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Original Contribution

Variation in Breast Cancer–Risk Factor Associations by Method of Detection: Results From a Series of Case-Control Studies

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Concerns about breast cancer overdiagnosis have increased the need to understand how cancers detected through screening mammography differ from those first detected by a woman or her clinician. We investigated risk factor associations for invasive breast cancer by method of detection within a series of case-control studies (1992–2007) carried out in Wisconsin, Massachusetts, and New Hampshire ($n = 15{,}648$ invasive breast cancer patients and 17,602 controls aged 40–79 years). Approximately half of case women reported that their cancer had been detected by mammographic screening and half that they or their clinician had detected it. In polytomous logistic regression models, parity and age at first birth were more strongly associated with risk of mammography-detected breast cancer than with risk of woman/clinician-detected breast cancer ($P \leq 0.01$; adjusted for mammography utilization). Among postmenopausal women, estrogen-progestin hormone use was predominantly associated with risk of woman/clinician-detected breast cancer (odds ratio (OR) = 1.49, 95% confidence interval (CI): 1.29, 1.72), whereas obesity was predominantly associated with risk of mammography-detected breast cancer (OR = 1.72, 95% CI: 1.54, 1.92). Among regularly screened premenopausal women, obesity was not associated with increased risk of mammography-detected breast cancer (OR = 0.99, 95% CI: 0.83, 1.18), but it was associated with reduced risk of woman/clinician-detected breast cancer (OR = 0.53, 95% CI: 0.43, 0.64). These findings indicate important differences in breast cancer risk factors according to method of detection.

breast neoplasms; case-control studies; mammography; mass screening; prevention and control

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

Utilization of mammographic screening for breast cancer in the United States increased dramatically throughout the late 20th century (1). The percentage of women aged 40 years or older who reported that they had had a mammogram in the past 2 years rose from 30% in 1987 to approximately 70% in 2000; since that time it has remained relatively stable (2). Approximately 60% of all breast cancers are now first detected through mammographic screening (3).

For many years it has been recognized that women with breast cancers detected by mammographic screening tend to have better survival rates than women whose breast cancers were self-detected or discovered by a clinician, even after adjustment for stage, tumor size, hormone receptor status, and other known tumor prognostic factors (4–9). Several lines of evidence suggest that many breast cancers diagnosed by mammographic screening may in fact represent overdiagnosis: cancers that would never have harmed the woman during her lifetime (10, 11). Overdiagnosis has emerged as a major issue in debates about breast cancer screening recommendations and in the management of breast cancers detected through mammographic screening (12, 13). These concerns reflect uncertainties in the natural history of breast cancers detected by mammographic screening.

It is not known whether breast cancer risk factors vary according to method of detection. Prior studies have recognized screening utilization as a potentially confounding factor when evaluating breast cancer risk factors (14, 15), but to our knowledge no investigators have reported risk factor

Table 1. Characteristics of Breast Cancer Cases and Controls, Collaborative Breast Cancer Study, 1992–2007

Characteristic	Controls ($n = 17,602$)		Cases			
			Mammography-Detected Breast Cancer ($n = 8,372$)		Woman/Clinician-Detected Breast Cancer ($n = 7,276$)	
	No.	%	No.	%	No.	%
Age group, years						
40–49	3,362	19.1	1,169	14.0	1,793	24.6
50–59	6,227	35.4	2,931	35.0	2,383	32.8
60–69	6,344	36.0	3,323	39.7	2,185	30.0
70–79	1,669	9.5	949	11.3	915	12.6
Menopausal status						
Premenopausal	4,003	22.7	1,598	19.1	1,996	27.4
Postmenopausal	12,564	71.4	6,340	75.7	4,768	65.5
Unknown	1,035	5.9	434	5.2	512	7.0
Education						
Less than high school	1,816	10.3	738	8.8	733	10.1
High school diploma	7,478	42.5	3,581	42.8	3,020	41.5
Some college	4,459	25.3	2,049	24.5	1,734	23.8
College degree	3,828	21.8	1,996	23.8	1,780	24.5
Unknown	21	0.1	8	0.1	9	0.1
No. of mammograms in 5 years preceding reference date						
0	2,465	14.0	0	0.0	1,708	23.5
1–2	3,966	22.5	1,131	13.5	1,325	18.2
3–4	2,860	16.3	1,300	15.5	1,036	14.2
≥5	8,311	47.2	5,941	71.0	3,207	44.1
Tumor stage at diagnosis						
Localized	NA	NA	6,114	73.0	3,817	52.5
Regional	NA	NA	1,472	17.6	2,667	36.7
Distant	NA	NA	53	0.6	261	3.6
Unknown	NA	NA	733	8.8	531	7.3
Histological subtype						
Lobular	NA	NA	705	8.4	793	10.9
Ductal	NA	NA	6,568	78.5	5,636	77.5
Mixed	NA	NA	409	4.9	317	4.4
Other	NA	NA	603	7.2	398	5.5
Unknown	NA	NA	87	1.0	132	1.8

Abbreviation: NA, not applicable.

associations separately for breast cancers detected by mammographic screening and breast cancers detected by the woman or her clinician. Such data could improve our understanding of breast cancer biology, inform breast cancer risk assessment, and help to guide the design of optimal screening and prevention strategies.

Our objective in this study was to evaluate established risk factor associations for invasive breast cancer according to method of detection, while accounting for variation in the frequency of mammography utilization. We used data from a series of collaborative breast cancer case-control studies conducted over a 15-year period in Wisconsin, Massachusetts, and New Hampshire.

METHODS

This study was performed with data from the Collaborative Breast Cancer Study, a series of consecutive breast cancer case-control studies conducted in Wisconsin, Massachusetts (excluding metropolitan Boston), and New Hampshire (16). The present analyses were restricted to the studies conducted between 1992 and 2007, during which both method of cancer detection and history of mammography utilization (in detail) were assessed. Extensive details on the individual case-control studies have been published elsewhere (17–21). The studies were approved by institutional review boards at the University of Wisconsin, Harvard University, and Dartmouth College.

