Nipple Aspirate Fluid Cytology and the Gail Model for Breast Cancer Risk Assessment in a Screening Population

Jeffrey A. Tice,[1] Rei Miike,[2] Kelly Adduci,[3] Nicholas L. Petrakis,[2] Eileen King,[2] and Margaret R. Wrensch[2]

[1]Division of General Internal Medicine, Department of Medicine, [2]Department of Epidemiology and Biostatistics, and [3]Cancer Center, University of California, San Francisco, San Francisco, California

Abstract

Background: **Recent guidelines suggest that chemoprevention with tamoxifen may be appropriate for women who have a 5-year risk of breast cancer greater than 1.66% calculated using the Gail model.**
Objectives: **To determine whether nipple aspirate fluid (NAF) cytology combined with the Gail model provides breast cancer risk assessment that is superior to either method alone.**
Methods: **Prospective observational cohort of 6,904 asymptomatic women. Breast cancer cases were identified through follow-up with the women and linkage to cancer registries. We used proportional hazards modeling to recalculate the coefficients for the predictor variables used in the Gail model. NAF cytology was added to create a second model. The two models were compared using the concordance statistic (*c*-statistic).**
Results: **During 14.6 years of follow-up, 400 women were diagnosed with breast cancer. There were 940 (14%) women with hyperplasia and 109 (1.6%) women with atypical hyperplasia found in NAF. Adding NAF cytology results to the Gail model significantly improved the model fit ($P < 0.0001$). The *c*-statistic for the Gail model was 0.62, indicating only modest discriminatory accuracy. Adding NAF cytology to the model increased the *c*-statistic to 0.64. NAF cytology results had the largest effect on discriminatory accuracy among women in the upper third of Gail model risk. The relative incidence for the highest quintile of risk score compared with the lowest quintile was 7.2 for the Gail model and 8.0 for the model including NAF cytology.**
Conclusion: **NAF cytology has the potential to improve prediction models of breast cancer incidence, particularly for high-risk women.** (Cancer Epidemiol Biomarkers Prev 2005;14(2):324–8)

Background

The Gail model is a multivariable statistical model that uses age, age at menarche, age at first live birth, family history of breast cancer, and number of breast biopsies to estimate breast cancer risk among individuals without a prior history of breast cancer (1). It was modified for the Breast Cancer Prevention Trial using Surveillance, Epidemiology, and End-Results data to update the underlying incidence rates and allow for different underlying rates based on race (2). Breast cancer risk estimation is recommended by the U.S. Preventive Services Task Force for all women considering chemoprophylaxis for breast cancer (3). The Gail model has been shown to accurately estimate the proportion of women who will develop breast cancer when used in large groups (2, 4, 5). However, it performs poorly at discriminating between individual women who will and will not develop breast cancer (5). Given the close balance between the risk and benefits of tamoxifen for most women considering chemoprophylaxis, discovering new strategies to improve the identification of women at very high risk for developing breast cancer is clinically important. Adding information from biological measurements to the risk model may improve prediction of the near-term risk of breast cancer.

Nipple aspiration is a minimally invasive procedure originally developed as a form of Papanicolau test for breast cancer. Prospective cohort studies have shown that cytology information from cells obtained from nipple aspiration predicts breast cancer incidence independent of traditional risk factors (6, 7). The objective of this study was to determine whether NAF cytology combined with Gail model risk assessment provides superior prognostic information to the Gail model alone.

Materials and Methods

Design and Study Cohort. We followed 8,338 women who participated in studies of nipple aspirate fluid (NAF) from 1972 to 1991 to determine their breast cancer status. This analysis is limited to the 6,904 women with complete follow-up who were free of breast cancer at study entry and were not diagnosed with breast cancer within 6 months of nipple aspiration. Written informed consent was obtained from each participant. The Committee on Human Research of the University of California, San Francisco approved this study.

