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Population-Attributable Risk Proportion of Clinical Risk Factors for Breast Cancer

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IMPORTANCE Many established breast cancer risk factors are used in clinical risk prediction models, although the proportion of breast cancers explained by these factors is unknown.

OBJECTIVE To determine the population-attributable risk proportion (PARP) for breast cancer associated with clinical breast cancer risk factors among premenopausal and postmenopausal women.

DESIGN, SETTING, AND PARTICIPANTS Case-control study with 1:10 matching on age, year of risk factor assessment, and Breast Cancer Surveillance Consortium (BCSC) registry. Risk factor data were collected prospectively from January 1, 1996, through October 31, 2012, from BCSC community-based breast imaging facilities. A total of 18 437 women with invasive breast cancer or ductal carcinoma in situ were enrolled as cases and matched to 184 309 women without breast cancer, with a total of 58 146 premenopausal and 144 600 postmenopausal women enrolled in the study.

EXPOSURES Breast Imaging Reporting and Data System (BI-RADS) breast density (heterogeneously or extremely dense vs scattered fibroglandular densities), first-degree family history of breast cancer, body mass index (>25 vs 18.5-25), history of benign breast biopsy, and nulliparity or age at first birth (≥30 years vs <30 years).

MAIN OUTCOMES AND MEASURES Population-attributable risk proportion of breast cancer.

RESULTS Of the 18 437 women with breast cancer, the mean (SD) age was 46.3 (3.7) years among premenopausal women and 61.7 (7.2) years among the postmenopausal women. Overall, 4747 (89.8%) premenopausal and 12 502 (95.1%) postmenopausal women with breast cancer had at least 1 breast cancer risk factor. The combined PARP of all risk factors was 44.3% (95% CI, 40.8%-47.8%) among premenopausal women and 43.2% (95% CI, 41.0%-45.5%) among postmenopausal women. High breast density was one of the most prevalent risk factors for both premenopausal and postmenopausal women and had the largest effect on the PARP; 28.9% (95% CI, 25.3%-32.5%) of premenopausal and 14.4% (95% CI, 12.6%-16.0%) of postmenopausal breast cancers could potentially be averted if all women with heterogeneously or extremely dense breasts shifted to scattered fibroglandular breast density. Among postmenopausal women, 16.4% (95% CI, 14.4%-18.4%) of breast cancers could potentially be averted if all overweight and obese women attained a body mass index of less than 25.

CONCLUSIONS AND RELEVANCE Most women with breast cancer have at least 1 breast cancer risk factor routinely documented at the time of mammography, and more than 40% of premenopausal and postmenopausal breast cancers are explained by these factors. These easily assessed risk factors should be incorporated into risk prediction models to stratify breast cancer risk and promote risk-based screening and targeted prevention efforts.

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One of the challenges in promoting the widespread utility of breast cancer risk prediction models has been the assertion that most women with a diagnosis of breast cancer have no established clinical breast cancer risk factors or are not considered to be high risk.[1,2] Although it is impossible to determine the cause of breast cancer in any individual case,[3] easily assessed risk factors that explain a substantial proportion of incident breast cancers can be used to stratify breast cancer risk for targeted screening[4] and primary prevention[5] and improve public health interventions to reduce breast cancer risk.

The population-attributable risk proportion (PARP) represents the proportion of disease cases in a population that would not have occurred in the absence of a risk factor. The PARP can be calculated for a single risk factor or combinations of risk factors and quantifies the proportion of cases averted if exposure to the risk factor was removed from the entire population, holding all other factors constant. The PARP incorporates both the prevalence of the risk factor and the magnitude of its association with disease; therefore, rare exposures with a high relative risk may explain a similar proportion of cases as common exposures with modest relative risks.

Previous studies of PARP have largely focused on quantifying the potential reductions in postmenopausal breast cancer incidence by intervening on modifiable factors.[6-13] Estimates of the proportion of postmenopausal breast cancers that could be averted through lifestyle interventions range from 26%[6,11] to 40.7%,[12] and estimates for combinations of nonmodifiable factors range from 37.3% to 57.3%.[6,12,14] To our knowledge, no studies have quantified the contributions of risk factors for premenopausal breast cancer, only 1 small study has included breast density as a risk factor,[15] and none have examined the PARP for breast density using the Breast Imaging Reporting and Data System (BI-RADS) scale,[16] which is the standard for reporting breast density in clinical practice in the United States.

