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ORIGINAL REPORT

Risk Factors and Tumor Characteristics of Interval Cancers by Mammographic Density

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Terms in blue are defined in the glossary, found at the end of this article and online at www.jco.org.

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ABSTRACT

Purpose
To compare tumor characteristics and risk factors of interval breast cancers and screen-detected breast cancers, taking mammographic density into account.

Patients and Methods
Women diagnosed with invasive breast cancer from 2001 to 2008 in Stockholm, Sweden, with data on tumor characteristics (n = 4,091), risk factors, and mammographic density (n = 1,957) were included. Logistic regression was used to compare interval breast cancers with screen-detected breast cancers, overall and by highest and lowest quartiles of percent mammographic density.

Results
Compared with screen-detected breast cancers, interval breast cancers in nondense breasts (≤ 20% mammographic density) were significantly more likely to exhibit lymph node involvement (odds ratio [OR], 3.55; 95% CI, 1.74 to 7.13) and to be estrogen receptor negative (OR, 4.05; 95% CI, 2.24 to 7.25), human epidermal growth factor receptor 2 positive (OR, 5.17; 95% CI, 1.64 to 17.01), progesterone receptor negative (OR, 2.63; 95% CI, 1.58 to 4.38), and triple negative (OR, 5.33; 95% CI, 1.21 to 22.46). In contrast, interval breast cancers in dense breasts (> 40.9% mammographic density) were less aggressive than interval breast cancers in nondense breasts (overall difference, $P = .008$) and were phenotypically more similar to screen-detected breast cancers. Risk factors differentially associated with interval breast cancer relative to screen-detected breast cancer after adjusting for age and mammographic density were family history of breast cancer (OR, 1.32; 95% CI, 1.02 to 1.70), current use of hormone replacement therapy (HRT; OR, 1.84; 95% CI, 1.38 to 2.44), and body mass index more than 25 kg/m^2 (OR, 0.49; 95% CI, 0.29 to 0.82).

Conclusion
Interval breast cancers in women with low mammographic density have the most aggressive phenotype. The effect of HRT on interval breast cancer risk is not fully explained by mammographic density. Family history is associated with interval breast cancers, possibly indicating disparate genetic background of screen-detected breast cancers and interval breast cancers.

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INTRODUCTION

Interval breast cancers are cancers diagnosed in the interval between two mammographic screening visits. They are either true interval cancers (not present at screen examination) or false negatives from screening, with the latter being partly a consequence of high breast density masking a tumor on the x-ray. It is known that interval breast cancers have a more aggressive phenotype compared with screen-detected cancers, with higher histologic grade, larger tumor size, higher TNM stage, more estrogen receptor (ER)/progesterone receptor (PR) negativity,[1-6] higher proliferation rates,[2,3,5-8] and more often a triple-negative phenotype,[2,9] highlighting the importance of identifying women at risk. Apart from high breast density and hormone replacement therapy (HRT) use, risk factors for interval breast cancer are not well established. Studies comparing family history between interval breast cancers and screen-detected breast cancers have been inconclusive.[2,3,7,8,10-13] Current HRT use has consistently been shown to be more common in interval breast cancers,[1-3,7,10] but whether this is explained

