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ORIGINAL PAPER

Breast cancer risk in older women: results from the NIH-AARP Diet and Health Study

Louise A. Brinton · Llewellyn Smith · Gretchen L. Gierach · Ruth M. Pfeiffer · Sarah J. Nyante · Mark E. Sherman · Yikyung Park · Albert R. Hollenbeck · Cher M. Dallal

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Abstract
Background Divergent risk factors exist for premenopausal and postmenopausal breast cancers, but it is unclear whether differences by age exist among postmenopausal women.
Methods We examined relationships among 190,872 postmenopausal women, ages 50–71 years recruited during 1995–1996 for the NIH-AARP Diet and Health Study, in whom 7,384 incident invasive breast carcinomas were identified through 2006. Multivariable Cox regression hazard ratios (HRs) and 95 % confidence intervals (CIs) were estimated for breast cancer risk factors by age (50–59, 60–69, ≥70 years).
Results The only factor showing significant statistical heterogeneity by age ($p_{het} = 0.001$) was menopausal hormone therapy duration, but trends were apparent across all ages and the strongest association prevailed among women 60–69 years. Although other risk factors did not show statistically significant heterogeneity by age, we did observe attenuated relations for parity and late age at first birth among older women [e.g., HR for age at first birth ≥30 vs. 20–24 = 1.62 (95 % CI 1.23–2.14) for women 50–59 years vs. 1.12 (0.96–1.31) for ≥70 years]. In contrast, risk estimates associated with alcohol consumption and BMI tended to be slightly stronger among the oldest subjects [e.g., HR for BMI ≥35 vs. 18.5–24.9 = 1.24 (95 % CI 0.97–1.58) for 50–59 years vs. 1.46 (1.26–1.70) for ≥70 years]. These differences were somewhat more pronounced for estrogen receptor positive and ductal cancers, tumors predominating among older women. Breast cancer family history, physical activity, and previous breast biopsies did not show divergent associations by age.
Conclusion Although breast cancer risk factor differences among older women were not large, they may merit further consideration with respect to individualized risk prediction.

Keywords Breast cancer · Risk · Age · Older women

L. A. Brinton (✉) · L. Smith · G. L. Gierach · R. M. Pfeiffer · S. J. Nyante · Y. Park · C. M. Dallal
Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD 20892, USA
e-mail: brinton@nih.gov

M. E. Sherman
Division of Cancer Prevention, National Cancer Institute, Bethesda, MD 20892, USA

A. R. Hollenbeck
AARP, Washington, DC, USA

Present Address:
C. M. Dallal
Department of Epidemiology and Biostatistics, School of Public Health, University of Maryland, College Park, MD 20742, USA

Introduction

It is well documented that breast cancer is strongly influenced by age, with incidence rates that rise rapidly prior to menopause, until they plateau and subsequently show less rapid rate increases [1]. Although it has been demonstrated that breast cancer risk factors differ between premenopausal and postmenopausal women, particularly with respect to the effects of family history of breast cancer, parity and obesity [2], less is known regarding whether there are additional variations in relationships according to age for women experiencing the highest incidence rates—namely postmenopausal women. Age-related differences in risk factor relationships could influence risk prediction

models, but few studies have specifically addressed effects with an emphasis on older women,

The heterogeneity of breast cancer by age is supported by different clinical characteristics, most notably by rising rates of hormone receptor positivity with increasing age [3]. Given that many risk factors differ by hormone receptor status [4], it would be expected that factors should show different patterns according to advanced ages at diagnosis. A few studies have suggested that the risk of breast cancer among women at older ages may be less influenced by reproductive behavior [5–7] and alcohol consumption [5], and more influenced by menopausal factors [5] and body mass [8], but it is unclear to what extent these differences reflect effects of divergent clinical characteristics. This includes not only hormone receptor status, but also histology and stage, factors that may be influenced by variations in screening practices for different ages.

Within the NIH-AARP Diet and Health Study, we had a unique opportunity to examine whether breast cancer risk factor associations changed with advancing ages among a large series of postmenopausal women.

Methods

Study population

The NIH-AARP Diet and Health Study was established in 1995–1996 when a questionnaire requesting information on demographic characteristics, dietary intake, and health-related behaviors was sent to 3.5 million AARP members. The study design has been described in detail elsewhere [9]. Those initially contacted were AARP members 50–71 years old residing in six US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and two metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). A total of 617,119 people (17.6 %) returned the questionnaire. Excluded were individuals who skipped substantial portions of the questionnaire, made significant recording errors or indicated eating <10 foods, did not indicate sex, or died or moved before their questionnaire was scanned. After these exclusions, the baseline study population included 241,227 female participants. Address changes were tracked annually through the National Change of Address Service, the processing of undeliverable mail and directly from participants. Vital status was tracked using the Social Security Administration Death Master File, the National Death Index, cancer registry linkages, and mailing responses. The NIH-AARP Diet and Health Study was approved by the Special Studies Institutional Review Board of the US National Cancer Institute.

Cancer incidence

Incident cases of breast cancer were identified by probabilistic linkage to cancer registries in the eight states of the cohort as well as Arizona, Nevada, and Texas in order to capture cancers occurring among participants who moved to those states during the follow-up period. These linkages were based on annually updated residence information and used first and last name, address, sex, date of birth, and social security number from the baseline questionnaire. The states of the cohort were chosen in part because their registries had been shown to validly identify at least 90–95 % of cancer cases [10]. All suspected matches underwent review. Dates of diagnosis and tumor characteristics were obtained from the registries. Histology was available from all eleven state registries and was defined using the International Classification of Diseases for Oncology Codes, 3rd edition [11]. Any primary incident invasive carcinoma of the breast was considered for this analysis, which included ductal (8,500, 8,523), lobular (8,520, 8,524), mixed (8,522), and other cases. Estrogen receptor (ER) status was available from eight of the state registries (not Florida, Pennsylvania, or Texas) and was classified as ER positive (+), ER negative (−), borderline or unknown.

Exposure assessment

Study participants were asked to provide information on demographic characteristics (e.g., race/ethnicity, level of education, and marital status), dietary characteristics (e.g., alcohol and caloric intake), and medical history (e.g., family history of cancer and previous biopsies). In addition, participants reported their current height and weight which was used to determine a participant's current body mass index (BMI, kg/m^2). A period of vigorous physical activity was defined as one of at least 20 min in the past 12 months that caused an increase in breathing or heart rate, or worked up a sweat. Women were also asked for the age of their first menstrual period, of the birth of their first child, and of their last menstrual period, as well as number of live births. In addition, they were asked whether they had even taken menopausal hormone therapy (MHT) and the duration of their use (years).