We aimed to estimate the proportion of breast cancers attributable to breast cancer risk factors commonly documented in clinical practice and used in breast cancer risk prediction models, including BI-RADS breast density. We used data from a large cohort of women undergoing mammography at facilities participating in the Breast Cancer Surveillance Consortium (BCSC).

Key Points

Question What proportion of premenopausal and postmenopausal breast cancers are attributed to commonly collected clinical risk factors?

Findings In this population-based, case-control, cohort study of 202 746 women, breast density and body mass index had the largest individual population-attributable risk proportion. Twenty-nine percent of premenopausal and 14% of postmenopausal breast cancers could be prevented if breast density in women with dense breasts was reduced to scattered fibroglandular densities on the Breast Imaging Reporting and Data System scale, and postmenopausal breast cancer incidence would be reduced by 16% if all women achieved a body mass index less than 25.

Meaning Clinical breast cancer risk factors explain a large proportion of breast cancer incidence and should be used in the clinical setting for risk stratification and targeted screening and prevention efforts.

Methods

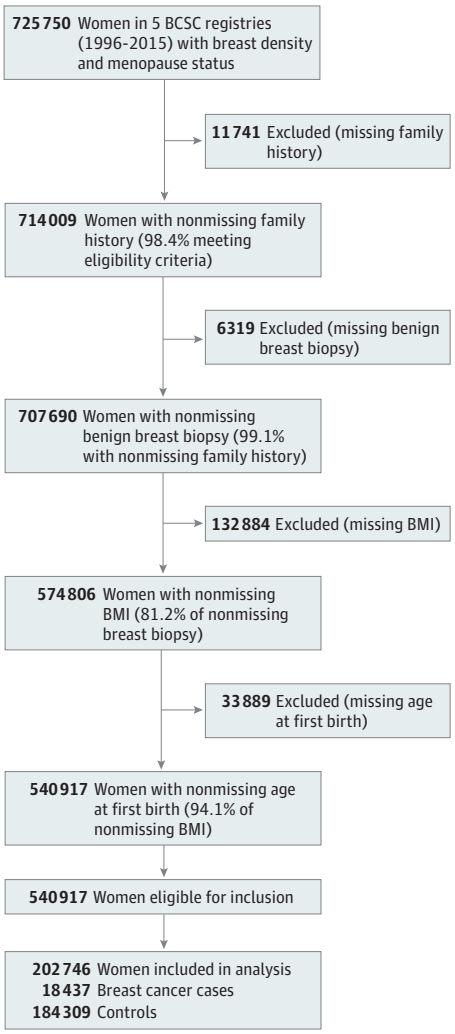
Study Population

Women with breast cancer and those serving as matched controls were selected from the BCSC, which comprises regional registries from across the United States that collect clinical characteristics and breast imaging data from community radiology facilities. Breast cancer diagnoses and tumor characteristics are obtained through linkage to pathology databases and regional Surveillance, Epidemiology, and End Results programs or state cancer registries. Each registry and the statistical coordinating center received institutional review board approval for either active or passive consenting processes or a waiver of consent to enroll participants, link data, and perform analytic studies. The present study received approval from the institutional review boards of the Group Health, North Carolina, San Francisco, Vermont, and New Hampshire registries. All procedures are Health Insurance Portability and Accountability Act compliant, and all registries and the statistical coordinating center received a federal certificate of confidentiality and other protection for the identities of women, physicians, and facilities. The BCSC cohort is described in further detail elsewhere.[17,18]

Five BCSC registries (New Hampshire, North Carolina, San Francisco, Vermont, and Group Health) contributed data for this analysis. Eligible cases were women aged 40 to 74 years who were diagnosed with invasive breast cancer or ductal carcinoma in situ between 1996 and 2015 and with a BI-RADS breast density measure and risk factor data available within 5 years before their diagnosis. Risk factors and strength of associations with invasive cancer and ductal carcinoma in situ are similar,[19,20] so both were included. Women with a history of breast cancer or missing menopausal status were excluded, as well as women with incomplete breast cancer risk factor data (**Figure**). We selected risk factor information associated with mammography examinations 1 year or more before diagnosis. For 4499 of 18 437 women (24.4%), risk factor information was not available more than 1 year before the diagnosis, and data from within a year of diagnosis were used. Risk factor information was collected a mean (SD) of 20.4 (15.46) months (range, <1-60 months) before breast cancer diagnosis. As a sensitivity analysis, we excluded cases with risk factor information obtained within 1 year of diagnosis and our findings remained unchanged.