Table 2. Overall Associations Between Breast Cancer Risk Factors and Breast Cancer Diagnosis, Collaborative Breast Cancer Study, 1992–2007

Characteristic	No. of Controls[a] (*n* = 17,602)	No. of Cases[a] (*n* = 15,648)	Multivariable Adjustment[b]		Additional Adjustment for Mammographic Screening[c]	
			OR	95% CI	OR	95% CI
First-degree family history of breast cancer						
No	15,132	12,243	1	Referent	1	Referent
Yes	2,470	3,405	1.70	1.61, 1.80	1.72	1.63, 1.83
Age at menarche, years						
<12	3,384	3,280	1	Referent	1	Referent
12	4,330	4,024	0.95	0.89, 1.02	0.95	0.89, 1.02
13	4,815	4,259	0.89	0.84, 0.95	0.90	0.84, 0.96
≥14	5,074	4,085	0.81	0.76, 0.87	0.81	0.76, 0.86
Age at first birth[d], years						
<20	3,082	2,218	1	Referent	1	Referent
20–24	7,698	6,349	1.12	1.04, 1.19	1.12	1.05, 1.20
25–29	3,504	3,394	1.27	1.18, 1.38	1.28	1.18, 1.38
≥30	1,378	1,612	1.46	1.32, 1.61	1.46	1.32, 1.61
Parity						
0	1,941	2,075	1	Referent	1	Referent
1	1,670	1,707	0.77	0.69, 0.87	0.77	0.69, 0.87
2	4,852	4,651	0.75	0.68, 0.83	0.75	0.68, 0.83
≥3	9,139	7,215	0.64	0.59, 0.70	0.64	0.59, 0.70
Age at menopause[e], years						
<45	3,576	2,521	1	Referent	1	Referent
45–49	3,283	2,899	1.24	1.14, 1.34	1.24	1.14, 1.35
50–54	4,536	4,456	1.36	1.27, 1.46	1.37	1.27, 1.47
≥55	1,686	1,672	1.34	1.22, 1.48	1.35	1.23, 1.48

Table continues

Cases

The cases were women diagnosed with a first invasive breast cancer reported to the cancer registries of the respective states. Age requirements varied over the course of the study, consisting of ages 50–79 years during 1992–1996 and ages 20–69 years in 1997–2007. Eligibility was further restricted to women with a published telephone number, a complete date of diagnosis reported to the cancer registry, and (for women aged less than 65 years) a driver's license verified by self-report. Of 20,793 eligible women, a total of 16,494 (79%) women with breast cancer participated in the study.

Controls

Controls from each state were chosen randomly from lists of female licensed drivers (ages <65 years during 1992–2003, all ages during 2004–2007) and Medicare beneficiary files (ages ≥65 years during 1992–2003). A stratified random sampling design was used to match the age distribution of the cases. Eligibility was restricted to women with a publicly available telephone number and no personal history of breast cancer. Of 23,812 eligible women, a total of 17,378 (73%) women participated.

Data collection

Information about the date of diagnosis, histological subtype, and stage of disease at diagnosis was obtained from each state's cancer registry. Structured telephone interviews were conducted to collect information from the study participants. The date of diagnosis was used as a reference date for each case. On average, the cases were interviewed approximately 16 months after the date of diagnosis. Each control participant was also assigned a reference date such that the state- and age-specific distribution of elapsed time between the reference date and the interview date was equivalent between cases and controls. The interviews ascertained information on demographic characteristics, height and weight 1 year prior to the reference date, complete reproductive and menstrual history, personal and family medical histories, breast cancer screening history, medication use, and lifestyle factors such as typical alcohol consumption 1 year prior to the reference date. Information about the woman's personal and family history of cancer was obtained at the end of the interview to maintain interviewer blinding. For 85% of cases and 93% of controls, the interviewers reported being unaware of the woman's case/control status until the end of the interview.

Table 2. Continued

Characteristic	No. of Controls[a] (*n* = 17,602)	No. of Cases[a] (*n* = 15,648)	Multivariable Adjustment[b]		Additional Adjustment for Mammographic Screening[c]	
			OR	95% CI	OR	95% CI
Postmenopausal hormone use[f]						
Never use	3,063	2,330	1	Referent	1	Referent
Estrogen only	1,293	1,027	1.15	1.04, 1.28	1.20	1.08, 1.33
Estrogen plus progestin only	845	918	1.46	1.30, 1.63	1.52	1.36, 1.70
Other	360	340	1.25	1.06, 1.47	1.30	1.10, 1.52
Alcohol consumption, drinks/week						
0	3,685	3,082	1	Referent	1	Referent
0.1–6.9	11,620	10,257	1.04	0.98, 1.10	1.05	0.99, 1.11
≥7	2,296	2,309	1.21	1.12, 1.31	1.22	1.13, 1.32
Postmenopausal BMI[g,h]						
<18.5	151	99	0.82	0.63, 1.08	0.80	0.61, 1.05
18.5–24.9	3,063	2,330	1	Referent	1	Referent
25.0–29.9	2,637	2,193	1.10	1.02, 1.19	1.10	1.02, 1.20
≥30.0	1,736	1,790	1.40	1.28, 1.53	1.41	1.29, 1.54
Premenopausal BMI[i]						
<18.5	62	48	0.81	0.55, 1.20	0.80	0.54, 1.18
18.5–24.9	2,197	2,094	1	Referent	1	Referent
25.0–29.9	1,280	1,179	0.96	0.87, 1.07	0.96	0.86, 1.06
≥30.0	983	780	0.82	0.73, 0.93	0.82	0.72, 0.92

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.
[a] Average value from 5 imputed data sets.
[b] ORs were mutually adjusted for all other risk factors in the table, in addition to age, state of residence, year of diagnosis, menopausal status, educational level, and interaction terms for interactions between BMI, postmenopausal hormone use, and menopausal status. Controls were the reference group for all estimates.
[c] ORs were additionally adjusted for mammography utilization in the 5 years prior to the reference date.
[d] Among parous women only.
[e] Among postmenopausal women only.
[f] Among normal-weight postmenopausal women.
[g] Weight (kg)/height $(m)^2$.
[h] Among postmenopausal women who had never used postmenopausal hormones.
[i] Among premenopausal women only.

All participants were asked to report whether they had undergone mammography in the 5 years prior to the reference date. Those indicating yes were then asked either to report the number of mammograms they had undergone during the 5-year period or to choose the most appropriate response option (1–2, 3–4, 5, or >5), depending on the study period. All cases were asked how their cancer was first discovered: whether the woman had first noticed it herself, it was discovered during a routine mammogram, it was first detected by a physician or health-care provider, or it was detected via other means (e.g., an unrelated medical procedure) (22).

Statistical analyses

Questionnaire data for 38 breast cancer cases and 37 controls were deemed unreliable by the interviewers because of inconsistent participant responses and were excluded. All analyses were restricted to women aged 40 years or older (*n* = 16,310 cases and 17,950 controls) to correspond with the earliest recommended age for initiation of screening in the general population. Breast cancers were categorized as mammography-detected if the woman reported initial discovery by routine mammogram (*n* = 8,439) and woman/clinician-detected if the woman reported initial discovery by herself (*n* = 6,269) or a clinician (*n* = 1,090). The few cases missing information on method of detection (*n* = 444) or reporting breast cancer detection via "other means" (*n* = 68) were excluded, as were participants with missing data on mammography utilization (*n* = 150 cases and 348 controls), leaving a final analysis sample of 17,602 controls, 8,372 mammography-detected breast cancers, and 7,276 woman/clinician-detected breast cancers.