Analytic population

For the present analysis, we excluded 15,760 participants whose questionnaires were completed by proxies, 23,957 who self-reported or were diagnosed with any cancer other than non-melanoma skin cancer before baseline, 18 who died or were diagnosed with cancer on the first day of follow-up, 1,300 who had extreme values for BMI (defined

as more than two inter-quartile ranges above the 75th ‰ or below the 25th ‰ of log-transformed BMI), 7,210 who reported premenopausal status, and 2,110 with unknown menopausal status. The final analytic population included 190,872 women, of whom 7,384 were diagnosed with invasive breast carcinoma during follow-up.

Statistical analysis

We used Cox proportional hazards regression (SAS 9.2.3 software, SAS Institute Inc., Cary, NC, USA), with age as the timescale to estimate the hazard ratios (HRs) and 95 % confidence intervals (CIs) of developing breast cancer in each age interval. Follow-up for a woman started at age at cohort entry and ended at an invasive breast cancer diagnosis or censoring. Women were censored at the earliest of the following: the end of follow-up (31 December 2006), an in situ (or unknown behavior) breast cancer diagnosis, or the date on which the participant moved out of the registry area or died from any cause. Women contributed person time to one or more age intervals (age 50–59, 69–69, ≥70 years) based on their ages at entry into and exit from the cohort.

Multivariable models were adjusted for established risk factors as determined by previous studies of postmenopausal breast cancer. Covariates included race (white, nonwhite, unknown), education level (high school or less, post high school or some college, college graduate, post-graduate, unknown), marital status (married, unmarried, unknown), age at menarche (≤10, 11–12, 13–14, ≥15 years, unknown), parity and age at first live birth (nulliparous, <20, 20–24, 25–29, ≥30 years, unknown), age and type of menopause (natural menopause at age: <45, 45–49, 50–54, ≥55 years, surgical/medical, unknown), use of MHT (never, former, current, unknown), BMI (<18.5, 18.5–24.9, 25–29.9, 30–34.9, ≥35.0 kg/m^2, unknown), alcohol intake (nondrinker, ≤5.0, 5.01–10.0, 10.01–20.0, 10.01–35.0, >35.0 g/day), history of breast cancer in a first-degree relative (no, yes, unknown), and number of previous breast biopsies (0, 1, ≥2, unknown). Statistical heterogeneity in the hazard ratios across the three age intervals was assessed using the Wald's test (p_{het}).

In addition, we examined whether the relationship between risk factors and breast cancer incidence differed by age and by ER status (ER+, ER−) or histologic type (ductal, lobular). For example, to obtain ER+ specific HR estimates, we fit Cox regression models where ER+ cases were defined as events and ER− cases were censored at the date of their diagnosis. In analyses of ER status, only those participants who reported living in a state that reported ER status at baseline were eligible. To examine the relationships between BMI, menopausal hormone use, and breast cancer risk, we assessed duration of MHT use according to three categories of BMI: normal/underweight (<25 kg/m^2), overweight (25–29.9 kg/m^2), and obese (≥30 kg/m^2). We also evaluated the converse, namely whether BMI relations differed according to menopausal hormone status.

To address potential biases, we ran sensitivity analyses, separately excluding women with extreme values for total caloric intake ($n = 1{,}679$), those who reported being in poor or fair health at baseline ($n = 24{,}532$), and those who reported no or infrequent recent breast cancer screening ($n = 38{,}041$) (among a subset of postmenopausal subjects who completed a second risk factor questionnaire). We also truncated follow-up time at 30 June 2002 (the date of the end of an influential study on menopausal hormone use and breast cancer) [12], changing the status of current hormone users to former at 30 June 2002. Finally, we assessed the impact of adjusting for year of birth in 5-year categories.

The proportional hazards assumption was evaluated by visual examination of Kaplan–Meir plots and by assessing time-dependent interactions between each exposure and age; no deviations of the assumption were observed (all $p > 0.05$). Tests for linear trend across categories of covariates were estimated from the Wald's test using an ordinal variable. p values of <0.05 were considered statistically significant. All tests of significance were two-tailed. Analyses were conducted using SAS 9.2.3 software, SAS Institute Inc., Cary, NC, USA.

Results

During an average 9.3 years (SD 2.7) of follow-up, the 190,872 women contributed the following person-years (pyrs) to their corresponding age intervals: 50–59 years (1,778,664 pyrs), 60–69 years (1,761,243 pyrs), and ≥70 years (1,720,507 pyrs). Among the 7,384 breast cancer cases, 809 (11.0 %) were diagnosed between 50 and 59 years of age, 3,864 (52.3 %) between 60 and 69 years, and 2,711 (36.7 %) at ages 70 years or beyond.

Table 1 shows the relationship of various reproductive factors with breast cancer risk for all study subjects and stratified by the three different age groups. Although there was no statistically significant heterogeneity across the three age groups for any of the parameters of interest–which included age at menarche, number of births, age at first birth, and age and type of menopause—there were some suggestive associations observed.

A trend of decreasing risk with increasing age at menarche that was observed among all cases was largely driven by a relationship among the women 70 years of age or older (RR for ≥15 vs. <10 = 0.81, 95 % CI 0.66–0.99), with little evidence that this factor related to risk among the younger women. In contrast, the number of births was

Table 1 Association between menstrual and reproductive history and breast cancer risk among postmenopausal women in the NIH-AARP Diet and Health Study, overall and stratified by age of follow-up

