Projecting Individualized Absolute Invasive Breast Cancer Risk in African American Women

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Background The Breast Cancer Risk Assessment Tool of the National Cancer Institute (NCI) is widely used for counseling and determining eligibility for breast cancer prevention trials, although its validity for projecting risk in African American women is uncertain. We developed a model for projecting absolute risk of invasive breast cancer in African American women and compared its projections with those from the Breast Cancer Risk Assessment Tool.

Methods Data from 1607 African American women with invasive breast cancer and 1647 African American control subjects in the Women's Contraceptive and Reproductive Experiences (CARE) Study were used to compute relative and attributable risks that were based on age at menarche, number of affected mother or sisters, and number of previous benign biopsy examinations. Absolute risks were obtained by combining this information with data on invasive breast cancer incidence in African American women from the NCI's Surveillance, Epidemiology and End Results Program and with national mortality data. Eligibility screening data from the Study of Tamoxifen and Raloxifene (STAR) trial were used to determine how the new model would affect eligibility, and independent data from the Women's Health Initiative (WHI) were used to assess how well numbers of invasive breast cancers predicted by the new model agreed with observed cancers.

Results Tables and graphs for estimating relative risks and projecting absolute invasive breast cancer risk with confidence intervals were developed for African American women. Relative risks for family history and number of biopsies and attributable risks estimated from the CARE population were lower than those from the Breast Cancer Risk Assessment Tool, as was the discriminatory accuracy (i.e., concordance). Using eligibility screening data from the STAR trial, we estimated that 30.3% of African American women would have had 5-year invasive breast cancer risks of at least 1.66% by use of the CARE model, compared with only 14.5% by use of the Breast Cancer Risk Assessment Tool. The numbers of cancers predicted by the CARE model agreed well with observed numbers of cancers (i.e., it was well calibrated) in data from the WHI, except that it underestimated risk in African American women with breast biopsy examinations.

Conclusions The CARE model usually gave higher risk estimates for African American women than the Breast Cancer Risk Assessment Tool and is recommended for counseling African American women regarding their risk of breast cancer.

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Gail et al. (1) obtained relative risk (RR) and attributable risk (AR) information from a case–control study of white women in the Breast Cancer Detection Demonstration Project (BCDDP) and

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BCDDP data on age-specific composite breast cancer incidence rates for white women. By combining relative risks, attributable risks, and composite incidence rates, they provided methods to project the probability that a white woman with a given set of risk factors would develop breast cancer during a subsequent time interval. Statisticians at the University of Pittsburgh modified the model by substituting breast cancer incidence rates from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI). They modified the attributable risks by using the BCDDP relative risk model and data on the distribution of risk factors in the SEER population (2). The modified model, called model 2 in Costantino et al. (3), has been evaluated in independent data and shown to be "well calibrated;" that is, the model accurately predicts the numbers of breast cancers that are observed in various subsets of the validation population (3,4). This model is incorporated in the Breast Cancer Risk Assessment Tool of the NCI and is available at http://www.cancer.gov/bcrisktool/.

The NCI Breast Cancer Risk Assessment Tool also permits projections for African American women and for women from other racial and ethnic groups, with the caveat that these projections are based on strong assumptions. In particular, it is assumed that the BCDDP relative risk model for white women applies to African American women and to women from other groups. Except for African American women, the population attributable risk for women from other ethnic and racial groups was assumed to be the same as for white women. The attributable risk for African American women in the SEER population, AR_{SEER}, was estimated from the formula $(1 - AR_{SEER}) = C(1 - AA_{BCDDP})$, where C is a SEER-to-BCDDP conversion factor and AA_{BCDDP} is the attributable risk estimated from sparse African American case data in the BCDDP. Because of the need to rely on these various assumptions rather than on sufficient empirical data on African American women and women in other racial and ethnic groups, the NCI Breast Cancer Risk Assessment Tool includes a disclaimer for African American women and for women in other groups, and the possibility that projections might be inaccurate in these groups has been a concern. Biased projections in particular racial/ethnic groups could result in women in those groups receiving misleading counseling and might mistakenly render some women ineligible for participation in breast cancer prevention trials. For example, it is possible that some African American women were not eligible to participate in the Study of Tamoxifen and Raloxifene (STAR) trial because their projected risks were lower than their actual risks (5). Consequently, there has been great interest in developing race- or ethnicity-specific adaptations of the "Gail" model (1,3) that are based on sufficient race- or ethnicity-specific data.

The Women's Contraceptive and Reproductive Experiences (CARE) Study gathered data on 1622 African American women with breast cancer and 1661 African American women without breast cancer (6). This study obtained information on the factors used in the original Gail model and thus afforded an opportunity to estimate relative and population attributable risks specific for African American women for that model. In this article, we use data from the Women's CARE Study and SEER data from 1994 through 1998 to build a model to project absolute invasive breast cancer risk for African American women, and we provide tables and figures to make projections and obtain approximate 95% confidence intervals (CIs) for the projections. We also compare these new projections with those from the current NCI Breast Cancer Risk Assessment Tool, assess the calibration of the CARE model in independent data from African American women in the Women's Health Initiative (WHI) (7), and evaluate how many African American women who were screened for the STAR trial (5) would have been eligible to participate had the CARE model been used instead of the NCI Breast Cancer Risk Assessment Tool.

CONTEXT AND CAVEATS

Prior knowledge

The Breast Cancer Risk Assessment Tool of the National Cancer Institute is widely used for counseling and determining eligibility for breast cancer prevention trials, but its validity for projecting risk in African American women is uncertain.

Study design

Data from the Women's Contraceptive and Reproductive Experiences (CARE) Study were used to develop a model. The model was validated with data from the Women's Health Initiative.

Contribution

The numbers of cancers predicted for African American women by the CARE model were higher than those predicted by the Breast Cancer Risk Assessment Tool and agreed well with the numbers of cancers observed among African American women in the Women's Health Initiative.

Implications

The CARE model is recommended for counseling African American women about their risk of breast cancer.

Limitations

The CARE model, like the Breast Cancer Risk Assessment Tool, should be used with caution or avoided for certain special populations, including African American women with a history of breast cancer or with mutations associated with an increased risk of breast cancer.

Methods and Data Sources

Data Sources

The study methods and participant accrual for the Women's CARE Study have been described in Marchbanks et al. (6). Women who were newly diagnosed with a first primary incident invasive breast cancer and aged 35–64 years were recruited from four SEER registry sites—Atlanta, Detroit, Los Angeles County, and Seattle—and from Philadelphia. Of the 1622 African American patients, 1233 (75%) came from SEER sites and 1607 had complete data on the risk factors that are used in the Gail model to project breast cancer risk. Younger patients and African American case patients were oversampled to achieve approximately equal numbers of case patients in each 5-year age category (6). Control subjects were obtained by use of random digit dialing methods and frequency matched with case patients on race, center, and 5-year age group. A total of 1647 African American control subjects were included in this analysis. Data from African American women in nine SEER registries [SEER 9 (8)], namely, San Francisco–Oakland,

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Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta, from January 1, 1994, through December 31, 1998, were used to estimate CARE sampling weights, as described below. Data from January 1, 1994, through December 31, 1998 from these nine SEER registries and from SEER registries in San Jose-Monterey and Los Angeles [SEER 11 (9)] were used to estimate the age-specific invasive breast cancer rates, as described below. The competing age-specific hazard of non-breast cancer mortality was obtained from data for African American women from January 1, 1996, through December 31, 2000, from the National Center for Health Statistics (10).

