Factors Contributing to Mammography Failure in Women Aged 40–49 Years

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Background: **Younger women (40–49 years) have lower mammographic sensitivity (i.e., greater proportion of cancers detected after a negative mammogram) than older women (≥50 years). We explored the effect of tumor growth rate, breast density, mammographic image quality, and breast cancer risk factors on mammographic sensitivity in younger and older women.** ***Methods:*** **We studied 576 women (n = 73 aged 40–49 years and n = 503 aged 50 years or older) who were diagnosed with invasive breast cancer between 1988 and 1993. Interval cancers were defined as those diagnosed within 12 or 24 months after a negative screening mammogram and before a subsequent mammogram. Tumor growth rate was assessed by mitotic figure count and Ki-67 positivity. The main outcome measures were percentage of women with interval cancer (1 – mammographic sensitivity) by age, odds ratio (OR) of interval cancer by age, and excess odds (i.e., the percentage of the odds ratio for age that was explained by individual covariates).** ***Results:*** **Interval cancers occurred in 27.7% of younger women and 13.9% of older women within 12 months (OR = 2.36, 95% confidence interval [CI] = 1.14 to 4.77) and in 52.1% of younger women and 24.7% of older women within 24 months (OR = 3.58, 95% CI = 2.15 to 5.97). Greater breast density explained 67.6% of the decreased mammographic sensitivity in younger women at 12 months, whereas rapid tumor growth explained 30.6% and breast density explained 37.6% of the decreased sensitivity in younger women at 24 months.** ***Conclusions:*** **Breast density largely explained decreased mammographic sensitivity at 12 months, whereas rapid tumor growth contributed to decreased mammographic sensitivity at 24 months. A 12-month versus a 24-month mammography screening interval may therefore reduce the adverse impact of faster growing tumors on mammographic sensitivity in younger women. [J Natl Cancer Inst 2004;96:1432–40]**

Mammography is the only available screening method proven to reduce breast cancer mortality, but it is imperfect. For example, mammography is less sensitive and results in less reduction of mortality in younger women (aged 40–49 years) than in older women (aged 50 years or older) *(1–6).* The lower reduction in mortality from mammography screening in younger women has led to considerable controversy over whether screening is effective in younger women *(2,7,8).*

Several factors may explain why younger women have lower mammographic sensitivity or, equivalently, higher rates of interval cancer (cancers detected clinically after a negative mammographic screen); one factor is breast density. It is well established that younger women have greater mammographic breast density than older women *(4,9,10)* and that greater breast density increases the risk that a cancer will be obscured on a mammogram *(11–14).* Breast density is also likely to influence mammographic quality. We previously reported that mammographic quality, particularly positioning of the breast during the mammogram, is associated with whether a tumor was missed at screening *(15).* However, we did not examine whether there were differences in mammographic quality by age after accounting for differences in breast density.

A second factor that may explain the higher rates of interval cancer in younger women is the rate of tumor growth. Several studies have shown that breast tumors in younger women grow faster than those in older women, and this difference results in greater rates of new cases arising in the interval after screening in younger women *(16–18).* This phenomenon is supported by the results of studies that have shown shorter preclinical screen-detectable times (time between the tumor arising and its detectability by mammography) for younger women than for older women *(19,20).*

A third factor is that younger women may have different distributions of other breast cancer risk factors than older women, including family history of breast cancer, prevalence and duration of hormone therapy use, body mass index, and menopausal status and other reproductive factors. Tumor characteristics, menopausal status, reproductive factors, body mass index, and family history have all been studied as predictors of the occurrence of interval cancer, with mixed results *(1,12,13).* Therefore, the extent to which these known breast cancer risk factors explain why younger women do not benefit as much as older women from screening mammography is unclear.

We undertook this analysis to explore factors that explain the lower sensitivity of mammography in younger women (aged 40–49 years). We evaluated the relative contribution of breast density, tumor growth properties, mammographic image quality, and breast cancer risk factors in explaining the excess odds of younger women being diagnosed with interval cancer. To our knowledge, this is the first study to measure all of these explanatory factors in the same sample of women to investigate the relative contributions of these factors to the decreased sensitivity of mammography in younger women. Understanding why

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younger women have lower mammographic sensitivity than older women could suggest ways to improve mammography for younger women or guide the development of other technologies for breast cancer screening among these women.

Subjects and Methods

Study Population

We conducted our study in a cohort of women diagnosed with invasive breast cancer because of symptoms or by clinical breast examination within 12 or 24 months after a negative screening mammogram (interval cancers) or following a positive screening mammogram (screen-detected cancers). We have previously examined breast density *(14),* mammographic quality markers *(15),* and tumor characteristics *(16)* in relation to risk of having an interval cancer in the same population of women. The specifics of the study population have been described in detail previously *(14–16).* Briefly, study subjects were women aged 40 years or older who were enrolled in Group Health Cooperative (GHC), a health maintenance organization with more than 400 000 members in western Washington State.

