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Title: Changes in mammographic density over time and the risk of breast cancer: an observational cohort study

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Keywords: Breast neoplasms; mass screening; longitudinal studies; mammographic density

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Abstract: Background: The effect of changes in mammographic density over time on the risk of breast cancer remains inconclusive.
Methods: We used information from four centers of the Breast Cancer Screening Program in Spain in the period 1996-2015. We analyzed individual level data from 117,388 women first screened age 50-54, with at least two screening examinations. Breast density was determined using the BI-RADS classification (A to D in increasing order) at earliest and latest screening examination. Adjusted Poisson regression models were used to estimate the relative risk (RR) and 95% confidence intervals (95%CI) of the association between changes in mammographic density and breast cancer risk over time.
Results: During an average 5.8 years of follow-up, 1592 (1.36%) women had a breast cancer diagnosis. An increase in density category increased breast cancer risk, and a decrease in density decreased the risk, compared with women who remained in the same BI-RADS category. Women whose density category increased from B to C or B to D had a RR of 1.55 (95%CI= 1.24-1.94) and 2.32 (95%CI= 1.48-3.63), respectively. The RR for women whose density increased from C to D was 1.51 (95%CI= 1.03-2.22). Changes in BI-RADS density were similarly associated with the risk for invasive cancer than for ductal carcinoma in situ.
Conclusions: Although a modest proportion of women changed BI-RADS density category, mammographic density changes modulated the risk of breast cancer and identified women at a differential risk. Using two longitudinal measures of BI-RADS density could help target women for risk-based screening strategies.

Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

ABSTRACT

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Keywords: Breast neoplasms; mass screening; longitudinal studies; mammographic density

Abbreviations: SFM: screen-film mammography; FFDM: full-field digital mammography; DCIS: ductal carcinoma in situ; RR: relative risk; BI-RADS: breast imaging reporting and data system.

BACKGROUND

Breast density is a major risk factor for breast cancer. Women with a high mammographic density are associated with a two-fold increased risk of breast cancer compared with women with scattered breasts density (1). Most studies investigating the association between mammographic density and breast cancer risk are based on a single breast density measure, with a wide variability in the time interval prior to diagnosis at which density was measured, most frequently between 1 and 10 years (1–3).

It is known that breast density declines with increasing age, particularly in perimenopausal women (4–7). In addition, menopause is associated with a reduction in breast density, caused by changes in hormonal exposure that reduce the number of epithelial and stromal elements in the breast (7). In Spain, the median age of natural menopause is estimated to be 51.7 years (8). Population-based mammography screening in most European countries, including Spain is targeted to women aged 50 to 69 years, which raises the hypothesis that the change in breast density over time may be more relevant to risk than breast density measured at a point in time.

Changes in mammographic density over time have been suggested to predict breast cancer risk (6,9–13). However, they found dissimilar results. While some studies showed that the risk increased with increasing mammographic density, and decreased with decreasing density (9–12), others did not find an association between mammographic density changes and the risk of breast cancer (6,13). It should be noted that most studies had a limited statistical power to provide conclusive evidence (6,10–13). Some studies lacked adjustment for time between breast density examinations (10,12), while other lacked adjustment for important confounders like hormone therapy or body mass index (9). In addition, different quantitative and categorical measures of breast density have been used to assess the association of mammographic density and the risk of breast cancer (3,14–19). Quantitative density measures are taken mainly in research settings. In the context of population-based screening programs, the American College of Radiology Breast Imaging

Reporting and Data System (BI-RADS) is the most common categorization used to classify mammographic breast density (20).

Assessing the change in mammographic density over a series of sequential participations in women targeted for mammography screening could help identify women at a higher risk and has the potential to add information to a more efficient management of breast cancer screening. We conducted a retrospective cohort study to assess if changes in BI-RADS mammographic density categories over time were associated with breast cancer risk in women biennially screened ages 50 to 69 years in a population-based mammography screening program.