To determine what impact the risk projection model that was based on the Women's CARE Study would have on eligibility criteria for entry into a breast cancer prevention trial, compared with the NCI Breast Cancer Risk Assessment Tool, we used data from 20278 African American women who were screened for entry into the STAR Trial from May 26, 1999, through July 15, 2004 (5). To assess the calibration of the CARE model, we used independent data on breast cancer incidence from 14059 postmenopausal African American women, aged 50–79 years, who entered the WHI study without a history of breast cancer (7). These women were recruited from September 1, 1993, through December 31, 1998, and followed for an average of 7.57 years (range = 0–11.2 years) to detect incident invasive breast cancer. Invasive breast cancers were diagnosed at ages from 50.6 to 86.4 years. In the WHI study, 40.5% of African American women were current or former users of hormone replacement therapy, compared with 50.0% of African American control subjects aged 50 years or older in the Women's CARE Study.

Analytic Approach

The basic approach has been given in Gail et al. (1). First, we developed a multivariable relative risk model from the CARE data applied to the risk factors in Gail et al. (1). Then, we obtained baseline age-specific breast cancer incidence rates by multiplying age-specific rates from SEER times one minus the population attributable risk estimated from CARE. Finally, we made absolute risk projections for an African American woman with specific risk factors by multiplying her multivariable relative risk times the baseline age-specific breast cancer incidence rate and taking competing mortality risks into account. Further details follow.

Initially, relative odds were obtained by use of logistic regression with the same independent variables and coding as described previously (1) (*see* coding in Table 1). In particular, the log relative odds model included main effects in the following five linear variables: age at birth of first live child (AGEFLB), coded as 0, 1, 2, or 3 for ages of younger than 20 years, 20–24 years, 25–29 years or nulliparous, or older than 29 years, respectively; number of biopsy examinations (NBIOPS), coded as 0, 1, or 2 for zero, one, or more than one biopsy examination, respectively, at the reference date (the case patient's date of diagnosis or the day on which the first telephone survey of the control subject's residence was conducted); number of affected relatives (NUMREL), coded as 0, 1, or 2 for zero, one, or more based on mother's and sisters' histories of breast cancer as of the reference date; age at menarche (AGEMEN) coded as 0,1, and 2 for age at menarche older than 14, 12–13, and younger than 12 years; and an indicator of age category (AGECAT) with a value of 1 for women aged 50 years or older and a value of 0 otherwise. The model also included the interactions AGEFLB × NUMREL and NBIOPS × AGECAT. The log relative odds parameters for the full model from CARE data were 0.185 (95% CI = −0.009 to 0.379) for NBIOPS, 0.0815 (95% CI = −0.016 to 0.180) for AGEMEN, 0.0014 (95% CI = −0.077 to 0.080) for AGEFLB, 0.424 (95% CI = 0.150 to 0.698) for NUMREL, 0.0262 (95% CI = −0.127 to 0.179) for AGECAT, −0.114 (95%CI = −0.369 to 0.141) for NBIOPS × AGECAT, and 0.0485 (95% CI = −0.161 to 0.258) for AGEFLB × NUMREL. Because the estimated effect of AGEFLB was nearly 0 and its interaction with NUMREL was small and not statistically significant, we omitted AGEFLB and AGEFLB × NUMREL from the CARE model. Omitting these two factors did not degrade the fit of the model, as judged by a likelihood ratio test (P = .88). Unreported models that used categorical rather than linear coding of the previous variables indicated no statistically significant evidence of lack of fit from the linear codes for NBIOPS and NUMREL. There was evidence of deviation from linearity for AGEMEN, however. A recoding of AGEMEN into two levels, 1 if age at menarche was 13 years or younger and 0 otherwise, fit the data adequately, compared with the saturated categorical coding (P = .17). This reduced model, which omitted AGEFLB and AGEFLB × NUMREL and recoded AGEMEN into only two categories, yielded risk projections with substantially greater precision than the full model. Hereafter, we present only the reduced model (*see* Tables 1 and 2).

To calculate the factor $F(t) = 1 - \mathrm{AR}(t)$, where $\mathrm{AR}(t)$ is the population attributable risk at age t, we modified the formula of Bruzzi et al. (11) to take into account the oversampling of younger case patients in the Women's CARE Study. If the risk factor distribution among case patients varies with age, the following reweighting procedure is necessary to ensure that the attributable risk corresponds to the general (SEER) population. Let j = 1, 2, 3, 4, 5, or 6 index the age ranges 35–39, 40–44, 45–49, 50–54, 55–59, and 60–64 years, respectively. Let Q_j be the proportion of case patients with breast cancer in age group j among African American women in the Women's CARE Study, as given in table 6 of Marchbanks et al. (6), and let P_j be the corresponding proportion of cases in SEER 9 from 1994 through 1998 (8). For women younger than 50 years of age, define $w_j = (P_j/Q_j)$ for j = 1, 2, or 3, and for women aged 50 years or older, define $w_j = (P_j/Q_j)$, for j = 4, 5, or 6. Let i = 1, 2, …, or 18 index the cross-classified risk factor categories for women younger than 50 years, and let r_i be the corresponding relative risk estimate from the logistic model, with $r_1 = 1.0$ corresponding to the referent level i = 1. For women younger than 50 years, we estimated $F(t) = (\Sigma w/r)/\Sigma w$, where the summation is over all case patients younger than age 50 years in the CARE sample, where $w = w_j$, if the case patient is in age interval j (j = 1, 2, or 3), and where $r = r_i$, if the case patient is in risk category i. Likewise, for women aged 50 years or older, we redefined r_i, for i = 1, 2, …, 18, because the effect of biopsy examinations on breast cancer risk is less in older women, and we computed $F(t)$ as described above, but now with weights w_j that are appropriate for the older woman. Using the age-specific invasive breast cancer incidence rates $h^*(t)$ for African American women from 1994 through 1998 from SEER 11 (9), we estimated the baseline hazard as $h_1(t) = h^*(t)F(t)$.

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The hazard $h_2(t)$ of risks of mortality from non-breast cancer causes was obtained from 1996 through 2000 national mortality data for African American women (10). Using formula 6 in Gail et al. (1), we combined information on h_1, h_2, and r_i to project individualized absolute risk for various initial ages, final ages, and combinations of risk factors.

For a woman with a given combination of risk factors leading to a relative risk r compared with a woman younger than 50 years with all risk factors at their lowest risk level, we computed the variance of the estimate of $rF(t)$, and confidence intervals on it, by using the influence function approach of Graubard and Fears (12). Details are provided in the Appendix. Because absolute risk is a monotone function of $rF(t)$ and because we regarded h^* and h_2 as known quantities, we obtained 95% confidence intervals for the absolute risk by evaluating equation 6 in Gail et al. (1) at the upper and lower 95% confidence limits on $rF(t)$.

