

Comparisons of Two Breast Cancer Risk Estimates in Women with a Family History of Breast Cancer¹

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Abstract

There is an increasing need for accurate prediction methods of assessing individual risk for breast cancer for both clinical and research purposes. The purpose of this study is to compare the Gail and Claus model risk estimates of breast cancer among women with a family history of breast cancer. This study presents risk estimates from two models of breast cancer risk in 491 women 18 to 74 years of age with a family history of breast cancer who were recruited to risk counseling clinical trials in Seattle, Washington between 1996 and 1997. These trials included women from the general population and additional samples of Ashkenazi Jewish, African-American, and lesbian women. We estimated and compared lifetime (to age 79) and 5-year risk for developing breast cancer using the National Surgical Adjuvant Breast and Bowel Project adaptation of the Gail model and the Claus model. About one-quarter of participants fell into the Gail “high” risk category ($\geq 1.7\%$ risk of developing breast cancer in the next 5 years). The average lifetime risk was estimated at 13.2% by the Gail model and 11.2% by the Claus model. Estimates from the two models were moderately and positively correlated ($r = 0.55$) with the Gail model yielding a higher estimate than the Claus model for most participants. If women with a family history of breast cancer are being counseled regarding decisions on genetic testing, tamoxifen use, or other preventive measures, presenting both Claus and Gail estimates may be the best option.

Introduction

“What are my chances, doc?” The anxiety reflected on a patient’s face as she utters that phrase is felt keenly by the

physician, not only in his or her own feelings about the health of the patient, but in the physician’s realization that he or she does not know how to estimate the patient’s “chances.” For those physicians who do venture into the numbers game and give patients estimates of how likely they are to get a disease or to survive a certain amount of time, the lay literature is replete with instances where patients proved their doctors wrong.

There is increasing need for accurate methods of assessing individual risk for both clinical and research purposes. In the clinical setting, risk assessment is used to make decisions on primary and secondary prevention practices (1). In research settings, risk assessment has been used to choose women for studies of primary prevention (2, 3) and breast cancer risk counseling (4, 5). The multitude of risk factors that affect risk of developing breast cancer (6) and the lack of information about specific genetic determinants of disease in most breast cancer cases (7) leads to a need for multivariate modeling for estimating breast cancer risk. Various models for estimating risk for breast cancer over discrete or lifelong periods of time have been developed (8). The accuracy of a model depends on the identification of risk factors, the accuracy of estimation of risk factor effects in specific populations, and accurate knowledge of an individual woman’s medical, familial, and demographic histories.

Two models of breast cancer risk levels, Gail *et al.* (9) and Claus *et al.* (10), have been published and used in clinical practice and research settings. The purpose of this study is to compare these two model risk estimates of breast cancer among 491 women with a family history of breast cancer enrolled in clinical trials of breast cancer risk counseling.

Materials and Methods

Study Populations. We recruited women for four randomized clinical trials of breast cancer risk counseling methods in the western Washington area between 1996 and 1997. The recruitment methods, described briefly in this study, are given in more detail elsewhere (11). The first and largest clinical trial included women with a family history of breast cancer who were interested in breast cancer risk counseling. The three other trials also included women interested in risk counseling but focused on women from three population groups of special concern. These additional women either had special issues with respect to inherited breast cancer or were from groups that have reported low levels of comfort with or access to the health care system: (a) Ashkenazi Jewish women; (b) African-American women; and (c) lesbian women. For the clinical trials in African-American and lesbian women, family history of breast cancer was not an eligibility requirement. For the current analysis, however, only women with a family history were included.

Women were recruited to the clinical trials in several ways. For the first trial, we used three recruitment methods. First, we identified breast cancer cases through incident breast cancer cases being recruited for population-based case-control

