Identification of Women at Increased Risk for Breast Cancer in a Population-based Screening Program[1]

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Abstract

A multivariate model to assess breast cancer risk was developed by Gail *et al.* (M. H. Gail, L. A. Brinton, D. B. Byar, D. K. Corle, S. B. Green, C. Schairer, and J. J. Mulvihill, J. Natl. Cancer Inst., *81:* 1879–1886, 1989) based on data analysis of the Breast Cancer Detection and Demonstration Project. We evaluated the model's usefulness for assigning women to risk groups for counseling and follow-up by applying it to the 1987 Texas Breast Screening Project data. We identified 3165 women with one or more first-degree relatives affected with breast cancer. The mean risk score for the group was 3.3 (range, 2.7–11.8), indicating a greater than 3-fold elevated risk. The mean risk score for the remaining 27,439 women without affected first-degree relatives was 1.5 (range, 1.24–3.2). Risk perception was found to be a motivator for participation. Women with a risk score greater than 5 perceived themselves to be at high risk for breast cancer. The perception of risk was related to the type of affected first-degree relatives: 80.0% of the women with three affected first-degree relatives and 71.5% of women whose mother and sister were both affected with breast cancer perceived themselves to be at high risk. The Gail model is potentially useful in the clinical setting because women at high risk for breast cancer can be entered into etiological studies, enrolled in primary prevention trials, or referred to programs seeking to improve compliance with screening mammography. The Gail model needs validation, but it is useful for estimating the risk of breast cancer in large populations.

Introduction

Family history of breast cancer in first-degree relatives is associated with an increased risk of developing the disease, and as many as 8% of the female population report having at least one affected first-degree relative (1). Research in the etiology of breast cancer is now focusing on women at increased risk, and many are being included in primary prevention efforts (2, 3). The ability to identify such women and classify others according to risk will enhance evaluations of prevention strategies, because these strategies are reported to produce differential effects in groups at varying risk. A method for efficiently identifying women at increased risk is necessary.

An assessment of the univariate relative risks associated with breast cancer has been available for some time (4–6). Recently, Gail *et al.* (7) developed a multivariate model that incorporates life events, clinical features, and familial risk factors for breast cancer. The model can estimate a relative risk for breast cancer among white women and estimate absolute risk of developing breast cancer in any desired interval of time. The model was derived from the Breast Cancer Detection and Demonstration Project data, but it has not been validated in another population.

In this study, we used the Gail model to determine the level of breast cancer risk for women who participated in a low-cost mammography screening project that was promoted by the media in the state of Texas. We wanted to determine whether the model could aid in identifying women who may be at increased risk of developing breast cancer. These women could then be entered in etiological studies, enrolled in primary prevention trials, or referred to programs that seek to improve compliance with screening mammography recommendations. We also wanted to investigate the ways in which women with different levels of estimated relative risk varied in their perception of developing breast cancer and in their behavior with respect to health maintenance.

Materials and Methods

Data Collection. The study population consisted of 38,000 women who completed a self-administered risk factor questionnaire. These women were among the 64,000 women who participated in the American Cancer Society's 1987 Texas Breast Screening Project. The TBSP[3] was promoted by a statewide media campaign and offered low-cost ($50) mammography. To be eligible for the TBSP, a woman had to be asymptomatic for breast cancer, be between the ages of 35 and 39 and never had a mammogram or be over age 39 and not had a mammogram in the past 12 months, and not be pregnant or

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[3] The abbreviation used is: TBSP, Texas Breast Screening Project.

lactating. Additional details of the project are described elsewhere (1).

The participants answered a 31-item questionnaire that took 10 to 15 min to complete. The questionnaire included information on demographics, prior mammographic screening, family history of breast cancer, perception of personal lifetime risk of breast cancer, perception of risk associated with mammographic screening, knowledge of risk factors known to be associated with breast cancer, health behaviors, and barriers to previous participation in mammography screening. Questionnaire responses were not reviewed with the project participants.