Although a computer program in GAUSS (13) is available to compute such confidence intervals for any combination of initial and final ages and risk factors, we prepared a graph that gives approximate confidence intervals by generating confidence intervals for a wide range of absolute risks corresponding to various choices of risk factors and risk projection intervals. We regressed the confidence limits calculated from the variance estimates shown in the Appendix on the absolute risk, $\varphi(x)$, and on $\varphi^2(x)$. We chose the points to which the regressions were fit to cover a broad range of absolute risks. For each of the following 14 starting ages 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, and 85 years, we considered projection intervals of length 5, 10, 15, 20, 25, 30, 35, 40, 45, 50, 55, 60, 65, and 70 years, subject to the constraint that the starting age plus the duration of the projection interval was no greater than 90 years. This yielded 105 possible age intervals over which projections were to be made. For each such age interval, we computed the absolute risk for each of the 18 possible risk factor combinations, resulting in 105 × 18 = 1890 pairs (upper confidence limit and absolute risk) and 1890 pairs (lower confidence limit and absolute risk). The regressions explained 98.7% of the variation in upper confidence limits and 98.1% of the variation in lower confidence limits. Thus, the loci (*see* Fig. 1) each provide a good fit to the calculated confidence limits in these 1890 scenarios. The coefficients a, b, and c in the regressions $a + b\,\varphi(x) + c\,\varphi^2(x)$ were (0.0004, 1.2325, and 0.6749, respectively) for the upper confidence limit and (−0.0004, 0.8287, and −0.5758, respectively) for the lower confidence limit.

To validate the CARE model, we checked its calibration by comparing observed numbers of invasive breast cancers with numbers expected by use of the model in independent data from African American women in the WHI. For women in various categories, such as ages 50–59 years, we computed a woman's probability of developing invasive breast cancer from the CARE model by use of her age at entry, risk factors, and the age she would attain if she survived to the end of the original WHI follow-up in 2004–2005. The sum of all such probabilities over women in category i was the expected count, E_i, which we compared with the corresponding observed number of women with incident invasive breast cancer, O_i. In each category, we computed an O/E ratio and a 95% CI with a lower limit of $(O/E)\exp(-1.96 \times O^{-1/2})$ and upper limit of $(O/E)\exp(+1.96 \times O^{-1/2})$. In addition, P values for the goodness-of-fit test were calculated within groupings of categories of the breast cancer risk factors including age at entry, age at menarche, number of biopsy examinations for women who were younger than 50 years and for women who were 50 years or older, and number of affected first-degree relatives. The P values for the goodness-of-fit tests within these groupings were obtained from the chi-square statistic, $\Sigma(O-E)^2/E$, with degrees of freedom equal to the number of mutually exclusive and exhaustive categories within the grouping.

The discriminatory accuracy of a risk projection model is often measured by the concordance statistic, also known as the area under the receiver operating curve (AUC). The AUC is the probability that a randomly selected case patient would have a higher projected absolute risk of invasive breast cancer than a randomly selected control subject (4). To estimate how much the factors in the CARE model contributed to discriminatory accuracy for women of a given age, we estimated age-specific concordance statistics in 5-year intervals from CARE data and computed the unweighted average of these age-specific concordance estimates. We used the nonparametric estimator in Wieand et al. (14), which accounts for ties and provides estimates of standard errors. All statistical tests for a single parameter were two-sided.

Results

Relative and Attributable Risks

Relative risks are needed to produce individualized estimates of absolute risk (1). Relative risks (and 95% confidence intervals) estimated from the logistic model for African American women in the Women's CARE Study are shown in Table 1, which also indicates the number of case patients and control subjects in various risk factor categories in the Women's CARE Study and the corresponding relative risks obtained with the NCI Breast Cancer Risk Assessment Tool (1). To use Table 1 for the CARE model, one does not require the factor AGEFLB; that is, relative risks do not depend on AGEFLB for the CARE model. However, AGEFLB was included in Table 1 to facilitate comparison with the NCI Breast Cancer Risk Assessment Tool.

We calculated attributable risks to convert SEER age-specific invasive breast cancer rates to baseline rates for an African American woman whose risk factors were all at their lowest levels. Except for the risk associated with the factor AGEMEN, the relative risks in Table 1 and log relative odds in Table 2 were lower than estimates from the Gail model 2 (1,3); hence, the estimated attributable risks were also lower for African American women. Indeed, the estimated attributable risks were approximately 0.27 for African American women in the Women's CARE Study compared with approximately 0.58 estimated for African American women for the NCI Breast Cancer Risk Assessment Tool (3). To be precise, estimates of $F(t) = 1 - \mathrm{AR}(t)$ were 0.7295 (95% CI = 0.6104 to 0.8228) for African American women younger than 50 years and 0.7440 (95% CI = 0.6258 to 0.8347) for African American women 50 years or older in the Women's CARE Study, compared with 0.4145 and 0.4228, respectively, for African American women in the NCI Breast Cancer Risk Assessment Tool. Because the conversion factors $F(t)$ were larger for African American women in the Women's CARE Study than in the NCI Breast Cancer Risk

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Table 1. Relative risks for African American women estimated from the Women's Contraceptive and Reproductive Experiences Study data and relative risks in Gail model (1)*

Risk factor (assigned code)		CARE RR (95% CI)†	Gail RR	No. of CARE case patients	No. of CARE control subjects
AGEMEN, y					
≥14 (0)		1.00 (referent)	1.00	309	387
12–13 (1)		1.31 (1.10 to 1.55)	1.10	839	784
<12 (2)		1.31 (1.10 to 1.55)	1.21	459	476
NBIOPS					
Age <50 y					
0 (0)		1.00 (referent)	1.00	661	704
1 (1)		1.20 (0.99 to 1.46)	1.70	90	102
≥2 (2)		1.44 (0.98 to 2.12)	2.88	50	25
Age ≥50 y					
0 (0)		1.00 (referent)	1.00	604	630
1 (1)		1.07 (0.97 to 1.19)	1.27	141	135
≥2 (2)		1.15 (0.87 to 1.52)	1.62	61	51
AGEFLB	NUMREL				
<20 y (0)	0 (0)	1.00 (referent)	1.00	550	594
	1 (1)	1.61 (1.32 to 1.96)	2.61	96	75
	≥2 (2)	2.59 (1.75 to 3.83)	6.80	7	2
20–24 y (1)	0 (0)	1.00 (referent)	1.00	385	436
	1 (1)	1.61 (1.32 to 1.96)	2.68	63	38
	≥2 (2)	2.59 (1.75 to 3.83)	5.78	7	3
25–29 y or nulliparous (2)	0 (0)	1.00 (referent)	1.55	333	359
	1 (1)	1.61 (1.32 to 1.96)	2.76	68	35
	≥2 (2)	2.59 (1.75 to 3.83)	4.91	1	3
≥30 y (3)	0 (0)	1.00 (referent)	1.93	83	91
	1 (1)	1.61 (1.32 to 1.96)	2.83	14	11
	≥2 (2)	2.59 (1.75 to 3.83)	4.17	0	0

* CARE = Contraceptive and Reproductive Experiences; RR = relative risk; CI = confidence interval; AGEMEN = age at menarche; NBIOPS = number of biopsy examinations; AGEFLB = age at birth of first live child; NUMREL = number of affected mother or sisters.