GHC has a population-based Breast Cancer Screening Program (BCSP) that women are invited to join when they turn 40 years old or when they join GHC *(21,22).* Women participating in the BCSP complete breast cancer risk factor questionnaires at program enrollment, and this information is updated at the time of each mammogram *(21,22).* Women enrolled in BCSP are sent recruitment and reminder letters when they are due for a mammogram. Between 1988 and 1993, women were issued an invitation for mammography as follows: annual mammography if they had previous breast cancer, atypical hyperplasia, or at least two first-degree relatives with breast cancer; biennial mammography if they had one first-degree relative with breast cancer or were 50 years old or older and had two or more minor risk factors (e.g., menarche before age 10, second-degree family history of breast cancer, previous negative breast biopsy); and mammography every 3 years if they were aged 40–49 years and had one or more minor breast cancer risk factors or were 50 years old or older and had no more than one minor risk factor *(21).* Women aged 40–49 years who did not have any minor risk factors were not invited for screening. However, all women enrolled in GHC are able to override the recommended interval and can have annual mammography if they wish.

To be eligible for this study, women had to be aged 40 years or older; to have had at least one BCSP screening mammogram between January 1, 1988, and December 31, 1993; to have been diagnosed with a first primary invasive breast cancer within 24 months after their index mammogram (i.e., the last screening mammogram before cancer diagnosis) but before any subsequent screening mammogram; to have no breast implants; and to have been enrolled continuously in GHC for at least 24 months following the index mammogram (unless they died in the interval). We linked women from GHC to the Seattle–Puget Sound Surveillance, Epidemiology, and End Results[1] cancer registry and identified 578 eligible women who were diagnosed with invasive breast cancer during the study period. One woman was subsequently excluded at her request and another woman was excluded because she was symptomatic at the time of her screening mammogram, leaving a total sample size of 576 *(14,16).* This study was reviewed and a waiver of consent was approved by the Institutional Review Boards at GHC and the Fred Hutchinson Cancer Research Center.

Interval and Screen-Detected Cancers

We recorded final mammographic evaluations according to the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) guidelines *(23).* For the main analyses we followed women for up to 24 months after their index screening mammogram for a diagnosis of breast cancer. Interval cancers were defined as cancers in women who had received a BI-RADS score of 1 or 2 (negative or benign finding) in the same breast as the final cancer diagnosis (n = 162). Screen-detected cancers were defined as cancers in women who had received a BI-RADS score of 3, 4, or 5 (probably benign finding—short interval follow-up suggested, suspicious abnormality—biopsy should be considered, or highly suggestive of malignancy—appropriate action should be taken) in the same breast as the final cancer diagnosis (n = 414, of whom 44 had a BI-RADS score of 3). In the total sample of 576 women, 73 cancers (38 interval and 35 screen-detected) were in women aged 40–49 years at the time of their index mammogram.

We also conducted separate analyses using 12 months of follow-up for cancer detection. We performed both the 12- and 24-month analyses to be consistent with the current U.S. Preventive Services Task Force's current guidelines and recommendations for breast cancer screening *(24).* When we conducted the 12-month analyses, we excluded all cancers detected between 12 and 24 months. That exclusion left 71 interval cancers and 393 screen-detected cancers, of which 13 interval and 34 screen-detected cancers were in younger women and 58 interval and 359 screen-detected cancers were in older women.

Breast Density

The expert radiologist who read all the index mammograms to measure breast density was blinded to age, year of mammogram, interval or screen-detected status, and cancer laterality. BI-RADS mammographic density categories were assigned in the contralateral breast *(23).* The mammographic density ratings were categorized into four groups: 1) almost entirely fat, 2) scattered fibroglandular tissue, 3) heterogeneously dense, and 4) extremely dense.

Mammographic Quality Variables

An expert mammography reader, who was a board-certified Mammography Quality Standards Act–qualifying physician, reviewed mammographic image quality. The reader was blinded to age, year of mammogram, interval or screen-detected status, and cancer laterality *(15).* Image quality was read on two mediolateral and two craniocaudal views; the worst quality rating of the four views was used. We used a grading scale that was developed specifically for this study to rate breast position, exposure, noise, contrast, compression, sharpness, artifact, and overall quality; details of the definitions have been reported elsewhere *(15,25).* The overall quality reading was a subjective rating delivered after reading the seven other categories. Each quality variable was rated on a five-point ordinal scale (from 1 [excellent] to 5 [poor]), which we categorized into pass (1 and 2), borderline (3), and fail (4 and 5). We further collapsed compression and exposure into pass (1 and 2) versus borderline

or fail (3, 4, and 5) because these variables did not have sufficient distribution in the failure category.