We studied two groups of women. Women in the first group (n = 3,633) were volunteers recruited from 1972 to 1980 from three sources: the University of California, San Francisco (UCSF) outpatient clinics (35%), the Merritt Hospital (Oakland, California) site of the Breast Cancer Detection and Diagnosis Project (59%), and several small community-based screening programs (6%). Women in the

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Requests for reprints: Jeffrey A. Tice, Division of General Internal Medicine, Department of Medicine, University of California, San Francisco, 1701 Divisadero Street, Suite 554, San Francisco, CA 94143-1732. Phone: 415-885-7866; Fax: 415-353-7932. E-mail: jtice@medicine.ucsf.edu

Table 1. Baseline characteristics of NAF cohort

Risk factor	Overall, *N* (%)	No breast cancer, *N* (%)	Breast cancer, *N* (%)
Age groups, y			
18-34	1,652 (24)	1,613 (25)	39 (10)
35-44	2,109 (31)	2,003 (31)	106 (26)
45-54	1,815 (26)	1,670 (25)	145 (36)
55+	1,328 (19)	1,218 (19)	110 (28)
Ethnicity			
White	4,921 (71)	4,618 (71)	303 (76)
Black	744 (11)	706 (11)	38 (9)
Asian	762 (11)	719 (11)	43 (11)
Latina	324 (5)	314 (5)	10 (3)
Other	139 (2)	133 (2)	6 (1)
Missing	14 (0.2)	14 (0.2)	
First-degree relatives with breast cancer			
0	5,886 (85)	5,575 (85)	311 (78)
1	769 (11)	703 (11)	66 (16)
≥2	53 (1)	44 (1)	9 (2)
Missing	196 (3)	182 (3)	14 (4)
Age at menarche			
≥14	1,610 (23)	1,526 (23)	84 (21)
12-13	3,626 (52)	3,414 (53)	212 (53)
<12	1,488 (22)	1,398 (21)	90 (23)
Missing	180 (3)	166 (3)	14 (3)
Age at first birth			
No full-term birth	2,480 (36)	2,359 (36)	121 (30)
<20	550 (8)	531 (8)	19 (5)
20-24	1,533 (22)	1,437 (22)	96 (24)
25-29	1,169 (17)	1,086 (17)	83 (21)
≥30	730 (11)	681 (11)	49 (12)
Missing	442 (6)	410 (6)	32 (8)
Number of breast biopsies			
0	4,929 (71)	4,686 (72)	243 (61)
≥1	1,767 (26)	1,623 (25)	144 (36)
Missing	208 (3)	195 (3)	13 (3)
Cytology			
No breast fluid	2,775 (40)	2,671 (41)	104 (26)
Unsatisfactory	453 (6)	419 (7)	34 (9)
Normal	2,627 (38)	2,454 (38)	173 (43)
Hyperplasia	940 (14)	863 (13)	77 (19)
Atypia	109 (2)	97 (1)	12 (3)

second group (n = 3,271) were volunteers recruited from 1981 to 1991 at UCSF hospitals and clinics or were UCSF employees. Over the 20-year recruitment period, participants completed an evolving series of baseline questionnaires that assessed standard breast cancer risk factors such as age, family history of breast cancer, parity, ethnicity, demographic factors, reproductive and menstrual history, and history of breast diseases and procedures.

Nipple Aspiration. We used the method of Sartorius (6) to obtain breast fluid by nipple aspiration from women in the cohort. The nipple was first cleaned with a detergent. A small plastic cup attached to a 10 mL syringe was placed over the nipple. Whereas the participant gently compressed the breast with both hands, the plunger was retracted to the 5 to 6 mL mark. If fluid did not appear at the nipple surface within 5 seconds, the plunger was withdrawn to the 10 mL mark and held for an additional 10 to 15 seconds. Up to three attempts were made on each breast. If no fluid appeared after these attempts, the participant was considered a non-yielder. Nipple aspiration was not attempted in women with retracted nipples. If fluid appeared, it was collected in capillary tubes and processed for cytology (8). Each breast fluid specimen was classified according to the most severe epithelial change observed: normal, mild hyperplasia, moderate hyperplasia, or atypical hyperplasia. For this report, mild and moderate hyperplasia were combined into a single category of hyperplasia. We classified participants according to the following categories: nipple aspiration attempted and fluid not obtained; fluid obtained but not satisfactory for cytologic diagnosis; normal cytology; epithelial hyperplasia without atypia; and epithelial atypia.