METHODS

Setting and study population

Population-based screening in Spain started in 1990 in a single setting and became nationwide in 2006. Breast cancer screening in Spain is government-funded, and follows the recommendations of the European Guidelines (21). The program is organized into administrative screening settings responsible for the local application of screening in their area (22). Screen-film mammography (SFM) was the default technique at start-up. Full-field digital mammography (FFDM) was introduced in the program in 2004 and was gradually widespread with a rate of 59% FFDM in 2015. The program has been previously described in detail elsewhere (22). In brief, women aged 50 to 69 years are biennially invited for a two-view mammography (craniocaudal, and mediolateral oblique). Screening mammograms are interpreted by trained breast radiologists. Prior mammograms are retrieved for comparison at subsequent screens. The Breast Imaging Reporting and Data System (BI-RADS) scale was used to classify mammograms. Women with screening mammograms scored with BI-RADS 3, 4, 5, or 0 are recalled for further assessments, including additional imaging, ultrasound and invasive procedures. If malignancy is ruled out, women are referred back to routine screening at two years. Women diagnosed with breast cancer are referred for treatment. All breast biopsies were histopathologically confirmed by trained pathologists.

Data were obtained from four centres of the mammography screening program in Spain (Costa de Ponent, Vallés Oriental, Sabadell-Cerdanyola, and Cantabria) that routinely gather information on mammographic density. Data for the study comprised information about women screened between January 1, 1996, and December 31, 2015. The centres collect information on screening and diagnostic mammography examinations, recall, furthers assessments and diagnosis results performed in their defined catchment areas. The study was approved by the Clinic Research Ethics Committee of Hospital del Mar Medical Research Institute (2015/6189/I). The review boards of

the institutions providing data granted approval for data analyses. This is an entirely register based study that used anonymised retrospective data and hence written consent was not required.

The initial reference population consisted of individual level data from all 231 700 women with at least two BI-RADS breast density examinations at screening mammography during the study period. Because we wanted to ensure representativeness of the population of women targeted for biennial screening mammography from age 50 to 69 years, we restricted the study population to women first screened ages 50–54 years. Thus, we excluded 114 289 women because they were 55 years or older at first screen. We also excluded 23 women because their earliest and latest examinations were less than 12 months apart. The final study sample consisted of 117 388 women.

Definition of study variables

Breast density was determined by radiologists at the time of screening mammography interpretation using the BI-RADS System (20) categories: almost entirely fat (A); scattered fibroglandular density (B); heterogeneously dense (C); or extremely dense (D). BI-RADS density measures were routinely obtained by radiologists as part of regular screening practice. We used breast density measures at the earliest and latest screening examination prior to a cancer diagnosis for each woman. The change in mammographic breast density was defined as a different BI-RADS density category reported at the latest examination compared to the earliest.

Breast cancer cases included all invasive cancers and ductal carcinoma in situ (DCIS) diagnosed within two years of the last screening examination in the study period. Breast cancer cases were identified from the screening centres databases, population-based cancer registries, the regional Minimum Basic Data Set, and hospital-based cancer registries.

Statistical Analysis

We used women as the unit of analysis. Because we analysed a dynamic cohort of women with different time spans and number of screening participations, we computed the time contribution at risk of each woman between mammographic density measures. Person-years at risk were calculated from the date of first mammographic density measure. Women were censored at date of last mammographic density examination prior to a breast cancer diagnosis (screen detected cancer or interval breast cancer).

We compared the frequency distributions of various risk factors (Bi-RADS category at earliest and latest mammographic density measure, breast density change stratified by BI-RADS density category at earliest measure, age at latest breast density measure, and time between earliest and latest density measure,) for women with and without breast cancer. To compare the frequency distribution, age at latest density measure was categorized into 5-year age groups (50-54, 55-59, 60-64, and 65-69 years), and time between earliest and latest density measures was categorized into 2 years intervals (<2, 2-4, 4-6, 6-8, and > 8 years). Breast cancer rates were calculated as number of breast cancer cases per 1000 women-years at risk. We used multivariable Poisson regression to estimate the relative risk (RR) and the 95% confidence interval (CI) of the association between breast density measures and breast cancer risk. Because use of SFM and FFDM coexisted over the time period in which density change was examined, we adjusted the models for the type of mammography women had at screening examinations (as a categorical variable [only SFM, only FFDM, or both]). In addition, all models were adjusted for screening centre, time (years) between earliest and latest examination (continuous variable), and year of baseline screen (continuous variable). Therefore, the number of incident breast cancer cases was analysed as a log-linear function of exposure time (t), mammographic density (d), screening centre (s), mammography type (m), and year of screen (y). The model was expressed as $\ln(\lambda_d) = \alpha + \ln(t_d) + \beta_d d + \beta_s s + \beta_m m + \beta_y y$; where α is the intercept, $\ln(t_d)$ is the time offset of the Poisson regression model given, where t_d is given by the time between earliest and latest examination, and β is the slope of the regression line for the