Tumor Markers

We collected paraffin-embedded primary breast tumor tissue samples that had been obtained before any adjuvant treatment was given *(16)*. Samples were examined microscopically for tumor characteristics and diagnosis and were evaluated by immunocytochemistry for expression of selected proteins by the study pathologist, who was blinded to interval cancer status and other clinical variables.

Mitotic cell counts were generated by using a standard method —the Nottingham modification of the Scarff–Bloom–Richardson grading scheme *(26)*. We assessed individual scores for mitotic figure count from histology slide review of 10 high-power fields; we classified less than 10 mitotic figures per 10 fields as low, 11–19 as intermediate, and more than 19 as high *(16,27,28)*. We carried out immunoperoxidase assays for Ki-67 proliferation-related antigen using MIB1 (DakoCytomation, Carpenteria, CA) on sections from a single tumor block for each subject. Results for Ki-67 staining were obtained by counting the positive tumor nuclei and the negative tumor nuclei in four high-power fields in tumor cells and averaging the counts over these fields *(16,27,28);* the Ki-67 index is the ratio of positive cells divided by the total number of nuclei averaged over four high-power fields. The range of tumor cell numbers in four fields for this study was 270–3650, and the median number of tumor cells assessed for Ki-67 staining over four fields was 1200 *(28)*.

Demographic and Breast Cancer Risk Factor Variables

We collected self-reported information on menopausal status, hormone therapy use, height, weight, and family history of breast cancer from the BCSP mammography questionnaire. Body mass index was calculated as weight (in kilograms) divided by height (in meters squared) and was categorized as underweight ($<$20), normal (20–24.9), overweight (25–29.9) and obese ($\geq$30) according to Bray *(29)*. We categorized women as premenopausal (n = 50), perimenopausal (n = 24), or postmenopausal (n = 495) on the basis of survey data and review of medical records. Results of the main analyses were similar for peri- and postmenopausal women (data not shown), so we analyzed these groups together.

We used GHC automated utilization data to compute the number of months between screening mammograms; this interval was based on the length of time between the last screening mammogram before diagnosis (i.e., the index mammogram) and the screening mammogram directly preceding the index mammogram. Screening intervals were characterized as being between 0 and 36 months (n = 191), as being greater than 36 months (n = 130), and as no previous mammogram if the index mammogram was a woman's first mammogram (n = 255), based on GHC's screening guidelines during the study period *(21)*.

Statistical Methods

All statistical tests were two-sided and used an alpha of .05. We used chi-square tests to evaluate differences in characteristics between younger and older women. We evaluated the sensitivity of mammography and interval cancer rate (i.e., 1 – mammographic sensitivity) by breast cancer risk factors, breast density, mammographic image quality variables, and tumor characteristics and used chi-square tests to evaluate the association of these characteristics with interval cancer versus screen-detected cancer. Mammographic sensitivity is equivalent to the proportion of women whose tumors were diagnosed within 24 months after a positive screening mammogram. We also report the proportion of women diagnosed with interval cancer by age group for selected factors under study.

We used unconditional logistic regression to calculate the odds ratio (OR) of interval cancer and the corresponding 95% confidence intervals (CIs), adjusted for screening interval, for younger (aged 40–49 years) versus older (aged 50 years or older) women. We added each explanatory factor to the model separately and reported the resulting odds ratio for interval cancer for younger versus older women. The odds ratio was calculated after controlling for the effect of individual explanatory factors to understand what explained the higher odds of interval cancer among younger women compared with older women. The percent excess odds was calculated as follows: (OR for age adjusted for screening interval – OR for age adjusted for screening interval + explanatory factor)/(OR for age adjusted for screening interval – 1) *(30)*. Percent excess odds measures the percent of the excess odds ratio (OR – 1) for younger versus older women having an interval cancer that can be explained by each factor. We systematically included in our multivariable model any factor that explained at least +10.0% of the excess odds for young women. The methods used to calculate excess odds for each explanatory factor ignore variables that are collinear (e.g., overall mammography quality and mammographic breast density). As a result, two factors that are correlated could individually account for a similar percentage of excess risk but, when examined in combination, explain less than their sum.

Results

Characteristics of the Study Population

The younger women in the study were more likely than the older women to be premenopausal; to have never used hormone therapy; to have had no previous mammogram; to have faster growing tumors, as measured by mitotic count and Ki-67-positive cells; and to have dense breasts on mammography (Table 1). Younger women also had more first-degree relatives with breast cancer than older women, because the BCSP brings women at high risk for breast cancer in for mammography screening at an earlier age. Younger women were also less likely to have passing mammogram quality scores for compression and noise.

