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Breast Cancer Risk Assessments Comparing Gail and CARE Models in African-American Women

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Abstract

The Gail model has been used to predict invasive breast cancer risk in women using risk factors of age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and number of previous benign breast biopsies. However, this model underestimates breast cancer risk in African-American women. The Contraceptive and Reproductive Experience (CARE) model has been developed to replace the Gail model in predicting breast cancer risk in African-American women. In a sample of 883 women who participated in the breast cancer screening program at Howard University Cancer Center, we compared the breast cancer risk estimates from the Gail model and the CARE model. The mean 5-year breast cancer risk was 0.88% (Range: 0.18–6.60%) for the Gail model and 1.29% (Range: 0.20–4.50%) for the CARE model. Using the usual cutoff-point of 1.67% or above for elevated risk, there is a significant difference in the proportion of women with elevated breast cancer risk between the Gail and the CARE models (McNemar's test, $p < 0.0001$). For both models, there was a significant mean risk difference between those with and without a family history of breast cancer (Wilcoxon rank-sum test, $p < 0.0001$). Our results confirm the need for validation of the Gail model in African-Americans and diversity in research. Although these findings are not perfect and perhaps not definitive, they are additive in the discussions during counseling and risk assessment in African-Americans. Furthermore, these findings will be complemented by new technologies such as genomics in refining our ability to assess risk.

The Breast Cancer Risk Assessment Tool, i.e., the Gail model (1), has primarily been used for counseling and to determine the eligibility for breast cancer prevention trials including the National Surgical Adjuvant Breast Project (NSABP) studies such as Breast Cancer Prevention Trial (BCPT) and the Study of Tamoxifen and Raloxifene (STAR) (2,3). Although the Gail model has been widely used in national chemoprevention trials, the validity of the model was unknown for minority populations since the original model was developed from a case control study using the Breast Cancer Detection Demonstration Project (BCDDP) comprising 200,000 white women (1,4).

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Disclosure
The authors have no conflicts of interest to declare.

Using data from Women's Contraceptive and Reproductive Experiences (CARE) study, Gail et al. (5) developed a model for breast cancer risk prediction in African-American women, the CARE model, using data from 1622 African-American women with invasive breast cancer and 1661 frequency matched controls. The CARE model uses the risk factors: age, age at menarche, age at first live birth, number of first-degree relatives with breast cancer, and number of previous benign breast biopsies. The CARE model reflects race-specific adaptations of the Gail model, focusing on African-American women that are based on sufficient ethnic-specific data.

The goal of the current study is to determine if the CARE model generates higher 5-year breast cancer risk estimates for African-American women than the Gail model. It is important to note that in the present study, the institution represented, Howard University Cancer Center/Hospital, reflects a population of women whose care is provided at a historical minority institution that has reported significant comorbidity as a barrier to participation in clinical research (6). Furthermore, the risk assessment forms completed in the STAR trial represented women throughout the country and from various recruitment strategies whereas in the present study, the cohort screening was not exclusively for clinical trial participation.

METHODS

A sample of African-American women who had undergone mammography at Howard University Hospital completed risk assessment forms between 2002 and 2005 to determine breast cancer risk estimates. The postmenopausal women were also being screened for potential enrollment into the STAR study during the recruitment period. The risk assessments were based on age at menarche, age at first live birth, number of affected relatives [mother and/or sister(s)], and number of previous benign biopsy examinations. The 5-year breast cancer risk was calculated for both the Gail and CARE models. Only women 35 years or older were considered in the analysis.

Statistical Analysis

The mean 5-year breast cancer risk between the Gail and CARE models were compared using the Wilcoxon signed-rank test. We compared the mean 5-year breast cancer risk between independent groups using the Wilcoxon rank-sum test. The proportion of women with elevated breast cancer risk (risk ≥ 1.67%) in the Gail and CARE models was compared using McNemar's test. Also assessed for the Gail and CARE models were the associations between breast cancer risk status (high versus low risk, ≥1.67% versus <1.67%) and selected characteristics using chi-squared tests.

Results

The mean age of the participants was 53.8 ±10.8 years with a minimum age of 35 years. Overall, approximately 21% of the African-American women had a 5-year breast cancer risk of at least 1.67 when calculated using the CARE model compared to 7% using the Gail model. The mean 5-year breast cancer risk was 0.88 (Range: 0.18–6.60%) for the Gail model and 1.29 (Range: 0.20–4.50%) for the CARE model.

The distribution of the risk assessment variables are presented in Table 1. Approximately 32% of the participants were 51–59 years old and 15.3% had at least one first-degree relative with breast cancer. In general, the CARE model risk predictions were higher than those from the Gail model in all categories of age at menarche, breast biopsy, age at first live birth; and in women 40 years and older, and those with at least one or no relatives with

breast cancer (Table 2). It is important to note the large differences in risk estimates for the women ≥60 years of age, for the Gail model (14.2%) and CARE model (51.7%).