covariates in the model. The time (years) between earliest and latest examination acted as the time scale in the models. All covariates included in the models were statistically significant. To avoid the confounding effect of age at screening examination we restricted our analyses to women aged 50-54 years at first screen only. This way, the time (years) between earliest and latest examination corresponds with the natural ageing of the population.

We evaluated the association of mammographic density at earliest and latest measure with breast cancer risk. For these analyses we used BI-RADS category B (scattered fibroglandular) as the referent group since this group was the most common. Also, we evaluated the change in Bi-RADS density category with breast cancer risk stratified by BI-RADS category at earliest examination. We used women whose density category did not change as the referent group within each BI-RADS category. Finally, we performed separate analyses for the risk of ductal carcinoma in situ and invasive breast cancer independently. Data were analysed using IBM® SPSS® v.21, and R statistical software version 3.2.3 (www.r-project.org). All tests were two-sided with a 5% significance level.

RESULTS

We analysed 117 388 women screened at least twice, of whom 1592 (1.36%) had a breast cancer diagnosis during the study period. At the earliest examination BI-RADS breast density B was the most common category for women with and without breast cancer (53.7% and 44.9%, respectively). Similarly, BI-RADS density B was also the most frequent category at the latest examination for women with and without breast cancer (59.3% and 55.7%, for women without and with breast cancer, respectively). The frequency of BI-RADS breast density categories A and B at earliest and latest examination were significantly higher for women without breast cancer, whereas BI-RADS breast density categories C and D were more frequent for women with a breast cancer diagnosis (Table 1). Compared with women without breast cancer, women with breast cancer had a greater proportion of women aged 60-64 years at the latest examination (Table 1).

Regarding mammographic density change, the average time between earliest and latest examination was 5.8 years, with a median of 4.1 years and an interquartile range of 6.0 years. Most frequently, women remained at density category B at earliest and latest examination (40.8%, and 33.1% for women without and with breast cancer, respectively) (Table 2). The proportion of women that remained at BI-RADS density A or B was significantly greater for women without breast cancer, whereas the proportion of women that remained at BI-RADS density C or D was greater for women with breast cancer. Among women without a breast cancer, 25.8% had a decrease, and 11.8% had an increase in breast density category, while among those with a breast cancer 34.0% experienced a decrease and 12.5% experienced an increase.

The crude rates and the adjusted RR of breast cancer calculated from the Poisson regression models are shown in Table 3. Compared with women with BI-RADS category B at the latest examination, women with BI-RADS density A had a lower rate of breast cancer (1.3 versus 2.1 cases per 1000 women-years, RR= 0.61; 95%CI= 0.52-0.73), while women with a BI-RADS category D had the highest rate of breast cancer (4.9 cases per 1000 women-years, RR= 2.18, 95%CI= 1.86-2.56). The

association between breast cancer risk and BI-RADS breast density category at the earliest measure followed a similar pattern, although the intensity of the association was somewhat weaker (Table 3).

Relative risks and rates (per 1000 women-years) of developing breast cancer were calculated for women who started in a given BI-RADS breast density category compared with women who experienced no change serving as the referent group (Table 4). In each strata, women who experienced an increase in mammographic density had an increased breast cancer risk, while those who experienced a decrease in breast density had a decrease in breast cancer risk, compared with women who remained in the same BI-RADS density category. Among women who moved to BI-RADS category C, the rates of breast cancer steadily increased from 2.9 per 1000 women-years for women who moved from B to C, to a rate of 3.4 women who moved from C and C, and 4.0 for women who moved from D to C, respectively. Among women with a BI-RADS category B at the earliest examination, the likelihood of developing breast cancer was higher for women who changed to C or D BI-RADS density category (RR= 1.55; 95%CI= 1.24-1.94, and RR= 2.32; 95%CI= 1.48-3.63), while the RR for women whose density increased from C to D was 1.51 (95%CI= 1.03-2.22).