Younger women were more likely to have interval cancers detected within 24 months of a negative screen (52.1%) than older women (24.7%). When we used a 12-month follow-up, the interval cancer rates were 27.7% for younger women and 13.9% for older women (data not shown). Among women of all ages, factors strongly associated with interval cancers included being premenopausal, being current or never users of hormone therapy, having a high mitotic figure count, having high Ki-67 positivity, and having dense breast tissue (Table 2). Mammographic noise and positioning were the mammography image quality factors that were most strongly associated with interval cancers. The same factors were associated with interval cancer

Table 1. Distribution of breast cancer risk factor and tumor characteristics, screening history, and mammographic image quality by age at screening mammogram

Characteristic	Age at screening: 40–49 years, No. (%) (N = 73)	Age at screening: ≥50 years, No. (%) (N = 503)	*P* value*
Breast cancer risk factors			
Menopausal status			<.001
Premenopausal	45 (68.2)	5 (1.0)	
Peri- or postmenopausal	21 (31.8)	498 (99.0)	
Missing information	7		
Body mass index (kg/m^2)			.172
Underweight (<20.0)	6 (8.2)	27 (5.4)	
Normal (20.0–24.9)	39 (53.4)	217 (43.1)	
Overweight (25.0–29.9)	15 (20.5)	156 (31.0)	
Obese (≥30.0)	13 (17.8)	103 (20.5)	
Family history of breast cancer†			<.001
No	29 (39.7)	335 (66.6)	
Yes	44 (60.3)	168 (33.4)	
Hormone therapy use			<.001
Current	8 (11.0)	140 (27.8)	
Former	6 (8.2)	171 (34.0)	
Never	59 (80.8)	192 (38.2)	
Time since last screening mammogram, mo			.091
0–36	19 (26.0)	172 (34.2)	
≥37	13 (17.8)	117 (23.3)	
No previous mammogram	41 (56.2)	214 (42.5)	
Tumor markers			
Tumor histology			.175
Invasive ductal	55 (87.3)	344 (79.6)	
Invasive lobular	0 (0.0)	41 (9.5)	
Tubular	5 (7.9)	23 (5.3)	
Mucinous	1 (1.6)	13 (3.0)	
Medullary	1 (1.6)	4 (0.9)	
Other	1 (1.6)	7 (1.6)	
Missing	10	71	
Mitotic figure count‡			<.001
Low	26 (41.9)	290 (67.3)	
Intermediate	16 (25.8)	84 (19.5)	
High	20 (32.3)	57 (13.2)	
Missing	11	72	
Average Ki-67 index, %§			<.001
<25	12 (19.0)	134 (31.8)	
26–50	9 (14.3)	100 (23.7)	
51–75	13 (20.6)	99 (23.5)	
>75	29 (46.0)	89 (21.1)	
Missing	10	81	
Mammographic breast density			<.001
Entirely fat	3 (4.3)	122 (25.4)	
Scattered fibroglandular	28 (40.0)	222 (46.3)	
Heterogeneously dense	29 (41.4)	122 (25.4)	
Extremely dense	10 (14.3)	14 (2.9)	
Missing	3	23	
Mammographic image quality scores			
Position			.412
Pass	11 (15.7)	68 (14.1)	
Borderline	39 (55.7)	237 (49.2)	
Fail	20 (28.6)	177 (36.7)	
Missing	3	21	
Compression			.025
Pass	45 (64.3)	369 (76.7)	
Borderline/fail	25 (35.7)	112 (23.3)	
Missing	3	22	
Exposure			.214
Pass	54 (77.1)	401 (83.2)	
Borderline/fail	16 (22.9)	81 (16.8)	
Missing	3	21	
Noise			.005
Pass	39 (55.7)	358 (74.3)	
Borderline	23 (32.9)	97 (20.1)	
Fail	8 (11.4)	27 (5.6)	
Missing	3	21	
Overall quality			.902
Pass	6 (8.6)	42 (8.7)	
Borderline	30 (42.9)	193 (40.0)	
Fail	34 (48.6)	247 (51.2)	
Missing	3	21	

*Two-sided chi-square test for difference in the characteristics between younger women (aged 40–49 years) and older women (aged 50 years or older).

†Defined as breast cancer in a first- or second-degree blood relative.

‡Mitotic figure count: <10 per 10 high-power fields = low; 11–19 per 10 high-power fields = intermediate; >19 per 10 high-power fields = high.

§Ki-67 index = the percent of positive tumor nuclei (number of positive tumor nuclei divided by the total number of nuclei) averaged over four high-power fields.

