Predicting the Cumulative Risk of False-Positive Mammograms

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Background: **The cumulative risk of a false-positive mammogram can be substantial. We studied which variables affect the chance of a false-positive mammogram and estimated cumulative risks over nine sequential mammograms.** ***Methods:*** **We used medical records of 2227 randomly selected women who were 40–69 years of age on July 1, 1983, and had at least one screening mammogram. We used a Bayesian discrete hazard regression model developed for this study to test the effect of patient and radiologic variables on a first false-positive screening and to calculate cumulative risks of a false-positive mammogram.** ***Results:*** **Of 9747 screening mammograms, 6.5% were false-positive; 23.8% of women experienced at least one false-positive result. After nine mammograms, the risk of a false-positive mammogram was 43.1% (95% confidence interval [CI] = 36.6%–53.6%). Risk ratios decreased with increasing age and increased with number of breast biopsies, family history of breast cancer, estrogen use, time between screenings, no comparison with previous mammograms, and the radiologist's tendency to call mammograms abnormal. For a woman with highest-risk variables, the estimated risk for a false-positive mammogram at the first and by the ninth mammogram was 98.1% (95% CI = 69.3%–100%) and 100% (95% CI = 99.9%–100%), respectively. A woman with lowest-risk variables had estimated risks of 0.7% (95% CI = 0.2%–1.9%) and 4.6% (95% CI = 1.1%–12.5%), respectively.** ***Conclusions:*** **The cumulative risk of a false-positive mammogram over time varies substantially, depending on a woman's own risk profile and on several factors related to radiologic screening. By the ninth mammogram, the risk can be as low as 5% for women with low-risk variables and as high as 100% for women with multiple high-risk factors. [J Natl Cancer Inst 2000;92:1657–66]**

A woman's cumulative risk of experiencing a false-positive mammogram is substantial. Among 2400 women who were 40–69 years of age at the beginning of our earlier study *(1)* and who were followed for a decade, the median number of mammograms received was four and 24% of the women had at least one false-positive mammogram. We estimated that the risk of a false-positive reading after 10 mammograms was 49.1% (95% confidence interval [CI] = 40.3%–64.1%) *(1)*.

Certain patient and radiologic characteristics affect the risk of a false-positive mammogram. Older age *(2–4)* and family history of breast cancer *(2)* lower the chance of a false-positive mammogram, whereas hormone replacement therapy *(5)* raises the risk. There is indirect evidence that the premenopausal state *(6)* and a previous breast biopsy *(7)* also raise the risk of a false-positive mammogram. Radiologic characteristics that affect the risk of a false-positive mammogram include the individual radiologist's tendency to identify abnormalities on mammograms *(8)*, whether previous mammograms are available for comparison *(9,10)* and, possibly, the interval between screening mammograms.

To our knowledge, there has not been a study to determine the combined effect of patients' risk profiles and radiologic characteristics on a woman's risk of experiencing a false-positive mammogram over multiple screening mammograms. Because a woman may have 30 or more screening mammograms over her lifetime, it could be clinically useful to know which characteristics contribute most substantially to the chance over time of a false-positive reading.

We undertook a study to determine which patient and radiologic characteristics affect the chance of a woman's experiencing a false-positive mammogram at her next mammographic examination and over a period of eight subsequent mammograms. We sought to identify characteristics that were the most powerful predictors of a false-positive mammogram after we controlled for the effects of other variables and the random effects of the radiologists in our sample. We also considered interaction of the independent variables.

Subjects and Methods

Setting and Patient Sample

The study sample of 2400 women was drawn from a cohort of female members of Harvard Pilgrim Health Care, Boston, MA, a large New England health maintenance organization (HMO). The cohort has been described in detail elsewhere *(1)*. Briefly, women between 40 and 69 years of age on July 1, 1983, who were enrolled continuously for 12 years (the last 2 years were used for follow-up information only) and who had computerized medical records at one of 11 HMO centers were randomly selected: 1200 women 40–49 years of age, 600 women 50–59 years of age, and 600 women 60–69 years of age. Exclusion criteria were a lapse in enrollment during the period from July 1, 1983, through June 30, 1995; health coverage outside Harvard Pilgrim Health Care; a history of breast cancer, a prophylactic mastectomy, or breast implants before July 1, 1983; or a prophylactic mastectomy or breast implants during the 10-year study period (July 1, 1983, through June 30, 1993). Trained abstractors, using standardized forms, abstracted specific data from the women's medical records for use in the study. The study was approved by the Human Studies Committee of Harvard Pilgrim Health Care.

We removed the records of 173 women who had no screening mammograms during the study period, leaving 2227 for study. Eighty-eight women who de-

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See "Notes" following "References."

veloped breast cancer during the 10 years were censored at the date of cancer diagnosis. Women also were censored at the time of the first false-positive mammogram. A total of 9747 screening mammograms were obtained. Ninety-one women (4.1%) had two or more false-positive screening mammograms that resulted in 357 mammograms (3.7%) being censored.

Definition and Classification of Screening Mammograms

A screening mammogram was defined as a bilateral mammogram that was performed on an asymptomatic woman with no abnormalities previously noted by clinicians or patients. The screening mammogram was classified as positive if there was a recommendation for nonroutine follow-up (repeat physical examination, diagnostic mammography within 12 months, ultrasound examination, or biopsy) or if the results were indeterminate or aroused a suspicion of cancer. A positive mammogram was further classified as false-positive if no breast cancer (invasive cancer or ductal carcinoma *in situ*) was diagnosed within 1 year.

Definition of Predictive Variables

We identified several radiologic and patient variables that might have an effect on the frequency of false-positive mammograms and defined them at the time of each mammogram. Radiologic variables included indication that the mammogram was compared with a previous mammogram and time since prior mammogram.

