50–59 years old, and 60 years and older.

Frequency was reported for each alcohol type in units of any of the following time intervals: day, week, month, year, or <1 year. Women also reported how many drinks consumed each time they drank in units appropriate for the type of alcohol (12 oz. bottle of beer, 4 oz. glass of wine, and 1.5 oz. of liquor). That information in addition to standard conversions[25] for grams of ethanol was used to calculate total grams of alcohol consumed per day for the six time periods. Lifetime alcohol intake was constructed using the number of years spent in the age interval as weights for total grams of alcohol consumed per day in each time period.[26]

As a measure of adiposity, BMI, weight (kg)/height $(m)^2$ was calculated from the self-reported height and weight 1 year before the date of diagnosis for cases and date of identification for controls.[27]

RPA was assessed by asking participants about all activities they had engaged in for at least 1 hour per week and 3 months or more in any year over their lifetime. Women who responded never having participated in any physical activity were classified as inactive. For women who replied ever having participated, the activity type, the ages the activity was started and stopped, and the number of hours per week and months per year the activity was engaged in were collected. This information was summed for all activities for each year of the woman's lifetime. The amount of lifetime physical activity was defined as exercise duration, in hours per week, from menarche to the reference date.[28]

NSAID use was defined using the women's report of their intake of aspirin, ibuprofen, and acetaminophen.[29] Ever use was defined as taking aspirin, ibuprofen, and/or acetaminophen at least once per week for 6 months or longer. Although acetaminophen is not an NSAID, it was included for comparison to account for potential misclassification.

HRT use was ascertained by identifying periods of exogenous hormone use during a woman's life. Interviewers used monthly calendars with information on reproductive and other life events to identify periods of HRT use. A color chart of estrogens and progestins marketed in the United States over the life span of the study subjects was shown to participants to enhance recall. Ever use of HRT was defined as history of HRT use in any form (pills, shots, creams, *etc.*) for any period of time before the reference date, including women who were currently using HRT.

Menopausal status was defined using information on date of last menstrual period, prior surgical information on hysterectomy or oophorectomy, cigarette smoking status, and HRT use.[5,6] Women were defined as postmenopausal if the last menstrual period was more than 6 months before the reference date or both ovaries were removed before the reference date. If a woman was using HRT or had undergone a hysterectomy without removing both ovaries, her menopausal status was first classified as unknown (11.8% of subjects).

To reduce the number of women with unknown menopausal status, information on age and smoking status was used. Specifically, a woman with unknown menopausal status was defined as postmenopausal if her reference age was greater than or equal to the 90th percentile age at natural menopause among the controls; for smokers, this age cutoff was 54.8 years, and for nonsmokers the cutoff was 55.4 years.

At the time of the interview, cases were asked to also sign a medical record consent form. Medical records were abstracted to determine clinical characteristics of the breast cancer diagnosis, including ER and PR status of the cases' first primary breast cancer.

Statistical methods

Unconditional logistic regression[30] was used to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between each of the factors of interest (alcohol intake, BMI, RPA, and NSAID use) and breast cancer, adjusting for potential confounders. All models included the frequency matching factor 5-year age group. These models also included an interaction term between the postmenopausal age group and the exposure of interest. The likelihood ratio test compared models with and without the interaction term to assess for effect modification (on a multiplicative scale) by the composite age/menopausal status variable,[30] and significance was defined as $p_{\text{interaction}} < 0.10$.[31,32]

Alcohol intake was evaluated as a categorical variable: never users, <15 g per day, 15–30 g per day, and ≥30 g per day. BMI was categorized using the standard World Health Organization classifications[33,34]: <25.0 kg/m^2, 25.0–29.9 kg/m^2, and >30 kg/m^2. Lifetime RPA was evaluated using inactive women (women reported never engaging in RPA) and quartiles based on the distribution among control women who reported ever engaging in RPA. NSAID use was categorized as a dichotomous variable (ever/never), where ever use was defined as taking aspirin, ibuprofen, and/or acetaminophen at least once a week for 6 months or longer.

Confounding was examined by the following factors, which were selected using a directed acyclic graph[35]: education, race, BMI (WHO categories), RPA (inactive and quartiles), daily caloric intake (kcal/day), migraine headaches (ever been diagnosed by a doctor), aspirin use (ever/never), ibuprofen use (ever/never), acetaminophen use (ever/never), and mammography (ever undergone mammography screening). Models with and without the confounders were compared, and variables were kept in the model if the change in estimate was at least 10% using a backward elimination strategy.