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studies at the Fred Hutchinson Cancer Research Center and through the breast cancer clinic at the University of Washington. Cases were asked to identify female relatives 18–74 years of age living in western Washington; 46% of cases provided information about potentially interested relatives, resulting in an eventual group of 47 women randomized to the counseling study. Second, we also recruited through a general press release to TV, radio, and print media announcing a study of counseling for women with a family history of breast cancer. We randomized an additional 357 women with a family history of breast cancer through these efforts. These women are referred to as the “general sample” in this study. The Ashkenazi Jewish, lesbian, and African-American samples were recruited through media, placements at health fairs, and community and religious organizations. Women had to meet the following eligibility criteria to be entered into one of the clinical trials: (a) general sample: 18–74 years of age, no personal history of breast cancer, had a history of breast cancer in a first- or second-degree relative but without a history suggesting a high penetrance autosomal dominant breast cancer inheritance gene (see below), and were willing to be randomized; (b) women recruited through Ashkenazi Jewish community: 18–74 years of age, no personal history of breast cancer, self-identified as Ashkenazi Jewish, history of breast cancer in a first- or second-degree relative but without a history suggesting a high penetrance autosomal dominant breast cancer inheritance gene (see below), and willing to be randomized; (c) women recruited through the African-American community: 18–74 years of age, no personal history of breast cancer, self-identified as African-American, and willing to be randomized; and (d) women recruited through the lesbian community: 18–74 years of age, no personal history of breast cancer, self-identified as lesbian sexual orientation, and willing to be randomized.

For this analysis, only women with a family history of breast cancer in one or more first- or second-degree relatives were included. We limited our sample to women for whom a breast cancer risk estimate could be derived. We excluded from any of the studies women ($n = 102$) who were likely to have a highly penetrant inherited gene such as *BRCA1* or *BRCA2* (12) or who had two or more first- or second-degree relatives in the same biological line with breast cancer diagnosed under age 50 or with ovarian cancer at any age because we thought these women should receive genetic counseling outside of a randomized clinical trial setting. For this analysis, we also excluded women with a daughter or half-sister with breast cancer, because not all of the models examined accommodated these possible family relations in their estimations. Finally, because we were focusing on specific race/ethnic groups, we included only Caucasians from the general sample (331 of the 357 were Caucasian) in this analysis. The lesbian group could have included any race or ethnic group. However, it turned out that all of the lesbian women in this study were non-Hispanic Caucasians. Therefore, the total sample size for this study was 491 women: 317 general sample women, 27 African-Americans, 65 lesbians, and 82 Ashkenazi Jews.

Data Collection. All of the participants were interviewed by phone with a standardized questionnaire before their randomization into their respective clinical trial. Among other questions, women were asked specific questions about family history of breast cancer, menstrual and reproductive history, and history of benign breast disease. We took complete pedigrees from all of the participants, both maternal and paternal, including daughters with breast cancer. However, we used only some of these family data because the models did not include all of

Table 1 Variables used in the Gail and Claus models

	Gail	Claus
Age	Yes	Yes
First-degree family history	Yes	Yes
	(mother, sisters, daughters ^a)	
Second-degree family history	No	Yes
Age at onset in relatives	No	Yes
Age at menarche	Yes	No
Age at first birth	Yes	No
No. of breast biopsies	Yes	No
Atypical hyperplasia	Yes	No
Race/ethnicity	Yes ^a	No

^a NSABP-modification.

the potential family relationships (see below). We measured perceived lifetime risk (13) by asking women the following question: “On a scale of 0 to 100, what do you think your chances of getting breast cancer are, where 0 is no chance of getting breast cancer and 100 means that you will definitely get it.”

Risk Assessment. As part of the counseling studies, we estimated lifetime and 5-year risk for developing breast cancer using two different models: the NSABP³ (14) adaptation of the Gail model (9) and the Claus model (Ref. 10; Table 1). These risk estimates were given to study participants as part of the counseling intervention. The risk estimates were not used to determine eligibility for the clinical trials.

The Gail model estimates the probability of an individual of a given age and set of risk factors developing invasive or *in situ* breast cancer over a specified interval (9, 15, 16). It was developed using data from a nested case-control subset of the 284,780 women participating in the BCDDP (17). These BCDDP women were predominantly Caucasian, 35–79 years of age, and receiving annual mammogram screening. The model includes risk factors that were major predictors of risk in the BCDDP and was derived from an unconditional logistic regression analysis. Risk factors (and their associated coded levels) include age [<50 (0); ≥ 50 (1)], age at menarche [<14 (0); 12–13 (1); <12 (2)], age at first live birth [<20 (0); 20–24 (1); 25–29 or nulliparous (2); ≥ 30 (3)], number of previous breast biopsies [0 (0); 1 (1); ≥ 2 (2)] and whether any biopsy showed atypical hyperplasia, and number of first-degree relatives (mother or sister) with breast cancer ([0 (0); 1 (1); ≥ 2 (2)]). Two interaction terms, age by number of previous breast biopsies and age at first live birth by number of first-degree relatives with breast cancer, are included in the model. The Gail model defines the log odds of developing breast cancer in the source population as:

$$\begin{aligned} \text{Log odds} = & -0.74948 + 0.09401 \times \text{age menarche} \\ & + 0.52926 \times \text{number of biopsies} + 0.21863 \\ & \times \text{age at first live birth} \\ & + 0.95830 \\ & \times \text{number of relatives with breast cancer} \\ & + 0.01081 \times \text{age } (<50 \text{ versus } 50+) \end{aligned}$$

³ The abbreviations used are: NSABP, National Surgical Adjuvant Breast and Bowel Project; BCDDP, Breast Cancer Detection Demonstration Project.