Table 2. Association of breast cancer risk factors, screening history, tumor characteristics, and mammographic image quality with screen-detected and interval breast cancers diagnosed within 24 months of the index mammogram*

Characteristic†	No. of subjects	Screen-detected (sensitivity)	Interval (1–sensitivity)	*P* value‡
Breast cancer risk factors				
Age at screening mammogram, y				<.001
40–49	73	47.9	52.1	
≥50	503	75.3	24.7	
Menopausal status				<.001
Premenopausal	50	36.0	64.0	
Peri- or postmenopausal	519	75.3	24.7	
Body mass index (kg/m^2)				.130
Underweight (<20.0)	33	63.6	36.4	
Normal (20.0–24.9)	256	68.8	31.3	
Overweight (25.0–29.9)	171	73.1	26.9	
Obese (≥30.0)	116	79.3	20.7	
Family history of breast cancer§				.156
No	364	73.9	26.1	
Yes	212	68.4	31.6	
Hormone therapy use				.008
Current	148	64.2	35.8	
Former	177	79.7	20.3	
Never	251	70.9	29.1	
Time since last screening mammogram, mo				.180
0–36	191	68.1	31.9	
≥37	130	70.0	30.0	
No previous mammogram	255	75.7	24.3	
Tumor markers				
Tumor histology				.001
Invasive ductal	399	70.7	29.3	
Invasive lobular	41	58.5	41.5	
Tubular	28	96.4	3.6	
Mucinous	14	35.7	64.3	
Medullary	5	60.0	40.0	
Other	8	50.0	50.0	
Mitotic figure count‖				<.001
Low	316	75.9	24.1	
Intermediate	100	67.0	33.0	
High	77	48.1	51.9	
Average Ki-67 index, %¶				<.001
<25	146	84.2	15.8	
26–50	109	67.9	32.1	
51–75	112	67.0	33.0	
>75	118	53.4	46.6	
Mammographic breast density				<.001
Entirely fat	125	80.0	20.0	
Scattered fibroglandular	250	80.4	19.6	
Heterogeneously dense	151	58.3	41.7	
Extremely dense	24	29.2	70.8	
Mammography image quality scores				
Position				.012
Pass	79	83.5	16.5	
Borderline	276	72.8	27.2	
Fail	197	66.0	34.0	
Compression				.448
Pass	414	72.7	27.3	
Borderline/fail	137	69.3	30.7	
Exposure				.400
Pass	455	70.1	29.9	
Borderline/fail	97	80.4	19.6	
Noise				.004
Pass	397	74.6	25.4	
Borderline	120	70.0	30.0	
Fail	35	48.6	51.4	
Overall quality				.042
Pass	48	79.2	20.8	
Borderline	223	76.2	23.8	
Fail	281	67.3	32.7	

*Screen-detected cancers include those in women whose index mammogram had a Breast Imaging Reporting and Data System (BI-RADS) score of 3, 4, or 5. Interval cancers include those in women whose index mammogram had a BI-RADS score of 1 or 2.

†Data were missing on seven women for menopausal status, on 81 for histology, on 83 for mitotic figure count, on 91 for Ki-67 index, on 26 for breast density, on 24 for position, on 25 for compression, on 24 for exposure, on 24 for noise, and on 24 for quality.

‡*P* values from two-sided chi-square test for difference in the characteristics of interval versus screen-detected cancers.

§Defined as breast cancer in a first- or second-degree blood relative.

‖Mitotic figure count: <10 per 10 high-power fields = low; 11–19 per 10 high-power fields = intermediate; >19 per 10 high-power fields = high.

¶Ki-67 index = the percent of positive tumor nuclei (number of positive tumor nuclei divided by the total number of nuclei) averaged over four high-power fields.

risk among younger and older women when the women were considered separately (Table 3; some data not shown).

Factors That Explain the Excess Odds of a Missed Cancer for Younger Women

Younger women were statistically significantly more likely than older women to have an interval cancer diagnosed within 12 months following a screening mammogram (OR = 2.36, 95% CI = 1.14 to 4.77) (Table 4). When histology was included in the model (invasive ductal versus other), the odds ratio increased (OR = 2.78), leading to a negative percent excess odds explained by histology (data not shown). This finding means that histology is not an explanatory factor for the increased interval cancer risk for younger women; indeed, it suggests that younger women would have an even higher interval cancer rate if they had a higher proportion of non-ductal invasive histology. In univariate analyses, breast density explained 67.6% of the total excess odds of having an interval cancer diagnosed within 12 months of a negative screening mammogram. Each of the mammographic quality variables explained more than 10.0% of the excess odds for cancers diagnosed within 12 months, with noise explaining the most (35.3%). However, when breast density was combined with all of the mammographic quality variables in a multivariable model, the overall percent of excess odds that could be explained (59.6%) was less than the total percentage explained univariately by mammographic breast density (67.6%, i.e., mammographic quality was not an independent explanatory factor).

Younger women were also statistically significantly more likely than older women to have an interval cancer diagnosed within 24 months of a screening mammogram (OR = 3.58, 95% CI = 2.15 to 5.97) (Table 4). Breast density, tumor growth (measured by mitotic count and Ki-67 index), and mammographic noise were the only factors that explained the relationship between age and having an interval cancer within 24 months; univariately, these three factors accounted for 37.6%, 30.6%, and 10.9% of the excess odds, respectively. We could explain 66.3% of the excess odds of having an interval cancer diagnosed within 24 months for younger women by accounting for breast density, tumor growth, and mammographic noise in a multivariable model.

