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Breast cancer risk assessment in women aged 70 and older

Pamela M. Vacek · Joan M. Skelly · Berta M. Geller

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Abstract Although the benefit of screening mammography for women over 69 has not been established, it is generally agreed that screening recommendations for older women should be individualized based on health status and breast cancer risk. However, statistical models to assess breast cancer risk have not been previously evaluated in this age group. In this study, the original Gail model and three more recent models that include mammographic breast density as a risk factor were applied to a cohort of 19,779 Vermont women aged 70 and older. Women were followed for an average of 7.1 years and 821 developed breast cancer. The predictive accuracy of each risk model was measured by its *c*-statistic and associations between individual risk factors and breast cancer risk were assessed by Cox regression. *C*-statistics were 0.54 (95% CI = 0.52–0.56) for the Gail model, 0.54 (95% CI = 0.51–0.56) for the Tice modification of the Gail model, 0.55 (95% CI = 0.53–0.58) for a model developed by Barlow and 0.55 (95% CI = 0.53–0.58) for a Vermont model. These results indicate that the models are not useful for assessing risk in women aged 70 and older. Several risk factors in the models were not significantly associated with outcome in the cohort, while others were significantly related to outcome but had smaller relative risks than estimated by the models. Age-related attenuation of the effects of some risk factors makes the prediction of breast cancer in older women particularly difficult.

Keywords Breast cancer · Risk assessment · Mammographic breast density · Elderly

P. M. Vacek (✉)
Departments of Medical Biostatistics and Pathology, University of Vermont College of Medicine, Hills Building, 105 Carrigan Drive, Burlington, VT 05405, USA
e-mail: pvacek@uvm.edu

J. M. Skelly
Department of Medical Biostatistics, University of Vermont College of Medicine, Hills Building, 105 Carrigan Drive, Burlington, VT 05405, USA

B. M. Geller
Departments of Family Practice, Radiology, and Health Promotion Research, University of Vermont College of Medicine, 1 South Prospect Street, UHC, Burlington, VT 05405, USA

Introduction

Although women aged 70 and older have the highest incidence of invasive breast cancer, they have lower rates of screening mammography than younger women [1–4]. It is unclear why fewer older women undergo breast cancer screening, but a lack of explicit guidelines for this age group is likely to be an important contributing factor. Despite evidence that less screening mammography among older women is associated with later stage at diagnosis and poorer survival [5–7], there is no consensus on whether or how often women aged 70 and older should be screened [8]. However, there is general agreement that screening recommendations for older women should be individualized based on health status and breast cancer risk [9–11].

A woman's breast cancer risk is an important consideration when making recommendations about screening mammography because screening is more beneficial for those at higher risk of developing the disease. Considerable effort has been directed at identifying risk factors and developing risk prediction models for breast cancer. The most widely used risk assessment tool is the Gail model,

which was first published in 1989 and includes the following risk factors: current age, age at menarche, age at first child's birth, number of first-degree relatives with breast cancer, and number of prior breast biopsies [12]. The model was subsequently modified to include a biopsy outcome of atypical hyperplasia as a predictor [13]. More recent models have included mammographic breast density, which has been consistently shown to be highly associated with breast cancer risk [14]. Chen et al. added both body weight and percent dense breast tissue, as measured by planimetry, to the risk factors in the revised Gail model [15, 16]. The resulting model did not include age at menarche or an interaction between childbearing age and family history of breast cancer because they were not statistically significant. Tice et al. added breast density to the original Gail model, using the American College of Radiology Breast Imaging and Data System (BI-RADS®) categories of almost entirely fat, scattered fibroglandular densities, heterogeneously dense, and extremely dense [17, 18]. This classification scheme is routinely used by most radiologists in the U.S. to characterize breast density as part of their mammographic assessment. Barlow et al. developed a model that included BI-RADS breast density, body mass index (BMI), postmenopausal use of hormone therapy, and surgical menopause, in addition to the risk factors in the original Gail model [19].