- 0.28804 × (number of biopsies × age)
- 0.19081 × (age first birth
- × number of relatives with breast cancer)

Odds ratios derived from this equation are combined with information on baseline age-specific hazard rates and competing mortality risks, and an absolute risk of breast cancer over a defined time interval is developed. The baseline age-specific breast cancer hazard rate, *i.e.*, the baseline hazard rate from a subject without known risk factors, was estimated from the BCDDP population. Hazard rates for age groups with sparse cases in the BCDDP population were estimated by rates from the Surveillance, Epidemiology, and End Results Program. Estimates of breast cancer probabilities were based on the assumption that dying of non-breast cancer causes was the same for all women. The NSABP Breast Cancer Prevention Trial modified the Gail model to use the 1983–1987 United States average annual invasive breast cancer rates and 1988 United States mortality rates for all of the causes other than breast cancer (14, 18, 19). It also incorporated specific attributable risk fractions for African-American women and included daughters as first-degree relatives.

Genetic models were developed by Claus *et al.* (10) and fit to the age-specific incidence data of breast cancer among first- and second-degree relatives of 4730 Caucasian breast cancer cases and 4688 Caucasian controls 20–54 years of age from the Cancer and Steroid Hormone study. The autosomal dominant major gene model was used to generate predicted risk for breast cancer in relatives of cases. An assumption was made that susceptibility to breast cancer and age at onset are both regulated by the same single diallelic major locus. Age-specific risks of breast cancer to a woman with one or two first- or second-degree relatives with breast cancer were estimated using the results of segregation analyses and are presented by age at breast cancer onset of the relatives. The Claus model assumes that both the relationship of the relative(s) and the age at onset of breast cancer are important in predicting risk; *e.g.*, thus a woman with two first-degree relatives diagnosed with breast cancer in their thirties has a greater than 40% chance of developing breast cancer in her lifetime according to the Claus model. Risk to mothers and sisters of cases is higher than risk to sisters of controls. Early age at onset in the index case increases risk further. Other risk factors, such as menopausal status and bilaterality of breast cancer, were not included in their model, because these factors did not add to the accuracy or precision of their estimates.

At the time of our study intervention delivery, the NSABP modification was not available. Therefore, study participants received the original version of Gail estimates. For the present analysis comparing risk estimates, however, we used the NSABP modification of the Gail model because we believed this modification likely improved the precision of the model (18) and because this is the version released by the National Cancer Institute for clinical use.⁴

Statistical Methods. For each member of our analysis, we calculated the 5-year risk from the NSABP modification of the Gail model. The NSABP Breast Cancer Prevention Trial defined a woman as eligible if she had the same 5-year risk for breast cancer as an average 60-year-old woman. This translated

into a risk of 1.7% for developing breast cancer in the next 5 years.

We limited our comparative analysis to the estimates of cumulative risk from present age to age 79, because this estimate was available for both models. We examined the association between estimates from the Gail and Claus models in several ways. First, we compared mean estimates of risk to age 79 provided by the two models for each of the four population groups. Then, to examine the degree of correlation between estimates from the two models, we computed Pearson and intraclass correlation coefficients for each of the four population groups. We then constructed a variable representing the difference between Gail and Claus estimates of risk to age 79. Finally, we examined factors that were related to this difference in risk using multiple linear regression analyses. All of the statistical analyses were performed using SAS (version 6.12; Refs. 20, 21).

Results

The four groups differed somewhat in their profiles of breast cancer risk factors (Table 2). The mean age of the four groups of women was comparable, although the Ashkenazi Jewish women were somewhat older. There was no significant difference among groups according to age at menarche, although a larger proportion of African-American women underwent menarche before age 12, and a larger proportion of Ashkenazi Jews had a late age at menarche. Lesbian women were significantly less likely to have ever been pregnant or to have had a live birth. Of those women who had ever had a live birth, the African-American women had a significantly lower age at first birth compared with the other three groups. The general sample women were significantly more likely to report a first-degree relative with breast cancer but less likely to report a second-degree affected relative. Approximately 16% of the general sample of Ashkenazi Jewish women had ever had a breast biopsy, compared with only 10.8% of lesbian women and none of the African-American women.