Patient variables included age, previous open biopsy or fine-needle aspiration during the study period, family history of breast cancer (if recorded), menopausal status, estrogen use, body mass index (BMI; calculated as [weight in kilograms]/[height in meters]^2), race, and median household income. Women for whom there was no comment regarding menopausal status were defined as postmenopausal if they were older than 50 years of age at the time of the mammogram. BMI was calculated for the years 1983–1987 and 1988–1993 from the first recorded patient weight in the periods 1983–1987 or 1988–1993 and from height recorded at any time. Median household income was estimated by matching the patient's home address to census tract data *(11)*.

We also included in the statistical model random effects for the widely varying frequency of false-positive readings by the radiologists in our study. Radiologists who read fewer than 25 mammograms in our sample of women were classified as "other." Those reading at least 25 mammograms and the group of "other" radiologists were coded as random effects for the statistical modeling. Statistically, these effects are viewed as random because the radiologists appear in our sample randomly.

Statistical Methods

We first examined the data using the mammogram, as opposed to the woman, as the unit of analysis and tested for a relationship between false-positive outcomes and variables of interest using contingency tables. Chi-square statistics from tests of independence of all factors were used to calculate P values. These initial analyses did not account for the longitudinal nature of the data.

Next, we used a cumulative risk–survival model with likelihood-based Bayesian inference to determine the effect of patient and radiologic characteristics on the risk of a first false-positive mammogram. (Risk of subsequent false-positive readings was not addressed.) These analyses used the woman as the unit of interest; time-dependent covariates and varying time between outcomes within and among patients were incorporated into the model. The Bayesian model was developed especially for this study *(12)*. It employs a Bayesian discrete hazard model with covariates and random effects, and we use Markov Chain Monte Carlo techniques *(13)* for estimation of cumulative risks and the effect of predictor variables. The model and estimation methods are described in more detail in the "Appendix" section; a brief description follows.

The Bayesian model allows for calculation of point and CI estimates for all unknown quantities, including the effect of patient and radiologic characteristics (regression parameters), radiologist effects, risk ratios, and cumulative risk for individuals. The discrete hazard model was chosen for several reasons. The time between mammograms was different between and within individuals, and the women in the study had a varying number of screening mammograms. Cumulative time to first false-positive mammogram is not an appropriate measure of risk. Rather, the patient incurred the risk by having the mammogram, and risk cumulated with the number of mammograms. Hence, we calculated the cumulative risk and the chance of a first false-positive mammogram at a given number of mammograms by use of time between occurrences as an explanatory variable in the regression model.

The cumulative risk is calculated through a sequence of probabilities. For the i^{th} woman at her k^{th} screening mammogram, let p_{ik} denote the probability of at least one false-positive reading within these first k readings; also, let q_{ij} be the probability of a false-positive reading given no false-positive in the previous $k-1$ screening mammograms. Therefore,

$$p_{ik} \equiv 1 - \prod_{j=1}^{k} (1 - q_{ij}(X_{ij})). \quad [1]$$

The q_{ij} values are modeled as a function of levels of the predictive variables (risk factors) X_{ij} at the j^{th} screening mammogram for the i^{th} patient.

Estimates of cumulative risks, risk ratios, and regression coefficients were made with the use of the Bayesian model and methods described in the "Appendix" section and in reference *(12)*. The estimation method we used is similar to maximum likelihood estimation. However, Bayesian models allow unknown parameters to have probability distributions as opposed to assuming that they are fixed, unknown values. Therefore, 95% CIs reported here are actually probability intervals for the parameters.

The effect of each explanatory variable on the cumulative false-positive risk was analyzed individually. To report the cumulative risk of a false-positive mammogram, we estimated risks for as many repeat mammograms as we had data for, and we report estimated risks at the first, fifth, and ninth mammograms. Cumulative risks require specification of variables for each mammogram in the sequence of nine mammograms. Many combinations of variables are possible; to simplify the reporting of estimated cumulative risks, variables (except for age) were artificially held constant throughout the mammographic history. For example, a woman who was premenopausal for the first mammogram remained classified as premenopausal through the ninth mammogram. To report the cumulative risks of age, we assumed that women began receiving mammograms at age 40, 50, 60, or 70 years and were 8 years older at the time of the ninth mammogram. In contrast to the estimated cumulative risks, the reported risk ratios are approximately constant across the number of mammograms and can be reported as the ratio of risks between a variable and its referent category (*see* the "Appendix" section). For example, if a risk ratio is 2.0 for a patient with characteristic X, the risk of a first false-positive mammogram is approximately twice that for a patient without this characteristic at any mammogram in a sequence of mammograms. (*See* the "Appendix" section for a more technical explanation of these approximate risk ratios.)

The considerable variability in radiologists' tendencies for reading mammograms as abnormal was modeled by use of random effects, as opposed to use of fixed-effect variables. We considered these effects random because the radiologists in the study are only a small sample of the population of radiologists; a different sample of women would generate a different sample of radiologists. In addition, the degree to which the same radiologist would tend to read mammograms as abnormal for a group of patients can be estimated through these random effects.

Pearson's correlation coefficient was used to calculate the correlation between the random effects and the radiologists' false-positive percentage from our sample. We used deviance statistics to determine if the random-effects model fit the data better than one without random effects. Deviance statistics are a goodness-of-fit measurement; a model with a small deviance explains more of the variation in the data than one with a large deviance.

The final analysis used the cumulative risk model with multiple explanatory risk factors. A variable was included in the multiple-variable model if the relative risk interval from the univariate analysis of its effect did not include 1.00. In this model, the actual value of the continuous variable at the time of each mammogram was used. For example, to report risk ratios in the univariate models, a continuous variable such as time between screenings was categorized into two categories ($\leq$18 months and >18 months) with the use of indicator variables. In the final model, however, time between screening mammograms was used as a continuous variable.

