Predicting Risk of Breast Cancer in Postmenopausal Women by Hormone Receptor Status

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For the Women's Health Initiative Investigators

Background Strategies for estrogen receptor (ER)–positive breast cancer risk reduction in postmenopausal women require screening of large populations to identify those with potential benefit. We evaluated and attempted to improve the performance of the Breast Cancer Risk Assessment Tool (i.e., the Gail model) for estimating invasive breast cancer risk by receptor status in postmenopausal women.

Methods In The Women's Health Initiative cohort, breast cancer risk estimates from the Gail model and models incorporating additional or fewer risk factors and 5-year incidence of ER-positive and ER-negative invasive breast cancers were determined and compared by use of receiver operating characteristics and area under the curve (AUC) statistics. All statistical tests were two-sided.

Results Among 147916 eligible women, 3236 were diagnosed with invasive breast cancer. The overall AUC for the Gail model was 0.58 (95% confidence interval [CI] = 0.56 to 0.60). The Gail model underestimated 5-year invasive breast cancer incidence by approximately 20% (P<.001), mostly among those with a low estimated risk. Discriminatory performance was better for the risk of ER-positive cancer (AUC = 0.60, 95% CI = 0.58 to 0.62) than for the risk of ER-negative cancer (AUC = 0.50, 95% CI = 0.45 to 0.54). Age and age at menopause were statistically significantly associated with ER-positive but not ER-negative cancers (P = .05 and P = .04 for heterogeneity, respectively). For ER-positive cancers, no additional risk factors substantially improved the Gail model prediction. However, a simpler model that included only age, breast cancer in first-degree relatives, and previous breast biopsy examination performed similarly for ER-positive breast cancer prediction (AUC = 0.58, 95% CI = 0.56 to 0.60); postmenopausal women who were 55 years or older with either a previous breast biopsy examination or a family history of breast cancer had a 5-year breast cancer risk of 1.8% or higher.

Conclusions In postmenopausal women, the Gail model identified populations at increased risk for ER-positive but not ER-negative breast cancers. A model with fewer variables appears to provide a simpler approach for screening for breast cancer risk.

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The Breast Cancer Risk Assessment Tool (i.e., the Gail model) is used to predict risk of invasive breast cancer (including both estrogen receptor [ER]–positive and ER-negative disease) in women 35 years of age or older (1,2). However, strategies to reduce breast cancer risk, including use of tamoxifen, raloxifene, and aromatase inhibitors, influence almost exclusively ER-positive disease, with the use of raloxifene and aromatase inhibitors limited to postmenopausal women (3,4). In addition, although many women could potentially benefit (5), risk–benefit considerations indicate that a large number of postmenopausal women must be screened to identify a population who gain net benefit from tamoxifen use (6,7). As a result, methods to rapidly identify a population of postmenopausal women at increased risk of ER-positive breast cancer are needed.

We therefore examined models of breast cancer risk in participants of the Women's Health Initiative (WHI). Our objective was to facilitate the identification of postmenopausal women at increased risk for ER-positive invasive breast cancer as candidates for potential risk reduction interventions.

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CONTEXT AND CAVEATS

Prior knowledge

Because many postmenopausal women must be screened to identify a population who will benefit from tamoxifen treatment for breast cancer risk reduction, methods to rapidly identify such a population are needed.

Study design

Data from the observational study and the clinical trial cohorts of the Women's Health Initiative were used. Four prediction models were investigated, including the Gail model (tested in the clinical trial cohort) and three logistic regression models (trained on the observational study cohort and tested on the clinical trial cohort).

Contribution

A model with only three risk factors—age, breast cancer in first-degree relatives, and previous breast biopsy examination—performed nearly as well as the Gail model for the prediction of estrogen receptor (ER)–positive breast cancer.

Implications

The new model with fewer variables than the Gail model may be as effective at identifying women at high risk for ER-positive breast cancer who would benefit from risk reduction interventions.

Limitations

Information on atypical hyperplasia, reproductive hormone levels, mammogram breast density, and bone mineral density, all risk factors for breast cancer, were not available. The Gail model was the only model evaluated; other models are in clinical use.

Participants and Methods

Study Population

The WHI is a large multicomponent study designed to test three chronic disease risk reduction strategies and to examine risk factors for these conditions in postmenopausal women. Details of the implementation of both the observational study with 93 676 participants and the four randomized clinical trials with 68 132 participants that evaluated menopausal hormone therapy, a low-fat dietary intervention, and calcium–vitamin D supplementation have been published (8). Briefly, women were recruited at 40 clinical centers in the United States largely through direct mailings (9). Postmenopausal women, who were aged 50–79 years and unlikely to move or die within 3 years, were eligible. Each randomized trial had additional eligibility requirements related to safety and the intervention under test. Potential participants who were not eligible or interested in the randomized trials entered the observational study. All clinical trials excluded women with a history of breast cancer and required that the baseline mammogram and clinical breast examination not be suspicious for breast cancer. Breast screening was not required for enrollment in the observational study enrollment. For these analyses, women with previous invasive breast cancer, previous noninvasive breast cancer, previous mastectomy, or less than 5 years follow-up were excluded, leaving 147 916 women who met all eligibility criteria.

All participants provided written informed consent. Human subjects committee approval at each participating institution was provided.

Data Collection

Participants provided data on demographics; medical, reproductive, and family medical histories; and lifestyle factors, such as smoking and alcohol use, and physical activity (10). Menopausal hormone therapy use (i.e., use of estrogen alone or combined estrogen plus progestin) was ascertained through an interviewer-administered questionnaire.