On average, the women considerably overestimated their own likelihood of developing breast cancer during their lifetime (Table 3). The general sample had the highest mean perceived lifetime risk, and all of the women reported a mean perceived lifetime risk of greater than 40%.

The NSABP-modified 5-year Gail risk estimate is presented in Table 4. About one-third of the general sample and the Ashkenazi Jewish women fell into the higher risk category, *e.g.*, the threshold value for eligibility for entering the NSABP Breast Cancer Prevention Trial ($\geq 1.7\%$ risk of developing breast cancer in the next 5 years). In comparison, only 3.7% of African-American and 18.5% of lesbian women were in this “high” risk category.

On average across all of the groups, the risk to age 79 for developing breast cancer was estimated at 13.2% by the NSABP-modified Gail model and 11.2% by the Claus model (Table 5). As shown in Table 5, the mean risk estimates differed significantly among all of the four groups, whereas the two models provided estimates that were moderately correlated (Fig. 1). With the exception of the African-American group, the Gail model on average produced a higher lifetime risk (unadjusted difference in risk to age 79 ranging from 1.8 to 2.5%). In a general linear model that adjusted for study populations, the following variables were statistically significant contributors to the difference in risk estimates between the two models: study group, baseline age, age at menarche, age at first live birth, history of breast cancer in a second-degree relative, and history

⁴ Internet address: <http://cancer.net.nci.nih.gov/testing.html>.

Table 2 Demographic and other risk characteristics of women by study population

	General sample (n = 317)	African-American (n = 27)	Lesbian (n = 65)	Ashkenazi Jewish (n = 82)
Age				
Mean (SD)	42.2 (11.0)	43.9 (11.5)	40.8 (8.7)	46.6 (9.9)
Range	20–73	25–72	24–66	27–70
Age at menarche				
≤11	58 (18.3) ^a	8 (29.6)	11 (16.9)	14 (17.1)
12–13	210 (66.2)	13 (48.1)	45 (69.2)	49 (59.8)
14+	49 (15.5)	6 (22.2)	9 (13.8)	19 (23.2)
Ever had a live birth	221 (69.7)	23 (85.2)	21 (32.3)	68 (82.9)
Age at first birth ^b				
≤24	63 (28.5)	12 (52.2)	6 (28.6)	15 (22.1)
25–29	67 (30.3)	3 (13.0)	6 (28.6)	22 (32.4)
30+	62 (28.1)	3 (13.0)	2 (9.5)	19 (28.0)
no live births	27 (12.2)	5 (21.7)	7 (33.3)	11 (16.2)
No. of first-degree relatives with breast cancer				
0	74 (23.2)	13 (48.1)	30 (46.2)	46 (56.1)
1	234 (73.8)	14 (51.9)	33 (50.8)	36 (43.9)
2+	9 (2.8)	0 (0)	2 (3.1)	0 (0)
No. of second-degree relatives with breast cancer				
0	161 (50.8)	12 (44.4)	24 (36.9)	22 (26.8)
1	114 (36.0)	11 (40.7)	35 (53.8)	48 (58.5)
2+	42 (13.2)	4 (14.8)	6 (9.2)	12 (14.6)
≥1 breast biopsy	52 (16.4)	0 (0.0)	7 (10.8)	13 (15.9)

^a Number (percentage).^b Among women who had ever been pregnant.

Table 3 Participants perceived lifetime risk (%) of developing breast cancer, by study population

Study population	N	Mean (SD)
General sample	317	51.3 (25.1)
African-American	27	51.3 (29.0)
Lesbian	65	45.6 (24.5)
Ashkenazi Jewish	82	44.3 (24.9)
Total	491	49.4 (25.3)

of one or more breast biopsies. A history of a first-degree affected relative did not significantly affect the estimated difference in risk. Taken together, these variables accounted for 48% of the variance in the difference in risk estimates between the Gail and Claus models.

We compared the proportions of women (all of the groups combined) who would be classified by either model as “above average” risk (defined as risk to age 79 of 12% or more; Ref. 22). If we assume the Gail model to be the “gold standard,” the Claus model shows low sensitivity (49.3%) and relatively high specificity (87.6%; Table 6). The predictive value of a positive Claus test is high, whereas a negative Claus test is associated with a negative Gail test in only half of study participants. Of note, only 25 women had both a Claus estimate higher than 12% and a Gail estimate lower than 12%.