Ascertainment and Validation of Breast Cancer Cases. Prospective follow-up methods for the cohort were presented in detail elsewhere (7, 9). Breast cancer status was initially ascertained through self-reports or next-of-kin reports if the participant was deceased. We identified cases by linking to the Northern California Cancer Center, the California Cancer Registry, and death certificates from the California Department of Health Services Center for Health Statistics Death Certificate Master Files.

Statistical Analysis. Data for risk factors were categorized according to the methods used for the Gail model. All missing data were coded according to the approach of the FORTRAN program used by the National Cancer Institute Risk Disk (BCPT.FOR, May 12, 2000). Specifically, for the number of first-degree relatives with breast cancer, missing values were categorized as 0; for age at menarche missing values were categorized as >14; for age at first birth missing values were categorized as < 20; and for number of breast biopsies missing values were categorized as 0. We used Cox proportional hazards regression to compare the distributions of time from study entry to breast cancer development. All models are adjusted for age at enrollment, ethnicity (White, Black, Asian, Latina), and year of entry into the study. We included a term for year of study entry in all models to adjust for any cohort effect due to the extended period of enrollment. Age was coded as a continuous variable. Ethnicity was coded using indicator variables with White as the reference group. The initial model included the risk factors used in the Gail model including the interaction terms for age and number of biopsies and for age at first live birth and family history (1, 2). Proportional hazards modeling was used to

Table 2. Comparison of original Gail model risk factor relative risks for breast cancer with those calculated using the NAF cohort

Risk factor		Gail	Model 1		Model 2	
		RR	RR	(95% CI)	RR	(95% CI)
Age at menarche						
≥14		1.00	1	(reference)	1	(reference)
12-13		1.10	1.11	(0.96-1.28)	1.09	(0.95-1.27)
<12		1.21	1.23	(0.92-1.64)	1.20	(0.89-1.60)
Age <50 years						
No previous biopsy		1.00	1.00	(reference)	1.00	(reference)
Previous biopsy		1.70	2.04	(1.55-2.69)	2.01	(1.52-2.64)
>1 previous biopsy		2.88				
Age ≥50 years						
No previous biopsy		1.00	1.00	(reference)	1.00	(reference)
Previous biopsy		1.27	1.71	(1.24-2.34)	1.69	(1.23-2.32)
>1 previous biopsy		1.62				
Age at first birth	No. first-degree relatives					
<20	0	1.00	1.00	(reference)	1.00	(reference)
	1	2.61	1.80	(1.17-2.75)	1.77	(1.16-2.70)
	2+	6.80	3.23	(1.38-7.55)	3.14	(1.35-7.31)
20-24	0	1.24	1.15	(1.01-1.30)	1.14	(1.01-1.30)
	1	2.68	1.85	(1.35-2.52)	1.83	(1.34-2.48)
	2+	5.78	2.97	(1.71-5.15)	2.92	(1.69-5.05)
25-29	0	1.55	1.32	(1.02-1.70)	1.31	(1.01-1.68)
	1	2.76	1.90	(1.37-2.61)	1.88	(1.37-2.59)
	2+	4.91	2.73	(1.64-4.52)	2.71	(1.63-4.49)
30+	0	1.93	1.51	(1.04-2.21)	1.49	(1.02-2.18)
	1	2.83	1.95	(1.24-3.05)	1.94	(1.24-3.03)
	2+	4.17	2.50	(1.17-5.36)	2.52	(1.18-5.38)
Cytology						
No breast fluid					1.00	(reference)
Unsatisfactory					1.17	(0.78-1.77)
Normal					1.46	(1.11-1.91)
Hyperplasia					2.22	(1.63-3.03)
Atypia					2.28	(1.24-4.22)

NOTE: All models are additionally adjusted for age, year of entry into the cohort, and ethnicity. Gail, relative risks as reported in original Gail model. Model 1, Gail model fitted to this data set; *c*-statistic 0.62. Model 2, Gail model plus NAF cytology; *c*-statistic 0.64.
Abbreviations: RR, relative risk; 95% CI, 95% confidence interval.

recalculate the coefficients for the predictor variables used in the Gail model. NAF cytology was added to create a second model. We calculated a risk score for each woman for both models by summing the product of the model coefficients by the woman's value for each variable in the model, including year of entry into the study. The two models were compared using the concordance statistic (*c*-statistic; ref. 10) and by comparing the incidence of breast cancer by quintiles of the risk score. We also calculated the incidence of breast cancer by nipple aspirate cytology results within tertiles of the Gail model risk score. For this analysis, we used tertiles rather than quintiles and combined atypia with hyperplasia to have sufficient numbers of events in each subgroup to give meaningful results.