Table 3. Percentage of breast cancers diagnosed within 24 months of a screening mammogram that are interval cancers in younger and older women by tumor growth characteristics, breast density, and overall mammographic quality

Characteristic	Percent interval cancers* in women aged	
	40–49 years	≥50 years
Mitotic figure count†		
Low	50.0	21.7
Intermediate	43.7	31.0
High	70.0	45.6
Average Ki-67 index, %‡		
<25	33.3	14.2
26–50	66.7	29.0
51–75	46.2	31.3
>75	65.5	40.4
Mammographic breast density		
Entirely fat	0.0	20.5
Scattered fibroglandular	46.4	16.2
Heterogeneously dense	48.3	40.2
Extremely dense	90.0	57.1
Mammographic noise		
Pass	53.9	22.4
Borderline	34.8	28.9
Fail	87.5	40.7
Overall mammographic quality		
Pass	16.7	21.4
Borderline	60.0	18.1
Fail	50.0	30.4

*Percent interval cancer = number of interval cancers/total number of breast cancers. Interval cancers include those in women whose index mammogram had a BI-RADS score of 1 or 2.

†Mitotic figure count: <10 per 10 high-power fields = low; 11–19 per 10 high-power fields = intermediate; >19 per 10 high-power fields = high.

‡Ki-67 index = the percent of positive tumor nuclei (number of positive tumor nuclei divided by the total number of nuclei) averaged over four high-power fields.

Factors That Explain the Excess Odds of a Missed Cancer for Premenopausal Women

To examine whether menopausal status was more strongly associated than age with mammographic sensitivity, we repeated the analyses using pre- versus postmenopausal status rather than younger versus older age. Nearly all (90.0%) of the premenopausal women were aged 40–49 years, but 31.8% of the women aged 40–49 years were peri- or postmenopausal at their index mammogram. Being premenopausal was a stronger risk factor for having an interval cancer than age; 64.0% of premenopausal women had interval cancers compared with 52.1% of younger women. The odds ratio for having an interval cancer diagnosed within 12 months of screening was 5.36 (95% CI = 2.47 to 11.66) for premenopausal women compared with peri- and postmenopausal women combined; the odds ratio for having an interval cancer diagnosed within 24 months increased to 6.37 (95% CI = 3.39 to 11.95). The key factors that explained the excess risk for premenopausal women were the same as those for younger women: breast density and mammographic noise at 12 months, and mitotic count, Ki-67 positivity, and breast density at 24 months (data not shown).

Varying the Definition of Interval Cancer

We conducted sensitivity analyses by varying the definitions used for interval and screen-detected cancers, such that we classified women with BI-RADS scores of 1, 2, or 3 as having interval cancer and BI-RADS scores of 4 or 5 as having screen-detected cancer (n = 97 interval and 367 screen-detected cancers for the 12-month interval, and n = 206 interval and 370 screen-detected cancers for the 24-month interval). Using the more inclusive definition for interval cancer decreased the odds ratio for younger women of having an interval cancer within 24 months as compared with older women (OR = 2.73, 95% CI = 1.65 to 4.52). Although the odds ratios differed depending on the interval cancer definition, the percent excess odds explained by the various factors were within 3% for both definitions (data not shown).

Discussion

Results from this study confirm results from earlier studies *(31)* that younger women (aged 40–49 years) are more likely than older women (aged 50 years or older) to be diagnosed with an interval cancer within 12 or 24 months after a screening

Table 4. The odds ratio (OR) with 95% confidence interval (CI) and excess odds of having an interval cancer within 12 or 24 months associated with being screened between the ages of 40–49 years compared with being screened at age 50 years or older*

Explanatory factors	Diagnosis within 12 months (n = 464)		Diagnosis within 24 months (n = 576)	
	OR (95% CI)†	% excess odds‡	OR (95%) CI†	% excess odds‡
Age at screening mammogram only	2.36 (1.14 to 4.77)		3.58 (2.15 to 5.97)	
Breast cancer risk factors				
Body mass index	2.31 (1.14 to 4.69)	3.7	3.50 (2.09 to 5.86)	3.1
Family history	2.56 (1.23 to 5.31)	−14.7	3.59 (2.13 to 6.08)	−0.4
Age at menarche	2.30 (1.14 to 4.67)	4.4	3.61 (2.16 to 6.03)	−1.2
Tumor growth rate				
Mitotic figure count	2.32 (1.09 to 4.93)	2.9	2.98 (1.69 to 5.25)	23.3
Ki-67 index	2.26 (1.06 to 4.85)	7.4	3.02 (1.70 to 5.35)	21.7
Mitotic figure count + Ki-67 index	2.13 (0.95 to 4.73)	16.9	2.79 (1.56 to 4.99)	30.6
Mammographic breast density	1.44 (0.63 to 3.28)	67.6	2.61 (1.49 to 4.57)	37.6
Mammographic quality				
Position	2.20 (1.03 to 4.69)	11.8	3.77 (2.21 to 6.42)	−7.4
Compression	2.01 (0.95 to 4.26)	25.7	3.46 (2.05 to 5.84)	4.7
Exposure	2.10 (0.99 to 4.44)	19.1	3.65 (2.15 to 6.20)	−2.7
Noise	1.88 (0.87 to 4.04)	35.3	3.30 (1.94 to 5.62)	10.9
All quality scores	2.09 (0.95 to 4.64)	19.9	3.70 (2.13 to 6.42)	−4.7
Multivariable model§	1.55 (0.64 to 3.76)	59.6	1.87 (0.98 to 3.56)	66.3