Discussion

One other study (23) has compared agreement between breast cancer risk assessment models. That study compared risk estimates from the original Gail model with the Claus model for 111 women attending a high-risk breast cancer clinic. They found a significant and positive correlation between estimates from the two models at a level similar to our findings. Also similar to our findings, they observed that the Claus estimates were lower than Gail estimates for the majority of women.

Table 4 Percentage of study participants “eligible for tamoxifen therapy”^a by the NSABP adaptation of the Gail model

Study population	N in study	Percentage high risk ^{a,b}
General sample	317	32.8
African-American	27	3.7
Lesbians	65	18.5
Ashkenazi Jews	82	31.7
Total	491	29.1

^a Defined as a 5-year risk of developing breast cancer of 1.7% or more.^b Test for equality of means, $P = 0.002$.

Nulliparity, a history of a breast biopsy, and a first-degree family history of breast cancer were the factors most affecting the difference in risk estimates. We found different factors affecting the differences between the two models, including study group, age, age at menarche, age at first live birth, history of breast cancer in a second-degree relative, and history of one or more breast biopsies.

Our finding of a lack of correlation between the women’s perceived risk and their estimated lifetime risk is similar to the findings of Black *et al.* (24), who queried 200 outpatients at one center who were 40–50 years of age and who had no family history of breast cancer. The researchers asked the women to estimate their probability of developing breast cancer over the subsequent 10 years and compared that estimate with a Gail model-derived risk estimate. They found that the women overestimated their probability of dying of breast cancer by more than 20-fold.

The Gail model has been tested for its ability to predict breast cancer incidence in several populations. In general, the Gail model is relatively accurate for women who receive annual mammographic screening but likely overestimates risk in younger women who do not receive annual mammographic screening (25–27). In the Breast Cancer Prevention Trial, the modified Gail model showed excellent prediction for prospec-

Table 5 Estimated risk of developing breast cancer between current age and age 79, by Gail and Claus methods, for study population

	Gail risk ^a to age 79 Mean (SD)	Claus risk to age 79 Mean (SD)	Difference: Gail – Claus ^{b,c}	Pearson correlation ^d	Intraclass correlation ^d
General sample (<i>n</i> = 317)	14.2 (4.3)	11.8 (5.1)	2.12 (0.19)	0.52	0.50
African-American (<i>n</i> = 27)	6.1 (2.3)	10.3 (3.4)	-3.33 (0.67)	0.50	0.24
Lesbian (<i>n</i> = 65)	13.2 (5.0)	10.9 (4.9)	2.84 (0.44)	0.72	0.66
Ashkenazi Jewish (<i>n</i> = 82)	11.3 (3.9)	9.5 (3.5)	2.48 (0.39)	0.51	0.46
All of the groups combined (<i>n</i> = 491)	13.2 (4.7)	11.2 (4.9)	1.99 (0.15)	0.55	0.50

^a NSABP-modification of Gail model.

^b Differences adjusted for age, age at menarche, age at first birth, number of first-degree relatives with breast cancer, number of second-degree relatives with breast cancer, and history of one or more breast biopsies.

^c Test of difference between the Gail and Claus estimates, $P < 0.001$ for all of the groups.

^d $P < 0.008$ among African-American group; $P < 0.001$ for all of the other groups.