All analyses were conducted using SAS statistical software (version 9.2; SAS Institute Inc., Cary, North Carolina). Risk factors for examination were selected a priori and included family history of breast cancer, age at menarche, age at first birth, parity, age at menopause, use of postmenopausal hormones, alcohol consumption, and body mass index (BMI). Fewer than

Table 3. Associations[a] Between Breast Cancer Risk Factors and Breast Cancer Diagnosis, According to Method of Detection, Collaborative Breast Cancer Study, 1992–2007

Characteristic	No. of Controls[b] (*n* = 17,602)	Mammography-Detected Breast Cancer			Woman/Clinician-Detected Breast Cancer			*P* Value[c]
		No. of Cases[b] (*n* = 8,372)	OR	95% CI	No. of Cases[b] (*n* = 7,276)	OR	95% CI	
First-degree family history of breast cancer								
No	15,130	6,474	1	Referent	5,769	1	Referent	
Yes	2,472	1,898	1.57	1.47, 1.69	1,507	1.67	1.55, 1.80	0.16
Age at menarche, years								
<12	3,384	1,844	1	Referent	1,435	1	Referent	
12	4,330	2,168	0.93	0.86, 1.01	1,856	0.97	0.89, 1.06	0.38
13	4,815	2,277	0.88	0.81, 0.95	1,982	0.92	0.84, 1.00	0.38
≥14	5,074	2,082	0.79	0.73, 0.86	2,003	0.85	0.78, 0.93	0.12
Age at first birth[d], years								
<20	3,082	1,118	1	Referent	1,100	1	Referent	
20–24	7,698	3,483	1.18	1.09, 1.29	2,866	1.03	0.95, 1.12	0.01
25–29	3,504	1,849	1.39	1.26, 1.53	1,544	1.13	1.02, 1.25	0.001
≥30	1,378	833	1.62	1.43, 1.84	779	1.32	1.16, 1.49	0.01
Parity								
0	1,941	1,088	1	Referent	987	1	Referent	
1	1,670	862	0.69	0.60, 0.79	845	0.88	0.76, 1.01	0.01
2	4,852	2,452	0.68	0.60, 0.76	2,199	0.82	0.73, 0.93	0.01
≥3	9,139	3,970	0.59	0.53, 0.66	3,244	0.70	0.63, 0.78	0.01
Age at menopause[e], years								
<45	3,576	1,412	1	Referent	1,109	1	Referent	
45–49	3,283	1,643	1.23	1.10, 1.37	1,255	1.22	1.10, 1.35	0.92
50–54	4,536	2,521	1.31	1.19, 1.43	1,934	1.39	1.26, 1.53	0.30
≥55	1,686	997	1.32	1.18, 1.48	676	1.31	1.16, 1.49	0.94

Table continues

10% of participants were missing data for any single variable. A multiple-imputation approach was used to impute 5 data sets with complete data, using a Markov chain Monte Carlo method with fully conditional specification (23). The imputation model contained a variable for method of detection and all of the risk factors and covariates described above.

A multivariable logistic regression model for overall breast cancer risk (regardless of method of detection) was used to produce odds ratios and 95% confidence intervals for breast cancer risk factors, with and without adjustment for history of mammography utilization (categorized as 0, 1–2, 3–4, or ≥5 mammograms in the 5 years preceding the reference date). The overall regression model included all risk factors under investigation as well as potential confounders identified a priori, including age (40–49, 50–54, 55–59, 60–64, 65–69, or 70–79 years), state of residence (Wisconsin, Massachusetts, or New Hampshire), reference year (1988–1991, 1992–1996, 1997–2001, or 2002–2007), menopausal status (premenopausal, postmenopausal, or unknown), and educational level (less than high school, high school diploma, some college, college degree, or unknown). The regression model also included cross-product interaction terms for interactions between BMI, postmenopausal hormone use, and menopausal status, since there is known effect modification among these factors (24). BMI was calculated as weight (kg) divided by the square of height (m) and was categorized as underweight (<18.5), normal (18.5–24.9), overweight (25.0–29.9), or obese (≥30). For all analyses, we present the main effects for 1) postmenopausal hormone use among normal-weight postmenopausal women; 2) BMI among postmenopausal women who had never used postmenopausal hormones; and 3) BMI among premenopausal women.

A multivariable polytomous logistic regression model was used to investigate variation in risk factor associations by method of detection. Stratified analyses were conducted among women with a history of regular mammography utilization (i.e., at least 3 mammograms in the past 5 years) and those with no mammography in the 5 years prior to the reference date. An additional multivariable polytomous logistic regression model was used to examine whether risk factor associations among regularly screened women varied by stage of diagnosis within each method-of-detection stratum.

Table 3. Continued

Characteristic	No. of Controls[b] (*n* = 17,602)	Mammography-Detected Breast Cancer			Woman/Clinician-Detected Breast Cancer			*P* Value[c]
		No. of Cases[b] (*n* = 8,372)	OR	95% CI	No. of Cases[b] (*n* = 7,276)	OR	95% CI	
Postmenopausal hormone use[f]								
Never use	3,063	1,154	1	Referent	1,176	1	Referent	
Estrogen only	1,293	521	0.89	0.78, 1.01	506	1.23	1.08, 1.40	<0.0001
Estrogen plus progestin only	845	497	1.14	0.99, 1.31	422	1.49	1.29, 1.72	0.002
Other	360	186	1.02	0.84, 1.25	154	1.23	1.00, 1.52	0.13
Alcohol consumption, drinks/ week								
0	3,685	1,600	1	Referent	1,482	1	Referent	
0.1–6.9	11,620	5,530	1.06	0.99, 1.14	4,727	0.99	0.92, 1.07	0.12
≥7	2,296	1,242	1.24	1.13, 1.37	1,067	1.14	1.03, 1.25	0.14
Postmenopausal BMI[g,h]								
<18.5	151	30	0.61	0.40, 0.92	68	1.05	0.77, 1.44	0.02
18.5–24.9	3,063	1,154	1	Referent	1,176	1	Referent	
25.0–29.9	2,637	1,278	1.31	1.18, 1.45	914	0.91	0.82, 1.01	<0.0001
≥30.0	1,736	1,058	1.72	1.54, 1.92	732	1.13	1.01, 1.27	<0.0001
Premenopausal BMI[i]								
<18.5	62	6	0.29	0.12, 0.67	42	1.08	0.72, 1.63	0.003
18.5–24.9	2,197	811	1	Referent	1,283	1	Referent	
25.0–29.9	1,280	558	1.19	1.04, 1.37	621	0.82	0.72, 0.92	<0.0001
≥30.0	983	424	1.21	1.04, 1.40	356	0.61	0.52, 0.71	<0.0001

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] ORs were mutually adjusted for all other risk factors in the table, in addition to age, state of residence, year of diagnosis, menopausal status, educational level, history of mammography utilization, and interaction terms for interactions between BMI, postmenopausal hormone use, and menopausal status.