Ten controls were matched to each breast cancer case on menopausal status, age and year of risk factor assessment, and BCSC registry data. Eligible controls had no breast cancer diagnosis between the year of risk factor assessment and the year of diagnosis of her matched case. For age and year of risk factor information, we matched to controls differing up to ±5 years, selecting controls with the closest match to the case. A total of 17 607 cases (95.5%) matched to 10 controls on age and year

Figure. Flowchart of Women in 5 Breast Cancer Surveillance Consortium (BCSC) Registries Eligible for the Study



The 5 BCSC registries include New Hampshire, North Carolina, San Francisco, Vermont, and Group Health. BMI indicates body mass index.

exactly, and 16 cases (0.09%) matched to fewer than 10 controls. A total of 18 437 women with breast cancer and 184 309 matched controls were included.

Exposure Assessment

Demographics and breast cancer risk factors were obtained through questionnaires completed at each mammography visit. Questionnaires included birth date, race, ethnicity, height, weight, first-degree family history of breast cancer, menopause status, parity, and age at first birth. Body mass index (BMI) (weight in kilograms divided by height in meters squared) was calculated as underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), obesity class I (30.0-34.4), and obesity class II or III (≥35.0).[21] History of benign breast biopsy was obtained by self-report and through linkages with pathology databases. The American College of Radiology's BI-RADS system, assigned by clinical radiologists, was used to classify breast density as a, almost entirely fat; b, scattered fibroglandular densities; c, heterogeneously dense; and d, extremely dense.[22]

Statistical Analysis

Analyses were stratified by menopausal status. We used descriptive statistics to assess differences in demographics and clinical characteristics for cases and controls. Risk factors selected a priori for analysis were dense breasts (heterogeneously dense or extremely dense), first-degree relative with breast cancer, history of benign breast biopsy, and nulliparity or age at first birth 30 years or older. We considered BMI of 25 or more to be a risk factor only for postmenopausal breast cancer. Multivariable conditional logistic regression, stratified by matched set, was used to estimate the odds ratios and 95% CIs associated with each risk factor.

The PARP was calculated using the generalized regression-based approach described by Bruzzi et al,[23] allowing for the calculation of joint PARP for combinations of risk factors. The multivariable combined PARP was measured by the equation

$$1-\sum_i \frac{pd_i}{RR_i},$$

where pd_i is the proportion of cases in stratum i of the risk factor distribution and RR_i is the multivariable adjusted relative risk associated with that stratum of the risk factor. Odds ratios from the multivariable conditional logistic regression models were used as relative risk estimates.[23] The PARP was calculated for individual risk factors and combinations of risk factors. For each factor, the reference level reported in **Table 1** is considered the low-risk category. For combinations of factors, the PARP represents the proportion of cases eliminated in the population if everyone shifted to the referent category for all included variables. When the referent category for PARP was not the lowest level of exposure, the lowest level of exposure was assumed to remain unchanged. The 95% CIs were calculated using bootstrapping.[24] All analyses were conducted in R, version 3.2.1 (R Foundation).

Results

A total of 5286 premenopausal women with breast cancer were matched to 52 860 women without breast cancer, and 13 151 postmenopausal women with breast cancer were matched to 131 449 women without breast cancer. The mean age of premenopausal women was 46.3 (3.7) years compared with a mean age of 61.7 (7.2) years for postmenopausal women. The sample was predominantly non-Hispanic white (>75% of women) with smaller percentages of Asian, Hispanic, and African American women. Women with breast cancer were more likely to have a first-degree family history of breast cancer, a history of benign breast biopsy, dense breasts, and an older age at first birth compared with the controls (Table 1). Postmenopausal women with breast cancer were more likely to be overweight or obese.