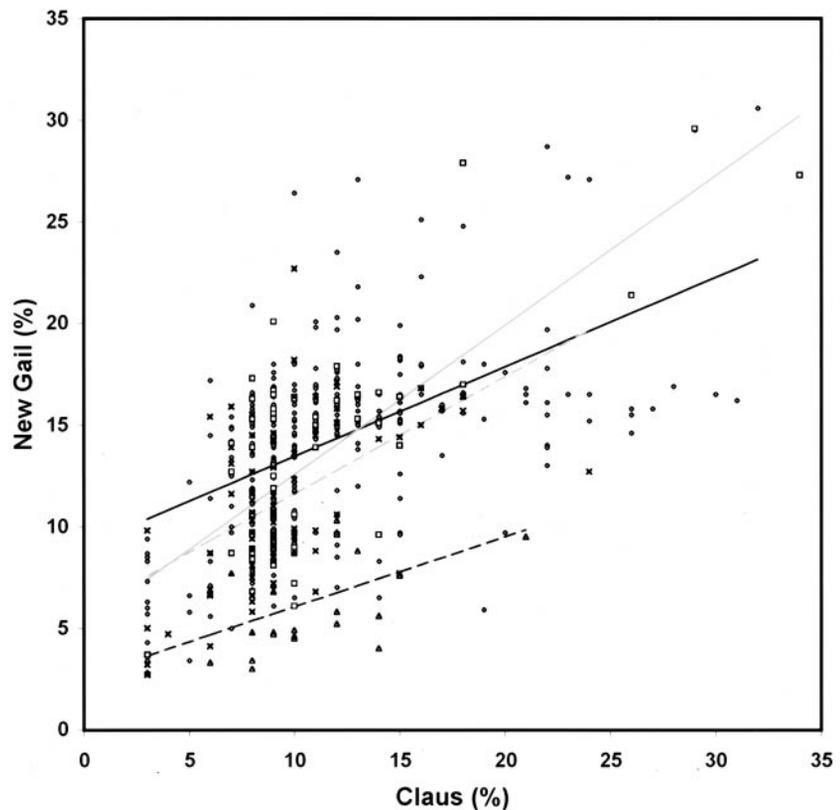


Fig. 1. Breast cancer risk by age 79. Gail versus Claus (*n* = 491). —, general sample; light gray solid line, lesbian; - - -, African-American; light gray dashed line, Ashkenazi Jewish; general sample (data); □, lesbian (data); △, African-American (data); ×, Ashkenazi Jewish (data).

tive breast cancer risk, with a ratio of observed to predicted cancers of 1.03 (95% confidence intervals, 0.88–1.21; Ref. 19). The Claus model has not been tested for its accuracy in predicting actual breast cancer risk.

There are several limitations to our data. First, some of the subgroups of women were small, *e.g.*, African-American women. This limits our ability to measure association in these subgroups. Second, the samples were not population based but rather represented women responding to recruitment for counseling studies and who were not judged by us as likely to be potential BRCA1 or BRCA2 carriers. To the extent that such women are different from other women, there may be bias in the data. Third, there is no “gold standard” for predicting the likelihood of developing breast cancer short of following women to occurrence of breast cancer or death. Fourth, the models are limited by the variables they use; *e.g.*, there are many established and tentative breast cancer risk factors that are not included in either model, including family history of

ovarian cancer or bilateral breast cancer, additional relatives with breast cancer, family history of male breast cancer, BRCA1 or BRCA2 carrier status, history of hysterectomy or bilateral oophorectomy, exogenous hormone use, endogenous hormone levels, body mass, bone mineral density, mammogram density, alcohol use, physical activity, diet, and race/ethnicity other than Caucasian and African-American. Finally, neither model is the best approach to risk assessment when a family history is consistent with autosomal dominant inheritance. In that case, it can be argued that a pedigree analysis is more useful for estimating risk because it enables the full family pattern to be taken into account in determining the likelihood that the person being assessed is at risk for an inherited predisposition. Often, information about second- or third-degree relatives is important in determining whether a high risk mutation is segregating in the family, and the pedigree analysis is more efficient than the Claus model in determining who in the family might have inherited the high-risk mutation.

Table 6 Sensitivity of Claus model for predicting individuals with above average risk ($\geq 12\%$ risk to age 79), assuming Gail model as gold standard^a

Claus risk (%)	NSABP-modified Gail risk		Total
	$\geq 12\%$	$< 12\%$	
$\geq 12\%$	146	25	171
$< 12\%$	150	170	320
Total	296	195	491

^a Sensitivity of Claus for measuring Gail, $146/296 = 49.3\%$; specificity of Claus for measuring Gail, $170/195 = 87.2\%$; predictive value of a positive Claus test, $146/171 = 85.4\%$; predictive value of a negative Claus test, $170/320 = 53.1\%$.

Nevertheless, our data provide some interesting and useful information. First, in this group of women with a family history responding to a recruitment for a counseling study and, therefore, who were concerned about their risk, less than one-third would be classified as high enough risk to be eligible for tamoxifen prevention therapy (14). Thus, whereas tamoxifen may be a viable prevention therapy for some high-risk women, there is need for alternative prevention methods for the majority of women who are at increased risk for breast cancer.

Second, the Claus model, which relies on an autosomal dominant inheritance, may have limited predictive validity for the majority of women with a family history of breast cancer. If women with a family history of breast cancer are being counseled regarding decisions on genetic testing, tamoxifen use, or other preventive measures, presenting both Claus and Gail estimates may be the best option (28).

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