We checked several possible interactions for their effect on the risk of a false-positive mammogram: 1) estrogen use with age, BMI, and family history of breast cancer; 2) age with the number of breast biopsies, previous breast biopsy or fine-needle aspiration, BMI, and comparison with the previous mammogram; and 3) time since the previous mammogram with comparison to the previous mammogram. No statistically significant interactions were found.

RESULTS

Over the 10-year study period, 2227 women obtained 9747[1] screening mammograms that were read by 93 radiologists; 531 (23.8%) women experienced at least one mammogram that fit our definition of a false-positive result. The overall percent of false-positive mammograms was 6.5% (634 of 9747), with a range of 2.6%–24.4% among the 35 radiologists who read at least 25 mammograms from our patient population. Of all 93 radiologists, 48 (52%) had false-positive percentages of 5% or less; 17 (18%) had percentages of more than 5% to 10%; and 28 (30%) had percentages of 10% or more.

In univariate analyses with mammograms as the unit of analysis, false-positive mammograms were related to several patient and radiologic variables (Table 1). The percentages of false-positive mammograms varied inversely by patient age from 7.9% in women aged 40–49 years to 4.4% in women aged 70–79 years. Previous breast biopsies, number of previous breast biopsies, a family history of breast cancer, premenopausal status, and estrogen use were all associated with higher frequency of false-positive mammograms. The percentages of false-positive mammograms within categories of race, income, and BMI were not statistically different. Of the radiologic variables, comparing the mammogram with a previous one lowered the percentages of

Table 1. Percentage of false-positive mammograms associated with selected patient and radiologic variables

Risk variable	No. of mammograms	% false-positive	P*
Patient clinical variables			
Age, y			
40–49	1993	7.9	<.01
50–59	3633	7.5	
60–69	2805	5.0	
70–79	1316	4.4	
Previous breast biopsy			
None	9109	6.1	<.01
Biopsy >2 y before	401	12.2	
Biopsy ≤2 y before	237	11.8	
No. of breast biopsies before screening mammogram			
None	9109	6.1	<.01
1	482	10.8	
2	92	13.0	
≥3	64	20.3	
Family history of breast cancer			
Yes	1975	7.8	.01
No	7772	6.2	
Menopausal status†			
Postmenopausal	8143	6.2	<.01
Premenopausal	1604	8.2	
Estrogen use			
Current user	1567	7.8	.03
Past user	293	8.2	
Never user	7887	6.2	
Body mass index, kg/m^2‡			
<21	1114	6.1	.21
21–24.9	3749	5.9	
25–26.9	1379	7.4	
27–29.9	1385	6.6	
≥30	1961	7.2	
Patient demographic variables			
Race			
Caucasian	7718	6.5	.80
Black	935	6.5	
Other	253	5.1	
Unknown	841	6.9	
Median household income§			
≤$40 000	2376	5.9	.26
$40 001–$50 000	2301	6.6	
$50 001–$70 000	2338	7.2	
>$70 000	2350	6.3	
Radiologic variables			
Stated comparison with previous mammogram			
Yes	5009	4.8	<.01
No/unknown‖	4738	8.3	
Time since last mammogram, mo¶			
≤18	4370	5.8	.10
>18	3252	6.7	

*P value was calculated with the use of the chi-square test for independence.

†Menopause year data are missing for 4043 mammograms (966 women); considered to have occurred at 50 years of age.

‡Body mass index = (weight in kilograms)/(height in meters)^2; data are missing for 159 mammograms (58 women).

§Data are missing for 382 mammograms (86 women); categories are approximately the quartiles of the data.

‖If no comment was in the medical record about comparison with previous mammogram, we assumed there was no comparison.

¶No prior mammogram for 2125 women.

false-positive screenings, while longer periods between mammograms were associated with slightly higher percentages (but the effect was not statistically significant).

Ignoring all explanatory variables, we estimated the risk that a woman will experience a false-positive mammogram as she underwent repeated mammographic screening over a decade. The estimated risk of having at least one false-positive mammogram was 7.4% (95% CI = 6.4%–8.5%) at the first mammogram, 26.0% (95% CI = 24.0%–28.2%) at the fifth mammogram, and 43.1% (95% CI = 36.6%–53.6%) at the ninth mammogram.

Table 2 shows the effect, calculated by use of the cumulative risk–survival model, of patient and radiologic variables on the cumulative risk that a woman will experience at least one false-

Table 2. Risk of a first false-positive mammogram associated with selected patient and radiologic variables