Overall, 89.8% (n = 4747) of premenopausal women with breast cancer and 95.1% (n = 12 502) of postmenopausal women with breast cancer had at least 1 risk factor, compared with

Table 1. Characteristics of Women With Breast Cancer and Controls Included in the Study Population, Breast Cancer Surveillance Consortium (1996-2015)

Characteristic	Women, No. (%)			
	Premenopausal		Postmenopausal	
	Control (n = 52 860)	Invasive and In Situ Cancer (n = 5286)	Control (n = 131 449)	Invasive and In Situ Cancer (n = 13 151)
Age, y				
40-49	41 120 (77.8)	4114 (77.8)	4711 (3.6)	471 (3.6)
50-59	11 740 (22.2)	1172 (22.2)	48 868 (37.2)	4882 (37.1)
60-69	NA	NA	54 153 (41.2)	5415 (41.2)
70-74	NA	NA	23 717 (18.0)	2383 (18.1)
Race/ethnicity				
White	40 054 (75.8)	4091 (77.4)	104 157 (79.2)	10 832 (82.4)
Black	1295 (2.4)	122 (2.3)	3323 (2.5)	279 (2.1)
Asian	5670 (10.7)	548 (10.4)	11 177 (8.5)	894 (6.8)
Hispanic	2719 (5.1)	208 (3.9)	5105 (3.9)	395 (3.0)
Other/mixed	3122 (5.9)	317 (6.0)	7687 (5.8)	751 (5.7)
Family history of breast cancer				
No	46 020 (87.1)	4181 (79.1)	109 827 (83.6)	10 035 (76.3)
Yes	6840 (12.9)	1105 (20.9)	21 622 (16.4)	3116 (23.7)
History of benign breast biopsy				
No	45 658 (86.4)	4193 (79.3)	102 741 (78.2)	9252 (70.4)
Yes	7202 (13.6)	1093 (20.7)	28 708 (21.8)	3899 (29.6)
Age at first live birth, y				
Nulliparous	11 729 (22.2)	1240 (23.5)	20 236 (15.4)	2350 (17.9)
Age <30 y	29 060 (55.0)	2615 (49.5)	97 101 (73.9)	9168 (69.7)
Age ≥30 y	12 071 (22.8)	1431 (27.1)	14 112 (10.7)	1633 (12.4)
BMI				
<18.5	924 (1.7)	106 (2.0)	2223 (1.7)	173 (1.3)
18.5-24.9	23 739 (44.9)	2642 (50.0)	45 341 (34.5)	4194 (31.9)
25.0-29.9	15 123 (28.6)	1456 (27.5)	43 937 (33.4)	4476 (34.0)
30.0-34.9	7192 (13.6)	616 (11.7)	23 321 (17.7)	2493 (19.0)
≥35.0	5882 (11.1)	466 (8.8)	16 627 (12.6)	1815 (13.8)
BI-RADS breast density				
Almost entirely fat (a)	2764 (5.2)	95 (1.8)	16 852 (12.8)	1014 (7.7)
Scattered fibroglandular densities (b)	17 256 (32.6)	1248 (23.6)	62 743 (47.7)	5749 (43.7)
Heterogeneously dense (c)	24 479 (46.3)	2803 (53.0)	44 686 (34.0)	5448 (41.4)
Extremely dense (d)	8361 (15.8)	1140 (21.6)	7168 (5.5)	940 (7.1)
Type of cancer				
Invasive	NA	3890 (73.6)	NA	10 313 (78.4)
In situ		1396 (26.4)		2838 (21.6)
No. of risk factors				
None	9749 (18.4)	539 (10.2)	11 222 (8.5)	649 (4.9)
1	20 793 (39.3)	1759 (33.3)	49 661 (37.8)	3803 (28.9)
2	17 509 (33.1)	2039 (38.6)	46 076 (35.1)	4807 (36.6)
3	4365 (8.3)	821 (15.5)	19 744 (15.0)	2914 (22.2)
≥4	444 (0.8)	128 (2.4)	4746 (3.6)	978 (7.4)

Abbreviations: BI-RADS, Breast Imaging Reporting and Data System; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable.