Table 5 shows the results of the multivariable analyses of BI-RADS category density change stratified by tumour invasiveness (DCIS or invasive cancer). Increases or decreases in BI-RADS breast density categories were similarly associated with increases or decreases in risk for DCIS and invasive tumours (RR_{DCIS}= 1.57; 95%CI= 1.02-2.42; and $RR_{Invasive}$= 1.49; 95%CI= 1.14-1.96 for women who changed from B to C density category).

DISCUSSION

In this analysis of data from 117 388 women first screened ages 50 to 54 years, and with follow-up of up to 20 years, we found that an increase in BI-RADS density category was associated with an increase in breast cancer risk, and that a decrease in mammographic density category was associated with a decrease in breast cancer risk, compared with women in whom BI-RADS mammographic density category remained unchanged. Mammographic density changes modulated the breast cancer risk and identified women at a higher risk.

The evidence from previous studies on whether changes in mammographic density over time influence breast cancer risk are inconclusive. However, it remains an important question to better identify high-risk women. Previous studies that used continuous measures of mammographic density found a non-significant relationship between changes in mammographic density and the risk of breast cancer (6,10,13). However, those studies had a limited sample size derived from its case-control design, and lacked sufficient time between mammographic examinations to allow for mammographic density changes to have a significant effect. Our findings, on the contrary, are in line with other studies using categorical measures for breast density, that reported an association between changes in mammographic density and breast cancer risk (9,10,12). Similarly to our findings, an increasing risk of breast cancer with increasing breast density over time has previously been reported (9,10,12). However, a decreasing risk of breast cancer with decreasing breast density was found in some studies (9,10), but not in others (12), possibly because of the small sample size in the latest. The discrepancy in the results reported between studies with continuous density measures and categorical measures may be explained by the fact that only broad density changes have an effect on breast cancer risk, and continuous density measures pool together small and large differences.

We found that changes in density categories over time were similarly associated with the risk for DCIS and invasive cancer. Nevertheless, estimates for DCIS had a reduced number of breast

cancer cases for some sub-groups resulting in wide confidence intervals, and thus the results should be interpreted with care. Most previous studies that have assessed the association of a single mammographic density separately for DCIS and invasive tumours found no differences in the direction and size of estimates (23–27). A pooled analysis from six studies showed that high mammographic density was strongly associated with breast cancer, but the intensity of the association was similar for DCIS and invasive tumours (24). However, other studies have suggested a stronger association between mammographic density and DCIS than that of invasive tumours (28,29). The stronger association has been attributed to the radiographic appearance of in situ cancers that might result in higher sensitivity of screening mammography for detection of DCIS as compared with invasive carcinoma (30). To our knowledge, this is the first study to assess the effect of mammographic density changes separately for the risk of DCIS and invasive cancer.

In agreement with most studies, we found that a single measure of breast density was associated with breast cancer risk (17–19,31). We observed that higher BI-RADS breast density categories were associated with an increased risk of breast cancer, with BI-RADS category D having the greatest risk, and BI-RADS category A the lowest. The differences in risk were observed for both BI-RADS density category measured at earliest and latest examination, with the estimates for latest examination being more prominently associated with an increased risk. This finding reinforces the existing evidence of a single mammographic density measure as a strong predictor of breast cancer risk. In our study, the density group women were moving from is also determinant of breast cancer risk. For example, the rates for A to B, B to B, C to B, and D to B, are steadily increasing (also were increasing the rates for B to C, C to C, D to C). This means that the risk was not uniquely determined by a single mammographic density measure, but it was also determined by the mammographic density change itself, and the density group women are moving from.