To approximate the Breast Cancer Detection and Demonstration Project population, our analysis included only non-Hispanic white women. Of the women who answered the questionnaire, 30,352 (84.3%) were white, and 7,560 (20.8%) reported a family history of breast cancer. Approximately 10% of the women reported a family history of breast cancer involving at least one first-degree relative.

Application of Model. We used the five variables identified by Gail *et al.* to be predictors of breast cancer risk: age at menarche; number of breast biopsies; age at first live birth; number of first-degree relatives with breast cancer; and current age. The relative risks derived from the logistic regression model were used to estimate the relative risks of the TBSP participants who reported having at least one first-degree relative with breast cancer. Because we did not include specific questions about the number of breast biopsies or age at first live birth, we modified the model variables to analyze our data. If a woman ever had a biopsy, we assigned her the risk associated with one biopsy. For parity status, we designated the women as either parous or nonparous, because we did not have information on age at first live birth. As a surrogate for age at first live birth, the parous women were assigned the relative risk for the 20- to 24-year-old age at first live birth group. This was not a severe limitation, because Gail *et al.* found that if a woman had one first-degree relative with breast cancer, risk was not associated with age at first live birth. The relative risks associated with breast cancer derived from Gail's model along with the number and percentage of women from the TBSP in each risk group are shown in Table 1. A summary relative risk was obtained for each woman by multiplying the risks for each factor from Table 1.

Statistical Analyses. We examined the demographic characteristics, lifetime expectation for developing breast cancer, mammographic screening practices, frequency of breast self-examination, and medical history to determine whether there were any differences in these factors between women who had at least one first-degree relative affected with breast cancer and those who did not. These results are reported as frequencies of those responding to the question. We made comparisons by risk score only for women with a family history, because of the small number of women with a moderate risk score among those without a family history. Mantel-Haenszel odds ratios and 95% confidence intervals were calculated to determine whether medical history and health behaviors differed among women with different degrees of risk as calculated by the model (8). For comparisons between perceived lifetime risk of breast cancer and its relationship to the affected first-degree relative, a Pearson's χ^2 test was done using SPSS-X statistical software (9). The comparisons between the affected relative and perception of lifetime risk of breast cancer were made for relative types that were mutually exclusive. In addition, SPSS-X software was also used to calculate risk scores and frequency distributions (9).

Table 1 Breast cancer risk factors and relative risks, for TBSP participants with and without a first-degree relative with breast cancer

Risk factor	Associated relative risk[a]	First-degree relative with breast cancer?			
		Yes		No	
		No.	(%)	No.	(%)
Age at menarche					
≥14	1.000	895	(28.3)	6507	(23.8)
12–13	1.099	1721	(54.4)	16035	(58.4)
<12	1.207	549	(17.3)	4897	(17.8)
Ever had a biopsy					
Age < 50 years					
No	1.000	1102	(34.8)	12190	(44.4)
Yes	1.698	129	(4.1)	1270	(4.6)
Age ≥50 years					
No	1.000	1567	(49.5)	11635	(42.4)
Yes	1.273	367	(11.6)	2344	(8.6)
Parity and no. of FDR[b] with breast cancer					
Parous					
0	1.244			23728	(86.5)
1	2.681	2532	(80.0)		
≥2	5.775	193	(6.1)		
Nulliparous					
0	1.548			3711	(13.5)
1	2.756	414	(13.1)		
≥2	4.907	26	(0.8)		

[a] Relative risk from Gail *et al.* (7).
[b] FDR, first-degree relatives.

Table 2 Distribution by risk score for individuals with first-degree relatives affected with breast cancer

Risk score	No.	%
2.7–2.9	1856	58.6
3.0–3.9	917	29.0
4.0–4.9	87	2.7
5.0–5.9	160	5.1
6.0–6.9	108	3.4
7.0+	37	1.2
Total	3165	100.0

Results

Demographics. Among women with a family history of breast cancer, 61.1% were over age 50 compared with 50.9% of the women under 50 without a family history ($P < 0.05$). There were no differences in the educational level between the two groups. Twelve % of the women with a family history were in the lowest income group (<$13,000) compared with 8.2% of women without a family history ($P < 0.05$).