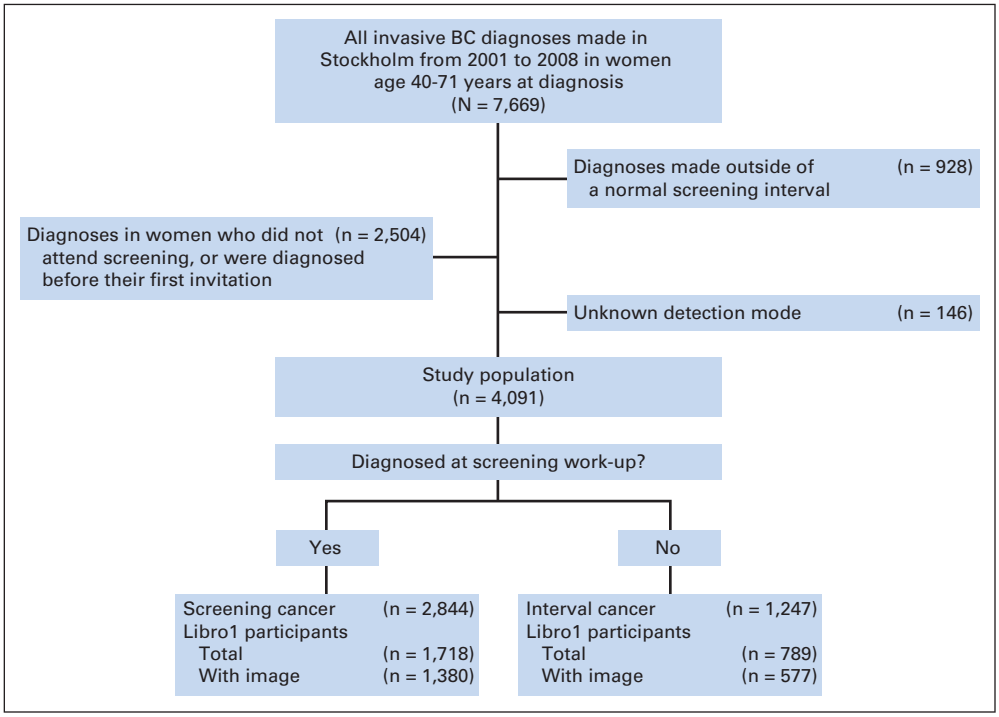

Fig 1. Flow chart of study creation, describing the initial cohort available for analysis, exclusions made, and final numbers of women with phenotype information (N = 4,091) and image and risk factor data (n = 1,957). BC, breast cancer.

by masking through increased mammographic density is not known. There is also little knowledge about associations between interval breast cancers and reproductive breast cancer risk factors.

We have previously found that interval breast cancers in women with low, but not high, breast density have worse prognosis compared with screen-detected breast cancers.[14] This suggests an importance of taking mammographic density into account when studying interval breast cancers. To our knowledge, no one has yet investigated whether tumor characteristics and risk factors of interval breast cancers differ by mammographic density when compared with screen-detected breast cancers. We compared established familial, reproductive, and hormonal breast cancer risk factors, as well as tumor characteristics, between screen-detected breast cancers and interval breast cancers in a large cohort of screening program participants, assessing associations in women with high and low mammographic density separately.

PATIENTS AND METHODS

Study approval was granted by the Regional Ethical Review Board in Stockholm, Sweden (Karolinska Institutet, DNR2009/254-31/4).

Setting

Phenotypic characterization was performed in the entire population of women diagnosed with screen-detected breast cancer and interval breast cancer from 2001 to 2008 in Stockholm, Sweden. Detailed questionnaire information and mammographic images were available for participants in the Libro-1 study nested in the aforementioned population.

Participant Recruitment and Data Collection

All women diagnosed with invasive breast cancer in Stockholm from 2001 to 2008 were identified through the Stockholm-Gotland Regional Breast Cancer quality register. Women who had been eligible for participation in the population-based screening program within the last 24 months of diagnosis (age 40 to 71 years at diagnosis, n = 7669) were all assessed for screening history. Dates of mammographic screening visits and information about the outcome of each visit were obtained through merges to the mammography screening database kept at the Stockholm-Gotland Regional Cancer Center. The database contains attendance and outcome of all visits undertaken within the population-based mammography screening program for Stockholm County. All Stockholm women age 50 to 69 have been invited to be screened at 24-month intervals since 1989, whereas women age 40 to 49 were included from mid-2005 and screened at 18-month intervals. Participation rate was 70%, recall rate was 3%, and detection rate was 0.5% for the study period.[15] Full details of the organizational and quality aspects of the Stockholm mammography screening program are described the publication by Lind et al.[15] Screen-detected breast cancer was defined as a breast cancer diagnosis made

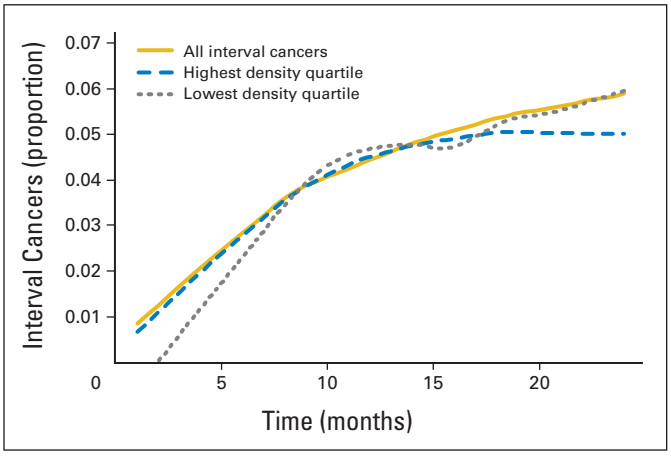

Fig 2. The distribution of interval cancer diagnoses in the population per each month of a 24-month screening interval, overall and by lowest and highest quartile of mammographic density. Expressed as proportion diagnosed per month (number of interval cancers diagnosed within each 30.5-day interval divided by the total number of interval cancers).

after a positive screen finding but before the next visit or end of a normal screening interval. Interval breast cancer was defined as a breast cancer diagnosis made after a negative screen but before the next visit or end of a normal screening interval. After excluding women diagnosed without a prior screening visit (n = 2,504), women diagnosed after a normal screening interval had passed (n = 928), and 146 women with uncertain mode of detection, 4,091 women with invasive screen-detected breast cancer or interval breast cancer were identified within the study period (Fig 1).

