Predictors of Mammographic Microcalcifications

Shadi Azam, MSc., Mikael Eriksson, MSc. Arvid Sjölander, PhD , Marike Gabrielson, PhD , Roxanna Hellgren, MD, PhD Kamila Czene, PhD, Per Hall, MD, PhD

Table of Contents

Supplementary Materials and Methods

Microcalcifications were measured, in both the mediolateral oblique and craniocaudal views, using the iCAD Computer-Aided Detection (M-Vu CAD®, Nashua, USA), software. The software is an FDA approved, class 3 device (PMA number P010038), with reproducibility being a part of the approval criteria. The probability of repeating detection of calcifications from the same breasts scanned on different mammography machines was 95.5% (+/- 3.4%) per image and 99.0% (+/-2.3%) per case. Previous results showed that the iCAD software is achieving a sensitivity of 92% in detecting suspicious microcalcification clusters [1, 2] with average specificity of 87% [3]. Clusters were defined according to a well-established neural network algorithm implemented by the iCAD software [2, 4] The software marks regions of interest on standard mammographic views to bring them to the attention of the radiologist.

Supplementary Tables

Table 1. Predictors of microcalcification clusters risk stratified by menopausal stats

Predictors	OR (95% CI)*	P-value†	P-value†	OR (95% CI) *	P-value †	P-value †
	Premenopausal women			**Postmenopausal** women		
Age baseline (years)§						
<50	1.00	Ref.		1.00	Ref.	
50-60	1.53 (1.40 to 1.67)	<0.001		1.25 (1.03 to 1.52)	0.02	
> 60	-	-		2.15 (1.77 to 2.62)	<0.001	
Continuous	1.06 (1.05 to 1.07)		<0.001	1.05 (1.05 to 1.06)		<0.001
BMI (kg/m^2)						
20.0-24.9	1.00	Ref.		1.00	Ref.	
25.0-29.9	0.79 (0.72 to 0.87)	<0.001		0.86 (0.81 to 0.92)	<0.001	
≥30.0	0.65 (0.56 to 0.74)	<0.001		0.87 (0.80 to 0.92)	0.002	
Continuous			<0.001			<0.001
Smoking status						
Never	1.00	Ref.		1.00	Ref.	
Former	0.95 (0.87 to 1.04)	0.29		0.83 (0.78 to 0.89)	<0.001	
Current	0.97 (0.86 to 1.11)	0.74		0.84 (0.76 to 0.93)	<0.001	
Alcohol consumption (gram/day) **						
0	1.00	Ref.		1.00	Ref.	
0.1-10	0.86 (0.78 to 0.95)	0.005		0.88 (0.81 to 0.95)	0.001	
>10	0.87 (0.76 to 1.02)	0.06		0.92 (0.84 to 1.01)	0.11	
Continuous			0.16			0.53
Physical activity, (MET-h per day)						
< 40	1.00	Ref.		1.00	Ref.	
40 – 44.9	0.98 (0.89 to 1.08)	0.89		0.96 (0.90 to 1.03)	0.35	
45.0 – 49.9	0.95 (0.85 to 1.06)	0.37		0.91 (0.83 to 1.03)	0.42	

≥ 50.0	0.93 (0.81 to 1.06)	0.32		0.96 (0.85 to 1.08)	0.52	
Continuous			0.28			0.20
Age at first birth (year)						
< 20	1.00	Ref.		1.00	Ref.	
20-25	0.99 (0.75 to 1.31)	0.94		0.81 (0.73 to 0.91)	<0.001	
> 25	0.93 (0.71 to 1.23)	0.61		0.68 (0.61 to 0.76)	<0.001	
Continuous			0.10			<0.001
Number of children						
0	1.00	Ref.		1.00		
1-2	1.00 (0.89 to 1.13)	0.92		0.95 (0.87 to 1.04)	0.30	
> 2	1.11 (0.96 to 1.27)	0.13		1.11 (1.02 to 1.22)	0.03	
Continuous			0.06			<0.001
Breast feeding duration (month)						
0	1.00	Ref.		1.00	Ref.	
1-5	0.92 (0.57 to 1.66)	0.91		1.18 (0.92 to 1.51)	0.18	
6-12	0.81 (0.54 to 1.28)	0.36		1.13 (0.92 to 1.39)	0.22	
>12	0.93 (0.63 to 1.43)	0.73		1.29 (1.07 to 1.58)	0.008	
Continuous			0.54			0.001
Time since last birth (year)						
<10	1.00	Ref.		Ref.	Ref.	
≥10	1.06 (0.95 to 1.19)	0.23		1.32 (0.84 to 2.20)	0.24	
Continuous			0.36			0.30
Age at menarche, (year)						
<13	1.00	Ref.		1.00	Ref.	
≥13	0.97 (0.90 to 1.06)	0.58		0.90 (0.83 to 0.95)	<0.001	
Continuous			0.16			<0.001
Oral contraceptive use						