† To obtain the multivariable relative risk, multiply the CARE relative risks for AGEMEN, NBIOPS, and NUMREL. Under the reduced CARE model depicted in this table, AGEFLB does not affect the relative risk, and any value of AGEFLB can be used to find the relative risk for NUMREL. One only needs to know if AGEMEN is less than or equal to 13 years to use the CARE model. If it is known that atypical hyperplasia was present on any biopsy, multiply the result by 1.82. If it is known that the woman had at least one biopsy examination and that no atypical hyperplasia was present in any biopsy specimen, then multiply the result by 0.93.

Assessment Tool, the baseline hazard estimate $h_1(t)$ for African American women was a larger fraction of the corresponding SEER breast cancer rates for African American women in the Women's CARE Study than in the NCI Breast Cancer Risk Assessment Tool. For African American women in the Women's CARE Study, we estimated the baseline hazard $h_1(t)$ to be 2.0, 8.2, 22.7, 49.3, 87.1, 136.7, 176.2, 212.4, 226.2, 267.4, 286.8, 298.3, 289.5, and 265.3 per 10^5 women-years, respectively, for the 14 age categories of 20–24, 25–29, …, 85–89. The corresponding mortality rates from non–breast cancer causes, $h_2(t)$, were 74.4, 101.7, 145.9,

Table 2. Log-odds estimates and their covariance estimates for the logistic model*

	NBIOPS	AGEMEN	NUMREL	AGECAT	NBIOPS × AGECAT
Parameter estimate	0.1822	0.2673	0.4757	0.0335	−0.1119
Covariance estimate	0.9807	−0.0187	−0.0451	0.2029	−0.9779
		0.7505	0.0352	0.0386	0.0064
			1.0017	−0.0341	−0.0115
				0.6098	−0.4205
					1.6926

* Relative risks in the body of the paper are obtained by exponentiation of the log-odds parameter estimates. For example, the relative risk associated with having one biopsy is exp(0.1822) = 1.20, as in Table 1. Variance estimates are the diagonal elements in the columns of the corresponding parameter estimates, and covariance estimates are shown as off-diagonal elements. These variances and covariances are needed to compute variances and confidence intervals for the relative risks and absolute risks for various combinations of risk factors. The variance and covariance estimates are 10^{-2} times the numbers shown. Unweighted logistic regression was fit to the data by maximum likelihood, with independent variable codes as defined for the reduced CARE model. The intercept was −0.3457. A model that included five dummy variables for the six 5-year age groups yielded very similar parameter estimates and is not shown. NBIOPS = number of previous biopsy examinations; AGEMEN = age at menarche; NUMREL = number of affected mother or sisters; AGECAT = 1 if age is 50 or more and 0 otherwise; NBIOPS × AGECAT = product of NBIOPS and AGECAT; CARE = Contraceptive and Reproductive Experiences; AGEFLB = age at birth of first live child. Precise codings for AGEMEN, NBIOPS, AGEFLB, NUMREL, and AGECAT are given in the "Analytic Approach" section of the "Methods and Data Sources."

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215.9, 315.1, 448.8, 632.3, 963.0, 1471.8, 2116.3, 3266.0, 4564.1, 6835.2, and 13,271.3 per 10^5 women-years, respectively.

Individualized Absolute Risk Projections for African American Women

To estimate absolute risks, one needs to specify relative risks and the age interval for the projection. Table 3 gives absolute risks for various initial and final ages and various initial relative risks. If the risk projection interval crosses age 50 years, one also needs to specify the relative risk at age 50 years, the so-called later relative risk in Table 3.

We now show by example how to compute individualized absolute risk by applying the information in Tables 1 and 3. Suppose one wishes to project risk over a 30-year period for a 30-year-old African American woman who began menstruating at age 14 years (AGEMEN = 0), whose mother but not whose sister had breast cancer (NUMREL = 1) and who has had one breast biopsy examination (NBIOPS = 1). It is unknown whether atypical hyperplasia was present. We obtain the woman's initial relative risk by multiplying relative risks corresponding to the factors in Table 1—namely, 1.00 (for AGEMEN = 0) × 1.20 (for NB1OPS = 1) × 1.61 (for NUMREL = 1) = 1.93. As in Gail et al. (1), we would recommend multiplying by 1.82 if it were known that any biopsy sample had atypical hyperplasia and by 0.93 if it were known that atypical hyperplasia was absent. Because a 30-year projection extends beyond age 50 years, we need to hypothesize the woman's risk factor status at age 50 years to compute her later relative risk. If we assume that none of her risk factors change, her later relative risk will be 1.00 × 1.07 × 1.61 = 1.72 because a history of a breast biopsy imposes less risk at ages 50 years or older. The 30-year absolute invasive breast cancer risk would be 6.26% if the initial and final relative risk were 2.0 (Table 3). An approximation can be obtained by linear interpolation as follows: 6.26 + [(4.56 − 6.26)(1.72 − 2.00)/(1 − 2)] + [(4.91 − 6.26)(1.93 − 2.00)/(1 − 2)] = 6.26 − 0.48 − 0.09 = 5.69%. In this interpolation, the value 4.56 corresponds to a later relative risk of 1.0 (Table 3). Thus, the term (4.56 − 6.26)[(1.72 − 2.00)/(1 − 2)] adjusts for the fact that the later relative risk is 1.72, instead of 2.00 or 1.00. The second term adjusts for the fact that the initial relative risk was 1.93, instead of 2.00 or 1.00. The interpolation approximation is close to the exact calculation of 5.71%.

A simple approximation can be used to estimate absolute risk over a 5-year interval. For 5-year risk projections, competing risks have little impact on the absolute risk, and the absolute risk can be approximated by simply multiplying the initial relative risk times the 5-year baseline risks (in percent) in Table 4. Thus the 5-year risk projection in the previous example would be approximately 1.93 × 0.113 = 0.22%. The exact 5-year risk estimate is also 0.22%.

Confidence Intervals on Risk Projections

A GAUSS (13) program provides confidence intervals that take into account random variation in estimates of relative and attributable risks from CARE data, as discussed in detail in the Appendix. Approximate 95% confidence intervals can be obtained from Fig. 1, which shows loci for upper and lower confidence limits, each plotted against the absolute risk projection. The width of the confidence interval increased with increasing absolute risk. The 95% confidence interval that was computed by the GAUSS program for the 30-year projection in the previous example was 4.57 to 7.11. The regressions in Fig. 1 yielded a similar approximate 95% confidence interval of 4.50 to 7.30. For most purposes, an adequately accurate confidence interval for the absolute risk estimate can be obtained from Fig. 1.