Tumor characteristics were obtained from merges to the Stockholm-Gotland Regional Breast Cancer quality register. Lymph node involvement was dichotomized into positive or negative. Tumor size was categorized as less than 20 mm, 20 to 40 mm, or more than 40 mm. ER and PR status were determined using radioimmunoassay or immunohistochemistry (IHC) with cutoff values of more than 10% positive cells for IHC and more than 0 fmol/μg DNA for radioimmunoassay assays. The information was recorded as negative or positive in the register according to local laboratories and existing treatment program. Human epidermal growth factor receptor 2 (HER2) status, assessed by IHC/immunocytochemistry and confirmed by fluorescence in situ hybridization analysis if protein levels from IHC/immunocytochemistry showed 2+ or 3+, was also recorded in the register as positive or negative. Triple-negative breast cancer was categorized based on ER, PR, and HER2 status. Information was essentially complete for tumor size and lymph node status, with less than 2% of patients with missing data, whereas more patients were missing data for ER and PR status (20%). HER2 status was included in the register from 2007 onward, with 13% of patients missing data on HER2 status. Grade was included from 2004, with 7% of patients missing data.

Detailed information on risk factors was available for women who were alive in 2009 and consented to participate in the Libro-1 study. Libro-1 was established by inviting all women in Stockholm with breast cancer who were younger than age 80 years at diagnosis and diagnosed between 2001 and 2008, as identified through Stockholm-Gotland Regional Breast Cancer quality register, to participate. Invitations were mailed out in 2009, together with informed consent documents and a link to an online questionnaire. Overall response rate was 62% (n = 5,715). For this study, only invasive interval breast cancers and screen-detected breast cancers were considered (n = 2,507; Fig 1).

HRT use was classified as current, past, or never; current use was defined as having used HRT pills during year of diagnosis. Pill HRT users who went off HRT before the year of diagnosis or users of patches or injections at any time

Table 1. ORs With Corresponding 95% CIs of Tumor Characteristics for Interval Cancers Compared With Screen-Detected Cancers

			Logistic Regression by Mammographic Density					Multinomial Logistic Regression by Interval Year				
	Full Cohort: Interval Cancers (n = 1,247) *v* Screen-Detected Cancers (n = 2,844)		Low Mammographic Density (≤ 20%): Interval Cancers (n = 100) *v* Screen-Detected Cancers (n = 389)		High Mammographic Density (> 40.9%): Interval Cancers (n = 293) *v* Screen-Detected Cancers (n = 197)			Interval Cancers Diagnosed in Year 1 (n = 456) *v* Screen-Detected Cancers (n = 2,844)		Interval Cancers Diagnosed at Year 2 (n = 791) *v* Screen-Detected Cancers (n = 2,844)		
Tumor Characteristic	OR	95% CI	OR	95% CI	OR	95% CI	*P**	OR	95% CI	OR	95% CI	*P**
Tumor size, mm												
< 20	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
20-40	2.20	1.89 to 2.57	1.96	1.16 to 3.27	1.53	1.03 to 2.29	.46	2.01	1.61 to 2.50	2.32	1.95 to 2.78	.25
> 40	2.57	1.93 to 3.43	4.90	1.85–13.05	1.96	0.77 to 5.07	.79	2.24	1.48 to 3.41	2.77	2.00 to 3.85	.36
Lymph nodes												
Negative	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
Positive	2.38	1.91 to 2.97	3.55	1.74 to 7.13	1.21	0.61 to 2.40	.03	2.25	1.65 to 3 to 08	2.46	1.91 to 3.15	.62
Grade†												
1	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
2	1.69	1.33 to 2.16	1.40	0.59 to 3.68	1.06	0.59 to 1.93	.61	1.52	1.05 to 2.22	1.78	1.33 to 2.40	.49
3	3.53	2.72 to 4.61	3.43	1.44 to 9.16	1.90	0.95 to 3.85	.31	3.48	2.36 to 5 to 15	3.56	2.60 to 4.88	.92
Estrogen receptor												
Positive	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
Negative	2.87	2.32 to 3.54	4.05	2.24 to 7.25	2.06	1.11 to 3.82	.11	2.85	2.13 to 3.83	2.87	2.26 to 3.66	.97
Progesterone receptor												
Positive	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
Negative	2.07	1.76 to 2.43	2.63	1.58 to 4.38	1.59	0.99 to 2.53	.15	2.27	1.79 to 2.88	1.96	1.62 to 2.37	.29
HER2†												
Positive	2.35	1.57 to 3.52	5.17	1.64 to 16.01	0.74	0.15 to 2.75	.03	2.46	1.40 to 4.32	2.29	1.44 to 3.65	.83
Negative	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
Triple negative†												
Yes	4.22	2.61 to 6.92	5.33	1.21 to 22.46	1.40	0.34 to 5.27	.12	4.72	2.52 to 8.84	3.94	2.28 to 6.83	.59
No	1.00	Ref	1.00	Ref	1.00	Ref		1.00	Ref	1.00	Ref	
Histology												
Ductal	1.00	Ref	1.00	Ref	1.00	Ref	.39	1.00	Ref	1.00	Ref	
Lobular	1.16	0.96 to 1.41	0.96	0.45 to 1.88	1.58	0.94 to 2.64		1.40	1.06 to 1.85	1.04	0.82 to 1.31	.17
Overall difference in estimate‡							.004					.06
Overall difference,‡ excluding histology							.008					.11