Characteristics	Overall				Age of follow-up categories (years)									
	Person-years	Cases (n = 7,384)	HR[1]	95 % CI	50–59			60–69			≥70			$p^2_{heterogeneity}$
					Cases n = 809	HR[1]	95 % CI	Cases n = 3,864	HR[1]	95 % CI	Cases n = 2,711	HR[1]	95 % CI	
Age at menarche (years)														
≤10	119,197	488	1.00	–	66	1.00	–	268	1.00	–	154	1.00	–	0.36
11–12	745,423	3,173	1.02	(0.93–1.12)	387	1.20	(0.92–1.55)	1,632	0.99	(0.87–1.13)	1,154	0.99	(0.84–1.17)	
13–14	740,833	3,070	0.98	(0.89–1.08)	298	1.05	(0.80–1.37)	1,605	0.98	(0.86–1.12)	1,167	0.94	(0.79–1.11)	
≥15	168,620	631	0.91	(0.80–1.02)	57	0.94	(0.65–1.34)	347	0.96	(0.82–1.12)	227	0.81	(0.66–0.99)	
Unknown	6,788													
p_{trend}				0.02			0.20			0.59			0.01	
Parity[3]														
Nulliparous	246,870	1,203	1.00	–	182	1.00	–	624	1.00	–	397	1.00	–	0.36
1	182,436	784	0.91	(0.83–1.00)	117	0.88	(0.69–1.11)	411	0.94	(0.82–1.06)	256	0.88	(0.75–1.03)	
2	458,674	1,879	0.84	(0.78–0.91)	251	0.80	(0.66–0.98)	1,009	0.86	(0.78–0.95)	619	0.83	(0.73–0.94)	
≥3	869,242	3,399	0.81	(0.75–0.86)	246	0.71	(0.58–0.87)	1,743	0.79	(0.72–0.87)	1,410	0.85	(0.76–0.96)	
Unknown	23,638													
p_{trend}				<0.0001			0.001			<0.0001			0.02	
Age at first birth (years)														
Nulliparous	246,870	1,203	1.25	(1.16–1.34)	182	1.34	(1.11–1.63)	624	1.25	(1.13–1.37)	397	1.22	(1.09–1.38)	0.12
<20	314,982	1,062	0.90	(0.84–0.97)	146	0.99	(0.81–1.22)	599	0.91	(0.83–1.00)	317	0.87	(0.76–0.98)	
20–24	776,419	3,044	1.00	–	284	1.00	–	1,606	1.00	–	1,154	1.00	–	
25–29	312,354	1,417	1.13	(1.06–1.21)	117	0.99	(0.79–1.23)	689	1.12	(1.02–1.22)	611	1.18	(1.07–1.31)	
≥30	101,042	520	1.28	(1.16–1.41)	65	1.62	(1.23–2.14)	260	1.35	(1.18–1.54)	195	1.12	(0.96–1.31)	
Unknown	29,194													
p^4_{trend}				<0.0001			0.02			<0.0001			<0.0001	

Table 1 continued

Characteristics	Overall				Age of follow-up categories (years)										$p^{2}_{\text{heterogeneity}}$
	Person-years	Cases (n = 7,384)	HR[1]	95 % CI	50–59			60–69			≥70				
					Cases n = 809	HR[1]	95 % CI	Cases n = 3,864	HR[1]	95 % CI	Cases n = 2,711	HR[1]	95 % CI		
Age and type of menopause															
Natural menopause (years)															
<45	123,272	459	0.84	(0.76–0.92)	36	0.68	(0.48–0.97)	209	0.80	(0.69–0.93)	214	0.91	(0.78–1.06)	0.37	
45–49	287,253	1,190	0.92	(0.86–0.99)	165	1.01	(0.83–1.23)	600	0.94	(0.85–1.04)	425	0.88	(0.78–0.98)		
50–54	497,569	2,276	1.00	–	265	1.00	–	1,154	1.00	–	857	1.00	–		
≥55	109,715	624	1.19	(1.09–1.30)	23	1.08	(0.71–1.66)	344	1.22	(1.08–1.38)	257	1.17	(1.02–1.35)		
Surgical/medical	717,726	2,625	0.73	(0.69–0.78)	308	0.70	(0.59–0.84)	1,409	0.75	(0.69–0.81)	908	0.72	(0.66–0.80)		
Unknown	45,325														
p^{4}_{trend}				<0.0001			0.14			<0.0001			0.001		

[1] Multivariable models adjusted for race, education level, marital status, age at menarche, parity and age at first live birth, age and type of menopause, MHT use, BMI, daily alcohol intake, family history of breast cancer in a first-degree relative, and number of previous breast biopsies

[2] Evaluates heterogeneity across categories of age of follow-up

[3] Multivariable models for parity do not adjust for age at first birth

[4] Trends for age at first birth do not include nulliparous women; trends for age and type of menopause do not include women with surgically/medically induced menopause

inversely related to risk within all three age groups, with some suggestion that it might be somewhat more strongly related to risk among the youngest as opposed to oldest women [HR for ≥3 vs. 0 births = 0.71 (95 % CI 0.58–0.87) for 50–59 years vs. 0.85 (0.76–0.96) for ≥70 years]. Similarly, a significant relationship with late age at first birth was observed within all age groups but was stronger among the youngest women [HR for ≥30 vs. 20–24 years = 1.62 (95 % CI 1.23–2.14) for 50–59 years vs. 1.12 (0.96–1.31) for ≥70 years].

Later age at natural menopause (>55 vs. 50–54 years) was significantly related to increased risk only among the women 60 years of age or older [HR 1.08 (95 % CI 0.71–1.66) for women 50–59 years, 1.22 (1.08–1.38) for 60–69 years, and 1.17 (1.02–1.35) for ≥70 years]. However, there was little difference in the relation of a surgical/medical menopause across the three age groups.

Risk was further examined according to a variety of lifestyle factors, including BMI, frequency of physical activity, alcohol consumption, and duration of MHT use (Table 2). The only factor showing significant heterogeneity by age was duration of MHT use ($p_{\text{het}} = 0.001$). Although there were significant linear trends with years of use in all age groups, the strongest association was observed for women in the 60–69 year age group (HR for ≥10 years MHT = 1.57, 95 % CI 1.43–1.73). In terms of other lifestyle factors, BMI was not significantly related to risk among the youngest age group, but significantly related to risk among the subjects 60 years of age or older [HR for BMI ≥35 vs. 18.5–24.9 kg/m^2 = 1.24 (95 % CI 0.97–1.58) for 50–59 years; 1.39 (1.24–1.57) for 60–69 years; 1.46 (1.26–1.70) for ≥70 years). In contrast, higher frequency of physical activity appeared to be significantly inversely related to risk only among women 60–69 years of age, with little evidence of a relation among the youngest or oldest women. Alcohol consumption was significantly related to risk only among the women 60 years of age or older [HR for >35 g/day vs. nondrinking = 1.10 (95 % CI 0.73–1.66) for 50–59 years, 1.42 (1.21–1.68) for 60–69 years, and 1.54 (1.27–1.87) for ≥70 years].

We also assessed risk in relation to a family history of breast cancer and a history of previous breast biopsies (Table 3). Subjects with a family history of breast cancer were at approximately at 50 % increased risk, which did not vary according to age. Similarly, a history of a previous breast biopsy, which conferred the highest risk if multiple biopsies were reported, remained significantly associated with risk across all three age intervals.

Since effects of BMI have been shown to be strongest in nonhormone users, we also conducted sensitivity analyses restricted to subjects who had never used menopausal hormones. These continued to show somewhat enhanced relationships of BMI among the women diagnosed at the older ages (data not shown).