81.6% (n = 43 111) of premenopausal controls and 91.5% (n = 120 227) of postmenopausal controls. Most premenopausal cases (56.5% [n = 2988]) had 2 or more risk factors compared with only 42.2% (n = 22 318) of premenopausal controls. Postmenopausal women, on average, had more risk factors, with 66.2% (n = 8699) of cases having 2 or more risk factors compared with 53.7% (n = 70 566) of the control women.

First-degree family history of breast cancer, history of benign breast biopsy, dense breasts, and nulliparity or age at first birth older than 30 years were associated with an increased risk of breast cancer (**Table 2**). Obesity was not associated with breast cancer risk among premenopausal women, but overweight and obese postmenopausal women were at a higher risk of breast cancer. This association showed a statistically significant positive association, with overweight, obesity class I,

Table 2. Odds Ratios and PARP of Breast Cancer Risk Factors in Women Undergoing Screening or Diagnostic Mammography[a]

	Women With Breast Cancer			
	Premenopausal (n = 58 146)		Postmenopausal (n = 144 600)	
Characteristic	OR (95% CI)[b]	PARP, % (95% CI)[c]	OR (95% CI)[b]	PARP, % (95% CI)[c]
Family history of breast cancer				
No	1 [Reference]	8.7 (7.3-10.1)	1 [Reference]	8.2 (7.2-9.1)
Yes	1.71 (1.59-1.84)		1.53 (1.46-1.60)	
BMI[d]				
Underweight	0.93 (0.76-1.15)	NA	0.79 (0.67-0.93)	16.4 (14.4-18.4)[e]
Normal	1 [Reference]		1 [Reference]	
Overweight	0.99 (0.93-1.07)		1.23 (1.17-1.28)	
Obesity class I	1.00 (0.91-1.10)		1.39 (1.31-1.47)	
Obesity class II or III	1.05 (0.94-1.18)		1.54 (1.45-1.64)	
History of benign breast biopsy				
No	1 [Reference]	6.9 (5.5-8.4)	1 [Reference]	8.6 (8.0-9.2)
Yes	1.50 (1.40-1.62)		1.41 (1.35-1.47)	
Age at first live birth				
Nulliparous	1.14 (1.05-1.22)	8.7 (4.8-12.7)	1.20 (1.14-1.26)	5.2 (4.2-6.2)
≤30 y	1 [Reference]		1 [Reference]	
>30 y	1.28 (1.19-1.37)		1.23 (1.16-1.30)	
BI-RADS breast density[f]				
Almost entirely fat	0.47 (0.38-0.58)	28.9 (25.3-32.5)[g]	0.62 (0.58-0.67)	14.4 (12.6-16.0)[g]
Scattered fibroglandular densities	1 [Reference]		1 [Reference]	
Heterogeneously dense	1.57 (1.46-1.69)		1.40 (1.34-1.45)	
Extremely dense	1.81 (1.65-1.99)		1.58 (1.46-1.71)	

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); NA, not applicable; OR, odds ratio; PARP, population-attributable risk proportion.

[a] Estimated by multivariable conditional logistic regression.

[b] Odds ratios presented were adjusted for family history of breast cancer, BMI, history of benign breast biopsy, age at first live birth, and Breast Imaging Reporting and Data System (BI-RADS) breast density.

[c] PARP calculated using multivariable adjusted ORs.

[d] Underweight, BMI less than 18.5; normal, 18.5-24.9; overweight, 25.0-29.9; obesity class I, 30.0-34.9; and obesity class II or III, 35.0 or more.

[e] PARP calculated for shifting everyone to normal weight and holding underweight constant.

[f] BI-RADS classification system: a, almost entirely fat; b, scattered fibroglandular densities; c, heterogeneously dense; and d, extremely dense.[22]

[g] PARP calculated for shifting the BI-RADS categories heterogeneously dense and extremely dense to scattered fibroglandular densities, and holding almost entirely fat constant.

and obesity class II or III women having 1.23, 1.39, and 1.54 times the odds of breast cancer relative to normal weight women.