Table 3. Projected absolute risk (%) of African American women developing invasive breast cancer within 5, 10, 20, or 30 years, by initial and later relative risks and by initial age and years of follow-up*

			Projected absolute risk, %			
			Initial relative risk			
Initial age, y	Years of follow-up	Later relative risk	1	2	5	10
20	5		0.01	0.02	0.05	0.10
	10		0.05	0.10	0.25	0.51
	20		0.40	0.81	2.00	3.96
	30		1.46	2.90	7.09	13.7
30	5		0.11	0.23	0.56	1.12
	10		0.36	0.71	1.77	3.50
	20		1.42	2.83	6.92	13.3
	30	1	3.18	4.56	8.58	14.9
	30	2	4.91	6.26	10.2	16.4
	30	5	9.89	11.2	14.9	20.8
	30	10	17.6	18.7	22.1	27.5
40	5		0.43	0.86	2.14	4.23
	10		1.09	2.17	5.34	10.4
	20	1	2.89	3.95	7.06	12.0
	20	2	4.65	5.69	8.75	13.6
	20	5	9.75	10.7	13.6	18.2
	20	10	17.6	18.5	21.1	25.3
	30	1	4.86	5.90	8.94	13.8
	30	2	8.47	9.47	12.4	17.1
	30	5	18.4	19.3	21.9	26.1
	30	10	32.4	33.1	35.3	38.7
50	5		0.88	1.75	4.23	8.46
	10		1.89	3.74	9.09	17.3
	20		3.96	7.75	18.2	32.9
	30		5.78	11.2	25.4	43.7
60	5		1.11	2.20	5.41	10.5
	10		2.29	4.52	10.9	20.5
	20		4.30	8.39	19.5	34.7
70	5		1.34	2.66	6.51	12.6
	10		2.47	4.87	11.7	21.9

* Later relative risk refers to relative risk at age 50 years for a woman who was initially younger than age 50 years. For a woman aged 50 years or older initially, no later relative risk is needed. Likewise, no later relative risk is needed unless the age at the end of follow-up exceeds 50 years.

Comparisons With the National Cancer Institute's Breast Cancer Risk Assessment Tool

For African American women, the attributable risk of breast cancer associated with the modeled risk factors was lower in the CARE model than in the NCI Breast Cancer Risk Assessment Tool. Consequently, baseline risk estimates were higher in the CARE model, as reflected in the higher 5-year baseline absolute risks in Table 4. The ratio of the baseline 5-year risk estimates of the CARE model to those of the NCI Breast Cancer Risk Assessment Tool was usually near 1.5 for women younger than 45 years and ranged from 2.0 to 2.4 for women aged 45–79 years.

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Table 4. Five-year absolute risks of invasive breast cancer (%) for African American women at the baseline level of risk (relative risk $r = 1.0$) for the Women's Contraceptive and Reproductive Experiences model and for the National Cancer Institute's Breast Cancer Risk Assessment Tool*

Age, y	Five-year absolute risk†		Ratio of CARE to BCRAT estimates
	CARE model	NCI BCRAT	
20–24	0.010 (0.008 to 0.011)	0.003	3.16
25–29	0.041 (0.035 to 0.048)	0.025	1.63
30–34	0.113 (0.098 to 0.131)	0.075	1.50
35–39	0.245 (0.212 to 0.284)	0.164	1.49
40–44	0.431 (0.372 to 0.499)	0.283	1.52
45–49	0.674 (0.582 to 0.780)	0.339	1.99
50–54	0.880 (0.765 to 1.013)	0.369	2.38
55–59	1.052 (0.913 to 1.210)	0.462	2.28
60–64	1.106 (0.961 to 1.273)	0.558	1.98
65–69	1.285 (1.117 to 1.479)	0.561	2.29
70–74	1.340 (1.164 to 1.542)	0.604	2.22
75–79	1.350 (1.173 to 1.554)	0.679	1.99
80–84	1.242 (1.079 to 1.429)	0.727	1.71

* CARE = Contraceptive and Reproductive Experiences; NCI = National Cancer Institute; BCRAT = Breast Cancer Risk Assessment Tool; CI = confidence interval; SEER = Surveillance, Epidemiology, and End Results.

† For the CARE model, these 5-year absolute risks (with 95% confidence intervals) were obtained by use of equation 6 in Gail et al. (1) with baseline age-specific invasive breast cancer incidence rates per 10^5 African American woman-years of 2.0, 8.2, 22.7, 49.3, 87.1, 136.7, 176.2, 212.4, 226.2, 267.4, 286.8, 298.3, 289.5, and 265.3, respectively, for the 14 age ranges 20–24, 25–29, …, 85–89. Corresponding non–breast cancer mortality rates, $h_2(t)$, were, respectively, 74.4, 101.7, 145.9, 215.9, 315.1, 448.8, 632.3, 963.0, 1471.8, 2116.3, 3266.0, 4564.1, 6835.2, and 13271.3. Composite age-specific invasive breast cancer incidence rates were obtained from data from 11 regions in the SEER Program for 1994–1998 (9) and 1996–2000 national non–breast cancer mortality rates from the SEER Program (10). The corresponding parameters for the BCRAT of the NCI are given for "model 2" in the appendix of Constantino et al. (3).

Counterbalancing this ratio was the ratio of relative risks, which were lower in the CARE model, except for AGEMEN (Table 1).

To understand the impact of these countervailing factors at various ages, we plotted 5-year absolute risks from the CARE model against those from the NCI Breast Cancer Risk Assessment Tool for each of the $3 \times 3 \times 12 = 108$ possible relative risks in the NCI Breast Cancer Risk Assessment Tool (Table 1) for women aged 35 (Fig. 2, A), 50 (Fig. 2, B), and 70 (Fig. 2, C) years. For women aged 35 years, estimates from the NCI Breast Cancer Risk Assessment Tool exceeded those from the CARE model in 90 (83%) of 108 risk factor combinations, as indicated by points below the equiangular line. Because women aged 35 usually have small 5-year risks, the differences in absolute risk estimated from the two models were small. For women aged 50 years, NCI Breast Cancer Risk Assessment Tool estimates were smaller than CARE model estimates in 89 (82%) of risk factor combinations (Fig. 2, B). Likewise, for women aged 70 years, the NCI Breast Cancer Risk Assessment Tool estimates were smaller than CARE model estimates in 78 (72%) of risk factor combinations (Fig. 2, C). Plots in Fig. 2 and other similar plots (not shown) indicate that the 5-year absolute risks from the CARE model tended to exceed those from the NCI Breast Cancer Risk Assessment Tool for women aged 45 years or older. For younger women, NCI Breast Cancer Risk Assessment Tool estimates tended to be larger than the CARE model estimates, especially for risk factor combinations corresponding to higher risks (Fig. 2, A).

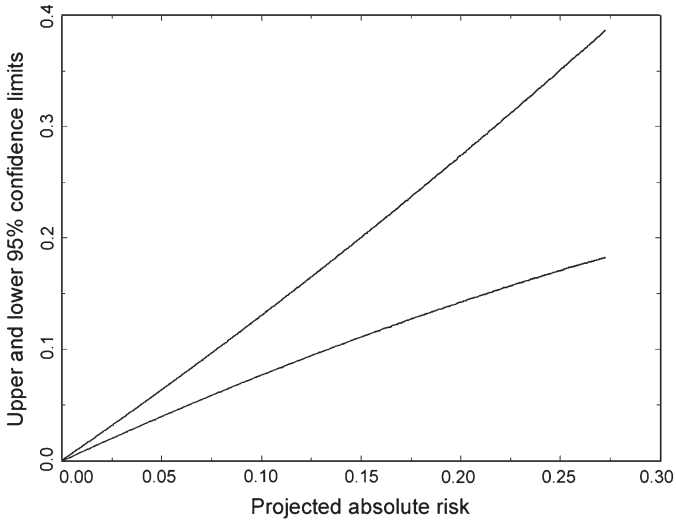

Fig. 1. Upper and lower 95% confidence limits for the estimated absolute risk of invasive breast cancer for African American women plotted against the projected absolute risk. Confidence limits were calculated as described in the "Analytic Approach" section of the "Methods and Data Sources" and in the Appendix.