Table 2 Association between body mass, physical activity, alcohol intake and menopausal hormone therapy (MHT) use and breast cancer risk among postmenopausal women in the NIH-AARP Diet and Health Study, overall and stratified by age of follow-up

Characteristics	Overall				Age of follow-up categories (years)									
	Person-years	Cases $n = 7{,}384$	HR[1]	95 % CI	50–59			60–69			≥70			$p^2_{\text{heterogeneity}}$
					Cases $n = 809$	HR[1]	95 % CI	Cases $n = 3{,}864$	HR[1]	95 % CI	Cases $n = 2{,}711$	HR[1]	95 % CI	
BMI (kg/m^2)														
<18.5	22,611	67	0.73	(0.58–0.93)	9	0.92	(0.47–1.78)	34	0.74	(0.52–1.04)	24	0.68	(0.45–1.02)	0.66
18.5–24.9	740,470	2,977	1.00	–	344	1.00	–	1,535	1.00	–	1,098	1.00	–	
25.0–29.9	568,598	2,362	1.10	(1.05–1.17)	242	1.04	(0.88–1.23)	1,248	1.14	(1.05–1.23)	872	1.08	(0.98–1.18)	
30.0–34.9	254,085	1,100	1.22	(1.13–1.31)	112	1.03	(0.83–1.29)	571	1.22	(1.11–1.35)	417	1.27	(1.13–1.43)	
≥35.0	138,518	652	1.39	(1.27–1.52)	86	1.24	(0.97–1.58)	355	1.39	(1.24–1.57)	211	1.46	(1.26–1.70)	
Unknown	56,580													
p_{trend}				<0.0001			0.14			<0.0001			<0.0001	
Physical activity in the past year														
Never/rarely	389,782	1,653	1.00	–	164	1.00	–	899	1.00	–	590	1.00	–	0.68
1–3 times/ month	253,466	1,069	0.98	(0.90–1.06)	138	0.98	(0.78–1.23)	583	0.93	(0.83–1.03)	348	1.07	(0.93–1.22)	
1–2 times/ week	373,076	1,540	0.95	(0.89–1.02)	191	1.02	(0.83–1.26)	807	0.90	(0.81–0.99)	542	1.02	(0.90–1.14)	
3–4 times/ week	448,834	1,877	0.95	(0.89–1.02)	201	1.04	(0.84–1.28)	958	0.90	(0.82–0.98)	718	1.02	(0.91–1.13)	
≥5 times/ week	292,883	1,160	0.91	(0.85–0.99)	107	0.88	(0.68–1.13)	583	0.86	(0.77–0.95)	470	1.01	(0.90–1.15)	
Unknown	22,821													
p_{trend}				0.02			0.56			0.003			0.97	
Alcohol intake (g/day)														
Nondrinker	528,444	2,046	1.00	–	187	1.00	–	1,032	1.00	–	827	1.00	–	0.57
≤5.0	836,800	3,407	1.01	(0.96–1.07)	421	1.15	(0.96–1.36)	1,821	1.03	(0.96–1.12)	1,165	0.95	(0.87–1.04)	
5.01–10.0	128,848	546	1.05	(0.95–1.15)	68	1.15	(0.87–1.53)	286	1.04	(0.91–1.18)	192	1.04	(0.89–1.22)	
10.01–20.0	160,427	725	1.11	(1.02–1.21)	72	1.12	(0.85–1.47)	376	1.10	(0.98–1.24)	277	1.12	(0.97–1.28)	
20.01–35.0	70,075	343	1.21	(1.08–1.36)	35	1.25	(0.87–1.80)	181	1.22	(1.04–1.43)	127	1.18	(0.98–1.43)	
>35	56,268	317	1.43	(1.27–1.61)	26	1.10	(0.73–1.66)	168	1.42	(1.21–1.68)	123	1.54	(1.27–1.87)	
p_{trend}				<0.0001			0.34			<0.0001			<0.0001	

Table 2 continued

Characteristics	Overall				Age of follow-up categories (years)										$p^2_{\text{heterogeneity}}$
	Person-years	Cases $n = 7{,}384$	HR[1]	95 % CI	50–59				60–69				≥70		
					Cases $n = 809$	HR[1]	95 % CI		Cases $n = 3{,}864$	HR[1]	95 % CI		Cases $n = 2{,}711$	HR[1]	95 % CI	
Duration of MHT use (years)															
Never	780,100	2,912	1.00	–	251	1.00	–		1,347	1.00	–		1,314	1.00	–	0.001
<5	342,906	1,376	1.16	(1.09–1.24)	276	1.28	(1.08–1.53)		744	1.23	(1.12–1.35)		356	1.02	(0.90–1.14)	
5–9	243,209	1,198	1.43	(1.33–1.54)	175	1.58	(1.29–1.94)		753	1.53	(1.40–1.68)		270	1.22	(1.06–1.39)	
≥10	378,865	1,792	1.46	(1.37–1.56)	97	1.30	(1.00–1.69)		966	1.57	(1.43–1.73)		729	1.37	(1.24–1.52)	
Unknown	35,782															
p_{trend}				<0.0001			0.001				<0.0001				<0.0001	

[1] Multivariable models adjusted for race, education level, marital status, age at menarche, parity and age at first live birth, age and type of menopause, MHT use, BMI, daily alcohol intake, family history of breast cancer in a first-degree relative, and number of previous breast biopsies

[2] Evaluates heterogeneity across categories of age of follow-up

As risk factor relationships can also vary by hormone receptor status and/or histology of the tumor, we examined risks within age groups by these parameters (Table 4). The relationships we observed according to the reproductive factors were generally less apparent for the ER negative (−) than positive (+) tumors, possibly reflecting small numbers among the former cases. Among the ER+ tumors, we continued to observe patterns generally similar to those observed for all tumors—namely significant heterogeneity by age for MHT duration, age at menarche relations that were restricted to the women diagnosed at the oldest ages, and somewhat enhanced associations for numbers of births among the youngest women. Further, for the ER+ tumors, BMI and alcohol consumption were most strongly related to risk among the oldest women, although the *p* for heterogeneity across age groups was not significant. In contrast to the other risk factors, a late age at first birth was a risk factor for both ER− and ER+ tumors, with relationships predominating among the younger participants.

We also assessed risks within subgroups of tumors defined by histology (ductal vs. lobular) (Table 5). The rarer lobular tumors generally showed inconsistent relationships with most of the established breast cancer risk factors, possibly owing to small numbers. However, among the ductal tumors, we continued to observe support for possible age heterogeneity in directions similar to what had generally been observed among all cases combined, as well as among the ER+ cases. Thus, ductal carcinoma risk associations with parity and age at first birth were slightly attenuated among the older women, and alcohol consumption slightly enhanced. Increased risk of ductal carcinoma associated with MHT use also showed significant heterogeneity by age, although there were significant trends with increasing durations of use in all age groups.