We also examined age/menopause-specific associations among potentially high-risk estrogen-related subgroups. First, we examined these associations further stratified by HRT use (ever/never). Second, we restricted examination of these associations among case women with ER+/PR+ tumors only. A sensitivity analysis, with models restricted to invasive breast cancer only, was also performed, but the results were similar (data not shown).

We used SAS version 9.3 (SAS Institute Inc., Cary, NC) to analyze the data.

Results

Postmenopausal respondents of the LIBCSP (Table 1), who resembled the overall study population, were predominantly white (93.9% of cases and 93.1% of controls) and highly educated women (43.9% of cases and 47.2% of controls had at least some college education) with a large portion (35.9% of cases and 39.9% of controls) of households having an annual income of $50,000+. Mean ages of the cases and controls were similar, where the mean age was 57.2 years for cases and 57.3 years for controls among the younger postmenopausal women (≤65 years), and 73.0 years for cases and 72.7 for controls among postmenopausal women age 65+ years.

Alcohol

Lifetime moderate alcohol intake of 15–30 g per day (about 1–2 drinks), compared to no alcohol intake, was associated with an increased incidence of postmenopausal breast cancer among women 65 and older (multivariable-adjusted OR = 1.79, 95% CI: 1.03–3.12), which was slightly higher in magnitude than the corresponding effect estimate among those younger than 65 years (OR = 1.31, 95% CI: 0.82–2.10, $p_{\text{interaction}} = 0.81$) (Table 2).

With regard to HRT use (Table 2), the magnitude of the positive association with moderate alcohol intake was slightly more pronounced among those who had never used HRT for women 65 and older (OR = 2.25, 95% CI: 1.13–4.47) than among women younger than 65 (OR = 1.60, 95% CI: 0.86–3.00), and the heterogeneity of the two ORs was not statistically significant ($p_{\text{interaction}} = 0.54$). Effect estimates for women who had ever used HRT, for both those younger than 65 and 65+, were similar ($p_{\text{interaction}} = 1.00$) and close to null.

Among women 65 years and older with ER+/PR+ cancer (Table 2), light (<15 g/day) and moderate alcohol intake, compared with no alcohol intake, were associated with an increased OR for postmenopausal breast cancer (OR = 1.38, 95% CI: 0.96–1.98 and OR = 1.76, 95% CI: 0.84–3.62, respectively), but the corresponding estimates among women younger than 65 years were close to 1.0 ($p_{\text{interaction}} = 0.71$). There was no association between heavy alcohol intake (≥30 g/day) and breast cancer incidence.

Body size

The BMI-postmenopausal breast cancer association among women 65 years and older (with ORs of 1.28 [95%

Table 1. Characteristics of the Postmenopausal Women Participants of the Long Island Breast Cancer Study Project, 1996–1997