The Gail model variables include age, ethnicity, age at menarche, age of the mother at the birth of her first live child, number of first-degree relatives with breast cancer (0, 1, or >1), number of previous breast biopsy examinations (0, 1, or >1), and the presence or absence of atypical hyperplasia in the biopsy specimen (http://brca.nci.nih.gov/brc/questions.htm). Calculations of 5-year risk estimates from the modified Gail model for women in this report were made by the National Surgical Adjuvant Breast and Bowel Project statistical center by following their usual coding procedures on data from individual WHI participants, courtesy of Dr Joseph Costantino. Because historical information on atypical hyperplasia was not collected in the WHI, all women with previous breast biopsy examinations are coded as "unknown" for this last variable.

Follow-up and Breast Cancer Ascertainment

Breast cancer incidence and mammography use were updated annually (in the observational study) or semiannually (in the clinical trial) by mail or telephone questionnaires. Self-reported breast cancers were verified by centrally trained WHI physician adjudicators who reviewed pathology reports (11). Final adjudication and coding were performed at the WHI Clinical Coordinating Center by use of the Surveillance, Epidemiology, and End Results Program (12). Only the 3263 invasive breast cancers diagnosed within 5 years of enrollment and confirmed by central review were included as events, 713 in situ breast cancers were excluded from analyses, and 144 680 women with no invasive breast cancer were coded as control subjects. The 363 case patients with missing or borderline information on ER status were excluded from subgroup analyses.

Statistical Analyses

Risk of invasive breast cancer was initially assessed with the Gail model and coded as a four-level nominal variable with categories of no invasive breast cancer or invasive breast cancer that was considered as ER-positive and progesterone receptor (PR)–positive tumors, ER-positive and PR-negative tumors, or ER-negative tumors. There were too few ER-negative invasive cancers to subdivide this group by PR status. After initial receiver operating characteristic (ROC) analyses, the two ER-positive invasive breast cancer categories were combined resulting in three final nominal variables of no invasive breast cancer, ER-positive invasive breast cancer, and ER-negative invasive breast cancer.

To explore whether other models could predict ER-positive and ER-negative breast cancer with similar or improved accuracy, the data were divided into the distinct observational study and clinical trial cohorts. The prediction models that we investigated were the Gail model, which was tested in the clinical trial cohort, and three logistic regression models, which were trained on the observational study cohort and tested on the clinical trial cohort. The first logistic regression model included the Gail model risk

Table 1. Baseline characteristics and breast cancer diagnosed within 5 years by cohort*

Characteristic	Observational study cohort enrolled (n = 83348)		Randomized clinical trial cohort (n = 64568)	
	No.	%	No.	%
No. of participants	83348	100	64568	100
Invasive breast cancer within 5 years of baseline				
No invasive breast cancer	81384	98	63296	98
ER-positive tumor	1489	2	923	1
ER-negative tumor	266	<1	195	<1
Borderline/unknown/missing	209	<1	154	<1
Age group at screening, y				
50–59	27227	33	22784	35
60–69	36824	44	29817	46
70–79	19297	23	11967	19
Ethnicity				
White	69835	84	52800	82
Black	6510	8	6558	10
Hispanic	3097	4	2635	4
American Indian	359	<1	274	<1
Asian/Pacific Islander	2399	3	1434	2
Unknown	1148	1	867	1
Age at menarche, y				
<12	18248	22	14080	22
12–13	45885	55	35329	55
≥14	18861	23	14939	23
Age at menopause, y				
<45	17624	22	13751	23
45–54	51234	64	37626	63
>54	11158	14	7963	13
At least one first-degree relative with breast cancer				
No	65841	85	52020	86
Yes	11816	15	8333	14
No. of previous breast biopsy				
0	63369	78	46306	80
1	12725	16	8444	15
>1	5550	7	3207	6
Parity				
Never pregnant/never had term pregnancy	10432	13	6843	11
1 child	7469	9	5363	8
2 children	21853	26	15049	23
≥3 children	43027	52	37003	58
Age at birth of first child, y				
<20	19817	26	16298	28
20–29	49191	65	37958	65
≥30	6312	8	4497	8
Cumulative of breastfeeding time				
Never	40276	49	30566	48
≤1 y	30448	37	23804	37
>1 y	11368	14	9411	15
Smoking				
Never	42200	51	32862	51
Past	35023	43	26074	41
Current	4980	6	4920	8
Alcohol, No. of drinks per day				
≤1	72720	87	57664	90
>1	10493	13	6702	10
Body mass index				
Normal (<25.0 kg/m^2)	33942	41	17688	28
Overweight (25 to <30 kg/m^2)	28045	34	22997	36
Obese (≥30 kg/m^2)	20397	25	23564	37
Physical activity, METs				
Inactive	10988	13	11030	19
<5	15545	19	13901	24
5–12	19479	24	14193	24
≥12	36396	44	19284	33

(Table continues)

Table 1 (continued).