A variety of sensitivity analyses, both excluding women (e.g., subjects with extreme values for caloric intake, those in poor or fair health, or those with no or infrequent breast cancer screening history) and truncating person years at the end of June 2002, resulted in no substantial changes to the results previously presented. Given small numbers of younger (50–59 years) women who developed ER− or lobular tumors, we also evaluated *p* values for heterogeneity comparing only the women aged 60–69 versus ≥70 years and also found no statistically significant differences.

Discussion

Given that breast cancer incidence rates increase with age and that the number of older women in the USA is increasing, it is important to understand the epidemiology of breast cancer among older women. In this large cohort

Table 3 Association between family history of breast cancer and number of previous breast biopsies and breast cancer risk among postmenopausal women in the NIH-AARP Diet and Health Study, overall and stratified by age of follow-up

Characteristics	Overall				Age of follow-up categories (years)								$p^2_{heterogeneity}$
	Person-years	Cases $n = 7,384$	HR[1]	95 % CI	50–59			60–69			≥70		
					Cases $n = 809$	HR[1]	95 % CI	Cases $n = 3,864$	HR[1]	95 % CI	Cases $n = 2,711$	HR[1]	95 % CI	
Family history of breast cancer in a female first-degree relative													
No	1,482,250	5,760	1.00	–	643	1.00	–	3,026	1.00	–	2,091	1.00	–	0.92
Yes	217,865	1,291	1.49	(1.40–1.59)	127	1.44	(1.19–1.74)	669	1.50	(1.38–1.63)	495	1.50	(1.36–1.66)	
Unknown	80,747													
Number of previous breast biopsies														
0	1,346,746	5,019	1.00	–	560	1.00	–	2,614	1.00	–	1,845	1.00	–	0.48
1	276,073	1,452	1.38	(1.30–1.46)	157	1.42	(1.19–1.69)	755	1.36	(1.25–1.48)	540	1.39	(1.26–1.53)	
≥2	147,198	878	1.59	(1.48–1.70)	87	1.67	(1.33–2.10)	476	1.66	(1.50–1.83)	315	1.47	(1.30–1.66)	
Unknown	10,844													
p_{trend}				<0.0001			<0.0001			<0.0001			<0.0001	

[1] Multivariable models adjusted for race, education level, marital status, age at menarche, parity and age at first live birth, age and type of menopause, MHT use, BMI, daily alcohol intake, family history of breast cancer in a first-degree relative, and number of previous breast biopsies

[2] Evaluates heterogeneity across categories of age of follow-up

of postmenopausal women, most risk factor relationships did not vary significantly by age, although we did observe some suggestive variations that might support potential etiologic differences.

Although previous studies have noted distinctive differences between risk factors for premenopausal versus postmenopausal onset breast cancers [2, 13], fewer have been able to assess risk factor differences among older women. By virtue of our study population, we had a unique opportunity to address this gap in research as all participants were aged 50 or older. However, there were challenges in interpreting some of the age differences given the relatively small number of younger (50–59 years) as compared to older women. In addition, it was difficult to compare our results to those of previous investigations because many of these studies had limited numbers within the age groups examined and the comparative age groups varied. For example, in some of the larger studies, older women were variously defined as 65 [6, 14], 70 [7, 8, 15], or 75 [5, 16] years or older.

Reproductive exposures have been the risk factors most commonly assessed in relation to later-onset breast cancers. Late menarche has been examined according to age at diagnosis among older women in several studies, with discrepant findings. While a lack of association with this parameter has been noted among older women [14], other studies have found either somewhat weaker [16] or stronger [6] inverse relationships among the oldest as compared to younger age groups. Our findings suggested little evidence of a relationship with age at menarche among younger women with the only significant inverse relationship seen among the older (≥70 years) subjects. We have no ready explanation for this, especially since we might have hypothesized stronger effects among younger women if recall was affecting the results. However, the variation by age that we observed was slight and not statistically significant.

Parity and late age at first birth have also been examined in several previous studies. Although some studies have failed to find relationships of breast cancer risk with either parity [5] or age at first birth [7] among older women, we, like two other investigations [6, 16], found the relationships of both factors somewhat attenuated among older as compared to younger women. Given that the effects of pregnancy on breast cancer risk are believed to operate, at least partially, though postpartum remodeling of breast tissue [17], it is not surprising that the effects would diminish with age. However, whether reproductive factors have no effect on the risk of the development of cancers at advanced ages or whether there is only a diminution with age has yet to be determined.

While the effect of reproductive factors on breast cancer risk appeared attenuated among older women in our study,

Table 4 Associations between reproductive and anthropometric variables and risk of ER positive and ER negative breast cancer among postmenopausal women in the NIH-AARP Diet and Health Study, overall and stratified by age of follow-up