[b] Average value from 5 imputed data sets.

[c] Test for difference in the risk factor association by method of detection.

[d] Among parous women only.

[e] Among postmenopausal women only.

[f] Among normal-weight postmenopausal women.

[g] Weight (kg)/height $(m)^2$.

[h] Among postmenopausal women who had never used postmenopausal hormones.

[i] Among premenopausal women only.

Sensitivity analyses were conducted to assess risk factor associations when restricting the definition of "regularly screened" to at least 5 mammograms in the past 5 years. All regression models were fitted separately to the 5 imputed data sets, and the results were combined for statistical inferences using the methods of Rubin (25). Wald tests of β coefficients in the polytomous regression model were used to assess whether there were statistically significant differences (at $\alpha = 0.05$) in risk factor associations according to method of detection.

RESULTS

Overall, 53.5% of cases were detected by mammographic screening and 46.5% were detected by the woman or her clinician. The mean age at the reference date was 58.4 years for controls, 59.7 years for women with mammography-detected cancers, and 57.8 years for women with woman/clinician-detected cancers. Compared with mammography-detected cases, participants with woman/clinician-detected cancers were more likely to be younger than 50 years of age (Table 1). Women with mammography-detected cancers reported higher rates of annual mammography utilization (71.0%) compared with controls (47.2%) and woman/clinician-detected cases (44.1%). Both case subgroups were slightly more likely to have completed college compared with controls. The predominant histological subtype was ductal for both mammography-detected (78.5%) and woman/clinician-detected (77.5%) cancers. Stage at diagnosis varied by method of detection; among breast cancers with known stage, 80.0% of mammography-detected cancers were localized, compared with 56.6% of woman/clinician-detected cancers.

Table 4. Associations[a] Between Breast Cancer Risk Factors and Breast Cancer Diagnosis Among Women With At Least 3 Mammograms in the Past 5 Years, According to Method of Detection, Collaborative Breast Cancer Study, 1992–2007

Characteristic	No. of Controls[b] (*n* = 11,171)	Detection Method						*P* Value[c]
		Mammography-Detected Breast Cancer			Woman/Clinician-Detected Breast Cancer			
		No. of Cases[b] (*n* = 7,241)	OR	95% CI	No. of Cases[b] (*n* = 4,243)	OR	95% CI	
First-degree family history of breast cancer								
No	9,373	5,546	1	Referent	3,246	1	Referent	
Yes	1,798	1,695	1.53	1.42, 1.66	997	1.61	1.47, 1.76	0.30
Age at menarche, years								
<12	2,186	1,591	1	Referent	865	1	Referent	
12	2,773	1,897	0.94	0.86, 1.03	1,115	0.97	0.87, 1.08	0.61
13	3,116	1,965	0.87	0.79, 0.95	1,135	0.85	0.77, 0.95	0.78
≥14	3,096	1,789	0.79	0.72, 0.86	1,129	0.84	0.75, 0.93	0.29
Age at first birth[d], years								
<20	1,855	976	1	Referent	627	1	Referent	
20–24	5,004	3,015	1.12	1.02, 1.23	1,657	0.94	0.84, 1.05	0.01
25–29	2,284	1,589	1.31	1.17, 1.47	930	1.07	0.94, 1.22	0.004
≥30	822	714	1.63	1.41, 1.88	462	1.32	1.12, 1.55	0.02
Parity								
0	1,206	946	1	Referent	567	1	Referent	
1	1,030	714	0.68	0.58, 0.80	494	0.94	0.78, 1.13	0.001
2	3,220	2,142	0.69	0.61, 0.79	1,361	0.86	0.74, 1.01	0.01
≥3	5,715	3,440	0.62	0.55, 0.70	1,821	0.75	0.65, 0.86	0.02
Age at menopause[e], years								
<45	2,340	1,246	1	Referent	631	1	Referent	
45–49	2,184	1,461	1.22	1.09, 1.37	751	1.23	1.08, 1.41	0.93
50–54	3,016	2,207	1.28	1.16, 1.41	1,157	1.42	1.25, 1.61	0.14
≥55	1,104	879	1.32	1.16, 1.50	396	1.39	1.19, 1.63	0.56

Table continues

Statistically significant associations with overall breast cancer risk were observed for all of the risk factors investigated (Table 2). Adjustment for mammography utilization generally had little impact on these findings.

Polytomous logistic regression models that adjusted for mammography utilization revealed that many risk factors varied in their strength of association according to the method of breast cancer detection (Table 3). Age at first birth and parity were more strongly associated with mammography-detected breast cancer (all P's ≤ 0.01). Estrogen-plus-progestin postmenopausal hormone use among normal-weight postmenopausal women was more strongly associated with woman/clinician-detected breast cancer ($P = 0.002$). The associations between BMI and breast cancer risk varied strongly by method of detection for both postmenopausal and premenopausal women (all P's ≤ 0.02). Among postmenopausal women who had never used postmenopausal hormones, there was a strong positive association between obesity and risk of mammography-detected breast cancer (odds ratio (OR) = 1.72, 95% confidence interval (CI): 1.54, 1.92) but only a modest association with woman/clinician-detected breast cancer (OR = 1.13, 95% CI: 1.01, 1.27). Among premenopausal women, there was a modest positive association between obesity and risk of mammography-detected breast cancer (OR = 1.21, 95% CI: 1.04, 1.40) but an inverse association between obesity and risk of woman/clinician-detected breast cancer (OR = 0.61, 95% CI: 0.52, 0.71).

In general, analyses restricted to women undergoing regular mammographic screening produced findings similar to those seen in all women, with the exception of BMI (Table 4). Among postmenopausal women, there was no longer evidence for an association between BMI and woman/clinician-detected breast cancer. Among premenopausal women, there was no longer evidence for a positive association between BMI and risk of mammography-detected breast cancer.