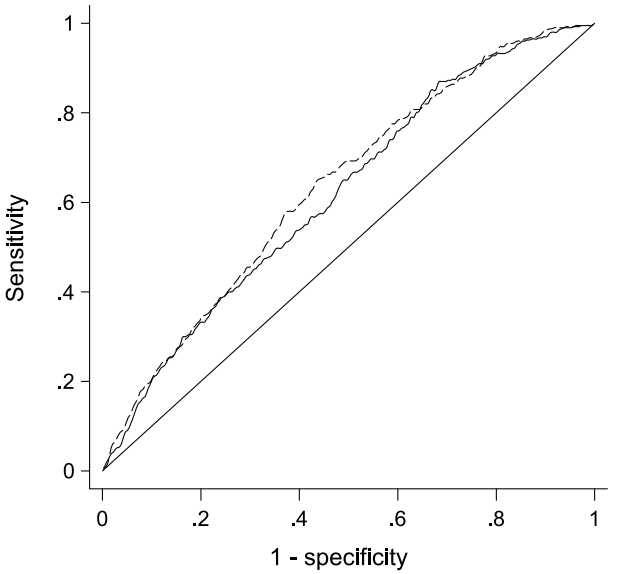

Figure 1. Receiver operating curves for predicting breast cancer: Gail model versus Gail plus NAF cytology. The received operating characteristic curves for the Gail model alone (*solid line*) and for the Gail model plus the NAF cytology results (*broken line*). Areas under the curves are 0.62 for the Gail model alone and 0.64 for the Gail model plus NAF. *Straight line:* ROC curve expected by chance alone.

Results

During 14.6 women-years of follow-up, 400 women were diagnosed with breast cancer. Table 1 shows the baseline characteristics of the women in this cohort. The women were young with a median age at enrollment of 43 years. The

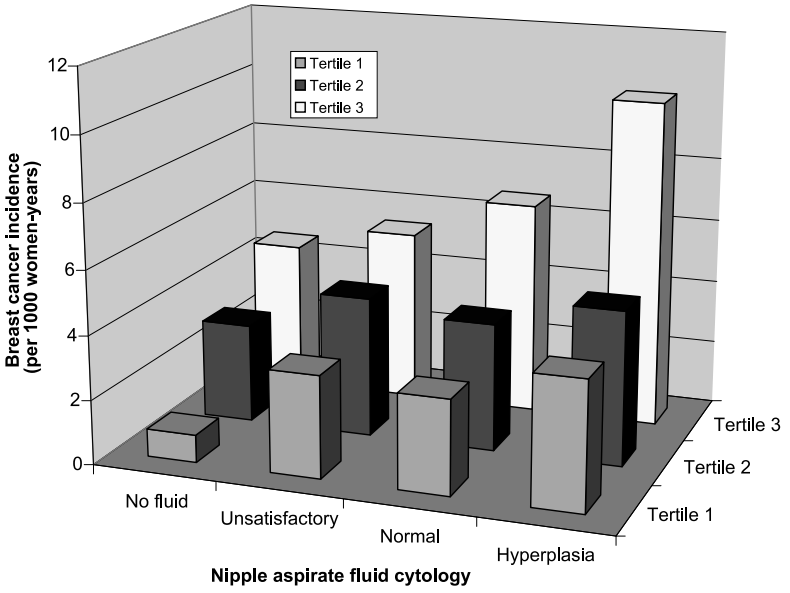

Figure 2. Breast cancer incidence by nipple aspirate cytology within tertiles of Gail model risk.