	Postmenopausal women <65 years		*Postmenopausal women 65+ years*	
	Cases	*Controls*	*Cases*	*Controls*
*Factor (*N, *%)*	*(*N = *488)*	*(*N = *552)*	*(*N = *518)*	*(*N = *438)*
Age [mean years (SD)]	57.2 (5.6)	57.3 (5.5)	73.0 (5.6)	72.7 (6.1)
Race				
White	454 (93.0)	502 (90.9)	488 (94.8)	420 (95.9)
Black	23 (4.7)	34 (6.2)	22 (4.3)	13 (3.0)
Other[a]	11 (2.3)	16 (2.9)	5 (1.0)	5 (1.1)
Education				
<High school	52 (10.7)	42 (7.6)	112 (21.8)	90 (20.6)
High school graduate	189 (38.8)	209 (37.9)	209 (40.7)	181 (41.4)
Some college or more	246 (50.5)	181 (41.4)	193 (37.6)	166 (38.0)
Annual household income				
<$25,000	50 (10.3)	75 (13.6)	206 (40.0)	176 (40.3)
$25,000–$49,999	169 (34.7)	182 (33.0)	217 (42.1)	161 (36.8)
$50,000+	268 (55.0)	295 (53.4)	92 (17.9)	100 (22.9)
BMI [mean, kg/m^2 (SD)]	27.3 (5.8)	27.1 (6.0)	27.5 (5.7)	26.0 (4.9)
Lifetime physical activity (average hours/week)				
None	105 (22.8)	111 (21.4)	156 (32.3)	118 (28.6)
Q1 (≤2.14)	85 (18.4)	88 (17.0)	81 (16.8)	85 (20.6)
Q2 (2.15–6.35)	102 (22.1)	97 (18.7)	74 (15.3)	58 (14.1)
Q3 (6.36–13.45)	77 (16.7)	121 (23.4)	87 (18.0)	61 (14.8)
Q4 (≥13.46)	92 (20.0)	101 (19.5)	85 (17.6)	90 (21.8)
Lifetime alcohol intake (average g/day)				
Nondrinkers	198 (40.6)	213 (38.7)	231 (44.6)	205 (46.9)
<15	217 (44.5)	267 (48.5)	223 (43.1)	186 (42.6)
15–30	49 (10.0)	40 (7.3)	43 (8.3)	25 (5.7)
≥30	24 (4.9)	31 (5.6)	21 (4.1)	21 (4.8)
Aspirin use (ever)	88 (18.8)	123 (24.5)	132 (26.7)	130 (33.2)
Ibuprofen use (ever)	62 (13.2)	79 (15.6)	33 (6.6)	39 (10.0)
Acetaminophen use (ever)	50 (10.8)	71 (14.0)	47 (9.4)	42 (10.7)
Cigarette smoker (ever)	293 (60.0)	343 (62.3)	266 (51.4)	211 (48.4)
HRT use (ever)	207 (42.5)	220 (39.9)	115 (22.3)	99 (22.6)
Mammography use (ever)	467 (95.7)	504 (91.3)	491 (95.0)	379 (86.5)
Stage of breast cancer				
In situ	87 (17.8)		58 (11.2)	
Invasive	401 (82.2		460 (88.8)	
Hormonal subtype of breast cancer				
ER+/PR+	218 (58.8)		169 (56.5)	
ER+/PR−	77 (20.8)		44 (14.7)	
ER−/PR+	12 (3.2)		18 (6.0)	
ER−/PR−	64 (17.3)		68 (22.7)	

[a]Other race primarily consisted of Asians, Pacific Islanders, and Alaska Natives.
SD, standard deviation; BMI, body mass index; HRT, hormone replacement therapy; ER, estrogen receptor; PR, progesterone receptor.

CI: 0.95–1.73] for BMI 25–29.9, and 1.83 [95% CI: 1.29–2.60] for BMI 30+) was stronger than among women younger than 65 years ($p_{interaction} = 0.07$) (Table 3).

On stratifying by HRT use, we found that increased odds for BMI with postmenopausal breast cancer among women 65 years and older were apparent among non-HRT users ($p_{interaction} = 0.21$) but not among HRT users ($p_{interaction} = 0.82$) (Table 3). For example, among women 65+ years, who did not report using HRT, ORs were 1.20 (95% CI: 0.85–1.69) and 2.14 (95% CI: 1.43–3.20) for overweight and obese BMI, respectively.

Associations were more pronounced among women 65+ years, but not among women younger than 65, with ER+/PR+ breast cancer, with corresponding ORs of 1.59 (95% CI: 1.06–2.39) and 2.92 (95% CI: 1.87–4.56) for overweight and obese women, respectively ($p_{interaction} = 0.01$) (Table 3).

Recreational physical activity

Lifetime average RPA was associated with an ~30% decrease in the odds of postmenopausal breast cancer among women 65+ years (OR = 0.69 for the highest quantile of RPA vs. inactive, 95% CI: 0.46–1.03), but not among women <65 years ($p_{interaction} = 0.05$) (Table 4).