To be useful for developing individualized screening recommendations, a model must have good predictive accuracy. Predictive accuracy is the ability to predict whether or not a specific woman will develop breast cancer and is measured by how well the risk estimates from a model differentiate those women who subsequently develop the disease from those who do not. Validation studies of currently available breast cancer risk models indicate that they have modest predictive accuracy [18–21]. In addition, the performance of the Gail model has been shown to vary depending on the population to which it is applied [21–24] and this is likely to be the case for the other models as well. None of the models has been specifically evaluated in women over the age of 69, so it is unclear how well they predict breast cancer in older women. To determine their usefulness as risk assessment tools for older women, we applied the original Gail model, the Tice modification of the Gail model and the Barlow model to a cohort of Vermont women aged 70 and older and examined their ability to predict a subsequent diagnosis of breast cancer. For the purpose of comparison, we also examined the performance of a model we previously developed using data from postmenopausal Vermont women, which has risk factors similar to the Barlow model but does not include previous breast procedure or surgical menopause as predictors. This model has not yet been validated but it would be expected to have an advantage over the other models since it was based on the population to which the women in the current study belong [25].

Materials and methods

Data sources

This study utilized data from the Vermont Breast Cancer Surveillance System (VBCSS) to assemble a cohort, obtain risk factor information and identify subsequent cases of breast cancer [26]. The VBCSS, a participating registry in the National Cancer Institute's Breast Cancer Surveillance Consortium [27], has collected information on all breast imaging and pathology performed in Vermont since 1994. It also obtains cancer information from the cancer registries in both Vermont and New Hampshire because some women from eastern Vermont receive medical care in New Hampshire. Risk factor information is obtained by questionnaire at the time of mammography. BI-RADS breast density is collected as part of the radiologists' mammography reports. To ensure completeness of follow-up, VBCSS data through 2009 for women in the study cohort were linked with health claims data from the Centers for Medicare and Medicaid Services (CMS) to identify breast cancers that were diagnosed outside of Vermont or New Hampshire.

Study cohort

We identified a cohort of 20,697 women aged 70 or older who had a mammogram in the VBCSS between 1996 and 2001, had not been previously diagnosed with breast cancer, and did not decline the use of their data for research. The date of a woman's first mammogram meeting these criteria was considered her entry date into the study. To exclude prevalent cancers, 918 women who were either diagnosed with cancer or lost to follow-up within a year of their entry mammograms were removed from the study cohort. Of the remaining 19,779 women, 97.7% were white, and 98.7% were non-hispanic. The majority (54.6%) were aged 70–74 at the time of entry into the study, 24.5% were aged 75–79, 13.0% were aged 80–84 and 7.9% were 85 or older. The Institutional Review Board at the University of Vermont approved the protocol for this project with an alteration of informed consent.

Follow-up

Invasive and in situ breast cancers diagnosed before January 1, 2010 were identified using both the pathology information in the VBCSS and the diagnosis codes in the Medicare claims data. For women who developed breast

cancer, the date of diagnosis was defined by the date of the first malignant biopsy. Follow-up for women who did not develop cancer was censored at either the last mammogram or benign biopsy recorded in the VBCSS or the last Medicare claims record, whichever came later. Medicare vital status data was used to verify that all women were alive at the time of censoring. The average follow-up for the 19,779 women in the cohort was 7.1 years, starting 1 year after the entry mammogram. This yielded 141,034 person years of follow-up for estimation of incidence rates.