Abbreviations: HER2, human epidermal growth factor receptor 2; OR, odds ratio; Ref, reference.
*Wald test of standardized differences in ORs between groups.
†HER2 was only recorded from 2007. Grade was recorded from 2004.
‡Wald test of sum of standardized differences in ORs between groups.

point were coded as past users. Women who had never used pills, patches, or injections, but may have used local HRT at any time, were coded as never users. Family history of breast cancer was defined as having a mother or sister with disease and was analyzed as a binary variable (yes or no). *BRCA1/2* mutation status was self-reported (yes or no, where no could mean not tested or tested negative). Parity was classified as none, one to two children, or three or more children. Age at menarche was categorized as ≤ or greater than 13 years old. Oral contraceptive use was categorized as never or ever. Body mass index (BMI) was calculated from self-reported weight and height at time of questionnaire and categorized as low (< 20 kg/m^2), normal (20 to 25 kg/m^2), and overweight (> 25 kg/m^2). Percentages of missing data were 0% to 5% for all questionnaire variables, except for *BRCA* (10%) and family history (8%).

Analog mammographic images were collected from radiology departments and digitized with an Array 2905HD Laser Film Digitizer (Array Corp, Tokyo, Japan). Mammographic density was measured with the area-based measure previously described by Li et al.[16] Briefly, an algorithm is taught to distinguish dense area from nondense area by training on image segmentation data measured by an experienced Cumulus[17] analyst, thus mimicking Cumulus. Percent mammographic density was assessed in prediagnostic mediolateral oblique view images of the cancer-free breast and categorized into quartiles, with cutoffs at 20%, 29.5%, and 40.9% in this population. Women with contralateral breast cancer arising within 3 months of diagnosis were not assessed for density (n = 163). An image matching our criteria was found for 1,957 (78%) of 2,507 individuals with questionnaire data.

Statistical Analysis

Binary logistic regression analysis was used to study tumor characteristics of interval breast cancers in the full population of patients with invasive screen-detected breast cancers or interval breast cancers (N = 4,091). We performed binary logistic regression analyses of interval breast cancers versus screen-detected breast cancers within separate strata of the highest and lowest mammographic density quartiles. Differences between estimates from each stratum were assessed for each exposure using the Wald test. We also assessed differences by the overall pattern, combining estimates for tumor size, lymph spread, ER status, PR status, HER2 status, triple-negative phenotype, grade, and histology into one score. The overall differences score was obtained by calculating the observed sum of standardized differences (sum of *z* statistics) for log-odds ratios (ORs) of low and high mammographic density and comparing it with the null distribution using a Wald test. The null distribution was generated from 1,000 simulated data sets scrambling the outcome variable to obtain null associations. As a secondary analysis, histology was omitted from the score to assess overall pattern of differences solely for factors related to prognosis.

Interval breast cancers diagnosed in the first or second year of the 2-year interval were compared separately with screen-detected breast cancers using multinomial logistic regression with screen-detected breast cancers as the reference group (population-based study; full population, N = 4,091). Differences between estimates for year 1 and year 2 interval breast cancers were assessed both separately for each exposure, using the Wald test, and overall, using the same approach of testing observed versus expected overall *z* statistics as described earlier for density. Sensitivity analysis was performed to assess main findings for tumor characteristics in the subgroup of women with questionnaire information.

Analysis of risk factors for interval breast cancer was performed in the cohort of women with density information (n = 1,957), using binary logistic regression. All explanatory variables were first tested separately in crude and age-adjusted models. Variables significantly associated with interval breast cancer after adjusting for age ($P < .05$) were tested in multivariable models. To address the impact of mammographic density on estimates, logistic regression was performed in strata of the highest and lowest mammographic density quartiles. Sensitivity analysis including women with missing density information was done. To assess potential survivorship bias among women who provided risk factor information, sensitivity analysis restricted to women diagnosed from 2004 to 2008 was performed. Data management was performed using SAS version 9.4 statistical software (SAS Institute, Cary, NC). Statistical analysis was performed in SAS version 9.4 and R version 3.1.0 (www.r-project.org.[18] All statistical tests were two-sided, with a cutoff at $\alpha = .05$.