For women who never used HRT, we observed an inverse association with postmenopausal breast cancer among women

Table 2. Odds Ratios and 95% Confidence Intervals for Postmenopausal Breast in Relation to Alcohol Intake, Long Island Breast Cancer Study Project 1996–1997

Lifetime alcohol use (g/day)	*Postmenopausal women <65 years*				*Postmenopausal women 65+ years*				p *for interaction*
	Cases	*Controls*	*OR*[a]	*95% CI*[a]	*Cases*	*Controls*	*OR*[a]	*95% CI*[a]	
Overall	*N* = 488	*N* = 552			*N* = 518	*N* = 438			
Nondrinkers	198 (40.6)	213 (38.7)	1.00		231 (44.6)	205 (46.9)	1.00		
<15	217 (44.5)	267 (48.5)	0.87	0.66–1.14	223 (43.1)	186 (42.6)	1.10	0.83, 1.46	
15–30	49 (10.0)	40 (7.3)	1.31	0.82–2.10	43 (8.3)	25 (5.7)	1.79	1.03, 3.12	
≥30	24 (4.9)	31 (5.6)	0.89	0.50–1.59	21 (4.1)	21 (4.8)	0.96	0.50, 1.85	0.81
Never used HRT	*N* = 280	*N* = 331			*N* = 400	*N* = 339			
Nondrinkers	134 (47.9)	143 (43.2)	1.00		186 (46.5)	168 (49.7)	1.00		
<15	106 (37.9)	148 (44.7)	0.83	0.58–1.18	168 (42.0)	138 (40.8)	1.15	0.83, 1.59	
15–30	29 (10.4)	21 (42.0)	1.60	0.86–3.00	31 (7.8)	16 (4.7)	2.25	1.13, 4.47	
≥30	11 (3.9)	19 (5.7)	0.70	0.31–1.59	15 (3.8)	16 (4.7)	0.97	0.45, 2.09	0.54
Ever used HRT	*N* = 207	*N* = 220			*N* = 115	*N* = 99			
Nondrinkers	64 (30.9)	69 (31.5)	1.00		42 (36.5)	37 (37.4)	1.00		
<15	110 (53.1)	119 (54.3)	0.87	0.56–1.36	55 (47.8)	48 (48.5)	0.95	0.52, 1.75	
15–30	20 (9.7)	19 (48.7)	1.11	0.53–2.33	12 (10.4)	9 (9.1)	1.10	0.41–2.96	
≥30	13 (6.3)	12 (5.5)	0.99	0.41–2.37	6 (5.2)	5 (5.1)	0.95	0.26–3.45	1.00
ER+/PR+ cases	*N* = 169	*N* = 552			*N* = 218	*N* = 438			
Nondrinkers	67 (39.6)	213 (38.7)	1.00		89 (40.8)	205 (46.9)	1.00		
<15	82 (48.5)	267 (48.5)	0.99	0.68–1.45	105 (48.2)	186 (42.6)	1.38	0.96–1.98	
15–30	13 (7.7)	40 (7.3)	1.09	0.54–2.18	14 (6.4)	25 (5.7)	1.76	0.84–3.68	
≥30	7 (4.1)	31 (5.6)	0.86	0.35–1.07	10 (4.6)	21 (4.8)	1.18	0.52–2.69	0.71

[a]Adjusted for age, BMI, and mammography.
OR, odds ratio; CI, confidence interval.

65+ years (OR = 0.65, 95% CI: 0.41–1.02) and null estimate for women younger than 65 (Table 4), but the effect estimates were based on small numbers. Similar patterns were observed among ever HRT users, although imprecise.

Finally, the strongest inverse association with RPA was noted for women diagnosed with ER+/PR+ postmenopausal breast cancer who were 65 years or older (OR = 0.62, 95% CI: 0.37–1.05), which was not evident among women younger than 65 (OR = 1.31, 95% CI: 0.76–2.26, $p_{\text{interaction}} = 0.01$) (Table 4).

Nonsteroidal anti-inflammatory drugs

As shown in Table 5, aspirin was associated with decreased odds of postmenopausal breast cancer, among women 65 and older (OR = 0.74, 95% CI: 0.55–1.00) as well

Table 3. Odds Ratios and 95% Confidence Intervals for Postmenopausal Breast in Relation to Body Mass Index, Long Island Breast Cancer Study Project 1996–1997