Among premenopausal women, the largest individual PARP was for breast density, with 28.9% (95% CI, 25.3%-32.5%) of breast cancers potentially removed by reducing breast density from BI-RADS heterogeneously or extremely dense breasts to scattered fibroglandular densities. The PARP for breast density increased to 65.5% (95% CI, 60.4%-70.6%) if all premenopausal women reduced their breast density to the lowest category of almost entirely fat. A more modest reduction of all women shifting to a single lower BI-RADS category would result in a PARP of 2.9% (95% CI, 1.5%-4.4%). Among premenopausal women, the combination of first-degree family history, history of benign breast biopsy, age at first birth, and breast density had a PARP of 44.3% (95% CI, 40.8%-47.8%) (**Table 3**).

Individual PARPs for first-degree family history, age at first birth, and history of benign breast biopsy were similar for premenopausal and postmenopausal breast cancer. However, overweight and obesity accounted for a modest proportion of postmenopausal breast cancers, with a PARP of 16.4% (95% CI, 14.4%-18.4%) if all obese and overweight women achieved a normal BMI. The estimated PARP for shifting all postmenopausal women to the BI-RADS category of almost entirely fat was 43.9% (95% CI, 39.6%-48.2%), whereas shifting only extremely or heterogeneously dense breasts to scattered fibroglandular densities was 14.4% (95% CI, 12.6%-16.0%). The PARP was 0.8% (95% CI, 0.4%-1.3%) for reductions of any single BI-RADS category. The combination of first-degree family history, history of benign breast biopsy, nulliparity or age at first birth older than 30 years, breast density (with scattered fibroglandular densities as reference) and BMI yielded a combined postmenopausal PARP of 43.2% (95% CI, 41.0%-45.5%) (Table 3).

Discussion

We found that routinely collected clinical risk factors included in breast cancer risk models may explain 44.3% of premenopausal and 43.2% of postmenopausal breast cancers. A moderate proportion of breast cancers can be attributed to high breast density alone, suggesting that behaviors or interventions that could facilitate reductions in breast density have the potential to eliminate a large proportion of breast cancers in both premenopausal and postmenopausal women. Overall, these easily assessed breast cancer risk factors are highly prevalent among premenopausal and postmenopausal women with breast cancer; more than half of the breast cancer cases in the population are attributable to these factors and thus they offer promise for risk-based screening and prevention strategies.

Table 3. PARP for Individual Risk Factors and Combinations of Factors[a]

Risk Factor	Breast Cancer, PARP (95% CI)	
	Premenopausal	Postmenopausal
2 Risk Factors		
Family history of breast cancer, breast density	35.0 (30.9-39.0)	21.4 (20.3-22.5)
History of benign breast biopsy, family history of breast cancer	14.8 (13.3-16.3)	16.0 (14.8-17.1)
History of benign breast biopsy, breast density	33.6 (30.4-36.8)	21.5 (19.6-23.5)
Breast density, BMI	NA	28.9 (26.4-31.5)
Family history of breast cancer, BMI	NA	23.2 (21.9-24.6)
History of benign breast biopsy, BMI	NA	23.7 (21.6-25.7)
Nulliparous or age at first birth ≥30 y, BMI	NA	20.9 (18.8-23.0)
Nulliparous or age at first birth ≥30 y, family history of breast cancer	16.6 (13.5-19.8)	13.0 (11.4-14.5)
Nulliparous or age at first birth ≥30 y, history of benign breast biopsy	15.0 (12.3-17.8)	13.3 (11.8-14.9)
Nulliparous or age at first birth ≥30 y, breast density	34.9 (31.2-38.2)	18.7 (16.7-20.7)
3 Risk Factors		
Family history of breast cancer, history of benign breast biopsy, breast density	39.1 (35.2-43.0)	27.9 (26.3-29.5)
Family history of breast cancer, history of benign breast biopsy, nulliparous or age at first birth ≥30 y	22.2 (19.8-24.6)	20.3 (18.8-21.8)
Family history of breast cancer, history of benign breast biopsy, BMI	NA	29.8 (27.6-31.9)
Family history of breast cancer, nulliparous or age at first birth ≥30 y, breast density	40.5 (36.2-44.8)	25.4 (23.6-27.1)
Family history of breast cancer, breast density, BMI	NA	34.7 (31.9-37.6)
History of benign breast biopsy, nulliparous or age at first birth ≥30 y, breast density	39.3 (36.0-42.5)	25.5 (23.7-27.3)
History of benign breast biopsy, breast density, BMI	NA	34.9 (32.8-37.1)
Family history of breast cancer, nulliparous or age at first birth ≥30 y, BMI	NA	27.3 (25.1-29.6)
History of benign breast biopsy, nulliparous or age at first birth ≥30 y, BMI	NA	27.7 (25.3-30.1)
Breast density, BMI, nulliparous or age at first birth ≥30 y	NA	32.6 (30.1-35.1)
4 Risk Factors		
Family history of breast cancer, history of benign breast biopsy, breast density, nulliparous or age at first birth ≥30 y	44.3 (40.8-47.8)	31.5 (30.0-33.1)
Family history of breast cancer, history of benign breast biopsy, breast density, BMI	NA	40.2 (37.7-42.6)
History of benign breast biopsy, nulliparous or age at first birth ≥30 y, breast density, BMI	NA	38.3 (35.8-40.7)
Family history of breast cancer, nulliparous or age at first birth ≥30 y, breast density, BMI	NA	38.1 (36.0-40.2)
Family history of breast cancer, nulliparous or age at first birth ≥30 y, history of benign breast biopsy, BMI	NA	33.5 (30.8-36.1)
5 Risk Factors		
Family history of breast cancer, history of benign breast biopsy, nulliparous or age at first birth ≥30 y, breast density, BMI	NA	43.2 (41.0-45.5)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); PARP, population-attributable risk proportion.