Characteristics	ER positive									
	Age of follow-up (years)									
	50–59			60–69			≥70			p^2_{het}
	Cases $n = 309$	HR[1]	95 % CI	Cases $n = 1{,}653$	HR[1]	95 % CI	Cases $n = 1{,}164$	HR[1]	95 % CI	
Age at menarche (years)										
≤10	26	1.00	–	126	1.00	–	66	1.00	–	0.26
11–12	148	1.07	(0.70–1.62)	676	0.86	(0.71–1.04)	506	0.99	(0.77–1.28)	
13–14	110	0.89	(0.58–1.37)	704	0.90	(0.74–1.09)	501	0.92	(0.71–1.19)	
≥15	24	0.95	(0.54–1.65)	141	0.85	(0.67–1.09)	85	0.71	(0.52–0.99)	
p_{trend}			0.30			0.66			0.01	
Parity[3]										
Nulliparous	78	1.00	–	266	1.00	–	177	1.00	–	0.35
1	48	0.88	(0.61–1.27)	185	1.00	(0.83–1.21)	106	0.83	(0.65–1.06)	
2	98	0.76	(0.56–1.04)	467	0.93	(0.80–1.09)	276	0.82	(0.67–0.99)	
≥3	82	0.65	(0.47–0.90)	696	0.78	(0.68–0.91)	591	0.80	(0.67–0.95)	
p_{trend}			0.01			0.0002			0.02	
Age at first birth (years)										
Nulliparous	78	1.39	(1.02–1.88)	266	1.25	(1.08–1.45)	177	1.35	(1.13–1.61)	0.25
<20	41	0.79	(0.54–1.13)	230	0.88	(0.75–1.02)	129	0.88	(0.72–1.07)	
20–24	106	1.00	–	648	1.00	–	458	1.00	–	
25–29	51	1.03	(0.73–1.44)	329	1.21	(1.06–1.39)	294	1.33	(1.15–1.55)	
≥30	28	1.58	(1.03–2.42)	138	1.58	(1.31–1.90)	88	1.17	(0.93–1.47)	
p^4_{trend}			0.02			<0.0001			0.001	
BMI (kg/m^2)										
<18.5	2	0.46	(0.11–1.85)	13	0.64	(0.37–1.12)	9	0.58	(0.30–1.13)	0.19
18.5–24.9	152	1.00	–	679	1.00	–	473	1.00	–	
25.0–29.9	84	0.85	(0.65–1.11)	527	1.14	(1.01–1.28)	368	1.10	(0.96–1.27)	
30.0–34.9	37	0.81	(0.56–1.17)	246	1.28	(1.10–1.49)	191	1.44	(1.21–1.71)	
≥35.0	31	1.06	(0.71–1.57)	139	1.33	(1.10–1.60)	85	1.46	(1.15–1.84)	
p_{trend}			0.78			<0.0001			<0.0001	
Alcohol intake (g/day)										
Nondrinker	77	1.00	–	421	1.00	–	355	1.00	–	0.23
≤5.0	150	0.94	(0.71–1.24)	793	1.09	(0.96–1.22)	474	0.91	(0.79–1.04)	
5.01–10.0	32	1.15	(0.76–1.75)	120	1.00	(0.82–1.23)	93	1.13	(0.90–1.42)	
10.01–20.0	26	0.82	(0.52–1.29)	173	1.13	(0.94–1.35)	128	1.13	(0.92–1.39)	
20.01–35.0	15	1.09	(0.62–1.91)	78	1.19	(0.93–1.52)	55	1.13	(0.85–1.50)	
>35.0	9	0.90	(0.45–1.81)	68	1.41	(1.09–1.83)	59	1.73	(1.31–2.29)	
p_{trend}			0.86			0.01			0.0003	
Duration of MHT use (years)										
Never	87	1.00	–	490	1.00	–	516	1.00	–	0.0002
<5	122	1.50	(1.13–1.99)	292	1.23	(1.06–1.42)	145	0.98	(0.81–1.18)	
5–9	64	1.58	(1.13–2.23)	390	1.90	(1.65–2.19)	134	1.38	(1.14–1.68)	
≥10	34	1.39	(0.89–2.16)	467	1.86	(1.61–2.14)	350	1.49	(1.28–1.73)	
p_{trend}			0.03			<0.0001			<0.0001	

Table 4 continued

Characteristics	ER negative									
	Age of follow-up (years)									
	50–59			60–69			≥70			p^2_{het}
	Cases $n = 97$	HR[1]	95 % CI	Cases $n = 309$	HR[1]	95 % CI	Cases $n = 220$	HR[1]	95 % CI	
Age at menarche (years)										
≤10	8	1.00	–	16	1.00	–	12	1.00	–	0.75
11–12	45	1.18	(0.56–2.52)	151	1.53	(0.91–2.56)	90	1.00	(0.54–1.82)	
13–14	35	1.09	(0.50–2.36)	112	1.16	(0.68–1.96)	97	1.00	(0.55–1.83)	
≥15	9	1.33	(0.51–3.48)	29	1.38	(0.75–2.56)	19	0.87	(0.42–1.80)	
p_{trend}			0.80			0.52			0.74	
Parity[3]										
Nulliparous	15	1.00	–	40	1.00	–	29	1.00	–	0.59
1	14	1.21	(0.58–2.52)	45	1.47	(0.96–2.26)	23	1.00	(0.57–1.73)	
2	35	1.33	(0.72–2.48)	75	0.95	(0.64–1.40)	44	0.73	(0.46–1.18)	
≥3	31	1.07	(0.56–2.04)	144	1.00	(0.70–1.44)	120	0.90	(0.59–1.36)	
p_{trend}			0.86			0.40			0.63	
Age at first birth (years)										
Nulliparous	15	1.00	(0.53–1.89)	40	0.98	(0.68–1.41)	29	1.06	(0.69–1.61)	0.15
<20	28	1.68	(1.00–2.85)	67	1.18	(0.88–1.60)	26	0.69	(0.44–1.06)	
20–24	31	1.00	–	130	1.00	–	105	1.00	–	
25–29	11	0.83	(0.41–1.67)	37	0.71	(0.49–1.03)	41	0.88	(0.61–1.27)	
≥30	10	2.18	(1.05–4.53)	28	1.71	(1.13–2.59)	14	0.90	(0.51–1.58)	
p^4_{trend}			0.77			0.85			0.50	
BMI (kg/m^2)										
<18.5	1	0.94	(0.13–6.89)	6	1.72	(0.76–3.92)	1	0.38	(0.05–2.74)	0.81
18.5–24.9	38	1.00	–	123	1.00	–	82	1.00	–	
25.0–29.9	31	1.16	(0.71–1.87)	93	1.05	(0.80–1.37)	76	1.21	(0.89–1.66)	
30.0–34.9	12	0.92	(0.48–1.79)	48	1.26	(0.90–1.77)	32	1.23	(0.81–1.87	
≥35.0	12	1.47	(0.75–2.89)	27	1.27	(0.83–1.95)	17	1.41	(0.83–2.41)	
p_{trend}			0.44			0.27			0.08	
Alcohol intake (g/day)										
Nondrinker	21	1.00	–	78	1.00	–	68	1.00	–	0.42
≤5.0	55	1.46	(0.88–2.44)	141	1.14	(0.86–1.51)	105	1.14	(0.84–1.56)	
5.01–10.0	7	1.20	(0.50–2.85)	27	1.40	(0.90–2.18)	11	0.79	(0.41–1.50)	
10.01–20.0	10	1.56	(0.72–3.36)	32	1.34	(0.88–2.04)	24	1.31	(0.81–2.11)	
20.01–35.0	3	1.05	(0.31–3.57)	18	1.75	(1.04–2.94)	10	1.26	(0.64–2.47)	
>35.0	1	0.44	(0.06–3.30)	13	1.63	(0.90–2.94)	2	0.35	(0.08–1.41)	
p_{trend}			0.93			0.01			0.85	
Duration of MHT use (years)										
Never	31	1.00	–	99	1.00	–	97	1.00	–	0.35
<5	27	0.89	(0.53–1.52)	74	1.43	(1.05–1.95)	36	1.24	(0.84–1.83)	
5–9	25	1.46	(0.83–2.56)	52	1.19	(0.84–1.69)	18	0.96	(0.58–1.61)	
≥10	12	0.91	(0.44–1.91)	80	1.36	(0.98–1.90)	63	1.25	(0.87–1.78)	
p_{trend}			0.68			0.12			0.27	

[1] Multivariable models adjusted for race, education level, marital status, age at menarche, parity and age at first live birth, age and type of menopause, MHT use, BMI, daily alcohol intake, family history of breast cancer in a first-degree relative, and number of previous breast biopsies

[2] Evaluates heterogeneity across categories of age of follow-up within each receptor subtype