Risk scores

Risk scores were computed based on each of four risk models: the original Gail model, the Tice modification of the Gail model, the Barlow model, and the Vermont model. A woman's score was obtained by multiplying the relative risk estimates associated with each of her risk factors, as specified by a particular model and thus represents her risk relative to a woman with none of the risk factors. Although the VBCSS collects information on all of the risk factors in the four models, question wording and coding necessitated a few modifications to the Gail and Tice models. These models use three categories for number of previous breast biopsies (0, 1, or $\geq$2). The VBCSS collects self-reported information about whether or not a woman had a prior biopsy, but not the number of biopsies. We therefore used two categories for this risk factor (0 or $\geq$1 biopsy) and assigned the latter category the weighted average of the relative risks associated with having one and having two or more previous breast biopsies. The weights corresponded to the proportions of women in these two categories in the cohort used to develop the model, and thus reflect the relative risk that would have been obtained if the two categories had been combined during model development. Age at menarche was also coded slightly differently than in the Gail model ($\leq$12, 13, or $\geq$14 instead of <12, 12–13 or $\geq$14). For the Barlow model, we did not include previous mammogram outcome as a risk factor because unlike the Barlow study we did not restrict our cohort to women with current and previous screening mammograms. The Gail, Tice, and Barlow models all accommodate missing risk factor information and we analyzed data both by including and excluding women with missing data. Similar results were obtained from the two analyses but, as expected, inclusion of missing data somewhat reduced predictive accuracy. We present only the results based on women with complete data for a particular model because this better reflects its performance.

Statistical analysis

For each risk model, women were classified into groups based on the quintiles of their risk score distributions. Breast cancer incidence was computed from the number of cases and number of person years of follow-up in each quintile. Age-adjusted incidence was computed as a weighted average of the rates in four age groups (70–74, 75–79, 80–84, $\geq$85) within each quintile, with the weights corresponding to the overall age distribution of person-years. The predicted incidence based on a particular risk model was obtained by using the incidence in the lowest quintile as a baseline. Predicted incidence in each of the other quintiles was then obtained by dividing its mean risk score by the mean risk score for the lowest quintile and multiplying it by the baseline incidence. We used this approach, rather than using reference rates from an external population to obtain predicted values, to eliminate the effect of potential calibration error on the predicted incidence. Cox regression was used to examine the relationship between risk scores and time to diagnosis of breast cancer. Because the risk score represents a relative risk and Cox regression fits an exponential equation, the natural logarithm of the risk score was used as the independent variable. Hence, if a risk model is accurate, the regression coefficient will be close to one and the relative risk estimate for a specified set of risk factors would correspond to the risk score. Cox regression was also used to assess relationships between individual risk factors and time to diagnosis of breast cancer. Age group, as defined above, was included in all Cox regressions as a time-varying covariate. Predictive accuracy of each risk model was measured by the concordance statistic (*c*-statistic) obtained from an empirical receiver–operator curve (ROC) analysis.

Results

There were 821 breast cancer cases among the 19,779 women in the cohort, 668 of which were invasive carcinoma. Neither the overall breast cancer incidence nor the incidence of invasive disease differed significantly between age groups (Table 1). The rates for invasive cancer were very similar to SEER estimates for a comparable time period except for women aged 85 and older [1]. We did not observe the lower incidence among these women that was evident in the SEER data.

The risk scores computed from each of the models were significantly associated with breast cancer risk in the Cox regression analyses ($P < 0.001$). However, the regression coefficients (β's) were all significantly lower than one ($\beta = 0.31$ for the Gail model, $\beta = 0.26$ for the Tice model, $\beta = 0.50$ for the Barlow model and $\beta = 0.54$ for the Vermont model) indicating that the observed increases in relative risk per unit of the risk score were much lower than predicted by the models. This can also be seen by examining breast cancer incidence across quintiles of the risk score distributions (Table 2). For each of the four risk models, the

Table 1 Breast cancer incidence by age

Age	Person-years	All breast cancers (invasive and in situ)			Invasive breast cancer			SEER data 2003–2007
		Number of cancers	Incidence per 1,000 person-years	95% CI	Number of cancers	Incidence per 1,000 person-years	95% CI	Invasive incidence per 1,000 person-years
70–74	25,912	142	5.48	4.62–6.45	114	4.40	3.63–5.28	4.30
75–79	53,021	309	5.83	5.20–6.51	258	4.87	4.29–5.50	4.56
80–84	38,374	220	5.73	5.00–6.54	180	4.69	4.03–5.43	4.40
≥85	23,727	150	6.32	5.35–7.78	116	4.89	4.04–5.86	3.49