Table 3. Breast cancer incidence by nipple aspirate cytology within tertiles of Gail risk score

NAF cytology	Gail risk score, tertile								
	1st			2nd			3rd		
	Number of events/women	RR (95% CI)	*P*	Number of events/women	RR (95% CI)	*P*	Number of events/women	RR (95% CI)	*P*
No breast fluid	9/842	1.0 (reference)	—	30/843	1.0 (reference)	—	65/1,090	1.0 (reference)	—
Unsatisfactory	7/140	2.6 (0.97-7.0)	0.058	11/138	1.2 (0.6-2.4)	0.653	16/175	0.9 (0.5-1.6)	0.723
Normal	39/954	2.4 (1.1-4.9)	0.022	70/948	1.3 (0.8-2.0)	0.232	64/725	1.1 (0.9-1.9)	0.516
Hyperplasia*	13/365	2.8 (1.2-6.5)	0.019	35/371	2.1 (1.3-3.4)	0.004	41/313	1.8 (1.2-2.7)	0.002

*Including atypical hyperplasia.

participants were predominantly Caucasian (71%), but there were substantial numbers of Blacks (11%) and Asians (11%). A substantial number of the women had hyperplasia (14%) in the NAF, but only 2% had atypia.

The coefficients for predictors included in the Gail model calculated using data from this cohort were similar to those reported in the original Gail model (Table 2). Adding NAF cytology results to the Gail model significantly improved the model fit ($P < 0.0001$) without any significant effect on the coefficients for variables used in the Gail model (Table 2). There was no significant interaction of NAF cytology results with age and the results were similar when limiting the analyses to 5- and 10-year follow-up. The *c*-statistic for the Gail model was 0.62 indicating modest discriminatory accuracy. Adding NAF cytology to the model only increased the *c*-statistic to 0.64 ($P = 0.006$). The receiver operating characteristic curves for prediction of breast cancer are shown in Fig. 1. The area under the curve (equivalent to the *c*-statistic) for the combined model is modestly greater than for the Gail model alone.

Figure 2 shows the incidence of breast cancer stratified by NAF cytology within tertiles of the Gail model risk score. Both variables were strongly associated with breast cancer incidence ($P < 0.0001$). Although the *P* value for the interaction between the two variables was not significant ($P = 0.16$), there was some variability in the relative risks for the NAF cytology results by tertile of Gail risk (Table 3). Women in the highest third of the Gail model risk score had the greatest range of breast cancer incidence by NAF cytology results and a larger increase in *c*-statistic with the addition of NAF results (0.57 to 0.61). The incidence for women in the third tertile was 10.3/1,000 woman-years among women with atypia or hyperplasia compared with 5.3/1,000 woman-years among women who did not yield fluid. In contrast, the breast cancer incidence for women in the lowest tertile with atypia or hyperplasia (2.2/1,000 woman-years) was only slightly higher than that for women who did not yield fluid (0.8/1,000 woman-years).

Table 4 presents the average incidence of breast cancer for women stratified by quintiles of predicted risk. Only 32% of the cases of breast cancer occurred in women in the highest quintile of risk (expect 20% by chance alone) when the Gail model was used to predict risk. The relative incidence for the highest risk quintile compared with the lowest quintile was 7.2. In contrast, 33% of the cases were in the highest quintile when NAF cytology was added to the model and the relative incidence increased to 8.0.

Discussion

Adding NAF cytology results to the predictor variables used to calculate the Gail risk for women modestly improved the discriminatory accuracy of the model (from *c*-statistic of 0.62 to 0.64). Clinically, the test information may be most useful for women at highest absolute risk by the Gail model because modest differences in relative risk are amplified. In this cohort, the incidence of breast cancer by NAF cytology ranged from 5.3 to 10.3 per 1,000 women years (non-yielder to hyperplasia/atypia) for women in the highest tertile of Gail risk. NAF cytology may be more informative in this population because women with multiple risk factors for breast cancer are more likely to produce NAF (11).

We preserved the categorization used in prior studies of NAF, but in this analysis hyperplasia and atypia had similar predictive power and could be categorized together without changing the study results. This may reflect the relative paucity of patients with atypia in our sample. In the other studies using biopsy specimens, the prevalence of atypia was much higher (12-15) although the largest study (16) had a prevalence of only 3% in 9,494 surgical biopsy specimens.