[3] Multivariable models for parity do not adjust for age at first birth

[4] Trends for age at first birth do not include nulliparous women

Table 5 Association between reproductive history and risk of ductal and lobular breast cancer among postmenopausal women in the NIH-AARP Diet and Health study, overall and stratified by age of follow-up

Characteristic	Ductal									
	Age of follow-up categories (years)									
	50–59			60–69			≥70			p^{2}_{het}
	Cases $n = 596$	HR[1]	95 % CI	Cases $n = 2{,}699$	HR[1]	95 % CI	Cases $n = 1{,}833$	HR[1]	95 % CI	
Age at menarche (years)										
≤10	48	1.00	–	179	1.00	–	106	1.00	–	0.78
11–12	287	1.23	(0.91–1.68)	1,162	1.06	(0.91–1.24)	761	0.95	(0.77–1.16)	
13–14	218	1.08	(0.78–1.48)	1,113	1.03	(0.88–1.21)	795	0.93	(0.76–1.14)	
≥15	43	1.00	(0.66–1.51)	236	0.98	(0.80–1.19)	166	0.86	(0.67–1.10)	
p_{trend}			0.37			0.47			0.21	
Parity[3]										
Nulliparous	142	1.00	–	421	1.00	–	283	1.00	–	0.32
1	75	0.72	(0.55–0.96)	280	0.93	(0.80–1.09)	172	0.83	(0.68–1.00)	
2	180	0.74	(0.59–0.93)	711	0.89	(0.78–1.00)	408	0.76	(0.65–0.89)	
≥3	189	0.71	(0.56–0.89)	1,230	0.81	(0.72–0.91)	952	0.80	(0.70–0.92)	
p_{trend}			0.01			0.0001			0.01	
Age at first birth (years)										
Nulliparous	142	1.47	(1.17–1.84)	421	1.19	(1.06–1.34)	283	1.27	(1.10–1.46)	0.04
<20	120	1.17	(0.93–1.48)	419	0.88	(0.79–0.99)	225	0.90	(0.77–1.04)	
20–24	200	1.00	–	1,153	1.00	–	798	1.00	–	
25–29	77	0.91	(0.70–1.19)	469	1.06	(0.95–1.18)	380	1.06	(0.94–1.20)	
≥30	45	1.56	(1.12–2.17)	173	1.26	(1.07–1.48)	123	1.02	(0.84–1.23)	
p^{4}_{trend}			0.63			0.0001			0.13	
BMI (kg/m^2)										
<18.5	7	0.96	(0.45–2.03)	22	0.70	(0.46–1.06)	19	0.79	(0.50–1.25)	0.98
18.5–24.9	252	1.00	–	1,058	1.00	–	742	1.00	–	
25.0–29.9	170	0.99	(0.82–1.21)	865	1.14	(1.04–1.25)	603	1.10	(0.99–1.23)	
30.0–34.9	88	1.09	(0.85–1.40)	401	1.24	(1.10–1.39)	268	1.20	(1.04–1.39)	
≥35.0	68	1.31	(0.99–1.73)	261	1.47	(1.28–1.70)	141	1.43	(1.19–1.72)	
p_{trend}			0.08			<0.0001			<0.0001	
Alcohol intake (g/day)										
Nondrinker	137	1.00	–	742	1.00	–	563	1.00	–	0.70
≤5.0	315	1.19	(0.97–1.46)	1,252	0.99	(0.90–1.08)	797	0.96	(0.86–1.08)	
5.01–10.0	51	1.20	(0.87–1.66)	200	1.01	(0.86–1.18)	126	1.00	(0.83–1.22)	
10.01–20.0	48	1.04	(0.74–1.45)	253	1.04	(0.90–1.20)	193	1.14	(0.97–1.35)	
20.01–35.0	24	1.18	(0.76–1.83)	131	1.24	(1.03–1.49)	79	1.07	(0.85–1.36)	
>35.0	21	1.21	(0.76–1.91)	121	1.44	(1.18–1.74)	75	1.37	(1.07–1.74)	
p_{trend}			0.50			0.0004			0.01	
Duration of MHT use (years)										
Never	192	1.00	–	942	1.00	–	893	1.00	–	0.004
<5	200	1.22	(1.00–1.50)	536	1.27	(1.14–1.41)	240	1.01	(0.88–1.17)	
5–9	129	1.51	(1.19–1.91)	519	1.52	(1.36–1.70)	171	1.14	(0.96–1.35)	
≥10	69	1.20	(0.89–1.63)	663	1.55	(1.39–1.74)	496	1.39	(1.23–1.57)	
p_{trend}			0.01			<0.0001			<0.0001	