Table 2 Incidence by risk-score quintiles for each risk model

Risk model	Quintile	No. of women[a]	Mean risk score	Person-years	No. of cases	Incidence per 1,000 person-years	95% CI
Gail	1	3,462	1.24	27,033	155	5.73	4.87–6.71
	2	2,034	1.52	16,071	94	5.85	4.73–7.16
	3	2,679	1.78	21,277	166	7.80	6.66–9.08
	4	2,028	2.23	16,433	118	7.18	5.95–8.60
	5	2,518	3.63	20,077	164	8.17	6.97–9.52
Tice	1	1,969	0.98	15,483	90	5.81	4.68–7.14
	2	1,860	1.31	14,472	96	6.63	5.38–8.10
	3	2,135	1.59	16,961	117	6.90	5.71–8.27
	4	1,989	2.13	15,707	117	7.45	6.16–8.93
	5	1,947	3.80	15,505	135	8.71	7.30–10.31
Barlow	1	2,103	1.50	15,163	61	4.02	3.08–5.17
	2	2,297	2.23	16,683	105	6.29	5.15–7.62
	3	2,217	2.67	15,942	98	6.15	4.99–7.49
	4	2,181	3.21	15,989	108	6.75	5.54–8.16
	5	2,204	4.37	15,822	120	7.58	6.29–9.07
Vermont	1	2,369	2.02	16,906	77	4.55	3.60–5.69
	2	2,280	2.93	16,351	89	5.44	4.37–6.70
	3	2,311	3.50	16,630	117	7.04	5.71–8.30
	4	2,228	4.12	16,092	93	5.78	4.67–7.08
	5	2,202	5.68	15,832	132	8.34	6.97–9.89

[a] Number of women with complete data for all risk factors in the model. Total samples sizes were 12,721 for the Gail model, 9,900 for the Tice model, 11,002 for the Barlow model, and 11,390 for the Vermont model

lowest and highest quintiles had the lowest and highest incidence, but trends over the five quintiles were not consistent and do not reflect the increase that would be expected based on the increase in the mean risk score relative to the first quintile (Fig. 1). Consistent with these results, the ROC analyses yielded *c*-statistics of 0.54 (95% CI = 0.52–0.56) for the Gail model, 0.54 (95% CI = 0.51–0.56) for the Tice model, 0.55 (95% CI = 0.53–0.58) for the Barlow, and 0.55 (95% CI = 0.53–0.58) for the Vermont model. Although these *c*-statistics were significantly higher than 0.50 (the value corresponding to a random association with outcome) they indicate poor predictive accuracy.

To gain insight into why the models performed poorly, we examined the associations between individual risk factors and outcome in our cohort (Table 3). Childbearing age, a predictor in all four of the risk models, was not associated with breast cancer risk among the women in our study. The relative risk associated with having two or more first-degree relatives with breast cancer was lower than in the Gail, Tice, and Barlow models. In addition, the interaction between family history and age at first child birth, which is included in the Gail and Tice model, was not significant in our cohort ($P = 0.52$ for improvement in fit with the addition of an interaction). The relative risks