Estimation of Relative Risk of Breast Cancer. For women with at least one first-degree relative affected with breast cancer, 31.7% had a moderate risk score (between 3 and 5), and 9.7% had a risk score greater than 5 (Table 2).

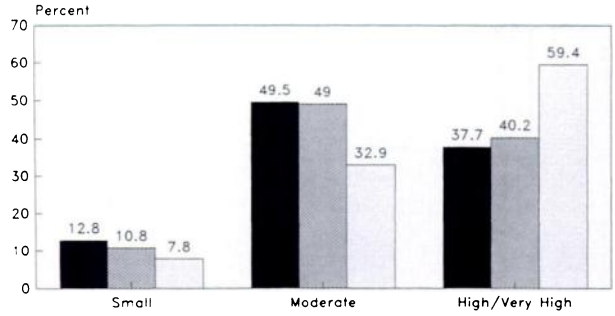

Fig. 1. Relative risk score by expectation of breast cancer. ■, <3; ▨, 3–5; □, 5+. *Numbers above columns*, percentage of women in that relative risk score group. $P < 0.0001$.

For the women without a family history, 99.8% had a risk score under 3, and the mean risk score was 1.5 ± 0.3 (SD). Of those women with a risk score greater than 5, 29.5% had one affected relative, 62.3% had two, and 8.2% had three. There were no differences by risk scores for women with affected first-degree relatives and by factors such as education, income, time since last clinical breast examination, and frequency of breast self-examination (data not shown).

Perceived Risk of Breast Cancer. Women with the highest estimated relative risk scores (≥5) were significantly more likely to perceive their lifetime risk of breast cancer to be high or very high ($\chi^2_{6df} = 73.97$; $P < 0.001$) compared with women in the lower risk categories (Fig. 1). When we examined the type of affected relative and its relationship to perceived risk, we found that 71.5% of the women with affected first-degree relatives perceived their risk to be very high when their mother and sister were affected (Table 3). Fewer than one-half of the women rated their risk as high or very high when their mothers had breast cancer, whereas when two first-degree relatives were affected, 39.3% perceived high risk. When they had three first-degree relatives affected with breast cancer, women perceived the highest risk (80.0%), but when their daughters or sisters were affected, fewer women perceived their risk to be high.

Motivation for Participation in Mammography Screening. Women with at least one first-degree relative affected with breast cancer ranked family history of breast cancer as the most important reason for participating in the TBSP. Women without a family history reported that American Cancer Society publicity was the most important reason to participate. The two groups rated as equally important reasons such as other media publicity, lower cost, and physician referral. The groups ranked similarly the reasons for not having mammography in the past: lack of physician referral; cost; transportation; time away from work; location of examining facility; or fear of pain. Perception of risk was an underlying global motivator, with the women's likelihood of participation linked to higher perception.

Medical History and Health-related Behavior. Proportionally more women with a family history of breast cancer reported ever having mammography than did women without family histories (Table 4). The two groups differed little in knowledge of breast self-examination; however, a significantly higher proportion of women with a family history performed monthly breast self-examination than women without a family history. The groups differed little in time since their last medical examinations; however, a significantly higher proportion of the women without a family history had a cervical cytology within the last year. We found no differential use of cervical cytology based on family history of breast cancer after adjusting for age. The two groups reported the same smoking pattern, with 27% of each group reporting that they had ever smoked and 16.8% reporting that they currently smoked. A higher proportion of women without a family history used birth control pills, 57%, compared to 49% of those with a family history.

The groups experienced similar biological life events such as age at menarche, parity, and menopause status. Mean age at menarche was 12.7 ± 1.5 years for both groups, and they had the same mean number of live births, 2.5 ± 1.2 children. In addition, there was no difference in the proportion of nulliparous women between the groups. Sixty-nine % of the women with a family history and 62% of women without a family history were postmenopausal.