Using the cutoff-point of 1.67% or above for elevated risk, there is significant difference in the proportion of women with elevated breast cancer risk between the Gail and the CARE models (McNemar's test, $p < 0.0001$). Among those with a family history of breast cancer, the mean risk was 1.57% for the Gail model and 1.88% for the CARE model. For both models, there was a significant mean risk difference between those with and without a family history of breast cancer (Wilcoxon rank-sum test, $p < 0.0001$) (Table 2).

Discussion and Conclusion

In the present study we estimated the 5-year risk for African-American women who underwent mammographic screening using the Gail and CARE models. It was observed that the CARE model had an estimated 5-year risk of 1.67% or greater in 21% of the study population compared to only 7% in the Gail model. However, among women at least 60 years of age, the difference observed between the two models is so wide that this may suggest that the CARE model is not a reliable estimate in this age group.

The CARE study provided interesting frequency distributions of the attributable risk for African-Americans. Gail et al. (5) revealed that the number of biopsies was not as important in African-Americans compared to whites. Moreover, the risk factor, ever had a biopsy, was more important than the number of biopsies.

One limitation of the CARE model that was cited by Gail et al. (5) is the low age-specific discriminatory accuracy base on the concordance or area under curve (AUC). As shown in our data, the differences in estimates using the CARE model was more than 3-fold greater than the estimates provided by the Gail model, among the women at least 60 years of age. If CARE is systematically overestimating risk in women >60 years of age then the use of this model in chemoprevention counseling will result in an inaccurate risk/benefit analysis and could ultimately lead to more harm than good in this population.

The Gail model also weighted biopsies less heavily in his development of the CARE model, but the subsequent validation using the Women's Health Initiative (WHI) cohort data showed that the CARE model was underestimating breast cancer risk in African-American women who had had a breast biopsy. Thus, biopsies should not have been weighted less heavily.

There are several models that have been developed to estimate breast cancer risk, although the Gail model is most frequently used, particularly for chemoprevention trials, and counseling. The CARE model is the only model to address breast cancer risk estimates in African-Americans. A program entitled RISK was developed by Benichou (7) that estimates the absolute risk of developing breast cancer for a woman between 20 and 80 years based on women undergoing annual screening with mammography. This model is known to over predict risk in young unscreened women (1,8–10). Another model developed risk projection for incidence breast cancer and in situ breast cancer that was based on family history that included the ages at onset in affected relatives (11,12). The theory underlying the Claus model is predicated on the fact that all familial risk is conferred by a single autosomal dominant gene.

A strength of this study is that data are collected from an institution which serves more than 95% African-Americans and broadens the utility and validation of the CARE Model. Future research which explores ways to improve the discrimination of the CARE model should

include similar cohorts. We were able to provide support of the important differences in attributable risks between African-American and Caucasian women.

The use of the CARE model has significant implications in the medical community regarding counseling African-American women at increased risk for developing breast cancer and the need to develop appropriate counseling messages for this population. Furthermore, the significance of the CARE model estimates indicates that more African-American women would be eligible for breast cancer chemoprevention studies. Based on the CARE model, increased numbers of African-American women would have been eligible for the national chemoprevention trials including STAR and BCPT. In addition, African-American women could be considered for pharmaceuticals with FDA approved indications for breast cancer risk reduction. Efforts need to be made to promote the education and enrollment of African-American women in breast cancer chemoprevention trials, since their risk is greater than previously estimated. It is plausible that the standard cutoff should be re-evaluated for African-American women. However, the approach may be regulatory since FDA approved indications for Tamoxifen or Raloxifene chemoprevention have been established.

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Table 1

Frequency Distribution of Risk Assessment Characteristics in African-American Women (n = 883)

Characteristic	Percentage (%)
Age (years)	
<40	9.5
40–49	28.5
50–59	32.5
≥60	29.5
Age at menarche (years)	
≥14	23.6
12–13	52.4
<12	24.0
Ever had biopsy	
No	72.2
Yes	27.8
First-degree relatives with breast cancer	
0	82.7
1	15.3
≥2	2.0
Age at first live birth (years) (parous women only)	
<20	33.2
20–24	35.4
25–29	18.1
≥30	13.3

Table 2

Percentage of African-American women with 5-year Breast Cancer Risk Estimates of 1.67% or Greater (n = 883)

Risk factor	Gail model	CARE model
1. CARE, contraceptive and reproductive experience.		
Age (years)		
<40	2.4	0
40–49	3.2	7.5
50–59	5.2	12.9
≥60	14.2	51.7
Age at menarche (years)		
≥14	5.3	9.6
12–13	7.0	25.2
<12	9.3	26.3
Ever had biopsy		
No	3.6	19.4
Yes	16.0	27.2
First-degree relatives with breast cancer		
0	1.6	13.6
1	25.2	56.3
≥2	100.0	83.3
Age at first live birth (years) (parous women only)		
<20	5.3	21.8
20–24	6.2	20.8
25–29	10.6	23.8
≥30	12.2	24.4