Risk variable	Cumulative risk by No. of mammograms			Risk ratio (95% confidence interval [CI])*
	1	5	9	
	Estimated % of women with a first false-positive result (95% CI)†			
Patient clinical variables				
Age at first mammogram, y				
40	10 (8–12)	34 (30–38)	55 (45–68)	2.00 (1.50–2.65)
50	8 (7–9)	28 (26–30)	46 (39–59)	1.59 (1.31–1.91)
60	6 (5–7)	23 (21–25)	39 (33–50)	1.26 (1.15–1.38)
70	5 (4–6)	19 (16–22)	33 (26–43)	1.00 (referent)
No. of breast biopsies before screening mammogram				
None	7 (6–8)	25 (23–27)	41 (35–52)	1.00 (referent)
1	11 (8–16)	37 (27–48)	58 (43–75)	1.63 (1.12–2.38)
2	11 (5–19)	36 (18–56)	56 (31–81)	1.55 (0.72–2.92)
≥3	22 (11–39)	62 (37–85)	84 (56–98)	3.43 (1.58–6.76)
Family history of breast cancer				
Yes	8 (7–10)	29 (26–34)	47 (39–60)	1.24 (1.03–1.51)
No	7 (6–8)	24 (22–27)	40 (34–51)	1.00 (referent)
Menopausal status‡				
Postmenopausal	6 (5–7)	21 (18–23)	36 (29–47)	1.00 (referent)
Premenopausal	7 (6–8)	24 (22–26)	40 (34–52)	1.16 (1.10–1.22)
Estrogen use				
Current user	9 (7–11)	31 (26–36)	48 (40–61)	1.35 (1.07–1.62)
Past user	11 (8–15)	36 (26–46)	56 (41–71)	1.62 (1.12–2.29)
Never used	7 (6–8)	24 (22–26)	39 (33–50)	1.00 (referent)
Body mass index, kg/m^2§				
19.0	7 (6–8)	24 (21–27)	39 (33–50)	1.00 (referent)
23.0	7 (6–8)	25 (22–27)	41 (34–51)	1.05 (0.95–1.10)
26.0	7 (6–8)	25 (23–27)	42 (35–52)	1.09 (0.97–1.17)
28.5	7 (6–9)	26 (24–28)	43 (36–54)	1.13 (0.97–1.27)
32.0	8 (6–9)	27 (24–30)	44 (37–56)	1.24 (0.99–1.53)
Patient demographic variables				
Race				
Caucasian	7 (6–8)	25 (23–27)	42 (35–52)	1.00 (referent)
Black	8 (6–10)	27 (22–33)	44 (35–58)	1.09 (0.86–1.39)
Other	6 (4–9)	22 (13–32)	36 (22–55)	0.84 (0.50–1.34)
Unknown	7 (5–9)	25 (19–30)	41 (30–54)	0.98 (0.70–1.24)
Median household income‖				
$40 000	7 (6–8)	26 (23–28)	42 (35–53)	1.00 (referent)
$50 000	7 (6–8)	25 (23–27)	42 (36–53)	0.99 (0.97–1.02)
$60 000	7 (6–8)	25 (23–27)	42 (35–53)	0.99 (0.94–1.04)
$70 000	7 (6–8)	25 (23–27)	42 (35–53)	0.99 (0.91–1.06)
Radiologic variables				
Stated comparison with previous mammogram				
Yes	4 (3–5)	18 (16–21)	33 (26–44)	1.00 (referent)
No/unknown	8 (6–9)	32 (29–35)	54 (45–67)	1.96 (1.64–2.34)
Time since last mammogram, mo				
≤18	7 (6–8)	24 (22–27)	41 (34–52)	1.00 (referent)
>18	8 (7–10)	27 (24–31)	ND¶	1.16 (0.92–1.43)
Radiologist random effect#				
Smallest	2 (1–5)	7 (2–19)	15 (5–32)	1.00 (referent)
Average	8 (6–8)	22 (16–30)	45 (38–56)	5.31 (1.66–6.30)
Largest	22 (8–45)	54 (23–83)	86 (46–98)	10.97 (1.96–16.88)

*Risk ratio for at least one false-positive mammogram at any mammogram. The relative risks are essentially ratios of the q_{ij} values (defined in the "Subjects and Methods" section) at two levels of the risk factor and are roughly constant across j, the screening number. If the interval for a risk factor contains 1.00, the risk factor is viewed as not statistically significant.

†See "Subjects and Methods" and "Appendix" sections for calculations.

‡Menopause year data are missing for 4043 mammograms (966 women); considered to have occurred at 50 years of age.

§Body mass index = (weight in kilograms)/(height in meters)^2; data are missing for 159 mammograms (58 women).

‖Data are missing for 382 mammograms (86 women); categories are approximately the quartiles of the data.

¶ND = not determined; >18-month category does not allow calculation of cumulative risk at nine mammograms.

#Based on 36 random effects; average effect was centered at zero.

positive mammogram at her first, fifth, or ninth mammogram. Each variable, except age, was held constant for all nine mammograms. Table 2 also presents point and interval estimates for risk ratios, i.e., risk relative to the baseline group for each risk variable.

The estimated effects of patient and radiologic variables on the cumulative risk of a woman's experiencing a false-positive mammogram (Table 2) and their effects on the risk of false-positive mammograms (Table 1) are similar in both direction and statistical significance. However, Table 2 enhances the information in Table 1 by estimating the effect of each variable over multiple mammograms. For example, whereas Table 1 shows that 20.3% of the mammograms in our sample were false-positive for women who had had three or more biopsies, Table 2 shows that a woman with three or more biopsies had an estimated 84% chance of experiencing a false-positive result by her ninth mammogram. Other patient characteristics that affected the cumulative risk of a false-positive mammogram in a statistically significant manner included young age, a family history of breast cancer, being premenopausal, and estrogen use. BMI, race, and median household income did not affect the cumulative risk. Of the radiologic variables, comparison with previous mammograms and the radiologist random effects statistically significantly affected the cumulative risk of a false-positive mammogram. The dichotomous variable indicating more than 18 months between mammograms was not statistically significant.

To clarify the radiologist random effects, we calculated the probability of false-positive results for three cases by use of a model that included only random effects: a radiologist with the smallest random effect, a radiologist with the average random effect (i.e., the effect of the radiologist is expected to be zero), and a radiologist with the largest random effect. If a typical woman in our sample had nine mammographic readings by the radiologist with the smallest effect, her estimated cumulative risk of a first false-positive reading would be 2%, 7%, and 15% at her first, fifth, and ninth screening mammograms, respectively. In contrast, if this same woman had mammograms read by the radiologist with the largest random effect, her estimated cumulative risk of a first false-positive reading would be 22%, 54%, and 86%, respectively. Averaged over all patient and radiologic variables and the 36 random effects, a woman's estimated cumulative risks were 8%, 22%, and 45% for the first, fifth, and ninth screening mammograms, respectively.

Table 3 lists patient and radiologic variables that affected the cumulative risk of a woman's experiencing a false-positive mammogram when considered in a multiple-variable model. Variables entered into the model included all statistically significant variables from Table 2, as well as the time between mammograms and BMI, which were statistically significant when analyzed as continuous variables (data not shown). Although several variables affected a woman's cumulative risk of a false-positive mammogram in the multiple-variable model, only multiple breast biopsies and radiologist random effects were associated with risk ratios greater than 2. To quantify the effect of the variability in radiologists, we considered the extreme risk ratio (i.e., the ratio of the most extreme pair of random effects). Holding all other risk factors constant, the relative risk of a false-positive reading, by the radiologists in our study, at a given mammogram could be as extreme as 16.37 (95% CI = 4.73–77.8). Other variables with statistically significant risk ratios between 1.0 and 2.0 included age, family history of breast cancer, estrogen use, no comparison with previous mammograms, and time between mammograms. Menopausal status and BMI were not statistically significant risk factors.