BMI (kg/m^2)	*Postmenopausal women <65 years*				*Postmenopausal women 65+ years*				p *for interaction*
	Cases	*Controls*	*OR*[a]	*95% CI*[a]	*Cases*	*Controls*	*OR*[a]	*95% CI*[a]	
Overall	*N* = 488	*N* = 552			*N* = 518	*N* = 438			
<25	201 (41.8)	246 (45.1)	1.00		231 (44.6)	205 (46.9)	1.00		
25–29.9	155 (32.2)	158 (29.0)	1.17	0.88–1.57	43 (8.3)	25 (5.7)	1.28	0.95–1.73	
≥30	125 (26.0)	141 (25.9)	1.09	0.80–1.48	21 (4.1)	21 (4.8)	1.83	1.29–2.60	0.07
Never used HRT	*N* = 280	*N* = 331			*N* = 400	*N* = 339			
<25	94 (34.2)	133 (40.8)	1.00		140 (35.6)	149 (45.6)	1.00		
25–29.9	88 (32.0)	99 (30.4)	1.19	0.80–1.77	135 (34.4)	118 (36.1)	1.20	0.85–1.69	
≥30	93 (33.8)	94 (28.8)	1.37	0.92–2.04	118 (30.0)	60 (18.4)	2.14	1.43–3.20	0.21
Ever used HRT	*N* = 207	*N* = 220			*N* = 115	*N* = 99			
<25	106 (51.7)	112 (51.4)	1.00		45 (39.5)	44 (44.9)	1.00		
25–29.9	67 (32.7)	59 (27.1)	1.24	0.79–1.94	50 (43.9)	33 (33.7)	1.52	0.82–2.82	
≥30	32 (15.6)	47 (21.6)	0.69	0.41–1.19	19 (16.7)	21 (21.4)	0.90	0.42–1.93	0.82
ER+/PR+ cases	*N* = 169	*N* = 552			*N* = 218	*N* = 438			
<25	67 (40.1)	246 (45.1)	1.00		64 (29.8)	193 (45.4)	1.00		
25–29.9	56 (33.5)	158 (29.0)	1.24	0.82–1.87	79 (36.7)	151 (35.5)	1.59	1.06–2.39	
≥30	44 (26.4)	141 (25.9)	1.13	0.73–1.75	72 (33.5)	81 (19.1)	2.92	1.87–4.56	0.01

[a]Adjusted for age and mammography.

Table 4. Odds Ratios and 95% Confidence Intervals for Postmenopausal Breast in Relation to Recreational Physical Activity, Long Island Breast Cancer Study Project 1996–1997

Lifetime RPA (hours/week)	*Postmenopausal women <65 years*				*Postmenopausal women 65+ years*				p *for interaction*
	Cases	*Controls*	*OR*[a]	*95% CI*[a]	*Cases*	*Controls*	*OR*[a]	*95% CI*[a]	
Overall	*N* = 488	*N* = 552			*N* = 518	*N* = 438			
None	105 (22.8)	111 (21.4)	1.00		156 (32.3)	118 (28.6)	1.00		
Q1 (≤2.14)	85 (18.4)	88 (17.0)	1.05	0.69–158	81 (16.8)	85 (20.6)	0.69	0.46–1.03	
Q2 (2.15–6.35)	102 (22.1)	97 (18.7)	1.11	0.75–1.65	74 (15.3)	58 (14.1)	0.91	0.59–1.41	
Q3 (6.36–13.45)	77 (16.7)	121 (23.4)	0.67	0.45–1.00	87 (18.0)	61 (14.8)	1.08	0.71–1.65	
Q4 (≥13.46)	92 (20.0)	101 (19.5)	0.99	0.66–1.47	85 (17.6)	90 (21.8)	0.69	0.47–1.03	0.05
Never used HRT	*N* = 280	*N* = 331			*N* = 400	*N* = 339			
None	70 (26.3)	74 (24.1)	1.00		125 (33.3)	96 (30.0)	1.00		
Q1 (≤2.14)	45 (16.9)	50 (16.3)	1.05	0.61–1.80	61 (16.3)	61 (19.1)	0.74	0.47–1.17	
Q2 (2.15–6.35)	57 (21.4)	61 (19.9)	1.10	0.66–1.83	61 (16.3)	45 (14.1)	1.00	0.62–1.64	
Q3 (6.36–13.45)	40 (15.0)	66 (21.5)	0.67	0.40–1.14	65 (17.3)	47 (14.7)	1.06	0.66–1.73	
Q4 (≥13.46)	54 (20.3)	56 (18.2)	1.09	0.65–1.82	63 (16.8)	71 (22.2)	0.65	0.41–1.02	0.27
Ever used HRT	*N* = 207	*N* = 220			*N* = 115	*N* = 99			
None	35 (18.0)	37 (17.5)	1.00		30 (28.6)	22 (23.9)	1.00		
Q1 (≤2.14)	40 (20.6)	38 (18.0)	0.99	0.51–1.92	20 (19.1)	24 (26.1)	0.54	0.24–1.26	
Q2 (2.15–6.35)	45 (23.2)	36 (17.1)	1.14	0.59–2.20	13 (12.4)	13 (14.1)	0.59	0.22–1.57	
Q3 (6.36–13.45)	36 (18.6)	55 (26.1)	0.63	0.33–1.20	21 (20.0)	14 (15.2)	1.00	0.41–2.47	
Q4 (≥13.46)	38 (19.6)	45 (21.3)	0.91	0.47–1.75	21 (20.0)	19 (20.7)	0.75	0.31–1.80	0.34
ER+/PR+ cases	*N* = 169	*N* = 552			*N* = 218	*N* = 438			
None	35 (21.3)	111 (21.4)	1.00		67 (32.2)	118 (28.6)	1.00		
Q1 (≤2.14)	26 (15.9)	88 (17.0)	1.00	0.55–1.83	34 (16.4)	85 (20.6)	0.70	0.42–1.18	
Q2 (2.15–6.35)	38 (23.2)	97 (18.7)	1.31	0.76–2.28	29 (13.9)	58 (14.1)	0.88	0.50–1.53	
Q3 (6.36–13.45)	26 (15.9)	121 (23.4)	0.68	0.38–1.22	46 (22.1)	61 (14.8)	1.33	0.80–2.22	
Q4 (≥13.46)	39 (23.8)	101 (19.5)	1.31	0.76–2.26	32 (15.4)	90 (21.8)	0.62	0.37–1.05	0.01