Discussion

We identified a large proportion of women in the TBSP who were at increased risk of breast cancer by estimating risk using a quantitative model. Of the women who participated in the TBSP, 31.7% were at moderate risk and 9.7% were at high risk of breast cancer. We found that an estimate of relative risk of breast cancer can be made in a short period of time in screening settings; therefore, the model has clinical utility.

Table 3 Perceived risk (percentage) of ever getting breast cancer by relationship to affected FDR[a]

Perceived risk	Relationship					
	Mother (n = 1819)	Sister (n = 952)	Daughter (n = 90)	Mother and sister (n = 95)	Two other FDRs[b] (n = 89)	Three FDRs (n = 25)
Small	7.8	18.8	23.3	3.2	13.5	8.0
Moderate	44.3	56.4	61.1	25.3	47.2	12.0
High	47.9	24.8	15.6	71.5	39.3	80.0

[a] FDR, first-degree relative.
[b] Includes two sisters or mother and daughter.
$\chi^2_{2df} = 168.03$; $P < 0.001$ (mother compared to sister).
$\chi^2_{2df} = 86.50$; $P < 0.001$ (mother compared to daughter).
$\chi^2_{2df} = 61.14$; $P < 0.001$ (mother and sister compared to daughter).
$\chi^2_{2df} = 13.29$; $P < 0.001$ (two FDRs compared to three FDRs).

Table 4 TBSP participants by medical history and health behavior

	First-degree relative with breast cancer?					
	Yes		No		OR[a]	95% CI
	No.	(%)	No.	(%)		
Benign breast disease	788	(25.5)	6,363	(23.6)	1.11	1.02-1.21
Breast biopsy	496	(15.7)	3,614	(13.2)	1.23	1.11-1.36
Ever had a mammogram	1,487	(47.3)	8,602	(31.6)	1.94	1.80-2.09
Knowledge of BSE	2,828	(90.3)	24,501	(90.1)	1.02	0.90-1.16
Frequence of BSE						
Never	280	(8.9)	2,792	(10.3)	1.00	
≥12 times/year	1,106	(35.4)	7,572	(27.9)	1.46	1.27-1.67
7-11 times/year	684	(21.8)	6,261	(23.0)	1.09	0.94-1.26
1-6 times/year	1,061	(33.9)	10,559	(38.8)	1.00	0.87-1.15
Time since last breast exam						
Never	56	(1.8)	482	(1.8)	1.00	
≤1 year	2,153	(68.6)	19,602	(71.9)	0.95	0.71-1.25
2 years	472	(15.1)	3,886	(14.3)	1.05	0.78-1.40
>3 years	453	(14.5)	3,285	(12.0)	1.19	0.88-1.59
Time since last cervical cytology						
Never	47	(1.5)	227	(0.9)	1.00	
<1 year	1,496	(47.8)	14,823	(54.5)	0.49	0.35-0.67
1-2 years	788	(25.2)	6,505	(23.9)	0.59	0.42-0.81
2+ years	795	(25.5)	5,624	(20.7)	0.68	0.49-0.94
Oral contraceptive use	1,538	(49.3)	15,380	(56.9)	0.74	0.68-0.79
Ever smoked	615	(27.2)	5,204	(27.0)	1.01	0.92-1.11

[a] OR, odds ratio; CI, confidence interval; BSE, breast self-examination.

The Gail model could simply express a numerical score for relative risk. The univariate models require more complicated information, however, such as a complete family history and breast laterality (4-6, 10-12). Through additional calculations provided by Gail *et al.*, the estimated relative risk scores can be converted to absolute risk scores by adjusting for an individual's current age (7). We used an estimate of relative risk, not absolute risk, in our calculation because our intent was to identify women at high risk and compare them with other women of the same age. For example, young women at high relative risk have increased absolute risks with prolonged person-years of observation (13).