Characteristic	Observational study cohort enrolled (n = 83348) No.	%	Randomized clinical trial cohort (n = 64568) No.	%
Length of unopposed estrogen use by category				
None	51782	62	42906	66
<5 y	10758	13	8966	14
5 to <10 y	6343	8	4214	7
10 to <15 y	4984	6	3281	5
≥15 y	9480	11	5200	8
Duration of estrogen + progestin use by category				
None	58765	71	49547	77
<5 y	11881	14	8151	13
5 to <10 y	6790	8	3979	6
10 to <15 y	3973	5	1991	3
≥15 y	1938	2	899	1

* Due to missing covariate information, not all levels of a particular categorical variable sum to the total number of participants. ER = estrogen receptor; METs = metabolic equivalents.

factors; the second model added parity, breastfeeding, smoking, alcohol, body mass index, physical activity, duration of previous estrogen-alone use, and duration of previous estrogen plus progestin use. The third, simpler model used only a subset of modified Gail model risk factors (age, number of first-degree relatives with breast cancer [coded as 0 or ≥1], and number of previous breast biopsy examinations [coded as 0, 1, or >1]).

The discriminatory accuracy of each model was assessed and compared by use of the ROC curve (R version 2.3 and R library ROCR, R Development Core Team, http://www.R-project.org) and the corresponding area under the curve (AUC). For models developed in the observational study cohort, the ROC and AUC were obtained by applying the models to the independent clinical trial cohort. ROC curves plot the true-positive rate (sensitivity) versus the false-positive rate (1 – specificity) at a continuum of thresholds; a participant is predicted to have breast cancer if her estimated probability of breast cancer exceeds a particular threshold. An ROC curve that corresponds to a fair-coin toss classifier (i.e., a nonpredictive model) is a straight line connecting the coordinates (0,0) to (1,1) and has an AUC of 0.50. An ROC curve that corresponds to a perfect classifier is a pair of vertical and horizontal lines connecting the coordinates (0,0) to (0,1) to (1,1) and has an AUC of 1.00.

To aid in our understanding of the ROC analysis, a single multinomial logistic regression model (in SAS PROC LOGISTIC version 9.1; SAS Institute, Cary, NC) was used in the pooled clinical trial and observational study cohorts to examine whether risk factors were associated with ER-positive and ER-negative invasive breast cancer, separately and combined, and whether the associations differed by receptor status. Specifically, the estimated coefficients of the risk factors were allowed to vary by ER status. This model included the Gail model risk factors and the additional risk factors described above; to increase power, family history of breast cancer was recoded as 0 or 1 or more. All risk factors were included regardless of statistical significance. Odds ratios (ORs), confidence intervals (CIs), and *P* values for tests of main effects and for tests of heterogeneity between tumor types were based on Wald statistics. All statistical tests were two-sided.

To estimate absolute risks and prevent downward bias, missing receptor status was dealt with by a multiple imputation model. Because the main goal of this particular analysis is estimation, data from the WHI observational study and clinical trials were combined. Calibration was verified by use of the Hosmer and Lemeshow goodness of fit test (13).

Results

Women in both the clinical trial and observational study cohorts were ethnically diverse and had a mean age of 63 years (range = 50–79 years), with 21% being 70 years or older (Table 1). Serial mammography was common, with an average of 0.7 mammogram per year in both cohorts. Given the large sample size, tests for statistical significance between cohorts were highly statistically significant for nearly all characteristics. There appeared to be substantive differences between the cohorts in age, ethnicity or race, body mass index, family history, previous benign breast biopsy examination, and use of hormone therapy. Among 147916 women eligible for these analyses, 3236 developed invasive breast cancer within 5 years. ER status was borderline or missing for 363 breast cancer patients, and 2412 ER-positive and 461 ER-negative invasive breast cancers were diagnosed.

The ROC curves for predicting invasive breast cancer by use of the Gail model 5-year risk probabilities for the 64 568 women in the WHI clinical trial produced an AUC of 0.58 (95% CI = 0.56 to 0.60). The AUC provided reasonable prediction of ER-positive and PR-positive tumors and ER-positive and PR-negative tumors (AUC = 0.60 for both). Given the similar ability to predict ER-positive and PR-positive tumors and ER-positive and PR-negative tumors, these categories were combined in subsequent modeling. For all ER-positive tumors, the usual Gail model threshold of 1.67%, used for defining increased risk, corresponds to approximately 50% sensitivity and 65% specificity. For ER-negative tumors, the Gail model was comparable to a random process (AUC = 0.50, 95% CI = 0.45 to 0.54) (Fig. 1).

The accuracy of the Gail model estimated probabilities (calibration) for estimating the incidence of invasive breast cancer was

assessed by comparing observed cases of breast cancer in the cohort with the number predicted by the Gail model (as the sums of the individual estimated Gail model probabilities of breast cancer). The Gail model 5-year risk estimate statistically significantly underestimated the number of breast cancers diagnosed within 5 years by approximately 20% (3236 observed versus 2562 expected, $P<.001$) with the disparity concentrated among those with lower Gail model risk estimates (≤1.37% expected 5-year risk). The total Gail model estimate was more closely aligned with the number of ER-positive breast cancers observed (Table 2).

To better understand this difference in predictive performance between estimated breast cancer incidence from the Gail model and the observed incidence in the WHI cohort, we examined breast cancer risk factors by hormone receptor status (ER-positive tumors, ER-negative tumors, and cancer-free for 5 years) (Table 3). In multinomial logistic regression analyses, the 5-year probability of ER-positive breast cancer in the entire cohort was statistically significantly associated with age, ethnicity, family history of breast cancer, number of previous breast biopsy examinations, age at menopause, parity, age at first birth, smoking status, alcohol use, and body mass index. African American women were at statistically significantly lower risk of ER-positive disease than white women (OR = 0.68, 95% CI = 0.54 to 0.85).