Assessment of the Impact of Using the Women's Contraceptive and Reproductive Experiences Model for Screening for Eligibility in the Study of Tamoxifen and Raloxifene Trial

To determine how the CARE model would affect eligibility for participation in breast cancer prevention trials compared with the NCI Breast Cancer Risk Assessment Tool, we generated CARE model estimates of 5-year breast cancer risk for 20278 African American women who were screened with the NCI Breast Cancer Risk Assessment Tool as part of the STAR trial (5). To be eligible for participation in STAR, a woman's 5-year risk had to be at least 1.66%. Overall, 13.8% of the population had 5-year risks of at least 1.66% from both models and 69.0% had risks of less than 1.66% from both models; thus the risks obtained from the models agreed for 82.8% of the screened women. Of the remaining 17.2% of screened women, 0.7% had a risk of at least 1.66% only with the NCI Breast Cancer Risk Assessment Tool and 16.5% had a risk of at least 1.66% only with the CARE model. Thus, 13.8% + 0.7% = 14.5% of the screened women satisfied the risk criterion with the NCI Breast Cancer Risk Assessment Tool, compared with 13.8% + 16.5% = 30.3% with the CARE model. The average estimated 5-year risk for this population increased from 1.03% for the NCI Breast Cancer Risk Assessment Tool to 1.45% for the CARE model. Among women younger than age 50 years, the average estimated 5-year risk rose from 0.7% to 0.9%. Among women aged 50 years or older, the average estimated 5-year risk increased from 1.19% to 1.75%. The 5-year risk was higher with the CARE model for 90.3% of the women screened.

Validation With Data From the Women's Health Initiative

Calibration of the CARE model was assessed by use of data from the 14059 African American women who entered WHI without a

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prior history of breast cancer (7). The average time of follow-up of this cohort was 7.57 years, and the standard deviation was 1.87 years. During follow-up, 350 African American women developed invasive breast cancer. From the risk factor profiles for breast cancer that were collected at entry, we used the CARE model to estimate the number of women who would be expected to develop invasive breast cancer among the WHI African American cohort members. The results of this assessment are presented in Table 5. The CARE model predicted well overall and in most categories, but the CARE model underestimated risk among women with a history of benign breast biopsy examinations.

Overall, the CARE model predicted that 323 women would develop breast cancer (Table 5). This value yielded an observed-to-predicted ratio of O/E = 1.08 (95% CI = 0.97 to 1.20), a value that is not statistically significantly different from 1.00 (P = .14), indicating that the observed and predicted values were similar to each other. The observed and predicted numbers of women with breast cancer for categories of age, age at menarche, and number of affected first-degree relatives were all reasonably close, and none of the goodness-of-fit P values testing the differences among categories of these risk factors approached statistical significance, indicating a good level of model calibration within categories of these factors (P = .30, .25, and .47, respectively, for these factors). For example, among women aged 50–59 years, the CARE model predicted 128.83 cancers, whereas 135 were observed, yielding O/E = 1.05 (95% confidence interval = 0.89 to 1.24). However, among women with a history of breast biopsy examination, the number of women predicted to develop breast cancer was statistically significantly lower than observed (P<.001). The observed-to-predicted ratio for those who had not had a biopsy examination was 0.97 (95% CI = 0.85 to 1.09), indicating a very good calibration for this group of women, who constitute 81% of the population. However, the ratios for women who had one biopsy examination and for those who had two or more biopsy examinations were 1.51 (95% CI = 1.20 to 1.92) and 1.65 (95% CI = 1.16 to 2.35), respectively, indicating that the CARE model underestimated the observed incidence of breast cancers in these segments of the population.

We estimated the age-specific concordance statistics for the age intervals 35–39, 40–44, …, 60–64 years as 0.568 (95% CI = 0.514 to 0.622), 0.553 (95% CI = 0.507 to 0.600), 0.578 (95% CI = 0.533 to 0.623), 0.566 (95% CI = 0.520 to 0.612), 0.560 (95% CI = 0.512 to 0.608), and 0.507 (95% CI = 0.454 to 0.559), respectively. The unweighted average age-specific concordance or AUC was 0.555 (95% CI = 0.535 to 0.575). Thus, the CARE model had only modest discriminatory accuracy.

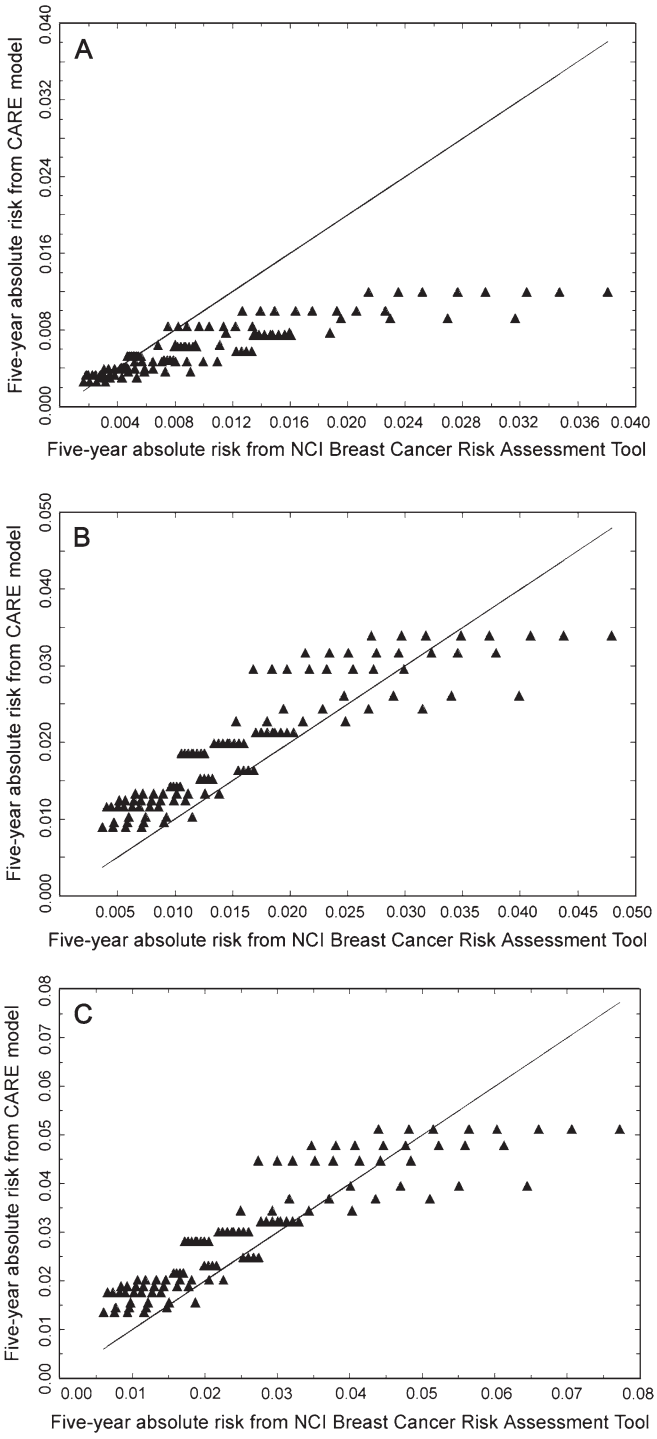

Fig. 2. Plots of 5-year projections of absolute invasive breast cancer risk in African American women from the Women's Contraceptive and Reproductive Experiences (CARE) model (ordinate) versus the Breast Cancer Risk Assessment Tool (BCRAT) of the National Cancer Institute (NCI) (abscissa). In each figure, the line of equality of the two projections is shown, together with solid triangles that correspond to the 108 combinations of risk factors in the NCI Breast Cancer Risk Assessment Tool. **A**) For women aged 35 years. **B**) For women aged 50 years. **C**) For women aged 70 years.