We predict that quantitative assessment using a multivariate model will improve health education by encouraging women to participate in screening and by simplifying counseling at their annual mammogram. Assessment using a multivariate model also will improve health education by clarifying risk perception. Self-ratings of risk varied with the number, age, and nature of kinship to affected relative(s). For example, women rated their risk higher if their mothers, rather than sisters or daughters, had breast cancer or if more than one first-degree relative, including the mother, were affected. A woman perceived her own risk to be higher if her mother or sister was diagnosed before, rather than after, age 40. Women whose daughters had breast cancer perceived themselves at low risk, regardless of the age of the daughter's diagnosis. Given quantitative risk estimates, women might refine such perceptions and improve health behavior (14-17).

Before risk can be determined the woman's age, perceived risk, and potential impact of any interventions should be considered by the clinician. A straightforward risk model based on self-reported information that is reliably recalled facilitates counseling, even in the absence of medical records. The model should allow updates to reflect changes in a person's life such as having a breast biopsy or having a first-degree relative diagnosed with breast cancer. Our data showed that women who perceived themselves at high risk of breast cancer were more likely than women who perceived themselves at low risk to have had at least one prior mammogram. However, none of the women complied with the recommended guidelines for periodic mammographic screening. Only 47% of all participants ever had a mammogram before the TBSP.

Women with an estimated relative risk greater than 5 perceived their risk of developing breast cancer to be high or very high compared with women with lower relative risks. A woman's perceived risk of developing breast cancer was influenced most by her affected family members. Because family history is the most important single variable in the Gail model, the model-derived relative risks correlate well with a woman's perception of her risk for developing breast cancer. We have not interviewed any of these women, and we do not know if they are aware of the complex effect that individual risk factors have on breast cancer risk. We plan to evaluate more completely the women with high relative risk scores. We will inform and follow the highest risk group in our study, the 10% of the TBSP population with at least one first-degree relative affected with breast cancer.

The Gail model needs validation, and we are attempting to provide this. The model also presents certain problems. It may not be appropriate for women with a single affected first-degree relative. In the original Gail analysis, 81.6% (4892 women) had no affected first-degree relative, whereas only 18.4 (1106 women) had an affected first-degree relative. Thus, risk was determined largely from women without affected first-degree relatives weighting the risk factors.

Another potential problem arises in the Gail model with the risk factor of age at first live birth. For women without an affected first-degree relative, Gail found that the relative risk increased with age at first live birth. Increased risk of breast cancer with elevated age at first live birth is consistent with many other studies (18) and has a plausible biological explanation based on terminal differentiation of breast cells stimulated by full-term pregnancy (18). Yet, for women with one affected first-degree relative, the model predicted that the relative risk of breast cancer did not depend on age at first live birth. This is puzzling, since the breast tissue differentiation would not depend on whether a woman has an affected first-degree relative. One possible explanation for this phenomenon comes from the determination of risk for women with two or more affected first-degree relatives. Their relative risk of breast cancer declined as the age at their first live birth increased. It is most likely that women with two or more first-degree relatives affected with breast cancer inherit their susceptibility.

For women with one first-degree relative affected with breast cancer, increasing age at first live birth was associated with increasing relative risk, even if breast cancer in the affected relative was a chance occurrence. But if breast cancer in the affected relative was due to an inherited susceptibility, the relative risk declined as age at first live birth increased. Without genetic markers, it is impossible to distinguish between a relative affected by chance and an affected relative with shared genes. Thus, the model found that women with at least one affected first-degree relative had no change in risk based on their age when their first child was born alive. This suggests that accurate measurement of risk for women with an affected first-degree relative should not be based on models derived from data sets in which more than 80% of the women do not have an affected relative. Other variables are likely to be more important than age at first live birth if the analyses are restricted to women with an affected first-degree relative.

In summary, despite these possible limitations, the Gail model, or a similar multifactorial model, should heighten public health awareness and reduce the possibility of inappropriate counseling. Model validation and refinement and an assessment of its impact on health behavior will be subjects of our future investigations.

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