Table 3. Estimated risk ratios associated with selected patient and radiologic variables in a multiple-variable model

Risk variable	Risk ratio* (95% confidence interval)
Patient clinical variables	
Age at first mammogram, y	
40	1.81 (1.29–2.54)
50	1.48 (1.19–1.86)
60	1.22 (1.09–1.36)
70	1.00 (referent)
No. of breast biopsies before screening mammogram	
None	1.00 (referent)
1	1.56 (1.03–2.38)
2	1.36 (0.61–2.49)
≥3	3.42 (1.55–5.92)
Family history of breast cancer	
Yes	1.24 (1.01–1.47)
No	1.00 (referent)
Menopausal status	
Postmenopausal	1.00 (referent)
Premenopausal	0.96 (0.77–1.20)
Estrogen use	
Current user	1.29 (1.02–1.59)
Past user	1.57 (1.02–2.27)
Never user	1.00 (referent)
Body mass index, kg/m^2†	
19.0	1.00 (referent)
23.0	1.05 (1.00–1.10)
26.0	1.09 (0.99–1.20)
28.5	1.14 (0.99–1.30)
32.0	1.18 (0.99–1.40)
Radiologic variables	
Stated comparison with previous mammogram	
Yes	1.00 (referent)
No/unknown	1.75 (1.44–2.07)
Time since last mammogram, y	
1	1.00 (referent)
2	1.21 (1.08–1.33)
3	1.46 (1.17–1.76)
Radiologist random effect‡	
Smallest	1.00 (referent)
Average	4.84 (1.91–19.3)
Largest	16.37 (4.73–77.8)

*Calculated relative to a woman who has all the characteristics of the referent categories.

†Body mass index = (weight in kilograms)/(height in meters)^2.

‡Average effect was centered at zero.

The point and interval estimates for the regression coefficients are given in Table 4. From these estimates, we estimated the cumulative risk of a first false-positive mammogram for women with the combination of risks producing the lowest, average, and highest chance of a false-positive mammogram over multiple screening mammograms. Fig. 1 shows how the effects of three different levels of the risk factors in Table 4 and the effect of radiologists with the three different levels of tendency for calling a mammogram abnormal (random effects) combine to affect the risk of a false-positive mammogram. Women with the combination of characteristics that predict a low risk of a false-positive mammogram are estimated to have a 0.7% (95% CI = 0.2%–1.9%) and a 4.6% (95% CI = 1.1%–12.5%) risk of experiencing a false-positive mammogram after one and nine mammograms, respectively, if their mammograms are read by a radiologist with the smallest random effect (which approximates

Table 4. Main effects coefficients under the full model*

Risk variable	Coefficient (95% confidence interval)
Patient variables	
Age in decades	−0.17 (−0.27 to −0.07)
No. of breast biopsies before screening mammogram	
None	1.00 (referent)
1	0.45 (0.04 to 0.86)
2	0.31 (−0.50 to 0.91)
⩾3	1.23 (0.45 to 1.78)
Family history of breast cancer	
Yes	0.21 (0.00 to 0.38)
No	1.00 (referent)
Estrogen use	
Current user	0.26 (0.02 to 0.47)
Past user	0.45 (0.02 to 0.83)
Never user	1.00 (referent)
Radiologic variables	
Stated comparison with previous mammogram	
Yes	1.00 (referent)
No/unknown	0.53 (0.36 to 0.72)
Years between mammograms	0.19 (0.08 to 0.28)

*The random effects for 35 radiologists (and a random effect for the other radiologists combined) were included in this model. The 36 random effect estimates are not shown here.

the radiologist with the smallest false-positive percentage). If these same women have their mammograms read by the radiologist with the highest random effect, they have a 54% (95% CI = 27%–82%) chance of experiencing a false-positive mammogram by their ninth mammogram. On the other hand, if women with the combination of risk factors producing the highest likelihood of experiencing a false-positive mammogram have their mammograms read by the radiologist with the lowest random effect, their estimated risk is 74% (95% CI = 23%–99%) after nine mammograms; this risk begins at 98.1% (95% CI = 69.3%–100%) at the first screening and rises to 100% (95% CI = 99.9%–100%) if their mammograms are read by the radiologist with the highest random effect. In fact, the estimated risk for these women reached 100% (95% CI = 98%–100%) by the fifth mammogram. Estimated cumulative risks for "average" women and a radiologist with the "average" random effect fall between these two extremes. While the radiologist random effects were included to explain variability in false-positive percentages, correlation of radiologists' false-positive percentages with their associated random effect was very high (r = .87). We can deduce that large (or small) effects are associated with high (or low) false-positive percentages.