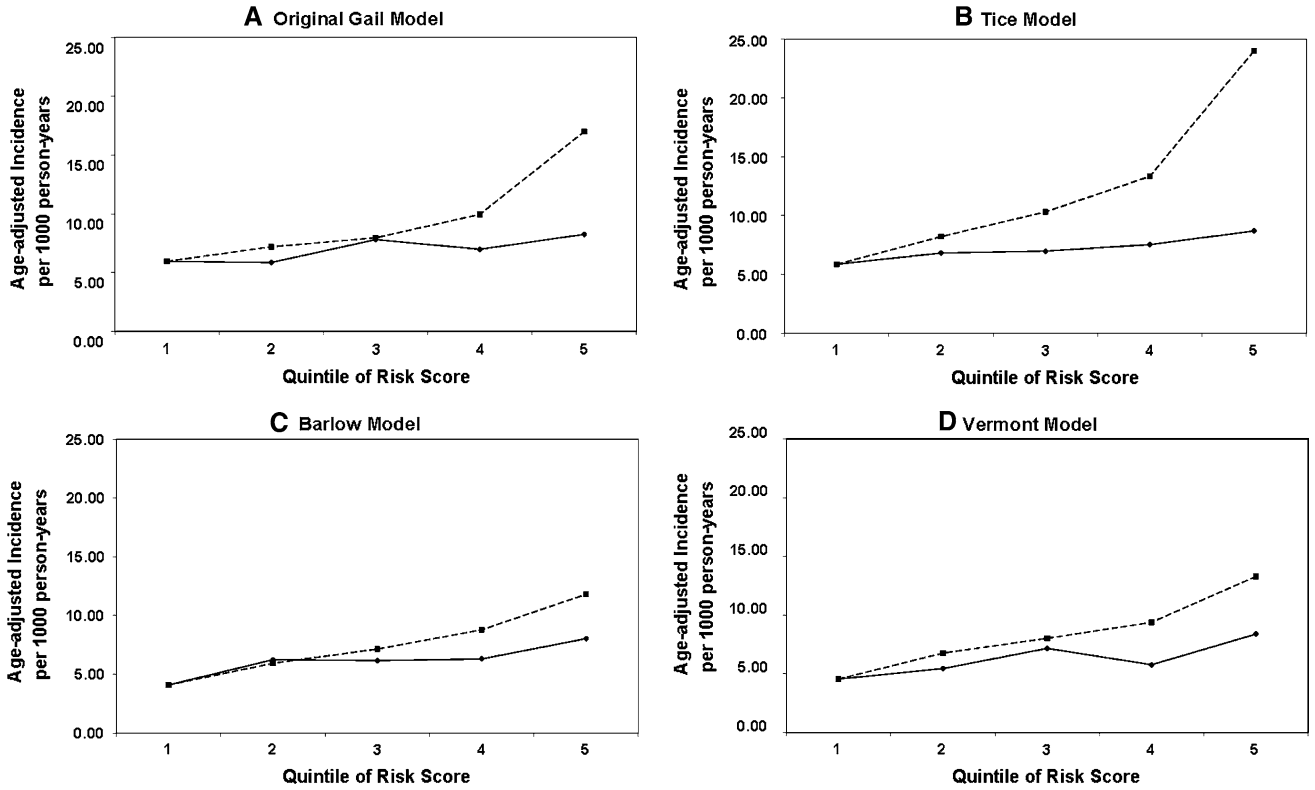

Fig. 1 Observed (—◆—) and predicted (- - ■ - -) incidence of breast cancer across quintiles of the risk score distributions for the original Gail model (**a**), the Tice modification of the Gail model (**b**), the Barlow model (**c**), and the Vermont Model (**d**). Rates for each quintile were adjusted to the overall age distribution of person-years. Predicted incidence was computed using the observed incidence in the lowest quintile as the baseline rate

associated with having had a prior breast procedure and prior biopsy were similar to those in the Barlow and Gail models, respectively, but surgical menopause and use of hormone therapy were not associated with breast cancer risk. The relative risk estimates for age at menarche, although not statistically significant, were similar to those in the Gail model.

The association between BMI and breast cancer risk was consistent with that predicted by the Barlow and Vermont models, but the effect of mammography breast density was less pronounced. The relative risk for BI-RADS category 2 compared to category 1 (1.9) was comparable to the Tice, Barlow, and Vermont models, which have relative risks ranging from 1.7 to 2.1. However, the relative risks for BI-RADS categories 3 and 4 (1.8 and 1.7, respectively) were lower than in the risk models, where the relative risks range from 2.4 to 3.0 for category 3 and 3.2 to 3.5 for category 4. Some of these discrepancies may be due to the fact that the relative risk estimates for a particular risk model are adjusted for all other variables in the model. However, when we included all risk factors in a Cox regression analysis, most of the multivariate relative risks were similar to those obtained from separate analysis of each risk factor (Table 3). Exceptions were the relative risks associated with family history of breast cancer and BMI, which were somewhat reduced after adjustment for the other risk factors. It should be noted, however, that the multivariate relative risks were based on only those subjects with complete risk factor information, so they are not directly comparable to those obtained from separate analysis of each risk factor.