[a]Adjusted for age, BMI, and mammography

as those younger than 65 (OR = 0.73, 95% CI: 0.53–0.99, $p_{\text{interaction}} = 0.97$).

While ibuprofen use was associated with an imprecise decreased odds of postmenopausal breast cancer among older women (OR = 0.65, 95% CI: 0.39–1.10), which was close to null for women younger than 65 ($p_{\text{interaction}} = 0.43$). Acetaminophen use was not associated with breast cancer incidence in either group of postmenopausal women.

When we examined these associations stratified by HRT use (Table 5), for women reporting ever use of HRT, there was decreased odds of breast cancer among women younger than 65 (OR = 0.56, 95% CI: 0.35–0.91) for aspirin use, which was not observed in women older than 65 (OR = 0.88, 95% CI: 0.49–1.60), but cell sizes were small. For those never having used HRT, there was a decrease in odds of breast cancer for women 65+ (OR = 0.69, 95% CI: 0.49–0.98) for aspirin use and a null association for women younger than 65 (OR = 0.90, 95% CI: 0.58–1.39).

Finally, when examining ER+/PR+ cases, aspirin use was associated with a 37% decreased incidence in postmenopausal women 65 and older (95% CI: 0.43–0.94), but not among women younger than 65 (OR = 0.73, 95% CI: 0.46–1.14) (Table 5).

Discussion

Among this population-based sample of women, associations between lifetime alcohol intake, BMI, lifetime RPA and postmenopausal breast cancer were stronger among women 65 years and older, than among women younger than 65. Furthermore, there was some suggestion that among those who never used HRT and those with ER+/PR+ cancers, these associations were generally more pronounced among women 65 years and older, but our effect estimates were imprecise. The only exception to this general finding is that use of aspirin and other NSAIDs was similarly inversely associated with postmenopausal breast cancer regardless of age.

Our findings of stronger associations between each of the modifiable risk factors and ER+/PR+ breast cancer underscore the importance of the estrogen pathway in breast carcinogenesis.[10,20–23] Furthermore, hormone responsive tumors are the predominant type of breast cancer among American women of all racial groups.[16] Thus, although our findings are based on a sample of primarily white women, our results may be generalizable to all women diagnosed with ER+/PR+ tumors, given it is unlikely that that the biology of breast cancer subtypes varies by race.