Risk factor associations for mammography-detected breast cancer among regularly screened women did not appear to

Table 4. Continued

Characteristic	No. of Controls[b] (*n* = 11,171)	Detection Method						*P* Value[c]
		Mammography-Detected Breast Cancer			Woman/Clinician-Detected Breast Cancer			
		No. of Cases[b] (*n* = 7,241)	OR	95% CI	No. of Cases[b] (*n* = 4,243)	OR	95% CI	
Postmenopausal hormone use[f]								
Never use	1,674	949	1	Referent	524	1	Referent	
Estrogen only	1,018	489	0.92	0.80, 1.06	384	1.27	1.08, 1.49	0.001
Estrogen plus progestin only	734	482	1.21	1.04, 1.40	393	1.60	1.35, 1.90	0.003
Other	288	176	1.07	0.87, 1.33	126	1.35	1.06, 1.72	0.09
Alcohol consumption, drinks/week								
0	2,154	1,329	1	Referent	767	1	Referent	
0.1–6.9	7,483	4,830	1.09	1.00, 1.18	2,831	0.96	0.87, 1.05	0.02
≥7	1,534	1,083	1.23	1.10, 1.37	646	1.06	0.94, 1.21	0.04
Postmenopausal BMI[g,h]								
<18.5	61	22	0.62	0.37, 1.02	27	1.36	0.84, 2.21	0.01
18.5–24.9	1,674	949	1	Referent	524	1	Referent	
25.0–29.9	1,454	1,039	1.28	1.14, 1.43	399	0.88	0.75, 1.02	<0.0001
≥30.0	945	873	1.72	1.52, 1.96	298	1.02	0. 85, 1.21	<0.0001
Premenopausal BMI[i]								
<18.5	33	4	0.24	0.08, 0.68	26	1.23	0.72, 2.10	0.002
18.5–24.9	1,206	676	1	Referent	755	1	Referent	
25.0–29.9	742	451	1.06	0.91, 1.24	332	0.71	0.61, 0.84	<0.0001
≥30.0	543	318	0.99	0.83, 1.18	185	0.53	0.43, 0.64	<0.0001

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] ORs were mutually adjusted for all other risk factors in the table, in addition to age, state of residence, year of diagnosis, menopausal status, educational level, history of mammography utilization, and interaction terms for interactions between BMI, postmenopausal hormone use, and menopausal status.

[b] Average value from 5 imputed data sets.

[c] Test for difference in the risk factor association by method of detection.

[d] Among parous women only.

[e] Among postmenopausal women only.

[f] Among normal-weight postmenopausal women.

[g] Weight (kg)/height (m)^2.

[h] Among postmenopausal women who had never used postmenopausal hormones.

[i] Among premenopausal women only.

vary by stage at diagnosis (Appendix Table 1). There was modest variation in the associations of age at first birth, alcohol consumption, and postmenopausal BMI with woman/clinician-detected breast cancer by stage at diagnosis. Postmenopausal obesity was positively associated with late-stage woman/clinician-detected breast cancer (OR = 1.26, 95% CI: 0.98, 1.62) but not early-stage woman/clinician-detected breast cancer (OR = 0.89, 95% CI: 0.71, 1.11; $P = 0.03$ for difference in risk estimates by stage). Similar results were obtained when these analyses of regularly screened women were restricted to those with at least 5 mammograms in the past 5 years (data not shown).

Among women without mammographic screening in the preceding 5 years (Table 5), most risk factor associations were consistent with those observed for overall breast cancer risk among all women, including elevated risk of woman/clinician-detected breast cancer with postmenopausal obesity. There was no longer evidence for a positive association between estrogen-plus-progestin hormone use and breast cancer risk; however, the number of cases in this subgroup was quite small and the confidence interval was wide.

DISCUSSION

Our results indicate that some risk factor associations for invasive breast cancer vary by method of detection. Most strikingly, elevated BMI among regularly screened postmenopausal women was associated with increased risk of mammography-detected breast cancer but not woman/clinician-detected breast cancer. Among regularly screened

Table 5. Odds Ratios[a] for Woman/Clinician-Detected Breast Cancer Among Women With No Mammography in the Past 5 Years, According to Breast Cancer Risk Factors, Collaborative Breast Cancer Study, 1992–2007

Characteristic	No. of Controls[b] (*n* = 2,465)	No. of Cases[b] (*n* = 1,708)	OR	95% CI
First-degree family history of breast cancer				
No	2,213	1,431	1	Referent
Yes	252	277	1.68	1.39, 2.03
Age at menarche, years				
<12	449	322	1	Referent
12	604	405	0.90	0.74, 1.10
13	595	462	1.03	0.85, 1.24
≥14	817	519	0.85	0.70, 1.02
Age at first birth[c], years				
<20	494	279	1	Referent
20–24	1,007	700	1.17	0.97, 1.40
25–29	455	320	1.09	0.87, 1.36
≥30	216	163	1.09	0.83, 1.45
Parity				
0	292	246	1	Referent
1	254	199	0.85	0.63, 1.15
2	600	450	0.81	0.62, 1.06
≥3	1,320	814	0.68	0.54, 0.87
Age at menopause[d], years				
<45	483	282	1	Referent
45–49	429	318	1.27	1.01, 1.59
50–54	631	464	1.27	1.03, 1.58
≥55	236	184	1.31	1.01, 1.70
Postmenopausal hormone use[e]				
Never use	618	427	1	Referent
Estrogen only	75	50	1.01	0.68, 1.49
Estrogen plus progestin only	25	8	0.57	0.25, 1.29
Other	27	13	0.65	0.32, 1.32
Alcohol consumption, drinks/week				
0	677	434	1	Referent
0.1–6.9	1,503	1,045	1.12	0.97, 1.30
≥7	285	229	1.28	1.02, 1.59
Postmenopausal BMI[f,g]				
<18.5	48	28	0.80	0.47, 1.35
18.5–24.9	618	427	1	Referent
25.0–29.9	517	355	1.00	0.83, 1.21
≥30.0	340	270	1.21	0.98, 1.50
Premenopausal BMI[h]				
<18.5	13	10	1.21	0.51, 2.85
18.5–24.9	307	226	1	Referent
25.0–29.9	203	136	0.92	0.69, 1.23
≥30.0	163	87	0.76	0.55, 1.05

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] ORs were mutually adjusted for all other risk factors in the table, in addition to age, state of residence, year of diagnosis, menopausal status, educational level, and interaction terms for interactions between BMI, postmenopausal hormone use, and menopausal status.

[b] Average value from 5 imputed data sets.

[c] Among parous women only.

[d] Among postmenopausal women only.

[e] Among normal-weight postmenopausal women.

[f] Weight (kg)/height (m)^2.

[g] Among postmenopausal women who had never used postmenopausal hormones.

[h] Among premenopausal women only.

premenopausal women, elevated BMI was associated with reduced risk of woman/clinician-detected breast cancer but not mammography-detected breast cancer. The results also indicated that postmenopausal estrogen-plus-progestin hormone use among regularly screened women was more strongly associated with woman/clinician-detected breast cancer than with mammography-detected breast cancer.

Despite the recognized influence of screening history on estimates of cancer risk factor associations (26, 27), we are unaware of any prior studies examining breast cancer risk factor associations by method of detection. One small study found no evidence for differences between screen-detected and symptom-detected breast cancer cases in age or breast cancer risk, as calculated by the Gail model; statistical power was insufficient to examine differences in individual risk factors (28). It has been widely recognized that many breast cancer risk factors are associated with utilization of mammographic screening (15, 29). Screening in turn increases the risk of breast cancer detection during a given period, by allowing detection of cancers that might not be clinically evident during that time frame (26). Nevertheless, previous studies have demonstrated that breast cancer risk factor associations persist after adjustment for mammography use (14, 15). Our results are consistent with these prior results, as we observed only modest attenuation of risk factor associations when adjusting for screening utilization.