[a] Family history of breast cancer, first-degree family history only; breast density, heterogeneously or extremely dense breasts with scattered fibroglandular densities as reference; BMI 25 or more.

Although breast density is a well-established, strong, and prevalent breast cancer risk factor, few studies have quantified the PARP of breast density and, to our knowledge, none have used the BI-RADS classification utilized in clinical practice. In a study of Canadian women, Boyd et al[15] found a PARP of 16% if women with more than 50% breast density reduced their breast density to 50% or less,[15] and this PARP was much greater (approximately 40%) for cancers detected within 12 months of a negative screening examination, reflecting the increased probability of a masking effect in dense breasts.[25] We found a PARP nearly 2-fold higher than that of Boyd et al if the breast density in all women shifted to the BI-RADS scattered fibroglandular density category and the PARP was unaltered in a sensitivity analysis excluding women with breast density measured within 1 year of diagnosis. Differences between our and Boyd et al's study may reflect distinctions between a classification of greater than 50% density using quantitative measures that include a smaller proportion of women with substantial amounts of density, whereas the qualitative BI-RADS classification of heterogeneously or extremely dense includes larger proportions of women.[26] Furthermore, the use of 50% or less as a reference category is likely to attenuate the relative risk used in the PARP, since the lit-

erature suggests that women with 10% to 50% breast density have an increased breast cancer risk compared with women with less than 10% density.[27]

We found that reductions in breast density among women with dense breasts would avert 28.9% of breast cancers among premenopausal women and 14.4% among postmenopausal women; such a reduction would prevent more cases than reducing any other risk factor in this study, with the exception of BMI in postmenopausal women. Studies of longitudinal changes in BI-RADS breast density suggest that a reduction of dense BI-RADS categories to a lower category reduced breast cancer risk relative to density that remained stable or increased.[28,29] Our results suggest that shifting the distribution of dense breasts to scattered fibroglandular breast density would result in a substantial reduction in breast cancers in the population. Reductions among women with dense breasts could potentially be achieved through increased breastfeeding, as well as primary prevention with tamoxifen citrate for those at highest risk,[30-33] and our results highlight the necessity for new approaches to reduce breast density that could be widely adopted without adverse consequences.