Discussion

The risk models examined in this study were not found to be useful for predicting breast cancer in our cohort of women aged 70 and older. The original Gail model, the Tice modification of the Gail model, and the Barlow models have been previously shown to have modest predictive accuracy for other age ranges. Studies of the original Gail model have reported *c*-statistics ranged from 0.58 to 0.74 [18, 20, 22, 28], while *c*-statistics for the Tice and Barlow models have been estimated as 0.67 and 0.62, respectively [18, 19]. In our study of women aged 70 and older all the models had lower predictive accuracy, with *c*-statistics of 0.54 for the Tice and Gail models and 0.55 for the Barlow and Vermont models.

Table 3 Risk factor prevalences and associations with breast cancer

	N	%	Age-adjusted relative risk	95% CI	Multivariate relative risk[a]	95% CI
First-degree relatives with breast cancer						
0	15,945	81.1	1.00		1.00	
1	3,332	17.0	1.34	1.13–1.56	1.12	0.90–1.41
≥2	372	1.9	1.16	0.72–1.88	0.94	0.47–1.30
Missing	130					
Age at menarche						
≥14	3,909	30.3	1.00		1.00	
13	4,539	35.2	1.19	0.93–1.53	1.33	0.96–1.85
≤12	4,456	34.5	1.25	0.96–1.61	1.37	0.98–1.92
Missing	6,875					
Age at first childbirth						
≤19	2,640	14.0	1.00		1.00	
20–24	7,825	41.4	0.93	0.75–1.15	0.86	0.65–1.15
25–29	4,397	23.2	0.99	0.79–1.25	0.81	0.59–1.12
≥30	1,877	9.9	0.96	0.72–1.28	1.00	0.69–1.47
Nulliparous	2,174	11.5	1.07	0.82–1.41	0.86	0.59–1.26
Missing	866					
Surgical menopause						
No	12,999	67.9	1.00		1.00	
Yes	6,153	32.1	1.02	0.88–1.18	1.08	0.88–1.32
Missing	627					
Current hormone therapy						
No	13,154	81.8	1.00		1.00	
Yes	2,923	18.2	1.01	0.83–1.23	1.02	0.81–1.30
Missing	3,702					
BMI (kg/m^2)						
<22.0	3,225	19.6	1.00		1.00	
22.0–24.9	4,117	25.1	1.22	0.96–1.56	1.09	0.80–1.48
25.0–27.4	3,507	21.4	1.26	0.98–1.62	1.13	0.83–1.55
27.5–29.9	2,154	13.1	1.43	1.09–1.88	1.26	0.89–1.78
≥30	3,419	20.8	1.69	1.33–2.16	1.49	1.06–2.98
Missing	3,357					
Breast density(BI-RADS)						
1. Almost entirely fat	1,710	14.4	1.00		1.00	
2. Scattered fibroglandular densities	9,600	64.2	1.90	1.39–2.60	1.91	1.30–2.81
3. Heterogeneously dense	3,270	21.9	1.82	1.29–2.56	1.84	1.21–2.81
4. Extremely dense	381	381.0	1.66	0.93–2.95	1.32	0.56–2.92
Missing	4,818					
Prior breast biopsy						
No	14,724	78.9	1.00		1.00	
Yes	3,937	21.1	1.26	1.08–1.48	1.30	1.06–1.60
Missing	1,118					
Prior breast procedure (including biopsy)						
No	14,531	77.9	1.00		1.00	
Yes	4,111	22.1	1.27	1.09–1.49	1.32	1.07–1.62
Missing	1,137					

[a] Relative risk estimates from a multivariate model fitted to data from 8,066 women with complete risk factor information. Prior breast biopsy and prior breast procedure are nearly identical variables, so their multivariate relative risks are adjusted for all other variables but not for each other