*Interval cancers include those in women whose index mammogram had a Breast Imaging Reporting and Data System (BI-RADS) score of 1 or 2.

†Each odds ratio represents the odds of a women aged 40–49 years being diagnosed with an interval cancer compared with a woman aged 50 or older adjusted for the explanatory factor listed in the left column and for screening interval. Odds ratios were all adjusted for time between index mammogram and previous screening mammogram: 0–36 mo, ≥37 mo, and no previous mammogram.

‡The percent of the excess odds of having an interval breast cancer for women aged 40–49 years compared with women aged 50 years or older that is explained by breast cancer risk factors, tumor markers, and mammographic quality, adjusted for mammographic screening interval. Percent excess odds explained = (OR for women aged 40–49 years adjusted for screening interval − OR for women aged 40–49 years adjusted for screening interval + one explanatory factor)/(OR for women aged 40–49 years adjusted for screening interval − 1).

§Includes all explanatory factors that explained at least +10.0% of the relationship between age at mammogram and odds of interval cancer in a univariate model; 12-month model includes density, position, compression, exposure, and noise; 24-month model includes density, mitotic count, Ki-67 index, and noise.

mammogram. The aim of this study was to expand on the previous findings by examining potential explanations for the increased risk of interval cancer in young women. We found that greater mammographic density is largely responsible for younger women being diagnosed with interval cancer within 12 months of a negative screen, whereas rapid tumor growth and mammographic breast density are the factors that largely accounted for having an interval cancer detected within 24 months of a negative screening mammogram. We further found that, except for menopausal status, traditional breast cancer risk factors (e.g., age at menarche, parity, family history) did not account for reduced mammographic sensitivity in younger women.

Breast density is not a fixed lifetime characteristic. Stromal and epithelial tissues, which appear white (dense) on a mammogram, decrease substantially with age and menopause *(10,32)* as fat content increases. Breast density is one of the strongest factors affecting mammographic sensitivity *(4,13,14,33).* Higher breast density was strongly associated with lower mammographic sensitivity in both the younger and older women in our cohort, with the relationship being stronger in the younger women. The Breast Cancer Surveillance Consortium (BCSC) *(34)* recently reported mammographic sensitivities adjusted for age, breast density, and hormone therapy use in 329 495 women aged 40–89 years from seven population-based mammography registries *(4).* Sensitivities, adjusted for age and hormone therapy use, were 87% for women with entirely fatty breasts but just 62.9% for women with extremely dense breasts. The sensitivities in young women found with the pooled BCSC populations were higher (65.6% for women aged 40–44 years and 69.7% for women aged 45–49 years) than those seen in our study (47.9%). However, the sensitivities reported by the BCSC were adjusted for age and hormone therapy use, and ours were not. The adjusted sensitivities from the BCSC ranged from 72.9% for women aged 50–54 years to 86.1% for women aged 80–89 years, which are more consistent with the unadjusted sensitivities we observed for women aged 50 years or older. The BCSC measures were also based on data from the mid- to late-1990s, when mammography had likely improved compared with mammography in the late 1980s and early 1990s *(35).* The excess odds that we report should reflect the differential effects of the factors studied, despite the differences in sensitivity expected with more recent mammography technology. Findings from both studies demonstrate the importance of the influence of breast density over mammographic sensitivities.

Our group has previously reported that younger women have faster growing tumors than older women *(16).* Faster growing tumors, as measured by higher Ki-67 positivity *(17)* and a higher mitotic rate *(18),* have been reported in two small studies of interval and screen-detected breast cancer. Gilliland et al. *(17)* reported that twice as many women younger than age 50 years had high Ki-67 positivity than women aged 50 years or older. In addition, there was a strong and independent relationship between increasing Ki-67 positivity and increasing risk of interval cancers *(17).* Other studies have shown that interval cancers are more likely to be fast growing than screen-detected cancers, but they have not specifically examined differences in growth rates by age *(36,37).* The analysis reported here supports the hypothesis that younger women have faster growing tumors than older women and that faster growing tumors, as defined by a high mitotic figure count and Ki-67 positivity, account for approxi-

mately one-third of interval cancers diagnosed within 24 months in younger women.