In our study population, 11.8% of women had an increase in mammographic density between the earliest and latest examination, which identifies a subset of women at an increased risk for breast cancer. Also, one in every four women experienced a decrease in mammographic breast density over time, which was associated with a decrease in risk. Because changes in mammographic density modulate the risk of breast cancer, this information can be used to identify high and low risk groups of women that can benefit from risk-stratified and personalized screening strategies. However, most women remained in the same breast density category (62.3%), and a single breast density measure can help determine their breast cancer risk, with denser breast representing a higher breast cancer risk. Models estimating the individual risk of breast cancer have shown that addition of breast density as a risk factor improves the discriminatory power of the model (32–35). A study predicting 5-year breast cancer risk found that using two-density measures did not substantially improve the overall discrimination compared with a model including only one density measure (34). Nevertheless, the study also showed that using both measures in women who experienced a decrease in breast density offered and improvement in risk classification that could be clinically relevant to recommend supplemental screening for women with dense breasts or several risk factors. Because high mammographic density reduces sensitivity of mammography and increases the risk of masking (36), women with dense breast could be targeted to shorter screening intervals, but also to the use of MRI or ABUS to improve sensitivity, increasing the efficiency of risk-based screening strategies (37,38). Women with an increase in breast density over time are at an increased breast cancer risk and should be informed about their increased risk and encouraged to regular screening participation.

The study has several limitations. Most of the change in mammographic density takes place around the age of menopause (7,39). As in most population-based breast cancer screening programs in Europe, breast cancer screening in Spain starts at age 50. Information on mammographic density

before this age is infrequent, overlapping with the age of menopause. However, the study of Kerlikowske et al. (9), included a large number of women younger than 50 years, and found that changes in mammographic density after age 50 had the greatest influence on breast cancer risk. Furthermore, increases in mammographic density observed in our study could be partially due to the moderate inter-radiologist reliability of BI-RADS density assessment, which could reflect density misclassification rather than a true density change (40–42). Reliability between readers using BI-RADS is modest (kappa statistic= 0.56) (43). Also, criteria for BI-RADS density classification has changed over time, particularly after publication in 2013 of the fifth edition of the BI-RADS guidelines. Women who may have previously been BI-RADS density category B are now defined as BI-RADS C if there is any dense area that could mask a tumour (44). It is likely that a proportion of women moving from B to C or C to B, which are the most common category changes, are due to poor inter-radiologist reliability or changes in BI-RADS density classification. Nevertheless, the BI-RADS classification has been shown to appropriately discriminate women at different risks for breast cancer, with a fourfold gradient in risk between BI-RADS categories A and D (45). In our study, radiologists performed breast density assessment as part of screening practice. Mammographic interpretation and breast density classification was performed by highly trained radiologists with more than 1000 screening mammograms read per year. Despite the moderate inter-rater agreement, our results are consistent with those published by other studies using BI-RADS breast density (1,9,46). Another limitation of the study is that information on confounding variables like body mass index, hormone therapy use, and menopausal status was lacking because the screening centres did not collect this information. These factors are known to be associated with mammographic density and with breast cancer risk. An increase in body mass index has been associated with a decrease in breast density (47), and cessation of hormone therapy use decreases mammographic density in some women (48). Adjusting for these and other confounding factors would have been desirable and could have refined our estimates. Nevertheless, previous studies have shown that additional adjustment did not substantially alter the estimates of the association

between mammographic density and breast cancer risk (1,18), neither the risk of mammographic density changes with breast cancer risk (9), which minimizes the expected impact of lack of adjustment for this potential confounders. Lastly, the proportion of women that changed BI-RADS breast density category was small, particularly those representing an increase in breast density over time, limiting our ability to identify associations for some sub-group analyses.

A major strength of this study is that data were obtained from a well-established population-based screening program with an average participation rate of 67% of invited women, and a re-attendance rate of 91.2% (49). We analysed information obtained from up to 20 years of follow-up, which guaranteed sufficient time to capture density changes correctly over time and to provide robust estimates. Because we wanted to minimize the confounding effect of age at examination and time between mammography examinations, we restricted our study population to women first screened ages 50–54 years and modelled the rate of breast cancer incidence by means of a longitudinal analysis. Choosing the younger 5-years age group at first screen ensured representativeness of the population of women targeted for screening mammography.

CONCLUSIONS

In summary, we found that although a modest proportion of women changed BI-RADS breast density category over time, the risk of breast cancer was modulated by mammographic density changes. An increase in BI-RADS density category was associated with increased breast cancer risk, and a decrease was associated with decreased risk. Using two longitudinal measures of BI-RADS breast density may help target women at higher future risk that could benefit from more intense screening strategies, particularly those experiencing increase in breast density over time.