The full model (all risk factors and the radiologist effects) gave an expected deviance of 844.1. The expected deviance for

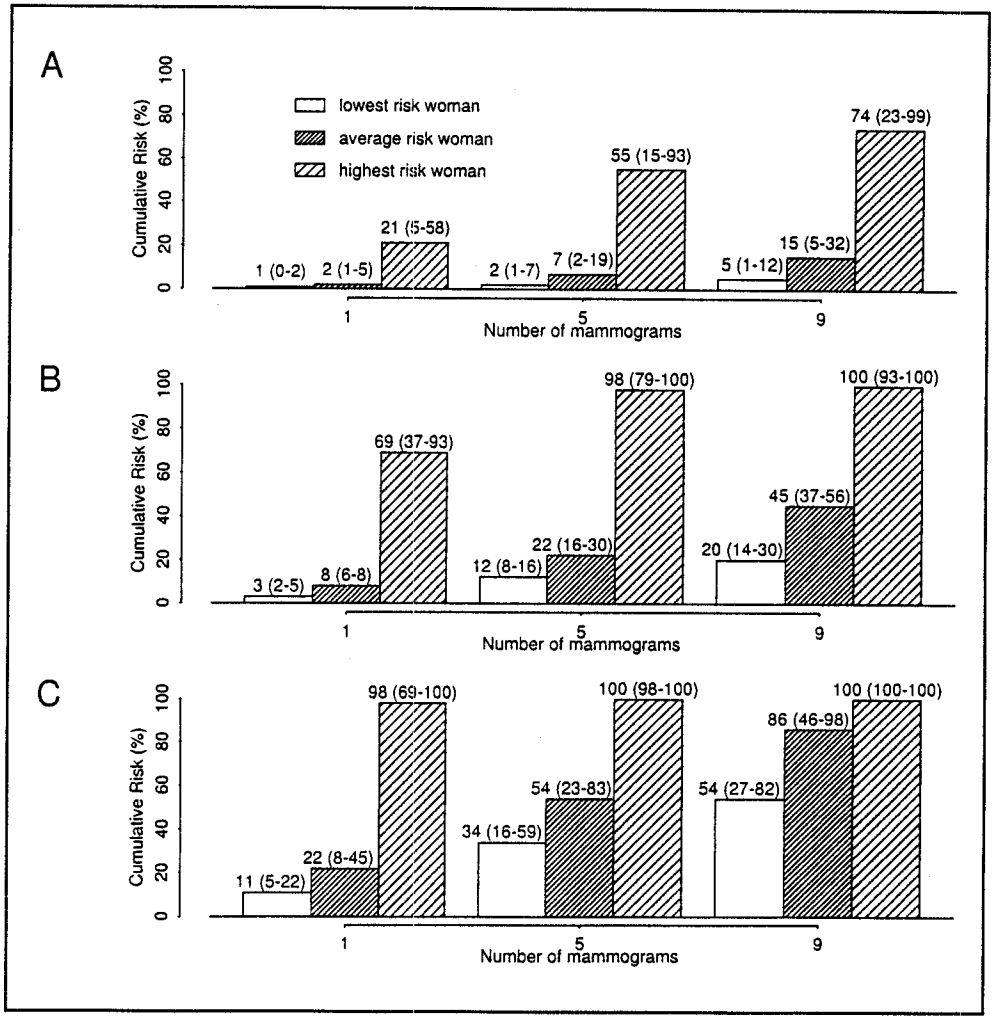

Fig. 1. Cumulative risk of a false-positive mammogram by patient risk and radiologist effect. **Bars** indicate the estimated cumulative risk for lowest-risk, average-risk, and highest-risk women when their screening mammograms are read by a radiologist with **A**) the lowest tendency for a false-positive mammogram, **B**) the average tendency, and **C**) the highest tendency. Lowest-risk variables are age 70 years at the first mammogram, body mass index (BMI, i.e., [weight in kilograms]/[height in meters]^2) of 19, no estrogen use, no breast biopsies, no family history of breast cancer, mammogram compared with previous one, and 1 year between screenings. Highest-risk variables are age 40 years at first mammogram, BMI of 32, current user of estrogen, three previous breast biopsies, family history of breast cancer, mammogram not compared with previous one, and 3 years between screenings. The average-risk woman has all characteristics at sample averages or proportions. **Numbers in parentheses** are 95% confidence intervals for the estimated risks.

the reduced model (all risk factors in the model except the radiologist effects) was 907.0. The difference in deviance (62.9) shows a reduction of roughly 7% when the radiologist effects are included. For binary response data, a reduction in deviance is analogous to an increase in R^2 for normally distributed response data.

Discussion

We found that four patient variables and three radiologic variables independently affected the risk of a false-positive mammogram over repeated screening mammograms. The patient variables were young age, an increasing number of previous breast biopsies, a family history of breast cancer, and current use of estrogen. The radiologic variables were a greater tendency of the radiologist to read a mammogram as abnormal, not comparing the mammogram with previous mammographic results, and a longer time period between previous and current mammograms. Most factors increased the likelihood of a woman's having a false-positive mammogram only modestly; except for the effect of the radiologist and the number of previous breast biopsies, the risk ratios for the independent effects of the other risk factors were under 2.0. However, because mammograms are obtained repeatedly and because the overall risk of a false-positive mammogram increases with multiple screening mammograms, even modest risk ratios substantially increased the cumulative risk of a woman's experiencing at least one false-positive mammogram. Taking into account all statistically significant risk factors, we estimate that the cumulative risk of experiencing a false-positive mammogram over nine screening mammograms can be as low as 5% for women with characteristics that make them at low risk or as high as 100% for women with multiple high-risk factors, even if the mammograms were read by a radiologist with an average tendency toward false-positive readings.

By using a Bayesian discrete hazard model with covariates and random effects, we were able to study women with varying and changing mammographic histories (such as number and timing of mammographic screenings), changing clinical characteristics (such as age and experience of breast biopsies), and varying radiologic factors (such as which radiologist read the mammogram and whether there was a comparison with previous mammograms). Our model demonstrates how risks for a false-positive mammogram vary over time in women with different sets of risk factors.

We found that the radiologist's random effect (tendency for reading a mammogram as abnormal) had the largest estimated effect on a woman's risk of experiencing a false-positive mammogram. The interpretation of this result requires understanding of random effects and the limitations of this dataset. First, the range of random effects depends on the number of radiologists studied. Our estimated risk ratios for the radiologist effects, therefore, are dependent on the number of radiologists in our sample. Second, random effects are used when there is interest in subjects outside those in a particular dataset. Generally, they are not interpreted as fixed effects. However, for the purposes of our analyses and for clarity of reporting, the radiologist effects in Table 2 are being interpreted as though they were fixed effects. Third, although 93 radiologists read the 9747 mammograms of the women in our sample, only 35 of them had 25 or more readings in the sample. We found wide variability in their false-positive percentages, from a low of 2.6% to a high of 24.4%. The implication of this wide range is that an effective model for the cumulative false-positive reading must include random radiologist effects to capture this variability. Our full model incorporates such effects.