Discussion

We combined data from African American women in the Women's CARE Study with invasive breast cancer rates for African American women in SEER and with national death rates for African American women from the National Center of Health Statistics for causes of death other than breast cancer to produce the CARE model for projecting absolute invasive breast cancer risk in African American women. Risk projections can be made from data in Tables 1 and 3, and corresponding approximate confidence intervals can be estimated from Fig. 1. Predicted numbers of incident breast cancers that were based on the CARE model agreed well with the numbers of incident breast cancers observed in independent data from the WHI. The CARE model tended to produce larger estimates of

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Table 5. Numbers of patients with invasive breast cancer observed and predicted from the Women's Contraceptive and Reproductive Experiences model among African American women participating in the Women's Health Initiative*

Breast cancer risk factor category	No. of women followed	Invasive breast cancer cases		O/E ratio (95% CI)	Goodness-of-fit *P* value
		No. observed	No. predicted		
Age at entry, y					
50–59	5892	135	128.83	1.05 (0.89 to 1.24)	.30
60–69	6000	166	144.13	1.15 (0.99 to 1.34)	
≥70	2167	49	50.44	0.97 (0.73 to 1.29)	
Age at menarche, y					
≥14	3645	80	68.57	1.17 (0.94 to 1.45)	.25
≤13	10414	270	245.31	1.06 (0.94 to 1.19)	
No. of biopsy examinations					
0	11361	250	259.06	0.97 (0.85 to 1.09)	<.001
1	1953	69	45.56	1.51 (1.20 to 1.92)	
≥2	745	31	18.78	1.65 (1.16 to 2.35)	
No. of affected first-degree relatives					
0	12422	286	263.85	1.08 (0.97 to 1.22)	.47
1	1434	54	48.56	1.11 (0.85 to 1.45)	
≥2	203	10	10.98	0.91 (0.49 to 1.69)	
Total No.	14059	350	323.40	1.08 (0.97 to 1.20)	.14

* O = observed; E = predicted; CI = confidence interval.

absolute invasive breast cancer risk than the NCI Breast Cancer Risk Assessment Tool in African American women aged 45 years or older. A GAUSS (13) computer program to produce absolute risk estimates with confidence intervals is available from the corresponding author (MHG) for research purposes and, especially, to facilitate further validation studies.

We initially used the same risk factors and coding that were in the original model of Gail et al. (1) to estimate relative risks and attributable risks for African American women with data from the Women's CARE Study and to compare these estimates with those from the NCI Breast Cancer Risk Assessment Tool. The final CARE model was more parsimonious because the variable, age at first live birth, and its interaction with number of affected first-degree relatives were omitted, and age at menarche was dichotomized (≤13 versus ≥14 years). This model fit the Women's CARE Study data well and yielded absolute risk estimates with smaller variance than for the coding used in the NCI Breast Cancer Risk Assessment Tool.

It is notable that, except for the variable AGEMEN, all the relative risk estimates from Women's CARE Study data for African American women were smaller than corresponding estimates for white women from the BCDDP (Table 1). Even within the Women's CARE Study, the effects of age at first live birth were less pronounced in African American women than in white women (15), as were the effects of family history of breast cancer (16). It is not surprising, therefore, that the average age-specific concordance statistic, 0.555 (95% CI = 0.535 to 0.575), was lower than reported for the original Gail model, 0.596 (17).

Estimates of 5-year absolute risk from the CARE model usually exceeded those from the NCI Breast Cancer Risk Assessment Tool for African American women aged 45 years or older, but the reverse was true for younger women. Had the CARE model been used to evaluate eligibility of African American women for the STAR trial, 30.3% of those screened would have had an estimated 5-year risk of 1.66% or greater, compared with 14.5% found to have such an estimated risk with the NCI Breast Cancer Risk Assessment Tool. Thus, use of the CARE model, instead of the current NCI Breast Cancer Risk Assessment Tool, should increase recruitment of African American women in future prevention trials that restrict eligibility to women with a 5-year projected risk of at least 1.66%.

Our validation study with independent WHI data indicated that the CARE model was well calibrated, in that it demonstrated good agreement between the number of women predicted to develop breast cancer by the CARE model and those observed in the entire WHI population of African American women and in most subgroups (Table 5). The CARE model underestimated the number of women who developed breast cancer among WHI African American women with one previous biopsy examination and with two or more previous biopsy examinations, however. We sought to explain this discrepancy by examining the types of biopsy examinations used in the Women's CARE Study and WHI. The WHI tabulations counted only surgical biopsy examinations, whereas, in the CARE analysis, we counted both surgical and needle biopsy examinations. The relative risks in the Women's CARE Study were higher for needle biopsy examinations than for surgical biopsy examinations, however. Thus, this difference in counting methods cannot explain the underestimation by the CARE model of the number of women who developed breast cancer among WHI women with surgical biopsy examinations. Perhaps other factors, such as frequency of screening or socioeconomic factors in the WHI population, contributed to the underestimation of risk by the CARE model. Further independent validation studies are required to determine whether CARE model estimates of relative risk agree with those derived from other datasets and whether CARE model estimates of absolute risk are well calibrated in independent cohorts, as has been shown for the NCI

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Breast Cancer Risk Assessment Tool for white women (3,4). Validation studies are especially needed for women younger than 50 years, because the WHI population consisted of women aged 50 years or older.

A limitation of the CARE model is that it has low age-specific discriminatory accuracy as measured by the concordance or AUC. The estimate of average age-specific AUC was 0.555 (95% CI = 0.535 to 0.575). Sometimes, as in the cardiovascular literature (18), investigators report the AUC for subjects of all ages, and, because age is a powerful predictor of disease, larger AUC values are obtained. When we computed the AUC from the CARE model with case patients and control subjects reweighted to correspond to their age distributions within the US population, in which women with incident breast cancer tend to be older than women without breast cancer, the AUC for the CARE model increased to 0.636 (95% CI = 0.617 to 0.655). The average age-specific AUC reflects the discriminatory accuracy provided by the risk factors in Table 2 (except for AGECAT) for women of comparable age.