The results likely reflect complex interactions between breast cancer biology and mammography detection characteristics for many established breast cancer risk factors. Mammography-detected breast cancers are more likely to be slow-growing cancers that spend a long period in a subclinical state. Woman/clinician-detected cancers arising among regularly screened women probably include both aggressive cancers that spent a short time in the subclinical state (i.e., they arose between screening mammograms) and those that were long present but difficult to detect via mammography. Notably, woman/

clinician-detected breast cancers are more likely to be hormone receptor–negative than those detected through mammographic screening (30, 31). Additionally, it is recognized that there is variation in risk factor associations by breast cancer subtype (32). For example, postmenopausal BMI is predominantly associated with risk of hormone receptor–positive breast cancer (24, 33). Our results are consistent with the idea that postmenopausal obesity primarily increases the risk of hormone receptor–positive cancers, which tend to be slower-growing and are thus conducive to detection by mammographic screening. This phenomenon could also contribute in part to the modest increases in the magnitude of association for age at first birth and parity for mammography-detected breast cancer compared with woman/physician-detected breast cancer, as there is evidence that these factors are primarily associated with hormone receptor–positive breast cancer (34). However, the heterogeneity in our findings among the risk factors thought to be predominantly associated with hormone receptor–positive breast cancer, including premenopausal BMI, suggests that the results cannot be explained entirely by variation in breast cancer hormone receptor status.

Some breast cancer risk factors, including postmenopausal hormone use and BMI, have been shown to be associated with the accuracy of mammographic screening (33, 35, 36). This variation in accuracy is most likely mediated through mammographic breast density, which can obscure breast cancers on a mammogram (36, 37). Estrogen-plus-progestin hormone use is positively associated with mammographic breast density, while BMI is inversely associated with mammographic density (37, 38). The elevated risk of woman/clinician-detected breast cancer with estrogen-plus-progestin hormone use (which increases mammographic breast density) may be due to the lower sensitivity of screening mammography in this group. The strong positive association between postmenopausal obesity and mammography-detected breast cancer may also partly reflect the enhanced sensitivity of screening mammography for women with elevated BMI, who tend to have less dense breasts (39), and possibly a reduced sensitivity of clinical breast examination among women with fatty breasts (40). Premenopausal obesity, which is well established as being protective overall for premenopausal breast cancer, was inversely associated with the risk of woman/clinician-detected breast cancer but was not associated with risk of screen-detected breast cancer among premenopausal women. This finding is difficult to interpret, but it may be that the decreased rate of breast carcinogenesis among obese premenopausal women is balanced by an elevated sensitivity of mammography, resulting in this null association.

Some risk factors appeared to have similar associations with risk of mammography-detected and woman/clinician-detected breast cancers. These included first-degree family history of breast cancer, age at menarche, and age at menopause. This may suggest that these factors influence risks of both slowly and quickly growing cancers and do not influence mammography performance. Alternatively, these risk factors could influence both cancer biology and mammography performance in ways that balance each other and lead to apparently comparable risk estimates for mammography-detected and woman/clinician-detected breast cancer.

Strengths of our study include its large size, its population-based design, and high participation rates. However, a number of limitations should be considered when interpreting these results. As with any case-control study, there is the potential for recall bias. However, we would not expect the accuracy of recall to vary among cases according to mode of cancer detection; thus, it appears unlikely that recall bias could explain our findings. We did not have data on mammographic breast density or tumor estrogen/progesterone receptor status for study participants; thus, we were unable to directly evaluate whether these factors mediated the observed variations in risk factors according to method of detection.

Method of detection for breast cancer cases was based on self-report. Mammography is used as both a screening tool and a diagnostic tool in breast cancer detection, which could have caused some confusion for women responding during the interviews. Although we could not assess the validity of participants' self-reports, the reliability of responses to this questionnaire item was assessed in a substudy of 179 breast cancer patients reinterviewed approximately 10 months after their initial study interview. Cohen's κ for classification of mode of detection as mammography-detected versus woman/clinician-detected was 0.91, indicating excellent reliability. Further, the percentage of breast cancers reported as mammography-detected in our study was quite similar to findings in national reports during the same time period (3), suggesting that most women accurately reported screening mammography history in the study interview. In our ascertainment of prior mammography utilization, we were unable to distinguish between screening mammography and diagnostic mammography. Such misclassification could have contributed to modest overadjustment when adjusting for prior mammography utilization in the regression analyses. Additionally, due to the use of categorical response options for the mammography utilization item during portions of the study period, some women undergoing regular biennial screening who had had 2 mammograms in the preceding 5 years were not categorized as regular screeners. Given the small percentage of women reporting 1–2 mammograms in the past 5 years, the impact of this limitation is expected to have been small.

These results have a number of implications for our understanding of breast cancer etiology and the design of screening and prevention strategies to reduce the burden of breast cancer. The variation we observed in risk factor associations by method of detection highlights the impact that mammography utilization and performance can have on the magnitude of observed risk factor associations. When interpreting the findings of other etiological breast cancer studies, it should be recognized that the mix of mammography-detected and woman/clinician-detected cases in the study population will influence the results. In future research, investigators seeking to understand breast cancer biology through epidemiologic studies of breast cancer molecular subtypes should also consider method of detection in their analyses. The development of risk-prediction tools and optimized risk-based screening strategies would also benefit from consideration of these patterns. For instance, among postmenopausal women undergoing regular screening mammography, the use of supplemental screening modalities may provide more benefit for women using estrogen plus progestin (who are at elevated risk of woman/clinician-detected breast cancer) than for obese women (who are not at an elevated risk of woman/clinician-detected

breast cancer). Finally, prevention efforts may potentially yield larger mortality reductions through the development of strategies to reduce the prevalence of risk factors for woman/clinician-detected breast cancer, which has a poorer prognosis. Epidemiologic studies that are able to classify breast cancers according to method of detection, combined with information on breast density and breast cancer subtype, will be most valuable in improving our understanding of breast cancer biology and elucidating new breast cancer screening and risk reduction strategies.