Similarly, associations for BMI and RPA (and to a more limited extent alcohol intake) with postmenopausal breast cancer in older women were more pronounced among non-HRT users. These results suggest that the impact of HRT on estrogen levels, and hence breast cancer incidence, may be dominant, and that any additional estrogen-like influence from BMI or physical activity cannot be discerned among women who are estrogen swamped from exogenous sources.[36–38]

Only four studies have considered whether modifiable lifestyle breast cancer risk factors vary by age and menopausal status, including Trentham-Dietz et al.[7] using the case–control Collaborative Breast Cancer Study (from Wisconsin, Massachusetts, and New Hampshire); Brinton et al.[8]

Table 5. Odds Ratios and 95% Confidence Intervals for Postmenopausal Breast in Relation to Nonsteroidal Anti-Inflammatory Drug Use, Long Island Breast Cancer Study Project 1996–1997

	Postmenopausal women <65 years				*Postmenopausal women 65+ years*				p *for*
NSAID use	*Cases*	*Controls*	*OR*[a]	*95% CI*[a]	*Cases*	*Controls*	*OR*[a]	*95% CI*[a]	*interaction*
Overall	*N*=488	*N*=552			*N*=518	*N*=438			
Aspirin use									
Never	380 (81.2)	380 (75.6)	1.00		362 (73.3)	262 (66.8)	1.00		
Ever	88 (18.8)	123 (24.5)	0.73	0.53–0.99	132 (26.7)	130 (33.2)	0.74	0.55–1.00	0.97
Ibuprofen use									
Never	408 (86.8)	428 (84.4)	1.00		464 (93.4)	352 (90.0)	1.00		
Ever	62 (13.2)	79 (15.6)	0.85	0.59–1.24	33 (6.6)	39 (10.0)	0.65	0.39–1.10	0.43
Acetaminophen use									
Never	413 (89.2)	435 (86.0)	1.00		451 (90.6)	349 (89.3)	1.00		
Ever	50 (10.8)	71 (14.0)	0.76	0.50–1.14	47 (9.4)	42 (10.7)	0.82	0.52–1.30	0.74
Never used HRT	*N*=280	*N*=331			*N*=400	*N*=339			
Aspirin use									
Never	216 (81.2)	237 (79.8)	1.00		288 (75.6)	205 (68.1)	1.00		
Ever	50 (18.8)	60 (20.2)	0.90	0.58–1.39	93 (24.4)	96 (31.9)	0.69	0.49–0.98	0.35
Ibuprofen use									
Never	234 (87.0)	259 (86.3)	1.00		359 (93.7)	272 (91.0)	1.00		
Ever	35 (13.0)	41 (13.7)	0.92	0.55–1.55	24 (6.3)	27 (9.0)	0.69	0.37–1.27	0.37
Acetaminophen use									
Never	237 (47.5)	262 (87.6)	1.00		348 (90.9)	272 (91.0)	1.00		
Ever	29 (10.9)	37 (12.4)	0.85	0.49–1.49	35 (9.1)	27 (9.0)	0.91	0.52–1.58	0.87
Ever used HRT	*N*=207	*N*=220			*N*=115	*N*=99			
Aspirin use									
Never	163 (81.1)	143 (69.4)	1.00		73 (65.8)	57 (62.6)	1.00		
Ever	38 (18.9)	63 (30.6)	0.56	0.35–0.91	38 (34.2)	34 (37.4)	0.88	0.49–1.60	0.26
Ibuprofen use									
Never	173 (86.5)	169 (81.6)	1.00		104 (92.9)	80 (87.0)	1.00		
Ever	27 (13.5)	38 (18.4)	0.78	0.44–1.38	8 (7.1)	12 (13.0)	0.64	0.23–1.79	0.67
Acetaminophen use									
Never	175 (89.3)	173 (83.6)	1.00		101 (89.4)	77 (83.7)	1.00		
Ever	21 (10.7)	34 (16.4)	0.66	0.35–1.25	12 (10.6)	15 (16.3)	0.58	0.24–1.39	0.94
ER+/PR+ cases	*N*=169	*N*=552			*N*=218	*N*=438			
Aspirin use									
Never	133 (81.1)	380 (75.6)	1.00		160 (75.1)	262 (66.8)	1.00		
Ever	31 (18.9)	123 (24.5)	0.73	0.46–1.14	53 (24.9)	130 (33.2)	0.63	0.43–0.94	0.78
Ibuprofen use									
Never	141 (85.5)	428 (84.4)	1.00		194 (91.1)	352 (90.0)	1.00		
Ever	24 (14.6)	79 (15.6)	1.03	0.62–1.72	19 (8.9)	39 (10.0)	0.88	0.47–1.65	0.97
Acetaminophen use									
Never	141 (87.6)	435 (86.0)	1.00		193 (89.8)	349 (89.3)	1.00		
Ever	20 (12.4)	71 (14.0)	0.95	0.55–1.66	22 (10.2)	42 (10.7)	0.83	0.47–1.49	0.98