Prior breast biopsy examination and body mass index were the only risk factors that were statistically significantly associated with ER-negative disease. The smaller number of ER-negative tumors may have precluded detection of some associations; however, the data indicate a different pattern of association for most factors with ER-positive disease than with ER-negative disease. For ER-negative cancers, odds ratios for age, family history, age at menopause, greater parity, smoking, and alcohol use were all close to 1.0. The association between breast cancer risk and chronologic age (P = .05), race or ethnicity (P = .01), and age at menopause (P = .04) differed statistically significantly across ER disease subtypes (Table 1). Age at menarche was not statistically significantly associated with either ER-positive or ER-negative breast cancer.

To determine whether other models could improve Gail model performance for prediction of ER-positive breast cancer, the effects of the Gail model risk factors were reestimated in a logistic regression model that used the WHI observational study cohort as a training set, and the resulting model was applied to WHI clinical trial cohort as a test set. This approach differed from the original approach in that it did not explicitly account for competing risks. However, only 5.3% of women in the observational study and 4.7% of women in the clinical trial died or were lost to follow-up within 5 years of enrollment. Expanding this model to add parity, breastfeeding, smoking, alcohol, body mass index, physical activity, duration of previous estrogen-alone use, and duration of previous estrogen plus progestin use produced ROC curves in a similar pattern with only slight improvements in the AUC statistics (Fig. 2). By focusing on only ER-positive tumors, we simplified the model to include only age, first-degree relatives with breast cancer (coded as 0 or ≥1), and number of previous breast biopsy examinations (coded as 0, 1, or >1) and we

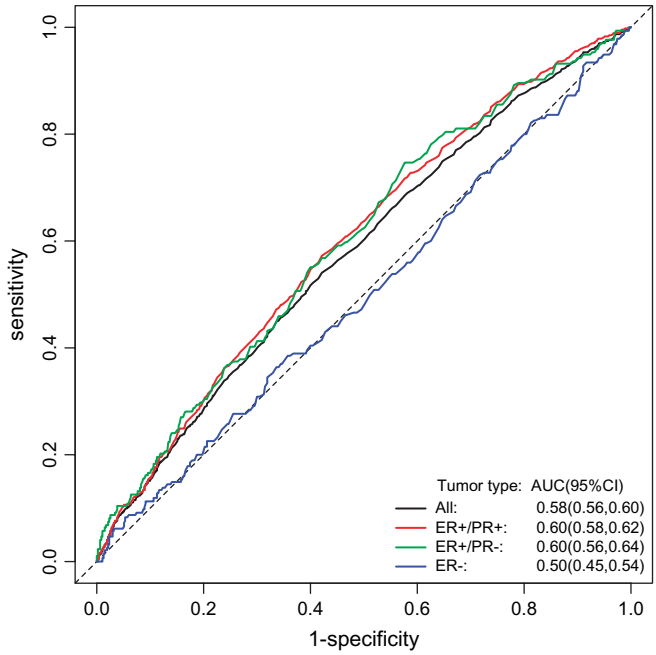

Fig. 1. Receiver operating characteristic analysis and corresponding area under the curve (AUC) statistics for Gail model of prediction of invasive breast cancer risk by receptor status evaluated on the Women's Health Initiative clinical trial cohort. ER = estrogen receptor; PR = progesterone receptor; CI = confidence interval.

Table 2. Comparison of observed number of invasive breast cancers with expected number from the Gail model of the clinical trial and observational study cohorts*

Gail model risk quintile, %	Expected invasive breast cancers from the Gail model	Observed invasive breast cancers in the entire cohort			
	Total No.	Total No.	Gail expected, %	ER+ tumor, No.	ER– tumor, No.
≤1.09	251	399	62.9	254	88
(1.09, 1.37]	377	568	66.3	411	85
(1.37, 1.68]	440	593	74.2	455	82
(1.68, 2.16]	559	733	81.7	566	95
>2.16	935	943	99.1	726	111
Total	2562†	3236	79.2	2412	461

* ER = estrogen receptor.

† The difference between the Gail model expected versus observed number of invasive breast cancers was statistically significantly different ($P<.001$). These data were based on a chi-square goodness of fit test with 5 df. The model was based on data from eligible case patients with invasive breast cancer within 5 years of baseline in the clinical trial and observational study cohorts from the Women's Health Initiative.

Table 3. Baseline characteristics and multivariable odds ratios* (95% confidence intervals) of invasive breast cancer cases (within 5 years of baseline) by tumor type of the clinical trial and observational study cohorts of the Women's Health Initiative†