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REFERENCES

1. Swan J, Breen N, Coates RJ, et al. Progress in cancer screening practices in the United States: results from the 2000 National Health Interview Survey. *Cancer*. 2003;97(6):1528–1540.
2. Breen N, Gentleman JF, Schiller JS. Update on mammography trends: comparisons of rates in 2000, 2005, and 2008. *Cancer*. 2011;117(10):2209–2218.
3. Breen N, Yabroff KR, Meissner HI. What proportion of breast cancers are detected by mammography in the United States? *Cancer Detect Prev*. 2007;31(3):220–224.
4. Gill PG, Farshid G, Luke CG, et al. Detection by screening mammography is a powerful independent predictor of survival in women diagnosed with breast cancer. *Breast*. 2004;13(1):15–22.
5. Dong W, Berry DA, Bevers TB, et al. Prognostic role of detection method and its relationship with tumor biomarkers in breast cancer: the University of Texas M.D. Anderson Cancer Center experience. *Cancer Epidemiol Biomarkers Prev*. 2008;17(5):1096–1103.
6. Shen Y, Yang Y, Inoue LY, et al. Role of detection method in predicting breast cancer survival: analysis of randomized screening trials. *J Natl Cancer Inst*. 2005;97(16):1195–1203.
7. Wishart GC, Greenberg DC, Britton PD, et al. Screen-detected vs symptomatic breast cancer: is improved survival due to stage migration alone? *Br J Cancer*. 2008;98(11):1741–1744.
8. Joensuu H, Lehtimäki T, Holli K, et al. Risk for distant recurrence of breast cancer detected by mammography screening or other methods. *JAMA*. 2004;292(9):1064–1073.
9. Buist DS, Abraham LA, Barlow WE, et al. Diagnosis of second breast cancer events after initial diagnosis of early stage breast cancer. *Breast Cancer Res Treat*. 2010;124(3):863–873.
10. de Gelder R, Heijnsdijk EA, van Ravesteyn NT, et al. Interpreting overdiagnosis estimates in population-based mammography screening. *Epidemiol Rev*. 2011;33(1):111–121.
11. Etzioni R, Gulati R, Mallinger L, et al. Influence of study features and methods on overdiagnosis estimates in breast and prostate cancer screening. *Ann Intern Med*. 2013;158(11):831–838.
12. Marmot MG, Altman DG, Cameron DA, et al. The benefits and harms of breast cancer screening: an independent review. *Br J Cancer*. 2013;108(11):2205–2240.
13. Esserman LJ, Thompson IM Jr, Reid B. Overdiagnosis and overtreatment in cancer: an opportunity for improvement. *JAMA*. 2013;310(8):797–798.
14. Joffe MM, Byrne C, Colditz GA. Postmenopausal hormone use, screening, and breast cancer: characterization and control of a bias. *Epidemiology*. 2001;12(4):429–438.
15. Cook NR, Rosner BA, Hankinson SE, et al. Mammographic screening and risk factors for breast cancer. *Am J Epidemiol*. 2009;170(11):1422–1432.
16. Newcomb PA, Trentham-Dietz A, Hampton JM, et al. Late age at first full term birth is strongly associated with lobular breast cancer. *Cancer*. 2011;117(9):1946–1956.
17. Newcomb PA, Storer BE, Longnecker MP, et al. Lactation and a reduced risk of premenopausal breast cancer. *N Engl J Med*. 1994;330(2):81–87.
18. Titus-Ernstoff L, Egan KM, Newcomb PA, et al. Exposure to breast milk in infancy and adult breast cancer risk. *J Natl Cancer Inst*. 1998;90(12):921–924.
19. Sprague BL, Trentham-Dietz A, Newcomb PA, et al. Lifetime recreational and occupational physical activity and risk of in situ and invasive breast cancer. *Cancer Epidemiol Biomarkers Prev*. 2007;16(2):236–243.
20. Nelson SE, Gould MN, Hampton JM, et al. A case-control study of the HER2 Ile655Val polymorphism in relation to risk of invasive breast cancer. *Breast Cancer Res*. 2005;7(3):R357–R364.
21. Nichols HB, Trentham-Dietz A, Sprague BL, et al. Effects of birth order and maternal age on breast cancer risk: modification by whether women had been breast-fed. *Epidemiology*. 2008;19(3):417–423.
22. Newcomer LM, Newcomb PA, Trentham-Dietz A, et al. Detection method and breast carcinoma histology. *Cancer*. 2002;95(3):470–477.
23. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res*. 2007;16(3):219–242.
24. Munsell MF, Sprague BL, Berry DA, et al. Body mass index and breast cancer risk according to postmenopausal

estrogen-progestin use and hormone receptor status. *Epidemiol Rev*. 2014;36(1):114–136.
25. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. New York, NY: John Wiley & Sons, Inc.; 1987.
26. Weiss NS. Adjusting for screening history in epidemiologic studies of cancer: why, when, and how to do it. *Am J Epidemiol*. 2003;157(11):957–961.
27. Joffe MM. Invited commentary: screening as a nuisance variable in cancer epidemiology: methodological considerations. *Am J Epidemiol*. 2003;157(11):962–964.
28. Burke JP, Power C, Gorey TF, et al. A comparative study of risk factors and prognostic features between symptomatic and screen detected breast cancer. *Eur J Surg Oncol*. 2008;34(2): 149–153.
29. Gross CP, Filardo G, Singh HS, et al. The relation between projected breast cancer risk, perceived cancer risk, and mammography use. Results from the National Health Interview Survey. *J Gen Intern Med*. 2006;21(2):158–164.
30. Kirsh VA, Chiarelli AM, Edwards SA, et al. Tumor characteristics associated with mammographic detection of breast cancer in the Ontario Breast Screening Program. *J Natl Cancer Inst*. 2011;103(12):942–950.
31. Porter PL, El-Bastawissi AY, Mandelson MT, et al. Breast tumor characteristics as predictors of mammographic detection: comparison of interval- and screen-detected cancers. *J Natl Cancer Inst*. 1999;91(23):2020–2028.
32. Althuis MD, Fergenbaum JH, Garcia-Closas M, et al. Etiology of hormone receptor-defined breast cancer: a systematic review of the literature. *Cancer Epidemiol Biomarkers Prev*. 2004; 13(10):1558–1568.
33. Kerlikowske K, Walker R, Miglioretti DL, et al. Obesity, mammography use and accuracy, and advanced breast cancer risk. *J Natl Cancer Inst*. 2008;100(23):1724–1733.
34. Phipps AI, Buist DS, Malone KE, et al. Reproductive history and risk of three breast cancer subtypes defined by three biomarkers. *Cancer Causes Control*. 2011;22(3): 399–405.
35. Banks E, Reeves G, Beral V, et al. Influence of personal characteristics of individual women on sensitivity and specificity of mammography in the Million Women Study: cohort study. *BMJ*. 2004;329(7464):477.
36. Carney PA, Miglioretti DL, Yankaskas BC, et al. Individual and combined effects of age, breast density, and hormone replacement therapy use on the accuracy of screening mammography. *Ann Intern Med*. 2003;138(3): 168–175.
37. Boyd NF, Guo H, Martin LJ, et al. Mammographic density and the risk and detection of breast cancer. *N Engl J Med*. 2007; 356(3):227–236.
38. Vachon CM, Kuni CC, Anderson K, et al. Association of mammographically defined percent breast density with epidemiologic risk factors for breast cancer (United States). *Cancer Causes Control*. 2000;11(7): 653–662.
39. Sprague BL, Gangnon RE, Burt V, et al. Prevalence of mammographically dense breasts in the United States. *J Natl Cancer Inst*. 2014;106(10):dju255.
40. Oestreicher N, White E, Lehman CD, et al. Predictors of sensitivity of clinical breast examination (CBE). *Breast Cancer Res Treat*. 2002;76(1):73–81.