The clinical history of multiple previous breast biopsies was the strongest patient predictor of a false-positive mammogram in our study. After we accounted for all other risk factors, the risk ratio for a history of three or more breast biopsies was 3.42 (95% CI = 1.55–5.92). Brenner and Pfaff *(7)* found mammographic changes in 50% of 293 women who had undergone excisional breast biopsies. The changes remained stable for 5 years. In contrast, Slanetz et al. *(14)* found that only 5% of 173 patients with previous excisional breast biopsies were recalled for additional imaging after screening mammograms, the same proportion as in women without a history of breast biopsy. In the latter study, the radiologists were aware of the biopsy history. In our study, with results more like those of Brenner and Pffaf *(7)*, radiologists did not necessarily know the patient's history, and our definition of biopsy included fine-needle aspiration and excisional breast biopsies.

We found that current use and past use of estrogen were associated with increased risk of a false-positive mammogram after adjusting for other variables. Laya et al. *(5)* found an adjusted risk ratio of 1.33 (95% CI = 1.15–1.54) for false-positive mammogram readings among current estrogen users (compared with our risk ratio of 1.29 [95% CI = 1.02–1.59] for current users) but no increased false-positive percentages among former estrogen users (compared with our risk ratio of 1.57 [95% CI = 1.02–2.27] for former users). We used medical records, not pharmacy records, to determine estrogen use, and it is possible that some of the women in our study continued the medication without notation in the record.

Most of our other results are consistent with findings of previous studies that investigated individual risk factors. For example, we found that younger age *(2–4)* and no comparison with previous mammograms *(9,10,15)* are associated with higher false-positive risks. However, in contrast to Kerlikowske et al. *(2)*, who found that the positive predictive value of abnormal mammographic readings was higher in women with first-degree relatives who had breast cancer than in women without a family history of breast cancer, we found that a family history of breast cancer was associated with a slightly increased risk of a false-positive mammogram. Elmore et al. *(16)* obtained results that were more consistent with our results; they found that, when radiologists knew of a family history of breast cancer, the number of diagnostic work-ups that they recommended for patients without cancer was increased.

Age and estrogen use change the mammographic appearance of the breast; the effects of family history of breast cancer and previous breast biopsies on mammographic appearance are less clear. It is possible, therefore, that some characteristics emerged as risk factors because of radiologists' reactions to the clinical information rather than to changes in mammographic appearance. Since no standard data-collection form was used in the multiple community radiology practices that did screening mammography in our retrospective study, we do not know the extent to which the radiologists were aware of the clinical information that predicted false-positive mammograms.

We found that some risk factors for false-positive mammograms are the same as those associated with risk of breast cancer. For example, a history of previous breast biopsies increases both

the risk of false-positive mammograms and the risk of future breast cancer *(17)*. The same is true for a family history of breast cancer *(18,19)* and estrogen use *(20–22)*. On the other hand, increasing age increases a woman's risk of breast cancer but decreases her risk of a false-positive mammogram.

Some of the risk factors for false-positive mammograms, such as age, previous breast biopsies, and family history of breast cancer, cannot be changed. However, all three radiologic variables can be modified. Community radiologists' percentages of false-positive readings have been shown to vary. Brown et al. *(8)*, in their national study of radiology facilities, found the overall average of practices' self-reported call-back rates was 11% (95% CI = 9%–13%) but varied from 3% to 57%; the average false-positive percentage was 10.7%. A report of the Agency for Health Care Policy and Research *(23)* suggests that fewer than 10% of screening mammograms should result in recommendations for further evaluation. Swedish mammographers' call-back rates were 2%–5% for any follow-up investigation and less than 1% for breast biopsy *(24)*. In The Netherlands, the referral rate for breast biopsy was 1%–1.3% *(25)*. Whether such low call-back rates (and, therefore, also false-positive rates) in other countries are at the expense of missing early breast cancers (false-negative mammograms) is not known and is an important issue if false-negative mammograms increase the mortality or morbidity from breast cancer.

Our retrospective study has a number of limitations. Most important, we do not know how well the model would work in a different setting with different women and different radiologists. The radiologists in our study had a lower average false-positive percentage (6.5%) than that of the national study by Brown et al. *(8)*. Our model was constructed with information gathered over a 10-year period, not necessarily from the time each woman began getting mammograms. If information were collected for these women starting with their first mammogram, the results of the study might be different. Our findings, therefore, should be validated in a separate study.

In our study, the number of women with more than five mammograms was relatively small, and the estimates of the cumulative risk of the first false-positive mammogram beyond five mammograms have wide CIs. We also did not know when in their menstrual cycles mammograms were performed for premenstrual women; time in the menstrual cycle has been shown to be associated with breast density *(26)* and mammographic accuracy *(27)*. Finally, we had no information on mammographic breast density, which has been shown to affect mammographic accuracy *(28)*.

Several studies *(29–33)* have found adverse effects, such as anxiety, distress, and intrusive thoughts, among women who have experienced false-positive mammographic readings. If our findings are replicated, it would be possible to develop a prediction equation that could be used to estimate the risk to an individual woman of a false-positive mammogram over multiple screening mammograms. This equation could be used alongside predictive models for the risk of developing breast cancer, such as that developed by Gail et al. *(34)* and recently modified by the National Cancer Institute, Bethesda, MD, for use in its Breast Cancer Risk Assessment Tool for Health Care Providers *(17)*, to help individual women better understand the competing risks they face from breast cancer and false-positive mammograms. Predicting the risk of false-positive mammograms may be an important way to educate women about screening and to deal with the occurrence of abnormal mammograms. If women understand their risks of false-positive mammograms, they might be less anxious when an abnormality is found. This important possibility needs investigation.