	No invasive breast cancer		Patients with ER-positive tumors				Patients with ER-negative tumors					
Characteristic	**No.**	**%**	**No.**	**%**	**OR (95% CI)**	***P* value‡**	**No.**	**%**	**OR (95% CI)**	***P*§**	***P* overall‖**	***P* homo¶**
Age group at screening, y						**<.001**				.98	**<.001**	**.05**
50–59	49124	34	630	26	1.00 (referent)		156	34	1.00 (referent)			
60–69	65104	45	1147	48	1.28 (1.14 to 1.44)		213	46	1.01 (0.78 to 1.31)			
70–79	30452	21	635	26	1.53 (1.33 to 1.76)		92	20	0.98 (0.71 to 1.37)			
Race or ethnicity						**.002**				.32	**.006**	**.01**
White	119815	83	2142	89	1.00 (referent)		369	80	1.00 (referent)			
Black	12862	9	114	5	0.68 (0.54 to 0.85)		59	13	1.41 (0.96 to 2.06)			
Hispanic	5641	4	60	2	0.74 (0.54 to 1.03)		17	4	0.90 (0.46 to 1.77)			
American Indian	625	0	6	0			2	0				
Asian/Pacific Islander	3755	3	62	3	1.02 (0.77 to 1.35)		11	2	1.17 (0.62 to 2.21)			
Unknown	1982	1	28	1			3	1				
No. of first-degree relatives with breast cancer						**<.001**				.44	**<.001**	.12
0	115456	86	1794	79	1.00 (referent)		347	81	1.00 (referent)			
≥1	19533	14	464	21	1.44 (1.28 to 1.62)		80	19	1.12 (0.84 to 1.51)			
No. of previous breast biopsy examinations						**<.001**				**.001**	**<.001**	.99
None	107550	79	1591	69	1.00 (referent)		303	70	1.00 (referent)			
1	20528	15	483	21	1.50 (1.34 to 1.69)		91	21	1.49 (1.14 to 1.96)			
≥2	8456	6	219	10	1.65 (1.41 to 1.94)		39	9	1.70 (1.17 to 2.48)			
Age at menarche, y						.27				.39	.35	.83
<12	31572	22	559	23	1.10 (0.96 to 1.26)		116	25	1.20 (0.87 to 1.66)			
12–13	79464	55	1297	54	1.01 (0.90 to 1.13)		248	54	1.01 (0.77 to 1.34)			
≥14	33091	23	540	23	1.00 (referent)		95	21	1.00 (referent)			
Age at menopause, y						**<.001**				.89	**<.001**	**.04**
<45	30785	23	412	18	1.00 (referent)		104	24	1.00 (referent)			
45–54	86865	64	1511	66	1.32 (1.16 to 1.51)		268	61	0.93 (0.70 to 1.24)			
>54	18619	14	383	17	1.55 (1.30 to 1.85)		64	15	0.93 (0.61 to 1.39)			
Parity						**<.001**				.63	**.003**	.38
Never pregnant/no term pregnancy	16841	12	346	14	1.00 (referent)		45	10	1.00 (referent)			
1 child	12560	9	209	9	0.63 (0.49 to 0.81)		31	7	0.76 (0.40 to 1.44)			
2 children	36067	25	629	26	0.71 (0.57 to 0.88)		125	27	1.04 (0.62 to 1.75)			
≥3 children	78368	54	1203	50	0.66 (0.54 to 0.81)		256	56	1.01 (0.62 to 1.65)			
Age at birth of first child, y						**<.001**				.17	**<.001**	.17
<20	35334	27	581	26	1.00 (referent)		100	24	1.00 (referent)			
20–29	85276	65	1388	63	1.08 (0.93 to 1.27)		279	68	1.41 (0.98 to 2.01)			
≥30	10504	8	250	11	1.56 (1.27 to 1.93)		32	8	1.45 (0.86 to 2.45)			
Cumulative breastfeeding time						.66				.17	.36	.13
Never	69290	49	1152	49	1.00 (referent)		221	49	1.00 (referent)			
≤1 y	53061	37	896	38	1.05 (0.94 to 1.17)		160	35	0.81 (0.63 to 1.05)			
>1 y	20335	14	325	14	1.03 (0.89 to 1.20)		72	16	1.05 (0.76 to 1.45)			
Smoking						**.001**				.96	**.009**	.25
Never	73524	51	1120	47	1.00 (referent)		239	53	1.00 (referent)			
Past	59655	42	1106	47	1.20 (1.09 to 1.32)		189	42	0.97 (0.77 to 1.22)			
Current	9699	7	145	6	1.12 (0.91 to 1.37)		27	6	1.02 (0.65 to 1.60)			
Alcohol consumption, drinks per day						**.02**				.75	0.08	.60
≤1	127608	88	2050	85	1.00 (referent)		408	89	1.00 (referent)			
>1	16743	12	359	15	1.17 (1.02 to 1.33)		50	11	1.06 (0.75 to 1.49)			
Body mass index						**<.001**				**.03**	**<.001**	.08
Normal (<25.0 kg/m^2)	50539	35	824	34	1.00 (referent)		163	36	1.00 (referent)			
Overweight (25 to <30 kg/m^2)	49958	35	838	35	1.14 (1.02 to 1.27)		134	29	0.83 (0.63 to 1.09)			
Obese (≥30 kg/m^2)	42924	30	729	30	1.26 (1.12 to 1.43)		162	35	1.21 (0.92 to 1.60)			

(Table continues)

Table 3 (continued).

Characteristic	No invasive breast cancer		Patients with ER-positive tumors				Patients with ER-negative tumors					
	No.	%	No.	%	OR (95% CI)	*P* value‡	No.	%	OR (95% CI)	*P*§	*P* overall‖	*P* homo¶
Physical activity, METs						.37				.38	0.41	.57
Inactive (0)	21514	16	359	15	1.00 (referent)		86	20	1.00 (referent)			
<5	28821	21	473	20	0.98 (0.84 to 1.15)		86	20	0.75 (0.53 to 1.06)			
5–12	32907	24	571	25	0.97 (0.84 to 1.13)		107	24	0.81 (0.58 to 1.14)			
≥12	54474	40	915	39	0.90 (0.78 to 1.04)		161	37	0.78 (0.57 to 1.07)			

* From a multivariable multinomial logistic regression model containing the predictors shown in the table and also adjusted for duration of baseline estrogen-only use and duration of estrogen plus progestin use.

† ER = estrogen receptor; OR = odds ratio; CI = confidence interval; homo = homogeneity. Boldface type indicates statistically significant *P* values. All statistical tests were two-sided.