To our knowledge, no prior studies have evaluated the PARP of clinical breast cancer risk factors in combination with breast density. However, our results are broadly consistent with previous literature evaluating nonmodifiable clinical risk factors, with PARP estimates ranging from 37.2%[6] to 57.3%[12] combining the risk factors of age at menarche, menopause, and first full-term pregnancy; parity; family history of breast cancer; and benign breast disease. Estimates of the PARP of BMI in postmenopausal women have been disparate across studies; Barnes et al[6] estimated a PARP of 2% by shifting all women to a BMI of 22.4 or lower, Mezzetti et al[9] estimated a PARP of 10.2% by shifting all women to a BMI of 23.3, and 3 additional studies found PARPs of 8.0%, 9.5%, and 24.8% by shifting women to a BMI of less than 25.[8,10,34] It is difficult to directly compare our results with previous findings because of different reference categories. Our finding of a PARP of 16.4% may reflect the high prevalence of overweight and obese postmenopausal women in the United States compared with studies in European populations. Our results suggest that excess bodyweight plays an important role in postmenopausal breast cancer, further reinforcing the need for weight reduction and management to prevent a substantial proportion of breast cancers. In the absence of interventions, the PARP for obesity will increase with the prevalence of obesity in the United States.[35]

Our study included more than 200 000 women from BCSC community breast imaging registries, which is broadly representative of the demographic composition of women in the United States[18] and with clinical risk factor distributions nearly identical to the distributions estimated in the population-based National Health Interview Survey (eFigure 1 and eFigure 2 in the Supplement). The BCSC 5- and 10-year absolute risk calculator was developed within the same cohort of women,[36,37] although the use of breast cancer risk models to identify women for primary and secondary preventions has been controversial, with a commonly expressed concern that most women with breast cancer have no known risk factors. We found that only 10% of premenopausal and less than 5% of postmenopausal breast cancers in our study had no clinical risk factors. The impact of assessing clinical breast cancer risk factors in combination with breast density is considerable, explaining more than half of premenopausal and postmenopausal breast cancers and identifying risk factors where targeted public health interventions would have the greatest impact. These factors represent clinically available information that can and should be used by clinicians to stratify breast cancer risk for improved risk-based screening and primary and secondary prevention efforts.[4]

Strengths and Limitations

Estimates of the PARP are sensitive to changes in category definitions that alter the prevalence and relative risk of the risk factor.[3,38] We chose categories based on clinical relevance, but examined how robust our findings were to changes in the reference group corresponding to ideal compared with more realistic interventions to change risk factor distributions. Close attention to risk factor prevalence should be considered when applying our results to other populations. We were unable to measure other behavioral and genetic risk factors; thus, our estimated PARP likely underestimates the joint PARP of all known risk factors. Our study uses risk factor and breast density information from 1996-2015—a period when the BI-RADS density category definitions changed. Despite these changes, there is no evidence of a difference in the distribution of breast density over time in the BCSC.[22] Studies have found mixed results for interrater and intrarater reliability of the BI-RADS categories[39-42]; however, relative risks for breast cancer are similar comparing BI-RADS with more objective quantitative density measurements.[43] Most importantly, BI-RADS is presently the only measure of breast density used routinely in clinical practice; thus, using BI-RADS enhances the clinical utility of our estimates for risk stratification and screening and prevention efforts.

Our study has several strengths, including collection of clinically available breast cancer risk factors. We provide novel insights into the contributions of breast density on a population level, reinforcing existing interventions to reduce breast density among high-risk women and the need for acceptable behaviors and novel interventions to reduce risk in women at high and average risk. Finally, we provide what we believe to be the first estimate of PARP for clinical risk factors in premenopausal women, and our results suggest that, with the exception of BMI, the PARP of most risk factors is similar among premenopausal and postmenopausal women.[44]

Conclusions

In what we believe to be the largest study of PARP in US women, we found that most premenopausal and postmenopausal women with breast cancer have at least 1 breast cancer risk factor, and that breast density and clinical risk factors may explain nearly half of breast cancer cases. These risk factors represent clinically available data that can and should be used to stratify risk, using established risk models that include breast

density, to promote risk-based screening and targeted prevention efforts. Future research should assess whether PARP estimates differ by molecular subtypes of breast cancer, where the magnitude and direction of risk factors may differ.[45-48]

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Study concept and design: Engmann, Miglioretti, Sprague, Kerlikowske.
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