APPENDIX

The Statistical Model

Similar to the familiar Kaplan–Meier *(35)* estimator in survival analysis, we obtain a product estimator for the cumulative risk of a false-positive mammogram. In particular, if p_{ik} denotes the probability of at least one false-positive for the i^{th} female within her first k mammograms, then $1 - p_{ik} = Pr$ (no false-positive in first k mammograms) $= Pr$ (no false-positive on first) $\bullet$ Pr (no false-positive on second given no false-positive on first) $\bullet\bullet\bullet$ Pr (no false-positive on k^{th} given no false-positive on the first $k - 1$)

$$\equiv \prod_{j=1}^{k} (1 - q_{ij}),$$

where $q_{ij} = Pr$ (false-positive at j^{th} mammogram given no false-positive in the previous $j - 1$). Hence, we obtain equation 1 in the text

$$p_{ik} \equiv 1 - \prod_{j=1}^{k} (1 - q_{ij}(X_{ij})). \quad [1]$$

Next, q_{ij} is a function of the vector of levels of the mammogram, X_{ij}. (In the univariate analysis of Table 2, X_{ij} is a scalar. In the multivariate analysis of Table 3, X_{ij} is a vector whose components are the variables in that table.) In particular, we propose

$$1 - q_{ij} = (1 - q_j)^{\exp(X_{ij}^T \beta)}. \quad [2]$$

In equation 2, $1 - q_j$ is interpreted as the probability of no false-positive at the j^{th} mammogram given no false-positive for the previous $j - 1$ mammograms, ignoring the risk factors. (This is equivalent to setting $\beta = 0$ in equation 2.) Alternatively, $h_j = -\log(1 - q_j)$ can be interpreted as the discrete hazard before the j^{th} mammogram, again ignoring risk factors, whence

$$h_{ij} \equiv -\log(1 - q_{ij}) = h_j \exp(X_{ij}^T \beta), \quad [3]$$

which is the standard proportional hazards equation *(36)*.

Estimation

In fitting a model to the data based on equation 2, it is convenient to work with the approximate likelihood function L of the unknown parameters h and β given the data,

$$L(h;\beta;data) = \prod_{j=1}^{K} h_j^{r_j - s_j} \exp\left(-\sum_{j=1}^{K} h_j A_j(\beta)\right) \prod_{s} \exp(X_{ik_i}^T \beta), \quad [4]$$

where K denotes the maximum number of screening mammograms for any woman in the study, k_i denotes, for the i^{th} woman, the number of screening mammograms until the first false-positive mammogram (or number of screening mammograms until the end of the study), s denotes the set of women with a first false-positive mammogram before the end of the study, r_j denotes the number of women with at least j screening mammograms and no false-positive mammogram within the first $j - 1$, s_j denotes the number with at least j screening mammograms and no false-positive mammogram within the first j, and

$$A_j(\beta) = \sum_{\{i:k_i \geq j\}} \exp(X_{ij}^T \beta).$$

The quantities in the parentheses on the left of the equation indicate that the likelihood function is a function of these three things.

The likelihood function in equation 4 is combined with weak prior information on h and β to obtain a Bayesian model where these parameters can be estimated with the use of Markov Chain Monte Carlo simulation methods *(13)*. The result is a distribution for each h_j and each component of β that enables point and interval estimates for these parameters—the discrete hazards h_j and the regression coefficients β (reported in Table 4). The q_{ij} (the probability of a false-positive at the j^{th} mammogram for the i^{th} woman given no false-positive in the previous mammograms) and p_{ik} (cumulative risks reported in Tables 2 and 3) are functions of h and β. Therefore, distributions for q_{ij} and p_{ik} can be determined from the distributions of h and β. Having these distributions also provides prediction of risks for new individuals; the only change is that new (possibly unobserved) vectors of levels of the risk factors are used in equation 2 and, hence, in equation 1.

Risk Ratios

Given two vectors of risk factor levels X_0 and X_1, the risk ratio at the j^{th} mammogram is defined as $q_j(X_1)/q_j(X_0)$. Because false-positive mammograms occur infrequently, $h_j(X_1) = -\log(1 - q_j[X_1) \approx q_j(X_1)$ and similarly $h_j(X_0) \approx q_j(X_0)$. Thus

$$q_j(X_1)/q_j(X_0) \approx \frac{h_j(X_1)}{h_j(X_0)} = \exp((X_1 - X_0)^T\beta)$$

so the risk ratio is roughly constant across j. The distributions for the risk ratios are determined from the distributions of h and β. In the univariate analysis of Table 2, X_0 is a baseline level against which X_1 is compared. In the extreme analysis, X_1 is the vector of highest risk levels, and X_0 is the vector of lowest risk levels. In the random-effects analysis, the term β includes regression coefficients for the independent variables and 36 random effects, one for each of the 35 radiologists who read at least 25 mammograms and one as a catch-all for the others. Effects of radiologists can be compared by use of risk ratios, with all other risk factors (the independent variables) held constant at a common level. For example, if the effect for radiologist 1 is denoted by θ_1 and the effect for radiologist 2 is denoted by θ_2, the risk of a false-positive mammogram for a woman whose mammogram is read by radiologist 1 relative to her risk if it is read by radiologist 2 is $\exp(\theta_1 - \theta_2)$.

Comparison of the full model (including radiologist random effects) with the reduced model (deleting these effects) uses estimates of the deviance $-2 \log L$ for each model, where L is calculated from equation 4. This method is comparable to the log-likelihood ratio statistic for testing an alternative hypothesis against the null.

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NOTES

[1]Numbers of screening and false-positive mammograms are slightly different from those in a previous publication *(1)* because small computing and data errors were discovered during the analyses for this study.

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