‡ From a multivariable multinomial logistic regression model, chi-square test to determine if the risk factor is predictive of ER-positive tumors.

§ From a multivariable multinomial logistic regression model, chi-square test to determine if the risk factor is predictive of ER-negative tumors.

‖ From a multivariable multinomial logistic regression model, chi-square test to determine if risk factor is predictive of either ER-positive or ER-negative tumors.

¶ From a multivariable multinomial logistic regression model, chi-square test to determine if odds ratios differ between ER-positive and ER-negative tumors for any level of risk factor.

obtained an AUC of 0.58 (95% CI = .56 to 0.60). The difference between the Gail model and the simplified model at the estimated 1.8% probability threshold was small and not statistically significant (difference = 0.02, 95% CI = –0.04 to 0.08) (Fig. 3). The absolute risk prediction results for ER-positive invasive breast cancer from the simplified model by age increments are shown in Table 4. To prevent the downward bias of the predicted 5-year risk of ER-positive invasive breast cancers, missing receptor status was dealt with by multiple imputations. The imputation model included age, ethnicity, and age at menopause. These variables were chosen from Table 3 because these variables suggested differing risks by receptor status.

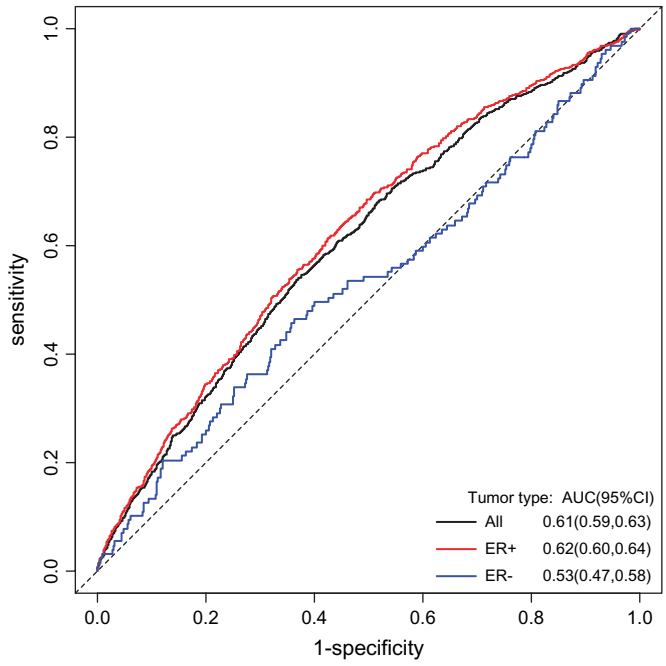

Fig. 2. Receiver operating characteristic analysis and corresponding area under the curve (AUC) statistics for Gail model prediction of invasive breast cancer risk plus additional risk factors by receptor status. The model was developed on a training set by use of the observational study cohort and evaluated by use of the clinical trial cohort. Variables in the training set analyses included Gail model factors (age, ethnicity, number of first-degree relatives with breast cancer [0, 1, or >1], previous breast biopsy examination [0, 1, or >1], age at menarche, and age at birth of first child) plus age at menopause, parity, breast feeding, smoking, alcohol, body mass index, physical activity, duration or previous estrogen-alone use, and duration of previous estrogen plus progesterone use. ER = estrogen receptor; CI = confidence interval.

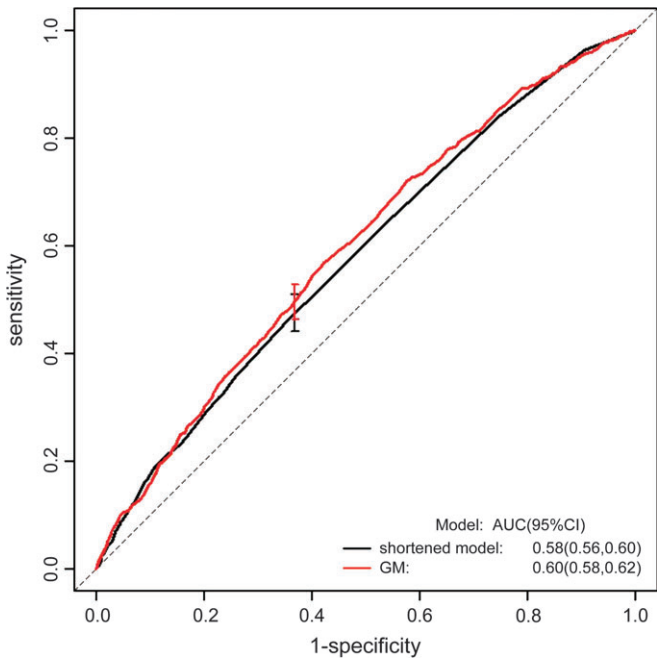

Fig. 3. Receiver operating characteristic analysis and corresponding area under the curve (AUC) statistics for Gail model prediction of estrogen receptor–positive invasive breast cancer risk and for a simpler model with fewer risk factors that was developed on a training set by use of the observational study cohort and evaluated by use of the clinical trial cohort. Variables in the simpler model include age, previous breast biopsy (0, 1, or >1), and number of first-degree relatives with breast cancer (0 or ≥1). **Error bars** = 95% confidence intervals (CIs) for the sensitivity for a cut point of 1.8%. GM = Gail model.