[a]Adjusted for covariates as follows: aspirin adjusted for age, BMI, and mammography; ibuprofen adjusted for age, BMI, mammography, and aspirin use; acetaminophen adjusted for age, BMI, mammography, and aspirin use.
NSAID, nonsteroidal anti-inflammatory drug.

using the cohort National Institutes of Health-American Association of Retired Persons (NIH-AARP) Study (from six United States and two metropolitan areas); Poynter et al.[9] using the cohort Iowa Women's Health Study (IWHS); and La Vecchia et al.[15] using data from three Italian case–control studies. Of the modifiable lifestyle factors examined in these studies, effect estimates did not vary across age groups except for BMI and alcohol intake. Thus, with the exception of physical activity, the lifestyle factor findings from other studies are mostly consistent with those reported here in the LIBCSP study population.

In addition to study design and study location, another issue that may have influenced any differences in study findings includes variations in exposure assessment. For example, the interview used by Trentham-Dietz et al.[7] was 40 minutes in duration and was administered by phone, while the NIH-AARP study[8] and IWHS[9] used mailed questionnaires. In comparison, the LIBCSP used a longer (100-minute) questionnaire format that was administered in-person and allowed for more comprehensive assessments. For example, we assessed adult physical activity across the life course using the approach developed by Bernstein et al.,[39] which generally takes about 20–30 minutes to administer. Similarly detailed assessments were used to assess life course body size and alcohol intake in the LIBCSP.

Still another variation in approaches includes the age range in the case–control studies, which were truncated in the studies by Trentham-Dietz et al.[7] and La Vecchia et al.,[15]

whereas our study had no upper age limit; thus, findings from the studies could also reflect differences in risk factor profiles by age. Another factor that may explain any inconsistencies in the results is the age category that each of the studies created. Our study and the study by Trentham-Dietz et al.[7] defined older women as those 65 and older (which maximizes study power within subgroups). In comparison, the studies by Brinton et al.[8] and La Vecchia et al.[15] used categories of 50–59 years, 60–69 years, and 70± years, while the study by Poynter et al.[9] used <75 years and 75± years age categories.

The study reported here has several limitations. There is a potential for bias in self-reported data, but given that our effect estimates are most pronounced in the ER+/PR+ cases, which is a biologically plausible subgroup, our findings may be less likely to be due to recall bias. Control LIBCSP participants had a lower response rate than cases,[24] which is a common occurrence in population-based case–control studies on breast cancer.[40] Despite our fairly large sample size, we lacked sufficient study power to consider more detailed exposure assessments (for example, aspirin dose), which would help to refine risk reduction strategies.

Strengths of our study include that the LIBCSP is population based, which enhances generalizability of our results. However, because the vast majority of women in this study were non-Hispanic white women, this may limit generalizability to this high-risk subgroup only. The LIBCSP questionnaire allowed for comprehensive assessment of multiple breast cancer risk factors over the life course. One particular strength is that the LIBCSP had no upper age limit for subject eligibility, including women up to 98 years, which aided our ability to consider whether risk factors for postmenopausal breast cancer vary by age.

Our findings are encouraging because they suggest that breast cancer incidence among older women may be, in part, modifiable. Earlier findings in the same LIBCSP study population found that other risk factors for breast cancer, including reproductive history and exogenous hormone use,[5,6] were no longer evident among women 65 years and older. The only exception was breastfeeding, where inverse associations persisted among the older women. Thus, it is possible that future interventions, focused on the modifiable factors that we consider here (alcohol intake, body size, physical activity, and aspirin use), could be implemented across the life course to reduce the incidence of postmenopausal breast cancer among older women.

Conclusions

In this population-based study with lifestyle factor information throughout the lifetime, we found that for women 65 years and older, alcohol intake and obesity increased postmenopausal breast cancer incidence, whereas RPA and aspirin use decreased incidence. In addition, these associations may be most pronounced for never users of HRT and for ER+/PR+ cancers. Our results suggest that life course interventions targeting these modifiable lifestyle factors could reduce the burden of postmenopausal breast cancer among older women.

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