Never	1.00			1.00	Ref.	
Ever	0.75 (0.67 to 0.96)	<0.001		0.86 (0.81 to 0.93)	<0.001	
MHT Status						
Never user	1.00	Ref.		1.00	Ref.	
Former user	0.85 (0.67 to 1.07)	0.18		0.92 (0.85 to 0.98)	0.02	
Current user	0.93 (0.67 to 1.25)	0.65		0.94 (0.82 to 1.07)	0.42	
Baseline mammographic area (cm^2)						
<9.0	1.00	Ref.		1.00	Ref.	
9.0- 19.9	1.12 (0.93 to 1.33)	0.20		1.26 (1.16 to 1.37)	<0.001	
20.0 – 40.0	1.43 (1.23 to 1.69)	<0.001		1.67 (1.54 to1.81)	<0.001	
>40	1.90 (1.63 to 2.23)	<0.001		2.11 (1.93 to 2.32)	<0.001	
Continuous			<0.001			<0.001
Family history of breast cancer						
No	1.00	Ref.		1.00	Ref.	
Yes	1.07 (0.96 to 1.20)	0.19		1.16 (1.07 to 1.25)	<0.001	
Overall PRS percentile						
0-20%	1.16 (0.82 to 1.65)	0.37		0.82 (0.64 to 1.06)	0.13	
20-40%	1.31 (0.93 to 1.83)	0.11		0.93 (0.73 to 1.19)	0.59	
40-60%	**1.00**	**Ref.**		**1.00**	**Ref.**	
60-80%	1.37 (0.98 to 1.92)	0.07		0.91 (0.71 to 1.17)	0.48	
80-100%	1.34 (0.96 to 1.87)	0.08		1.15 (0.91 to 1.47)	0.23	
Continuous			0.24			0.002

Abbreviations: BMI = Body mass index; MET = The metabolic equivalent of task; MHT = Menopausal hormone therapy; PRS= Polygenic risk score; CI = confidence interval, Ref. = Reference

*Adjusted Models: age, BMI, at baseline

† P-value is performed at the two-sided 0.05 significance level

§ Not adjusted for age at baseline

‖Not adjusted for BMI at baseline

** adjusted for age. BMI, and smoking

Table 2. A detailed description of the associations between breast cancer risk factors with microcalcification cluster risk, mammographic density and breast cancer risk

Predictors	**Suspicious microcalcification clusters***	**Mammographic density †**	**Breast cancer risk §**
	OR (95% CI)	**β (95% CI)**	**HR (95% CI)**
High Age	2.51 (2.28 to 2.77)	–8.25 (–9.19 to –7.31)	2.32 (1.88 to 2.85)
High MD	2.08 (1.93 to 2.25)	-	2.24 (1.76 to 2.85)
High PRS	1.22 (1.06 to 1.48)	0.14 (0.06 to 0.21) ‖	1.61 (1.57 to 1.65) **
Family history of breast cancer	1.13 (1.06 to 1.22)	1.67 (0.99 to 2.36)	1.76 (1.44 to 2.15)
More children	1.11 (1.02 to 1.20)	–5.95 (–6.75 to –5.14)	0.82 (0.62 to 1.10)
Longer period of breast feeding	1.22 (1.03 to 1.46)	2.29 (0.51 to 4.06)	0.81 (0.56 to 1.17)
High BMI ‡	0.87 (0.80 to 0.92)	–20.54 (–22.13 to –18.96)	1.26 (0.73 to 2.17)
Current smoking	0.89 (0.82 to 0.96)	–0.94 (–1.70 to –0.17)	1.08 (0.82 to 1.41)
Alcohol consumption	0.90 (0.84 to 0.97)	1.67 (0.90 to 2.44)	1.05 (0.79 to 1.38)
Physical activity	0.94 (0.86 to 1.03)	–1.75 (–2.58 to –0.92)	0.79 (0.56 to 1.14)
Late menarche	0.92 (0.88 to 0.97)	0.83 (0.33 to 1.32)	1.06 (0.88 to 1.27)
High age at first birth	0.72 (0.65 to 0.79)	2.40 (1.24 to 3.55)	1.39 (1.10 to 1.77)
Oral contraceptive use	0.84 (0.79 to 0.89)	–0.53 (–1.23 to 1.67)	0.90 (0.72 to 1.12)
MHT use	0.91 (0.85 to 0.97)	3.90 (2.58 to 5.21)	1.86 (1.28 to 2.71)