Table 4. Predicted 5-year risk* (%) of estrogen receptor–positive invasive breast cancer in postmenopausal women: simplified model

Participants	No biopsy	1 biopsy	>1 biopsy
No first-degree relative with breast cancer			
All postmenopausal women			
Age, y			
50–54	1.0	1.6	1.8
55–59	1.3	2.0	2.3
60–64	1.6	2.4	2.7
65–69	1.7	2.5	2.9
70–74	1.9	2.8	3.2
≥75	1.9	2.8	3.2
African American postmenopausal women			
Age, y			
50–54	0.7	1.2	2.2
55–59	0.6	1.0	1.8
60–64	1.1	1.7	3.2
65–69	1.2	1.9	3.6
70–74	0.9	1.4	2.6
≥75	0.8	1.3	2.3
≥1 first-degree relative with breast cancer			
All postmenopausal women			
Age, y			
50–54	1.5	2.3	2.6
55–59	2.0	2.9	3.4
60–64	2.3	3.4	4.0
65–69	2.5	3.7	4.3
70–74	2.7	4.1	4.7
≥75	2.8	4.1	4.7
African American postmenopausal women			
Age, y			
50–54	1.0	1.7	3.1
55–59	0.8	1.4	2.6
60–64	1.5	2.5	4.5
65–69	1.7	2.7	5.0
70–74	1.2	2.0	3.7
≥75	1.1	1.8	3.3

* Predicted 5-year risk of estrogen receptor–positive invasive breast cancer by age category, number of first-degree relatives with breast cancer (0 or ≥1), and number of previous breast biopsy examinations (0, 1, or >1).

All women older than 55 years with either a previous biopsy examination or a first-degree relative with breast cancer had a 5-year risk of invasive breast cancer that was greater than 1.8%. In an exploratory analysis, the same process was applied to African American participants in the clinical trial and observational study cohorts. For these African American women, women aged 60 years or older with a previous biopsy examination and a positive family history of breast cancer had a 5-year risk greater than 1.8% (Table 4).

Discussion

In a large cohort of postmenopausal women (50–79 years of age at entry), the discriminatory performance of the Gail model was similar to that observed in previous studies (14,15), but it underestimated the observed 5-year invasive breast cancer incidence by approximately 20%. Discriminatory performance and model calibration were somewhat better for estimating population-based risk of ER-positive breast cancers, but the performance of the Gail model for predicting ER-negative breast cancers was equivalent to chance alone. Incorporation of several additional risk factors provided only a small improvement in prediction. However, a simpler model that incorporated fewer variables was nearly as accurate as the Gail model in predicting ER-positive breast cancer risk and would be more accessible for routine and rapid prescreening in the prevention or routine care setting, in which breast cancer risk is only one measure among the many requiring assessment.

In our analyses, the association of putative risk factors with breast cancer prediction varied by ER status. For ER-positive breast cancers among postmenopausal women, the Gail model components of age, ethnicity, age of the mother at birth of her first live child, number of first-degree relatives with breast cancer, and number of prior breast biopsy examinations were statistically significantly associated with breast cancer risk. Age at menarche was not associated with risk. Also associated with the risk of an ER-positive tumor were age at menopause, parity, and body mass index. In contrast, only prior breast biopsy examination and body mass index were statistically significantly associated with the risk of ER-negative breast cancer, although the smaller number of patients with ER-negative breast cancer may have limited our ability to detect some associations, particularly for race or ethnicity.

Although the Gail model has been validated for predicting total breast cancer risk in several settings (14,15), including both pre- and postmenopausal women, the utility of the Gail model for predicting ER-positive compared with ER-negative breast cancers in postmenopausal women has not been previously recognized to our knowledge. In these analyses, a woman's age, a Gail model component, was associated only with the risk of ER-positive breast cancer but not with the risk of ER-negative breast cancer. As a result, the Gail model appears to have the ability to differentially predict breast cancer risk by receptor subgroup in postmenopausal women.

Despite its well-documented predictive performance (14,15), the Gail model statistically significantly underestimated breast cancer incidence in the WHI cohort of postmenopausal women. The initial four studies that validated the original Gail model included not only postmenopausal women but also some much younger premenopausal women (1,16–18), and two of these studies (17,18) entered women no older than 54 and 61 years at entry, respectively. In these studies, mammography was not prespecified and was rarely used before the mid-1980s. Because tumors detected by mammography are more likely than those detected by other means to be ER-positive tumors than ER-negative tumors (19) and older women are substantially more likely than younger women to develop ER-positive tumors (20), it is likely that these older studies did not optimally detect ER-positive disease. In contrast, the WHI cohort included only postmenopausal women who were 50 years or older, with a substantial number older than 70 years, and had comprehensively used mammography. In addition, a secular change in breast biopsy procedures had occurred, beginning in the early 1990s, away from open surgical biopsy examination to the common use of image-guided percutaneous core biopsy examinations, which are associated with less morbidity and a lower threshold for use (21). As a result of these changes, the breast biopsy rate per 100 000 Medicare beneficiaries increased by 43% between

1999 and 2004 (22). These factors likely contributed to a more comprehensive ascertainment of all patients with breast cancer in the WHI cohort, especially for those with ER-positive disease, and likely enhanced our ability to discriminate between the influences on ER-positive and ER-negative disease. Future development of breast cancer risk models, consequently, should consider premenopausal and postmenopausal women separately and segregate risk by hormone receptor status.