RESULTS

We identified 4,091 women diagnosed with invasive breast cancer either through mammography screening or during a screening interval (Fig 1). Of the 4,091 cancers, 70% (n = 2,844) were screen-detected breast cancers and 30% (n = 1,247) were interval breast cancers. Of the interval breast cancers, 63% (n = 791) were diagnosed in the second year after a mammography screen, with no apparent difference in year-wise distribution between dense and nondense breasts (Fig 2).

Overall, interval breast cancers had worse phenotype compared with screen-detected breast cancers, as measured by ORs (Table 1). Women with questionnaire information were no different from the full cohort (Appendix Table A1, online only). When comparing interval breast cancers according to time since last screen, interval breast

Table 2. Risk Factors in Patients With Interval and Screen-Detected Breast Cancers Among the 1,957 Women With Image and Risk Factor Data Available

Factor	Interval Cancer		Screen-Detected Cancer	
	No. of Patients	%	No. of Patients	%
Age at diagnosis, years				
Mean	59.2		59.8	
SD	6.1		5.7	
40-49	20	3.5	28	2
50-59	284	49.2	576	41.7
60-72	273	47.3	776	46.2
% Mammographic density				
Mean	35.0		30.0	
SD	15.5		15.5	
Quartile-based % mammographic density categories				
< 20.5%	100	17.3	389	28.2
20.5%-29.4%	119	20.6	368	26.7
29.5%-40.9%	161	27.9	330	23.9
> 40.9%	197	34.1	293	21.2
HRT use				
Never	196	35.6	573	43.8
Past	219	29.8	540	41.3
Current	135	24.6	194	14.8
Missing	27		73	
BMI, kg/m^2				
Mean	24.6		26.0	
SD	3.8		4.3	
< 20	29	5.2	44	3.3
20-25	331	58.8	620	46.6
> 25	203	36.6	667	50.1
Missing	14		49	
Family history of cancer in mother or sister				
No	423	78.5	1037	82.1
Yes	116	21.5	226	17.9
Missing	38		117	

Abbreviations: BMI, body mass index; HRT, hormone replacement therapy; SD, standard deviation.

cancers detected within a year of a negative screen were not more aggressive than those detected after 13 to 24 months (overall differences, Wald test $P = .06$; excluding histology, $P = .11$). In contrast, analysis by strata of high and low mammographic density showed differences. Interval breast cancer in the low mammographic density stratum had the worst phenotype, with higher frequencies of grade 3 disease (OR, 3.43; 95% CI, 1.44 to 9.16), ER-negative status (OR, 4.05; 95% CI, 2.24 to 7.25), PR-negative status (OR, 2.63; 95% CI, 1.58 to 4.38), HER2-positive status (OR, 5.17; 95% CI, 1.64 to 16.01), triple-negative status (OR, 5.33; 95% CI, 1.21 to 22.46), tumor size more than 40 mm (OR, 4.90; 95% CI, 1.85 to 13.05), and lymph node involvement (OR, 3.55; 95% CI, 1.74 to 7.13) compared with screen-detected breast cancers. For women with dense breasts, there was no detectable difference between screen-detected breast cancers and interval breast cancers except for tumor size and ER status (Table 1). Significant interactions between mammographic density and phenotype were found for lymph node involvement and HER2 status. The overall phenotype of interval breast cancers relative to screen-detected breast cancer was significantly more aggressive among the nondense breasts (Wald test for overall differences, $P = .004$; excluding histology, $P = .008$).

The distribution of general breast cancer risk factors significantly associated with interval breast cancer is shown in Table 2. ORs from the crude and age-adjusted analysis of general breast cancer risk factors are listed in Table 3. Current HRT use, high mammographic density, low BMI, and family history of breast cancer were more common in patients with interval breast cancers. None of the reproductive risk factors under study or *BRCA* mutation status was found to be significantly different between groups, although the point estimates indicated higher risk among *BRCA* mutation carriers (Table 3). In multivariable analysis (Table 4), the OR for family history was 1.32 (95% CI, 1.02 to 1.70), after adjusting for age and mammographic density. The point estimate was higher among nondense breasts than dense breasts. The effect of current HRT use persisted after