Abbreviations: β = beta coefficient, BMI = body mass index, CI = confidence interval, HR = hazard ratio, MD = mammographic density, MHT = menopausal hormone therapy, OR = Odds ratio, PRS = polygenic risk score

Point estimates are from the same dataset (KARMA Cohort) [5-7], except for the association between PRS and risk of breast cancer[5].

All variables are coded the same in two previous studies, except for BMI[6] and MD[5]

* Logistic regression used

† **Determinants of Mammographic Density Change**, Azam et al., 2019 [6]

Exclusion criteria: no informed consent, missing information in age and/or BMI, previous breast cancer, other cancers, breast enlargement and/or breast reduction, other breast surgeries, age at mammogram outside 40-70 years, women with < 3 examinations, screening interval outside 12-36 months

Population: 31,782 women

MD measurement: STRATUS dense area (cm^2)

Statistical analyses: Linear regression used, adjusted for age, BMI, menopausal status at baseline

§ **Mammographic Density Change and Risk of Breast Cancer**, Azam et al., 2019 [5]

Exclusion criteria: no informed consent, missing information in age and/or BMI, previous breast cancer, other cancers, breast enlargement and/or breast reduction, other breast surgeries, women with < 2 examinations

Population: 43,810 women, 43,247 healthy women, 563 breast cancer cases

MD measurement: STRATUS dense area (cm^2)

Statistical analyses: Cox proportional hazards regression used, adjusted for age and BMI at baseline. Due to small number of breast cancer cases the associations between some of the risk factors and risk of breast cancer did not reach the statistical significance.

‖ **Heritability of Mammographic Breast Density, Density Change, Microcalcifications, and Masses**, Holowko et al., 2020 [7]

The point estimate is taken from our most recent publication using the KARMA cohort, PRS was calculated for 9,365 women using 313 SNPs, linear regression used

** **Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes**, Mavadat et al., 2019 [8]

The point estimate is taken from a most up-to-date and comprehensive breast cancer polygenic risk score study, including 313 SNPs, logistic regression used

‡ increased risk for breast cancer only seen among postmenopausal women

Supplementary References

1. iCAD. Breast Health Solutions: Advanced Cancer Detection Built on Artificial Intelligence 2019-09-27.

2. Food and Drug Administeration - Summary of Safety and Effectiveness Data Mammoreader - iCAD.

3. Cole EB, Zhang Z, Marques HS, Edward Hendrick R, Yaffe MJ, Pisano ED. Impact of computer-aided detection systems on radiologist accuracy with digital mammography. *AJR American journal of roentgenology* 2014;**203**: 909-16.

4. Jeffrey C, WehnesJames P, MonacoDavid S, HardingJames H, PikeAnbinh T, HoLawrence M H. Microcalcification detection classification in radiographic images. *United States Patent and Trademark* 2014.

5. Azam S, Eriksson M, Sjolander A, Hellgren R, Gabrielson M, Czene K, Hall P. Mammographic Density Change and Risk of Breast Cancer. *Journal of the National Cancer Institute* 2019.

6. Azam S, Sjolander A, Eriksson M, Gabrielson M, Czene K, Hall P. Determinants of Mammographic Density Change. *JNCI cancer spectrum* 2019;**3**: pkz004.

7. Holowko N, Eriksson M, Kuja-Halkola R, Azam S, He W, Hall P, Czene K. Heritability of Mammographic Breast Density, Density Change, Microcalcifications, and Masses. *Cancer research* 2020;**80**: 1590-600.

8. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, Tyrer JP, Chen TH, Wang Q, Bolla MK, Yang X, Adank MA, et al. Polygenic Risk Scores for Prediction of Breast Cancer and Breast Cancer Subtypes. *American journal of human genetics* 2019;**104**: 21-34.