Other groups have examined the risk factors associated with breast cancer in hormone receptor subgroups (20,23–25). In a meta-analysis of observational studies, parity and age at first child's birth were associated with ER-positive and PR-positive tumors but not with ER-negative and PR-negative breast cancers (22). In another report (19), statistically significant heterogeneity among the four ER and PR categories was observed for some risk factors but not for prior breast biopsy examinations, family history of breast cancer, alcohol use, and height. Direct comparison with our analyses was precluded by differences in study populations, breast cancer receptor categories, and the risk factors examined.

Despite evaluation of multiple additional risk factors, we did not identify a model that would clearly improve the accuracy of risk prediction for ER-positive breast cancers over that of the Gail model. However, we did identify a simpler model with only three variables—age, family history of breast cancer in first-degree relatives, and previous breast biopsy examination—which had predictive accuracy approaching that of the Gail model.

Although many women could potentially benefit from tamoxifen use, there has been reluctance to incorporate Gail model breast cancer risk assessment in routine clinical practice (6,26–28). In one survey (6), only 11% of California primary care physicians had used the Gail model for risk assessment in the past year. In a recent national survey of primary care providers (29), only 16% agreed that "it is easy to determine" who is eligible for breast cancer risk reduction strategies and only 25% had prescribed tamoxifen for risk reduction in the past year. As a result, development of new, simpler risk models is an identified research priority (30). The simplified model described above provides a straightforward approach to initial screening for risk of ER-positive breast cancer in postmenopausal women and does not require computer use. Women who were 55 years or older with either a first-degree relative with breast cancer or a previous breast biopsy have 5-year risk of 1.8% or higher (which is higher than the Gail model threshold of 1.67%).

In previous analyses of the WHI cohort (31), African American women were identified as being at substantially lower risk for ER-positive breast cancer but at substantially higher risk for ER-negative, high-grade breast cancers with poor prognosis. These analyses suggest that African American women who were 60 years or older with a first-degree relative with breast cancer and a previous breast biopsy examination may have a 5-year breast cancer risk of 1.8% or higher. Given the sample size in this subgroup, additional studies are needed to confirm this finding. Because evaluation of the Gail model in multiethnic populations that include African American women have been preliminary (32–33) or disappointing (34), further model development in minority populations of African American and Hispanic women is a research priority.

The demonstration that the Gail model and our proposed simpler model can predict the risk of ER-positive breast cancer has several clinical implications. Although the selective estrogen receptor modulator (SERM) tamoxifen is approved by the Federal Drug Administration (FDA) for breast cancer risk reduction (35), a large number of postmenopausal women must be screened to identify potential candidates. By one calculation, only one of 142 screened postmenopausal women who were 60–79 years has a favorable balance for tamoxifen use (6). The SERM raloxifene has recently been approved by the FDA for breast cancer risk reduction in postmenopausal women as well and has a somewhat more favorable side effect profile (36). The current Gail model or our simpler model could identify populations of postmenopausal women appropriate for further consideration for breast cancer risk reduction interventions. For interactions with individual women in the clinic, the limitations of any risk assessment estimate should be acknowledged and the risk or benefit of any intervention should be carefully considered (3,26).

Benign breast disease, a recognized breast cancer risk factor, may be able to integrate hormone exposures and breast tissue response that lead to mammographic breast alterations and indications for a biopsy examination. In the future, histologic subclassification of benign breast disease (nonproliferative versus proliferative and the magnitude of lobular involution), which further differentiates breast cancer risk (37–39), may lead to more reliable risk estimation.

The strengths of this study include the prospective design, a large racially representative population that is well characterized for breast cancer risk factors and has serial assessment of mammography use, central adjudication of breast cancer pathology reports, and information on breast cancer hormone receptor status. In addition, the risk assessment models evaluated in this report were developed in one WHI population (the observational study cohort) and independently tested in a separate population (the clinical trial cohort), in which many of the risk assessment procedures and breast cancer outcomes were determined similarly.

Our study has several limitations. Information on atypical hyperplasia, a Gail model component, was not available in our cohort. However, the Gail model does allow for missing histologic subclassification and that was how we coded the WHI data. We evaluated only one model and recognize other risk prediction models are in clinical use (29). We selected the Gail model because it is the most commonly cited model, is the most frequently used by care providers in the United States, and is the basis for the FDA approved indication for use of tamoxifen for prevention.

Another study limitation is that reproductive hormone levels, mammogram breast density, and bone mineral density, which are strongly associated with breast cancer risk (40–43), were not available for these analyses. However, analyses incorporating these risk factors have provided mixed results. Although estrogen levels have been commonly related to breast cancer (40,43,44), in a randomized trial involving women at relatively high risk of breast cancer, estrogen and testosterone levels were not associated with either subsequent breast cancer risk or risk reduction by tamoxifen (45). The addition of mammographic breast density has not improved (46) or only modestly improved (47,48) breast cancer prediction over the Gail model. To our knowledge, the influence of bone mineral density addition to Gail model prediction has not been reported. At present, therefore, the role of these three factors on

the assessment of breast cancer risk in routine clinical practice remains to be determined.

In summary, we found that among postmenopausal women who receive regular mammographic examinations, the Gail model predicts ER-positive breast cancer risk at the population level but does not predict the risk of ER-negative tumors. A model incorporating only age, family history of breast cancer, and previous breast biopsy examinations provides a simpler approach for initial identification of populations of postmenopausal women at elevated risk for ER-positive breast cancer who may benefit by further evaluation for risk reduction interventions. Future attempts to improve breast cancer risk models should consider premenopausal and postmenopausal women separately and segregate risk by hormone receptor status.

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