Table 5 continued

Characteristics	Lobular									
	Age of follow-up categories (years)									
	50–59			60–69			≥70			p^2_{het}
	Cases $n = 68$	HR[1]	95 % CI	Cases $n = 398$	HR[1]	95 % CI	Cases $n = 332$	HR[1]	95 % CI	
Age at menarche (years)										
≤10	6	1.00	–	27	1.00	–	20	1.00	–	0.50
11–12	26	0.88	(0.36–2.16)	147	0.87	(0.58–1.32)	141	0.91	(0.57–1.45)	
13–14	29	1.08	(0.45–2.64)	187	1.11	(0.74–1.67)	143	0.85	(0.53–1.36)	
≥15	7	1.20	(0.40–3.60)	36	1.00	(0.60–1.65)	26	0.69	(0.38–1.23)	
p_{trend}			0.48		0.18				0.16	
Parity[3]										
Nulliparous	7	1.00	–	64	1.00	–	39	1.00	–	0.22
1	17	3.11	(1.27–7.58)	48	1.10	(0.75–1.60)	40	1.45	(0.93–2.27)	
2	23	1.78	(0.75–4.22)	111	0.92	(0.67–1.26)	76	1.07	(0.72–1.59)	
≥3	19	1.28	(0.52–3.13)	168	0.76	(0.56–1.03)	171	1.10	(0.77–1.58)	
p_{trend}			0.58			0.02			0.85	
Age at first birth (years)										
Nulliparous	7	0.53	(0.23–1.22)	64	1.34	(0.99–1.82)	39	1.13	(0.78–1.63)	0.18
<20	4	0.23	(0.08–0.65)	51	0.85	(0.61–1.17)	31	0.84	(0.56–1.25)	
20–24	32	1.00	–	153	1.00	–	120	1.00	–	
25–29	16	1.31	(0.71–2.42)	86	1.44	(1.10–1.89)	97	1.79	(1.36–2.35)	
≥30	7	1.78	(0.77–4.10)	36	1.96	(1.35–2.83)	37	2.00	(1.38–2.90)	
p^4_{trend}			0.0002			<0.0001			<0.0001	
BMI (kg/m^2)										
<18.5	0	–	–	3	0.61	(0.20–1.92)	0	–	–	0.93
18.5–24.9	30	1.00	–	167	1.00	–	140	1.00	–	
25.0–29.9	22	1.10	(0.63–1.92)	130	1.13	(0.90–1.43)	109	1.09	(0.85–1.40)	
30.0–34.9	6	0.65	(0.27–1.59)	57	1.22	(0.90–1.66)	53	1.34	(0.97–1.85)	
≥35.0	8	1.40	(0.62–3.14)	29	1.18	(0.79–1.77)	21	1.22	(0.76–1.95)	
p_{trend}			0.73			0.12			0.04	
Alcohol intake (g/day)										
Nondrinker	17	1.00	–	76	1.00	–	101	1.00	–	0.01
≤5	35	1.00	(0.56–1.81)	217	1.62	(1.25–2.11)	127	0.82	(0.63–1.06)	
5.01–10.0	6	1.10	(0.43–2.82)	35	1.63	(1.08–2.44)	25	1.05	(0.68–1.64)	
10.01–20.0	8	1.34	(0.57–3.17)	42	1.57	(1.07–2.30)	35	1.09	(0.74–1.62)	
20.01–35.0	2	0.82	(0.19–3.58)	16	1.38	(0.80–2.37)	21	1.53	(0.95–2.47)	
>35.0	0	–	–	12	1.33	(0.72–2.45)	23	2.31	(1.46–3.66)	
p_{trend}			0.62			0.15			0.0003	
Duration of MHT use (years)										
Never	21	1.00	–	138	1.00	–	165	1.00	–	0.22
<5	18	0.89	(0.47–1.70)	75	1.16	(0.87–1.54)	50	1.16	(0.84–1.60)	
5–9	20	2.02	(1.03–3.94)	75	1.37	(1.02–1.85)	36	1.33	(0.92–1.92)	
≥10	8	1.16	(0.47–2.87)	108	1.59	(1.19–2.11)	79	1.28	(0.95–1.73)	
p_{trend}			0.24			0.001			0.07	

[1] Multivariable models adjusted for race, education level, marital status, age at menarche, parity and age at first live birth, age and type of menopause, MHT use, BMI, daily alcohol intake, family history of breast cancer in a first-degree relative, and number of previous breast biopsies

[2] Evaluates heterogeneity across categories of age of follow-up within each histologic subtype

[3] Multivariable models for parity do not adjust for age at first birth

[4] Trends for age at first birth do not include nulliparous women

we actually found stronger relations of BMI among our oldest study subjects, as has been observed in several other investigations [8, 18–20]. BMI is well documented as showing discrepant relations with breast cancer risk according to menopausal status, with inverse associations having consistently been seen for cancers of premenopausal onset and direct associations observed for postmenopausal cancers [21, 22]. The latter relation is accepted as deriving from the peripheral conversion of androgens to active estrogens in fat tissue [23]. Thus, a stronger relationship of obesity to breast cancers at older ages may reflect that these cancers may be more prone to the influence of endogenous estrogens. This might also explain the slightly enhanced risks associated with alcohol consumption for cancers occurring in the oldest women given that there is evidence that this risk factor may operate through estrogenic mechanisms [24]. The stronger relation of obesity to later-onset cancers would also be consistent with findings that more recent weight gain is a stronger predictor of breast cancer than weight earlier in life [25, 26].

Of all the risk factors examined, the only one that showed significant variation across the age groups was that of duration of MHT use. If not merely a chance finding, the significance of the interaction might reflect varying prevalences of exposure across the age groups, given that there were significant trends according to this parameter in all age groups. The statistical heterogeneity could also reflect that the strongest relationship was observed among women ages 60–69 years, which had the largest number of subjects. Our interpretation of this finding was also complicated by the absence of information on the baseline questionnaire on types of hormones prescribed, which is known to affect risk of all tumors as well as tumor subtypes.

We also examined risk in relation to age at menopause, a factor that has been consistently and positively related to breast cancer risk [27], presumably reflecting effects of prolonged circulating estrogens. This is not a parameter that has generally been thought to show discrepant results by age [14]. Similarly, in the present study, we also did not observe significant heterogeneity by age but did note slightly stronger relations for the older subjects. Although the differences were not pronounced, this would be consistent with the notion that it can take between 10 and 15 years for menopause to fully exert its effects on breast cancer risk [28]. Given this, we would have also expected to have seen some heterogeneity according to relations with surgical menopause, a factor found not to affect risk of breast cancer in older women in one investigation [7]. However, the association with surgical menopause in our study may have been obscured by the inclusion of both women with a hysterectomy, which has not generally been related to substantial alterations in breast cancer risk [29]—as well as those with a bilateral oophorectomy, which can substantially reduce subsequent breast cancer risk [30].

Although a family history of breast cancer is known to be a stronger predictor of risk for very early-onset cancers [31, 32], most studies have not shown variation in relations across the spectrum of older ages [5, 16], in agreement with results from our study. We also did not observe consistent differences according to age for a variety of other accepted breast cancer risk factors, including previous breast biopsies and levels of physical activity.

While we examined associations with all breast cancers in the cohort, it is well recognized that the disease is extremely heterogeneous, with distinctive relationships according to various clinical parameters [33, 34]. Divergent effects by both hormone receptor status [4] and histology [35, 36] have been reported. Although there is a fair amount of inconsistency in the literature regarding risk factor associations within clinical subgroups, there are some suggestions of stronger relationships of alcohol consumption with ER+ as compared to ER− tumors [37], BMI and menstrual factors with ductal as compared to lobular cancers [35], and menopausal hormone use with lobular as compared to ductal cancers [38, 39]. However, even when we controlled for this variation, we continued to observe some possible heterogeneity by age, particularly with respect to attenuated relations among older women for some of the reproductive parameters and increased risks of BMI and alcohol consumption. Not surprisingly, these relationships mainly prevailed for the tumors that are most common among older women, notably the ER+ and ductal tumors.

Given that breast cancer incidence rates increase with age and that more women are living longer, it can be expected that greater numbers of women will be diagnosed with breast cancer at older ages in the future [40]. It is also well documented that less screening mammography among older women is associated with later stage at diagnosis and poorer survival [41–43]. It is therefore important to determine whether the standard risk factors apply to such women. Our analysis suggests generally similar risk profiles for such cancers, with possibly a slight attenuation for reproductive factors and a modest enhancement for obesity and alcohol consumption. Although these differences among older women were not large, they may merit further consideration with respect to individualized breast cancer risk prediction, as has been detailed in several recent investigations [7, 44, 45].

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