Table 3. Risk Factors for Interval Breast Cancer

	Crude Model: Interval *v* Screen-Detected Breast Cancer			Age-Adjusted Model: Interval *v* Screen-Detected Breast Cancer		
Factor	OR	95% CI	*P* for Trend	OR	95% CI	*P* for Trend
Age at diagnosis, years			< .001			
< 50	1.00					
50-59	0.69	0.38 to 1.25				
> 60	0.49	0.27 to 0.89				
Mammographic density			< .001			< .001
< 20%	1.00			1.00		
20%-29.4%	1.26	0.93 to 1.70		1.28	0.90 to 1.81	
29.5%-40.9%	1.90	1.42 to 2.54		1.84	1.31 to 2.57	
> 40.9%	2.62	1.97 to 3.48		2.89	2.09 to 4.00	
Age at menarche, years						
< 13	1.00			1.00		
≥ 13	1.11	0.89 to 1.38		1.13	0.92 to 1.39	
Age at first birth, years			.19			.24
< 20	1.00			1.00		
20-25	1.31	0.90 to 1.90		1.34	0.92 to 1.94	
> 25	1.35	0.93 to 1.96		1.34	0.92 to 1.95	
Parity, No. of children			.35			.49
0	1.00			1.00		
1-2	0.89	0.68 to 1.18		0.91	0.69 to 1.20	
≥ 3	0.85	0.61 to 1.28		0.89	0.64 to 1.32	
Oral contraceptive usage						
Never	1.00			1.00		
Ever	1.19	0.93 to 1.51		1.12	0.88 to 1.43	
Hormone replacement therapy			< .001			< .001
Never	1.00			1.00		
Past	1.18	0.95 to 1.49		1.32	1.04 to 1.66	
Current	2.04	1.55 to 2.67		2.18	1.65 to 2.87	
Body mass index, kg/m^2			< .001			< .001
< 20	1.00			1.00		
20-25	0.81	0.50 to 1.32		0.79	0.49 to 1.30	
> 25	0.46	0.28 to 0.76		0.47	0.28 to 0.75	
Family history* (mother or sister)						
No	1.00			1.00		
Yes	1.26	0.98 to 1.62		1.29	1.01 to 1.67	
BRCA1/2 mutation						
No	1.00			1.00		
Yes	2.37	0.88 to 6.34		2.17	0.80 to 5.89	

*Family history is defined as having a mother and/or sister(s) with breast cancer.

Table 4. Multivariable Analysis of Breast Cancer Risk Factors Showing ORs With Corresponding 95% CIs for Interval Cancers Relative to Screen-Detected Cancers

	All Interval Cancers *v* Screen-Detected Cancers		Low Mammographic Density (≤ 20%): Interval Cancers *v* Screen-Detected Cancers		High Mammographic Density (> 40.9%): Interval Cancers *v* Screen-Detected Cancers	
Exposure	OR	95% CI	OR	95% CI	OR	95% CI
Hormone replacement therapy use*						
Never	1.00		1.00		1.00	
Past	1.21	0.95 to 1.54	2.03	1.22 to 3.38	1.35	0.84 to 2.17
Current	1.84	1.38 to 2.44	2.42	1.67 to 5.04	2.47	1.49 to 4.08
Body mass index, kg/m^2*						
< 20	1.00		1.00		1.00	
20-25	0.77	0.46 to 1.27	1.12	0.22 to 5.60	0.72	0.29 to 1.78
> 25	0.49	0.29 to 0.82	1.08	0.22 to 5.35	0.38	0.15 to 0.97
Family history (mother or sister)†						
No	1.00		1.00		1.00	
Yes	1.32	1.02 to 1.70	1.66	0.96 to 2.87	1.28	0.77 to 2.11

Abbreviation: OR, odds ratio.
*Model: Interval cancer as outcome, and age, body mass index, hormone replacement therapy use, and percent mammographic density as covariates.
†Model: Interval cancer as outcome, and family history, age, and percent mammographic density as covariates. Family history is defined as having a mother and/or sister(s) with breast cancer.

adjustments for mammographic density, BMI, and age at diagnosis (OR, 1.84; 95% CI, 1.38 to 2.44) and was present in both the lowest and highest quartile of mammographic density (Table 4). The effect size associated with BMI was essentially unchanged after adjustments for mammographic density, age, and HRT use. The effect was still observed in the top quartile of mammographic density but was not present in the lowest mammographic density quartile (Table 4). Including women without images in the analysis did not change estimates, except that the effect of high age at menarche reached statistical significance (OR, 1.22; 95% CI, 1.02 to 1.46). In sensitivity analysis of survivor bias, the estimate for family history increased, whereas estimates for HRT weakened (Appendix Table A2, online only).

DISCUSSION

In this study, we appraised clinicopathologic and risk factor differences between screen-detected breast cancers and interval breast cancers and the implications of mammographic density on obscuring tumors that should have been detected at screening. Interval breast cancers in nondense breasts were associated with aggressive tumor characteristics compared with screen-detected breast cancers in nondense breasts, whereas interval breast cancers in dense breasts were phenotypically more similar to dense screen-detected breast cancers. Current HRT use, BMI, and family history were risk factors associated with interval breast cancer.