An analysis of losses associated with misclassification errors indicates that a well-calibrated prediction model with modest discriminatory accuracy may be useful for some applications, such as counseling on the use of tamoxifen to prevent breast cancer, even if the model is not discriminating enough for screening a general population (19). The AUC is inherently a retrospective quantity that can be estimated from a sample of case patients and control (noncase) subjects; in fact, the AUC is the probability that the projected risk from a randomly selected case patient will exceed that from a randomly selected control subject. However, the AUC does not describe how well a model will predict breast cancer risk prospectively. For example, if a model includes age only and predicts that every woman in the age range 60–64 years has a 1.7% risk of breast cancer in the next 5 years, then the AUC will be 0.50. Some would mistakenly construe this to mean that the model does not perform any better than a coin flip in predicting who will or will not get breast cancer. In fact, if one predicted that none of these women would be diagnosed with invasive breast cancer in the next 5 years, one would predict correctly for 100 − 1.7 = 98.3% of the women.

Nonetheless, it would be desirable to increase the discriminatory accuracy of the CARE model by adding additional strong risk factors. Adding the percentage of dense area on a mammogram to risk factors in the NCI Breast Cancer Risk Assessment Tool increased the average age-specific AUC by approximately 0.05 in white women (17). Apart from the need to develop and validate such a model for African American women, the use of such a model would require more expense and effort than obtaining the data on the risk factors in Table 2. Whether that effort is warranted would depend on the application.

One must be aware of additional limitations of the CARE model. Confidence intervals are wider for women with large projected risk than for women with small projected risk (Fig. 1). In addition, the Women's CARE Study was limited to women aged 35–64 years; thus, estimates of the baseline hazards from ages 20–34 and 66–89 years rely on extrapolation of the term (1 − AR). The stability of our estimates of (1 − AR) gives some reassurance, however; the estimates of (1 − AR) were 0.729 from women aged 35–49 years and 0.744 for women aged 50–64 years.

The CARE model, like the NCI Breast Cancer Risk Assessment Tool, should be used with caution or avoided for certain special populations. The CARE model will tend to underestimate risk in African American women with a previous history of invasive or in situ breast cancer and in African American women known to carry mutations associated with an increased risk of breast cancer, such as mutations in the BRCA1 or BRCA2 genes. Likewise, African American women who received substantial doses of radiation to the breast at a young age, such as those treated for Hodgkin lymphoma, are also likely to have much higher risk than is predicted by the CARE model (20). The CARE model will probably overestimate risk in African American women who are not periodically screened for breast cancer with mammography. On the basis of the WHI validation assessment, one should be aware that the CARE model may underestimate risk in African American women with previous breast biopsy examinations. Further validation efforts are needed to assess this issue.

Despite these limitations, the CARE model appears to offer more valid and usually larger estimates of invasive breast cancer risk for African American women than the currently available NCI Breast Cancer Risk Assessment Tool. Although we are aware of the need for additional validation studies, we recommend the CARE model for counseling African American women and for determining the eligibility of African American women for breast cancer prevention trials.

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Notes

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Appendix: Method Used to Calculate Confidence Limits on Absolute Risk Estimates

Let a be the age at the beginning of the risk projection interval and τ be the duration of the risk projection interval. The absolute risk from ages α to $\alpha+\tau$ for a woman with risk factors $x^*(t)$ (which change when a woman ages to $t \geq 50$ years) is given by $\pi = \int_a^{\alpha+\tau} h_0^*(t)\{I_1(t)H_1 + I_2(t)H_2\}\exp\{-\int_a^t [h_0^*\{I_1(u)H_1 + I_2(u)H_2\} + h_2(u)]du\}dt$, where $H_1 = \hat{F}_1\exp(\hat{\beta}^T x^*), H_2 = \hat{F}_2\exp(\hat{\beta}^T x^*)$ $\hat{F}_1 = \hat{F}(t)$ for women aged $t < 50$ years, $\hat{F}_2 = \hat{F}(t)$ for women aged $t \geq 50$ years, $I_1(t) = 1$ for $t < 50$, and 0 for $t \geq 50$, and $I_2(t) = 1 - I_1(t)$.

We assume that $h_1^*(t)$ and $h_2(t)$ are known without error. The variance of the absolute risk, π, is obtained from the delta method as, $D^T\Phi D$ where $D^T = (\partial\pi/\partial H_1, \partial\pi/\partial H_2)$ and Φ is the covariance of $(H_1, H_2)^T$. Confidence intervals on π are obtained by putting symmetric confidence intervals on $\ln\{\pi/(1-\pi)\}$ and transforming back to limits on π.

To estimate Φ, we applied the influence function method given by Graubard and Fears (12). Note that $H_1 = S_1/S_2$, where $S_1 = \sum_{j=1}^{N} w_j Y_j I_{1j}\exp\{\hat{\beta}^T(x_j - x_{0j} + x^*)\}$ and $S_2 = \sum_{j=1}^{N} w_j Y_j I_{1j}$.

The summation is over all N case patients and control subjects. The weights w_j were defined in the "Analytic Approach" section of the "Methods and Data Sources", separately for case patients younger than 50 years old and for case patients 50 years or older. The weights for control subjects are 1.0. In these expressions, $Y_j = 1$ or 0, depending on whether person j is a case patient or control subject, I_{1j} is 1 if the jth person is aged younger than 50 years and 0 otherwise, x_j is the vector of covariates, including intercept, for subject j, and x_{0j} is the corresponding vector with all changeable risk factors set to their lowest risk level. A variable, such as the indicator for age 50 years or older, would not change in this calculation. The influence of observation j on H_1 is $Z_j = S_2^{-1}\{\Delta_j(S_1) - H_1\Delta_j(S_2)\}$, where

$$\Delta_j(S_1) = w_j Y_j I_{1j}\exp\{-\beta^T(x_j - x_{0j} - x^*)\} + \frac{\partial S_1}{\partial \beta}\Delta_j(\beta),$$

$$\Delta_j(\beta) = \left\{\sum_{j=1}^{N} x_j x_j^T P_j(1-P_j)\right\}^{-1}\exp\{-\beta^T(x_j - x_{0j} - x^*)\},$$

$$P_j = \exp(\beta^T x_j)\{1+\exp(\beta^T x_j)\}^{-1}$$

$$\frac{\partial S_1}{\partial \beta} = -\sum_{j=1}^{N} w_j Y_j I_{1j}(x_j - x_{0j} - x^*)\exp\{-\beta^T(x_j - x_{0j} - x^*)\},$$

$$\Delta_j(S_2) = w_j Y_j I_{1j}.$$

Similar influences V_j can be calculated for H_2. The pairs (Z_j, V_j) are assumed to be random samples from four separate strata, corresponding to case patients aged younger than 50 years, control subjects aged younger than 50 years, case patients aged 50 years or older, and control subjects aged 50 years or older. The variance of H_1 is estimated as $\sum_{s=1}^{4}\{n_s/(n_s-1)\}\sum_{j=1}^{n_s}(Z_j - \bar{Z}_s)^2$, where n_s is the number of subjects in stratum s and $\bar{Z}_s$ is the stratum mean. The variance of H_2 is estimated similarly from V_j and the covariance of H_1 and H_2 is estimated as $\sum_{s=1}^{4}\{n_s/(n_s-1)\}\sum_{j=1}^{n_s}(Z_j - \bar{Z}_s)(V_j - \bar{V}_s)$.

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