The speed of tumor growth can have a large impact on mammographic sensitivity, particularly if younger women have biennial mammography screening and faster growing tumors. We found that mammographic sensitivity was only 48.0% among younger women for the 24-month follow-up but was 72.3% (data not shown) when the follow-up was limited to 12 months; for the same follow-up intervals, sensitivities in older women were 75.3% and 86.2% (data not shown), respectively. For younger women, the effect of mammographic breast density and tumor growth rate on mammographic sensitivity was additive for 24 months of follow-up (percent excess odds for density = 37.6%, for tumor growth = 30.6%, and for density plus tumor growth = 66.3%), whereas breast density was a much stronger driver of lower sensitivity at 12 months. It is important to note that our study was not powered to examine mammographic sensitivity and tumor growth by breast density to determine whether decreasing mammography screening intervals would improve sensitivity for women with different breast densities. However, the data suggest that screening younger women with heterogeneously or extremely dense breasts at a 12-month screening interval would increase mammographic sensitivity compared with screening at a 24-month interval.

We used rigorous standards to assess image qualities that differ from those used by accreditation bodies, which give a pass/fail rating to one submitted "best" film. As a result, a higher proportion of women failed our quality measures than would have failed on the basis of accreditation standards. Individually, mammographic quality variables explained 11.8%–35.3% of the excess odds of having an interval cancer within 12 months (19.9% for all quality variables together, and 24.3% [data not shown] for overall quality) and mammographic breast density explained 67.6%. However, only 59.6% of the excess odds were explained when all mammographic quality variables were combined with breast density in a multivariable model. It is important to note that the method we used to calculate excess odds ignores correlated variables, which could explain why no more of the excess odds were accounted for in the multivariable model than in the univariate model with density alone. These findings suggest that image quality alone does not explain the lower mammographic sensitivity in younger women independent of mammographic breast density and that what is sometimes interpreted as mammographic breast density may also be a reflection of poor mammographic quality. These data, and data from other populations *(34)*, support the need for improved imaging modalities in women with dense breasts.

Screening recommendations continue to group women by age into women aged 40–49 years and women aged 50 years or older *(5)*, so we used these groups for the main results of our report. One of our findings was that menopausal status was more strongly related than age to mammographic sensitivity. Nevertheless, we found that the same factors explained the poorer mammographic sensitivity for premenopausal women and for younger women. Our findings for menopausal status should be interpreted with caution because our population included only 50 premenopausal women and, as a result, our estimates are less stable, as indicated by the wider confidence intervals. Boyd et al. *(32)* recently examined how breast density changes during menopause in a longitudinal study; they concluded that menopausal status has a greater effect than age on breast density. Their finding, along with our data, suggests that both menopausal status and breast density, rather than age alone, should be considered in discussions between women and their health care providers about mammography screening frequency.

Our study has some limitations. During the study period, approximately 62% of women aged 40–49 years and 77% of women aged 50 years or older at GHC reported ever having had a mammogram, and 43% of women aged 40–49 years and 54% of women aged 50 years or older at GHC reported having had a mammogram within the previous 2 years *(38)*. GHC's mammography screening guidelines differ by age, such that younger women who get screened tend to be higher-risk women (e.g., those with a positive family history) than the younger women who do not get screened or who get screened less frequently. Therefore, our findings may be most applicable to higher-risk women aged 40–49 years. We did attempt to control for these differences by adjusting for screening interval and by examining the relative contribution of traditional breast cancer risk factors, including family history.

This study also has several strengths. Information on tumor characteristics, breast density, and mammography quality variables was collected and reviewed in a consistent way by experts who were blinded to whether a woman's cancer was interval or screen-detected. In addition, this study is the first, to our knowledge, in which risk factor data and information on tumor markers, breast density, and mammographic quality variables were available for the same population-based group of women who were all part of a mammography screening program. It is also the first, to our knowledge, to model how these factors explain decreased mammographic sensitivity among young women.

In summary, breast density was the most important factor that explained lower mammographic sensitivity in younger women, regardless of the length of follow-up. In younger women, rapidly growing tumors accounted for 16.9% of the excess odds of interval cancer within 12 months and 30.6% of the excess odds of interval cancer within 24 months. Thus, mammography screening of younger women at 12- versus 24-month intervals may remove the adverse effect of faster growing tumors on mammographic sensitivity but will not remove the adverse effect of breast density on mammographic sensitivity.

There are 21.7 million women in the United Stages aged 40–49 years, approximately 50% of whom have dense breasts. It may be that digital mammography, computer-aided detection, magnetic resonance imaging, and/or ultrasound can improve cancer detection in women with dense breast tissue *(39,40)*. Our data support continued efforts to improve mammographic quality in young women with dense breasts, further study of appropriate screening intervals in this population, and further research to elucidate potential complementary imaging modalities.

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NOTES

[1]SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

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