DECLARATIONS

Conflict of interests: The authors declare that they have no conflicts of interest

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Table 1: Characteristics of the study population for women with and without a breast cancer diagnosis. All women aged 50-54 at earliest examination.

	No breast cancer (n=115 796)	Breast cancer (n= 1592)	p
BI-RADS breast density at earliest examination			< 0.05
A	17 818 (15.4)	124 (7.8)	*
B	62 171 (53.7)	715 (44.9)	*
C	20 456 (17.7)	342 (21.5)	*
D	15 351 (13.3)	411 (25.8)	*
BI-RADS breast density at latest examination			< 0.05
A	20 975 (18.1)	158 (9.9)	*
B	68 704 (59.3)	887 (55.7)	*
C	19 305 (16.7)	366 (23.0)	*
D	6 812 (5.9)	181 (11.4)	*
Age at latest breast density measure			< 0.05
50-54	37 513 (32.4)	480 (30.2)	
55-59	48 938 (42.3)	679 (42.7)	
60-64	21 042 (18.2)	337 (21.2)	*
65-69	8 303 (7.2)	96 (6.0)	
Time between earliest and latest breast density measure			
< 2 y	8 917 (7.7)	135 (8.5)	
2-4 y	39 430 (34.1)	550 (34.5)	
4-6 y	22 476 (19.4)	292 (18.3)	
6-8 y	14 461 (12.5)	198 (12.4)	
> 8 y	30 512 (26.3)	417 (26.2)	

* Different at p< 0.05 in a two-sided test of equality for column proportions (z-test). Tests are adjusted using the Bonferroni correction for multiple comparison.

Table 2: Distribution of mammographic density change between earliest and latest breast density measures across BI-RADS density categories for women with and without a breast cancer diagnosis. All women aged 50-54 at earliest examination.

BI-RADS breast density on earliest and latest examination stratified by earliest density measure	No breast cancer N=115 796 (column %)	Breast cancer N= 1592 (column %)	p
Earliest BI-RADS density = A			< 0.05
A : A	12 509 (10.8)	68 (4.3)	*
A : B	5 167 (4.5)	54 (3.4)	*
A : C	123 (0.1)	1 (0.1)	
A : D	19 (0.0)	1 (0.1)	
Earliest BI-RADS density = B			
B : A	7 948 (6.9)	78 (4.9)	*
B : B	47 274 (40.8)	527 (33.1)	*
B : C	6 084 (5.3)	90 (5.7)	
B : D	865 (0.7)	20 (1.3)	*
Earliest BI-RADS density = C			
C : A	411 (0.4)	10 (0.6)	
C : B	10 619 (9.2)	169 (10.6)	*
C : C	7 974 (6.9)	130 (8.2)	*
C : D	1 452 (1.3)	33 (2.1)	*
Earliest BI-RADS density = D			
D : A	107 (0.1)	2 (0.1)	
D : B	5 644 (4.9)	137 (8.6)	*
D : C	5 124 (4.4)	145 (9.1)	*
D : D	4 476 (3.9)	127 (8.0)	*

* Different at p< 0.05 in a two-sided test of equality for column proportions (z-test). Tests are adjusted using the Bonferroni correction for multiple comparison.

Table 3: Rate and adjusted relative risk of developing breast cancer based on BI-RADS measured at earliest and latest examination. (1)

Bi-RADS breast density	Women-years	N of breast cancer cases	Rate per 1000 women-years	Adjusted RR (95%CI) (2)
At earliest examination				
A	104 391	124	1.2	0.60 (0.49-0.73)
B	352 619	715	2.0	Ref.
C	113 144	342	3.0	1.49 (1.31-1.70)
D	112 701	411	3.6	1.68 (1.49-1.91)
At latest examination				
A	125 085	158	1.3	0.61 (0.52-0.73)
B	415 299	887	2.1	Ref.
C	105 704	366	3.5	1.69 (1.50-1.91)
D	36 767	181	4.9	2.18 (1.86-2.56)

BI-RADS, A = almost entirely fat; B = scattered fibroglandular; C = heterogeneously dense; D = extremely dense

CI, confidence interval; RR, relative risk;

(1) Based on 2 separate Poisson regression models for breast density at earliest examination, and at latest examination.