The distribution of tumor characteristics between interval breast cancers and screen-detected breast cancers overall was in full agreement with the literature, with interval breast cancers being larger at diagnosis and of higher grade, displaying more lymph node involvement,[1-6] and more often being ER/PR negative,[2-4,6] HER2 positive,[8] or triple negative.[2,9] Interval breast cancers were not significantly different in phenotype whether they had been diagnosed 1 or 2 years after last screen. Instead, we found the interval breast cancer phenotype to differ by mammographic density, with nondense interval breast cancers having a significantly worse phenotype than dense interval breast cancers, compared with screen-detected breast cancers. In support of this, Domingo et al[19] performed a retrospective review of interval breast cancers, dividing them into true or missed, and reported true interval cancers to be associated with a worse phenotype, with true interval breast cancers also exhibiting weaker associations with mammographic density than missed interval breast cancers. Moreover, in previous work from our group, we found survival of patients with interval breast cancers to be poorer only in patients with nondense breasts, after adjusting for tumor size at diagnosis.[14] Together, these results suggest that interval breast cancers in nondense breasts are enriched for aggressive, true interval cancers.

We observed an increased risk of interval breast cancer among women with a mother or sister with breast cancer. In concordance with this, we found a two-fold increase in odds for interval breast cancer among *BRCA* mutation carriers, although the patient numbers were too low for these results to be conclusive. However, previous studies of *BRCA* mutations have found a lowered sensitivity of the mammography screening test for carriers,[20-22] in line with our results. Previous literature on family history and interval breast cancer reports conflicting results, using varying definitions of family history and low patient numbers (ranging from 47 to 375 patients with interval cancer.[2,3,7,8,10-13] We found that there is a small effect of family history on the risk of interval cancer, but results will need to be confirmed in other, larger studies.

Overweight women were more likely to have screen-detected breast cancers, a finding that persisted after adjusting for age, HRT, and mammographic density. BMI has been reported to be positively associated with high-proliferating tumors[23] but negatively associated with percent mammographic density.[24] Together, this makes the BMI associations with interval detection difficult to interpret in a logistic regression setting without distinguishing true from false interval breast cancers, because an effect of BMI on growth rate is likely hidden

by an opposite effect through the negative association with mammographic density. Notably, the negative association with BMI was not seen among the breasts with low density where the least favorable interval cancer phenotype was present.

We confirmed a higher risk of interval breast cancer, relative to screen-detected breast cancer, among current users of HRT, which has been previously shown in the literature.[1-3,7,10,25] The association was attenuated, but not removed, after adjustments for age, mammographic density, and BMI and was present also in nondense breasts, indicating an effect beyond mere masking. During our study period, HRT users were advised to attend sporadic screening at private mammography clinics outside of the screening program, creating surveillance bias for this group, which may in part explain this phenomenon.

This study has limitations that must be acknowledged. A proportion of interval breast cancers are missed screen-detected breast cancers, partly a result of high mammographic density masking the tumor from detection.[19] Thus, we performed an analysis stratified by the highest and lowest quartile of density to obtain separate risk estimates. For the Stockholm Screening program, an estimated 22% of cancers were missed at screening.[26] *BRCA* status may have been misclassified if women not tested were in fact carriers, which could underestimate any true effect. For family history, we did not have information on daughters with breast cancer. This could attenuate any true effect of family history. Another limitation is that risk factor analysis may have been influenced by survivor bias because the questionnaire data were available for women still alive in 2009. If so, our results from the risk factors could underestimate any true effects relating to aggressive cancers. In sensitivity analysis restricting our risk factor analysis to patients diagnosed in 2004 or later, point estimates did not change overall. However, among the patients with nondense breasts, we saw a decrease in the effect size of current HRT use and an increase in the point estimate for family history (Appendix Table A2).

Our study has several strengths given the sample size and quality and quantity of data available. For main analysis of tumor characteristics, we have population-based data, giving us one of the largest interval breast cancer versus screen-detected breast cancer breast cancer cohorts hitherto studied. In addition, we have the combination of tumor characteristics, detailed questionnaire data, and area-based mammographic density measurements available for 1,957 women, enabling us to address the impact of mammographic density on prognostic factors and risk factors of interval cancers in one of the largest interval breast cancer studies to date.

In conclusion, interval breast cancers and screen-detected breast cancers show disparate clinicopathologic features and are associated with several breast cancer risk factors differently. Interval breast cancers among women with low mammographic density have the most aggressive phenotype, indicating enrichment of true interval breast cancers within this group. In the future, screening programs should shift from solely age-based to individual risk–based programs. Diagnostic modality and screening intervals for individual women could be decided based on risk factors such as mammographic density and genetic background.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

HER2/*neu* (human epidermal growth factor receptor 2): also called ErbB2. HER2/*neu* belongs to the epidermal growth factor receptor (EGFR) family and is overexpressed in several solid tumors. Like EGFR, it is a tyrosine kinase receptor whose activation leads to proliferative signals within the cells. On activation, the human epidermal growth factor family of receptors are known to form homodimers and heterodimers, each with a distinct signaling activity. Because HER2 is the preferred dimerization partner when heterodimers are formed, it is important for signaling through ligands specific for any members of the family. It is typically overexpressed in several epithelial tumors.