(Appendix follows)

Appendix Table 1. Associations[a] Between Breast Cancer Risk Factors and Breast Cancer Diagnosis Among Women With At Least 3 Mammograms in the Past 5 Years, According to Method of Detection and Tumor Stage at Diagnosis, Collaborative Breast Cancer Study, 1992–2007

Characteristic	Detection Method and Stage at Diagnosis									
	Mammography-Detected Breast Cancer					Woman/Clinician-Detected Breast Cancer				
	Localized		Advanced		*P* Value[b]	Localized		Advanced		*P* Value[b]
	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI	
First-degree family history of breast cancer										
No	1	Referent	1	Referent		1	Referent	1	Referent	
Yes	1.55	1.43, 1.69	1.40	1.21, 1.62	0.18	1.66	1.49, 1.85	1.52	1.33, 1.73	0.26
Age at menarche, years										
<12	1	Referent	1	Referent		1	Referent	1	Referent	
12	0.97	0.87, 1.07	0.87	0.74, 1.03	0.26	0.95	0.83, 1.08	0.99	0.84, 1.16	0.68
13	0.88	0.80, 0.98	0.77	0.65, 0.91	0.13	0.83	0.73, 0.96	0.88	0.75, 1.03	0.59
≥14	0.81	0.73, 0.90	0.71	0.60, 0.84	0.15	0.77	0.67, 0.88	0.93	0.79, 1.10	0.05
Age at first birth[c], years										
<20	1	Referent	1	Referent		1	Referent	1	Referent	
20–24	1.12	1.00, 1.24	1.18	0.98, 1.42	0.59	0.94	0.81, 1.08	0.93	0.79, 1.09	0.91
25–29	1.30	1.15, 1.47	1.36	1.09, 1.70	0.68	1.08	0.91, 1.27	1.03	0.85, 1.25	0.69
≥30	1.64	1.40, 1.92	1.75	1.33, 2.30	0.65	1.15	0.93, 1.42	1.57	1.25, 1.98	0.03
Parity										
0	1	Referent	1	Referent		1	Referent	1	Referent	
1	0.65	0.54, 0.78	0.70	0.51, 0.95	0.65	0.92	0.73, 1.16	0.97	0.74, 1.27	0.76
2	0.68	0.59, 0.79	0.69	0.53, 0.89	0.95	0.88	0.72, 1.07	0.87	0.69, 1.10	0.98
≥3	0.60	0.53, 0.69	0.63	0.50, 0.81	0.72	0.72	0.60, 0.87	0.82	0.66, 1.02	0.35
Age at menopause[d], years										
<45	1	Referent	1	Referent		1	Referent	1	Referent	
45–49	1.21	1.06, 1.38	1.29	1.05, 1.59	0.57	1.33	1.13, 1.56	1.10	0.86, 1.42	0.19
50–54	1.26	1.13, 1.40	1.43	1.17, 1.74	0.23	1.28	1.10, 1.49	1.59	1.31, 1.93	0.06
≥55	1.27	1.10, 1.46	1.59	1.23, 2.05	0.09	1.29	1.05, 1.58	1.53	1.18, 1.98	0.26
Postmenopausal hormone use[e]										
Never use	1	Referent	1	Referent		1	Referent	1	Referent	
Estrogen only	0.89	0.76, 1.04	0.86	0.63, 1.17	0.81	1.32	1.08, 1.60	1.00	0.76, 1.30	0.08
Estrogen plus progestin only	1.18	1.01, 1.39	1.29	0.96, 1.73	0.60	1.68	1.37, 2.07	1.54	1.20, 1.98	0.56
Other	0.99	0.78, 1.25	1.50	1.02, 2.21	0.05	1.42	1.06, 1.90	1.25	0.86, 1.81	0.56
Alcohol consumption, drinks/week										
0	1	Referent	1	Referent		1	Referent	1	Referent	
0.1–6.9	1.11	1.02, 1.22	1.01	0.87, 1.18	0.27	0.95	0.84, 1.08	0.97	0.85, 1.12	0.80
≥7	1.25	1.11, 1.41	1.21	0.98, 1.49	0.76	1.16	0.99, 1.36	0.90	0.74, 1.09	0.03
Postmenopausal BMI[f,g]										
<18.5	0.66	0.38, 1.16	0.55	0.17, 1.79	0.78	1.67	0.95, 2.93	1.08	0.49, 2.42	0.34
18.5–24.9	1	Referent	1	Referent		1	Referent	1	Referent	
25.0–29.9	1.29	1.13, 1.47	1.12	0.87, 1.44	0.30	0.75	0.61, 0.91	1.11	0.88, 1.39	0.01
≥30.0	1.70	1.48, 1.96	1.81	1.40, 2.35	0.64	0.89	0.71, 1.11	1.26	0.98, 1.62	0.03

Table continues

Appendix Table 1. Continued

Characteristic	Detection Method and Stage at Diagnosis									
	Mammography-Detected Breast Cancer					Woman/Clinician-Detected Breast Cancer				
	Localized		Advanced		*P* Value[b]	Localized		Advanced		*P* Value[b]
	OR	95% CI	OR	95% CI		OR	95% CI	OR	95% CI	
Premenopausal BMI[h]										
<18.5	0.16	0.04, 0.67	0.62	0.15, 2.65	0.17	1.58	0.87, 2.85	0.52	0.18, 1.50	0.05
18.5–24.9	1	Referent	1	Referent		1	Referent	1	Referent	
25.0–29.9	1.03	0.86, 1.23	1.12	0.83, 1.50	0.61	0.63	0.51, 0.78	0.79	0.63, 0.99	0.12
≥30.0	0.89	0.73, 1.09	1.25	0.92, 1.72	0.05	0.47	0.37, 0.61	0.65	0.49, 0.86	0.08

Abbreviations: BMI, body mass index; CI, confidence interval; OR, odds ratio.

[a] ORs were mutually adjusted for all other risk factors in the table, in addition to age, state of residence, year of diagnosis, menopausal status, educational level, history of mammography utilization, and interaction terms for interactions between BMI, postmenopausal hormone use, and menopausal status.

[b] Test for difference in the risk factor association by stage at diagnosis within each method of detection.

[c] Among parous women only.

[d] Among postmenopausal women only.

[e] Among normal-weight postmenopausal women.

[f] Weight (kg)/height $(m)^2$.

[g] Among postmenopausal women who had never used postmenopausal hormones.

[h] Among premenopausal women only.