The Gail, Tice, and Barlow models were based on women undergoing screening and Gail excluded women with a previous abnormal mammogram, while Barlow included previous mammogram outcome as a predictor in his model. Although the women in our study had at least one mammogram in the VBCSS, some women had only diagnostic mammograms and we did not use outcome from a previous mammogram as a predictor in computing the Barlow model. Furthermore, the Barlow model was developed to predict breast cancer within a year of a screening mammogram and we looked at outcome over an extended period of time. The models may perform better for older women undergoing screening mammography and, in the case of the Barlow model, if the result of the previous screening mammogram was included as a predictor. On the other hand, the Vermont model was developed using a population that included some of the women in this study and was applied exactly as specified, but it had no better predictive accuracy than the other models.

Results from the analyses of specific risk factors indicated that all of the models over-predict the influence of some risk factors for the women in our cohort. We found no association between breast cancer risk and age at first childbirth, current use of hormone therapy or surgical menopause. The relative risk associated with a family history of breast cancer was lower than predicted by the models, especially for women having two or more first-degree relatives with the disease. There also was no evidence of an interaction between age at first childbirth and family history of breast cancer, which is a feature of the Gail and Tice models. In addition, breast density was less strongly associated with breast cancer risk than predicted by the Tice, Barlow, and Vermont models.

Previous studies have indicated that the effects of some risk factors vary with age. A cooperative reanalysis of data from 52 epidemiologic studies documented an age-related decline in the risk associated with a family history of breast cancer [29]. BMI has been consistently found to be inversely related with breast cancer risk in premenopausal women and positively related with risk in postmenopausal women [30]. Barlow developed separate models for pre and post-menopausal women and his relative risk estimates for family history of breast cancer and mammographic breast density are higher for pre than postmenopausal women [19]. Our results from this study suggest that the influence of these and other risk factors may further diminish as a woman gets older and the age-related increase in risk starts to predominate.

Our findings pertaining to mammographic breast density are of particular interest because density is one of the most promising markers of breast cancer risk. The risk associated with higher density (BI-RADS categories 3 and 4) was lower than observed in other studies and was comparable to category 2. BI-RADS breast density categories are somewhat subjective and it is possible that breast density is more difficult to assess in older women. More quantitative methods of assessing breast density have been developed and might have yielded different results. However, postmenopausal breast density is known to decline with age [31], and two studies with longitudinal measurements found women with the highest breast density remained at high risk of breast cancer even if their breast density declined over time [32, 33]. The histological features and age-related changes in breast tissue are complex and it is possible that the decline in density associated with age does not involve those tissue components most relevant to breast cancer development [34].

Limitations

Our data did not enable us to reliably determine whether a woman had more than one prior biopsy and this may have slightly reduced the performance of the Gail and Tice models. We also could not code age at menarche exactly as specified in these models, but this would have had little effect on the results because relative risk estimates for our categories were similar to those for the Gail model and relative risks for the Tice model are close to 1.0 for this variable. We did not apply the revised version of the Gail model or the Chen model [13, 16] because we could not reliably assess prior atypical hyperplasia. This has been shown to be an important risk factor and may improve breast cancer prediction in older women [35]. Finally, we excluded women with missing risk factor information to better evaluate model performance, but this could introduce selection bias and hence affect the generalizability of results. However, we obtained similar results when we included women with missing data, using the conventions described for each risk model to compute risk scores.

Implications

There is considerable interest in developing individualized breast cancer screening recommendations that take into account a woman's risk of developing the disease [36–38]. This could be particularly useful for women aged 70 and older because the benefits of screening are less certain in this age group. Unfortunately, accurate prediction of breast cancer is proving to be very difficult. Except for BRCA1 and BRCA2 gene mutations, which are strongly associated with early-onset breast cancer, most breast cancer risk factors have a modest influence on risk. The results of this study indicate that the effects of some risk factors are

attenuated in older women, making risk prediction even more difficult for this age group. New risk factors and biomarkers for breast cancer are clearly needed, as well as statistical models that allow their effects to vary with age.

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