(2) All models adjusted for time between screening mammography examinations (offset), screening center, mammography type, and year of screen

Table 4: Rate and adjusted relative risk of developing breast cancer based on BI-RADS category density change stratified by BI-RADS density category at earliest examination [(1)]

BI-RADS breast density on earliest and latest examination stratified by earliest density measure	Women-years	N of breast cancer cases	Rate per 1000 women-years	Adjusted RR (95%CI) [(2)]
Earliest BI-RADS density = A				
A : A	69 328	68	1.0	Ref.
A : B	34 205	54	1.6	1.68 (1.13-2.50)
A : C	755	1	1.3	NE
A : D	102	1	9.8	NE
Earliest BI-RADS density = B				
B : A	50 907	78	1.5	0.79 (0.62-1.00)
B : B	266 499	527	2.0	Ref.
B : C	30 857	90	2.9	1.55 (1.24-1.94)
B : D	4 357	20	4.6	2.32 (1.48-3.63)
Earliest BI-RADS density = C				
C : A	3 848	10	2.6	0.63 (0.33-1.22)
C : B	65 291	169	2.6	0.70 (0.55-0.89)
C : C	37 866	130	3.4	Ref.
C : D	6 140	33	5.4	1.51 (1.03-2.22)
Earliest BI-RADS density = D				
D : A	1 003	2	2.0	0.47 (0.12-1.95)
D : B	49 305	137	2.8	0.60 (0.47-0.77)
D : C	36 226	145	4.0	0.94 (0.73-1.19)
D : D	26 168	127	4.9	Ref.

BI-RADS, A = almost entirely fat; B = scattered fibroglandular; C = heterogeneously dense; D = extremely dense

CI, confidence interval; RR, relative risk; NE, not estimable.

(1) Based on 4 separate Poisson regression models for each category of BI-RADS breast density at earliest examination

(2) All models adjusted for time between screening mammography examinations (offset), screening center, mammography type, and year of screen

Table 5: Rate and adjusted relative risk of DCIS and invasive cancer separately based on BI-RADS category density change stratified by BI-RADS density category at earliest examination [1]

BI-RADS breast density on earliest and latest examination stratified by earliest density measure	Women-years	DCIS		Invasive	
		N of breast cancer cases	Adjusted RR (95%CI) [2]	N of breast cancer cases	Adjusted RR (95%CI) [2]
Earliest BI-RADS density = A					
A : A	69 328	14	Ref.	50	Ref.
A : B	34 205	15	1.88 (0.84-4.22)	38	1.83 (1.15-2.92)
A : C	755	1	NE	0	NE
A : D	102	0	NE	1	NE
Earliest BI-RADS density = B					
B : A	50 907	19	0.65 (0.40-1.04)	56	0.82 (0.61-1.08)
B : B	266 499	152	Ref.	364	Ref.
B : C	30 857	24	1.57 (1.02-2.42)	62	1.49 (1.14-1.96)
B : D	4 357	5	1.79 (0.73-4.36)	13	2.29 (1.31-3.98)
Earliest BI-RADS density = C					
C : A	3 848	2	0.38 (0.09-1.59)	8	0.79 (0.38-1.66)
C : B	65 291	59	0.87 (0.56-1.36)	102	0.62 (0.47-0.83)
C : C	37 866	31	Ref.	94	Ref.
C : D	6 140	7	1.28 (0.56-2.91)	25	1.61 (1.03-2.50)
Earliest BI-RADS density = D					
D : A	1 003	1	NE	1	NE
D : B	49 305	59	0.79 (0.52-1.20)	75	0.52 (0.38-0.72)
D : C	36 226	45	1.03 (0.66-1.60)	93	0.88 (0.65-1.20)
D : D	26 168	37	Ref.	84	Ref.

BI-RADS, A = almost entirely fat; B = scattered fibroglandular; C = heterogeneously dense; D = extremely dense

CI, confidence interval; RR, relative risk; NE, not estimable.

(1) Based on 8 separate Poisson regression models for each category of BI-RADS breast density at earliest examination and tumor invasiveness (DCIS and invasive cancer). Tumor invasiveness was unknown for 55 breast cancer cases.

(2) All models adjusted for time between screening mammography examinations (offset), screening center, mammography type, and year of screen