logistic regression analysis: a multivariable regression model in which the log of the odds of a time-fixed outcome event (eg, 30-day mortality) or other binary outcome is related to a linear equation.

population-based study: a study in which the patients are drawn from a defined population in a manner that is representative of the source population studied. Such a design can avoid bias arising from the selective factors that guide affected individuals to a particular medical facility, allowing for greater generalizability of the findings.

triple-negative phenotype: breast tumors that are negative for progesterone and estrogen and that underexpress HER2.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Risk Factors and Tumor Characteristics of Interval Cancers by Mammographic Density

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Appendix

Table A1. Tumor Characteristics for Interval Cancers and Screen-Detected Cancers in the Full Cohort and Women With Questionnaire Data

	All Women						Women With Questionnaire Data					
	Screen-Detected Cancer		Interval Cancer		Interval Cancers *v* Screen-Detected Cancers		Screen-Detected Cancer		Interval Cancer		Interval Cancers *v* Screen-Detected Cancers	
Tumor Characteristic	No. of Patients	%	No. of Patients	%	OR	95% CI	No. of Patients	%	No. of Patients	%	OR	95% CI
Tumor size, mm												
< 20	2,061	74	654	55	1.00	Ref	1,269	75	438	57	1.00	Ref
20-40	629	22	439	37	2.20	1.89 to 2.57	370	22	272	36	2.13	1.76 to 2.58
> 40	114	4	93	8	2.57	1.93 to 3.43	58	3	53	7	2.65	1.80 to 3.90
Lymph nodes												
Negative	2,658	94	1,061	86	1.00	Ref	1,616	94	686	88	1.00	Ref
Positive	181	6	172	14	2.38	1.91 to 2.97	98	6	97	12	2.33	1.74 to 3.13
Grade*												
1	504	27	106	15	1.00	Ref	300	26	73	15	1.00	Ref
2	976	53	346	48	1.69	1.32 to 2.15	624	55	241	50	1.59	1.18 to 2.13
3	358	20	266	37	3.53	2.72 to 4.59	213	19	166	35	3.20	2.31 to 4.44
Estrogen receptor												
Positive	2,144	91	727	78	1.00	Ref	1,326	92	496	80	1.00	Ref
Negative	210	9	204	22	2.87	2.32 to 3.54	121	8	124	20	2.74	2.09 to 3.60
Progesterone receptor												
Positive	1,714	75	530	59	1.00	Ref	1,063	75	361	60	1.00	Ref
Negative	586	25	375	41	2.07	1.76 to 2.43	357	25	291	40	1.99	1.63 to 2.44
HER2*												
Positive	59	9	51	18	2.35	1.57 to 3.52	46	11	40	19	1.97	1.23 to 3.16
Negative	633	91	233	82	1.00	Ref	390	89	155	81	1.00	Ref
Triple negative*												
Yes	30	4	45	16	4.22	2.60 to 6.86	21	5	28	15	3.45	1.90 to 6.26
No	653	96	232	84	1.00	Ref	409	95	148	85	1.00	Ref
Histology												
Ductal	1,941	70	184	69	1.00	Ref	1,180	71	112	71	1.00	Ref
Lobular	297	13	837	15	1.16	0.96 to 1.41	231	14	545	15	1.05	0.82 to 1.34

Abbreviations: HER2, human epidermal growth factor receptor 2; Ref, reference.
*HER2 recorded from 2007. Grade recorded from 2004.

Table A2. Sensitivity Analysis of Survivor Bias: Multivariable Logistic Regression of Interval Breast Cancers Versus Screen-Detected Breast Cancers Using Only Diagnoses From 2004 to 2008

	Main Analysis		Interval Cancers: Low Mammographic Density (≤ 20%)		Interval Cancers: High Mammographic Density (> 40.9%)	
Factor	OR	95% CI	OR	95% CI	OR	95% CI
Hormone replacement therapy*						
Never	1.00		1.00		1.00	
Past	1.13	0.84 to 1.52	1.58	0.84 to 2.99	1.66	0.92 to 3.01
Current	1.54	1.04 to 2.28	1.47	0.48 to 4.52	2.53	1.28 to 4.99
Body mass index, kg/m^{2}*						
< 20	1.00		1.00		1.00	
20-25	0.76	0.40 to 1.45	0.61	0.11 to 3.47	0.48	0.16 to 1.42
> 25	0.44	0.23 to 0.86	0.54	0.10 to 2.97	0.30	0.10 to 0.93
Family history (mother or sister)†						
No	1.00		1.00		1.00	
Yes	1.30	0.94 to 1.79	2.08	1.06 to 4.10	1.37	0.73 to 2.56

Abbreviation: OR, odds ratio.
*Model: Age, body mass index, hormone replacement therapy use, and percent mammographic density as covariates.
†Model: Family history, age, and percent mammographic density as covariates.