The composition of the cohort limits the strength of our conclusions in several ways. First, the 20-year period over which the cohort was assembled occurred during a time of changing incidence patterns for breast cancer (17). We adjusted for this by including year of entry into each model, but ideally cohort studies enroll participants over a short period of time to minimize cohort effects. Furthermore, some of the data used by the Gail model to calculate 5-year risk of invasive breast cancer were limited in this data set. We did not have data on how many prior biopsies had been done, nor did we know whether the pathology showed atypical hyperplasia. However, there were very few missing data. Most variables needed to calculate the Gail risk had less than 3% missing data and these were coded according to the method used by the National Cancer Institute Gail Risk Calculator.

Table 4. Breast cancer incidence by quintile of predicted risk

Quintile	Model 1		Model 2	
	Breast cancer, *N* (%)	Incidence per 1,000 woman-years	Breast cancer, *N* (%)	Incidence per 1,000 woman-years
1st	29 (7)	1.2	28 (7)	1.2
2nd	73 (18)	3.3	62 (16)	2.9
3rd	84 (21)	4.2	77 (19)	3.8
4th	85 (21)	4.6	101 (25)	5.4
5th	129 (32)	7.8	132 (33)	8.0
RR, 5th to 1st quintile (95% CI)	7.2 (4.5-11.1)		8.0 (5.3-11.9)	

The Gail model was originally developed using logistic regression in using a nested case-control design limited to 5 years of follow-up (1). Our cohort had longer follow-up and used proportional hazards modeling, but limiting the analysis to a 5-year follow-up period or using logistic regression produced similar estimates for the coefficients. By recalculating the coefficients for the Gail model risk factors, we optimized the predictive ability of the model in this data set. The fact that the *c*-statistic for the Gail model in this data set (0.62) was higher than that calculated for the Nurses Health Study (ref. 5; 0.58) suggests that there was no significant bias against the Gail model in our analyses. Because our model was developed and validated using the same data set, our estimates for the c-statistic are likely to be overly optimistic.

Another potential weakness of this study is the relatively young age of the women. Only 19% of the women are over 55 and nearly one in four are younger than 35, the age cutoff used in the development of the Gail model. However, younger women are more likely to benefit from NAF examination. Risk benefit analysis of tamoxifen use based on data from the Breast Cancer Prevention Trial (18) reported that tamoxifen was overall most beneficial in younger women as they were at much lower risk for the adverse effects of tamoxifen (stroke, venous thromboembolic disease, and uterine cancer) and they have a longer life expectancy. Prior work has shown that young women with risk factors for breast cancer are more likely to produce NAF (11, 19). Thus, as has been suggested by others (20), NAF may be most useful in helping premenopausal women with elevated Gail risk in making the decision about whether or not to use chemoprophylaxis.

However, even our model including NAF had modest discriminatory accuracy. Rockhill et al. (21) recently evaluated the discriminatory accuracy of the most sophisticated log-incidence model developed by Graham and Colditz (22, 23) based on ideas proposed by Pike et al. (24, 25) using prospective data from the Nurses' Health Study. The complete model incorporated 18 risk factors including those of the Gail model, alcohol intake, use of hormone therapy, height, and body mass index. Even this complex and sophisticated model was only modestly accurate at identifying which women would be at highest risk of developing breast cancer (*c*-statistic 0.63). A common feature of all of the models proposed to date is the lack of data measuring the biological state of the women at the time of risk assessment. Proposed biomarkers such as NAF cytology, breast density, bone mineral density, and serum hormone levels may enhance the accuracy of new risk models, although most do not seem to be strong enough risk factors to have a dramatic effect on discriminatory accuracy. Novel approaches, such as proteomic analysis of serum or NAF, may be needed to achieve sufficient discriminatory accuracy to appropriately target chemopreventive therapy.

Our results support the hypothesis that atypia or hyperplasia on NAF cytology can modify the estimated risk of breast cancer obtained from the Gail model, particularly for patients with higher Gail risk. NAF cytology has the potential to improve prediction models of breast cancer incidence. However, these results must be calibrated to national incidence data and validated in an independent study population before they can be incorporated into clinical practice.

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