Radiology

ORIGINAL RESEARCH • BREAST IMAGING

Identification of Women at High Risk of Breast Cancer Who Need Supplemental Screening

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Background: Mammography screening reduces breast cancer mortality, but a proportion of breast cancers are missed and are detected at later stages or develop during between-screening intervals.

Purpose: To develop a risk model based on negative mammograms that identifies women likely to be diagnosed with breast cancer before or at the next screening examination.

Materials and Methods: This study was based on the prospective screening cohort Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA), 2011–2017. An image-based risk model was developed by using the Stratus method and computer-aided detection mammographic features (density, masses, microcalcifications), differences in the left and right breasts, and age. The lifestyle extended model included menopausal status, family history of breast cancer, body mass index, hormone replacement therapy, and use of tobacco and alcohol. The genetic extended model included a polygenic risk score with 313 single nucleotide polymorphisms. Age-adjusted relative risks and tumor subtype specific risks were estimated by using logistic regression, and absolute risks were calculated.

Results: Of 70 877 participants in the KARMA cohort, 974 incident cancers were sampled from 9376 healthy women (mean age, 54 years ± 10 [standard deviation]). The area under the receiver operating characteristic curve (AUC) for the image-based model was 0.73 (95% confidence interval [CI]: 0.71, 0.74). The AUCs for the lifestyle and genetic extended models were 0.74 (95% CI: 0.72, 0.75) and 0.77 (95% CI: 0.75, 0.79), respectively. There was a relative eightfold difference in risk between women at high risk and those at general risk. High-risk women were more likely to be diagnosed with stage II cancers and with tumors 20 mm or larger and were less likely to have stage I and estrogen receptor–positive tumors. The image-based model was validated in three external cohorts.

Conclusion: By combining three mammographic features, differences in the left and right breasts, and optionally lifestyle factors and family history and a polygenic risk score, the model identified women at high likelihood of being diagnosed with breast cancer within 2 years of a negative screening examination and in possible need of supplemental screening.

Online supplemental material is available for this article.

Numerous studies have shown that mammographic screening leads to reduced mortality from breast cancer and that adjuvant therapy reduces the risk of recurrence (1,2). As a consequence, breast cancer mortality has steadily decreased during the past decades. However, breast cancer is still the most common cause of cancer death in women globally (3).

Although screening mammography reduces breast cancer mortality by approximately 20% (range, 2%–40%) (4,5), the optimal screening protocol is still uncertain. Screening and age intervals are intensively debated, whereas the risk of developing breast cancer and masking of an existing tumor during mammographic screening are less often taken into consideration (6). In a population of women attending regular biennial screening, approximately 25% of all cancers are detected in the interval between mammographic screening examinations (7,8). An interval cancer is missed, is masked, or is a fast-growing cancer that develops between two screening examinations (9).

We previously developed a risk model in which image features and lifestyle factors were used to predict the risk of breast cancer before or at the next screening examination, including 433 patients with breast cancer (10). We have now expanded the model to include a polygenic risk score (PRS) based on 313 single nucleotide polymorphisms, added estimates for tumor subtypes, improved image features, included 1153 patients with breast cancer, and validated the model in three external cohorts including 717 patients with breast cancer. With this risk model we aimed to create a protocol that has the potential to guide

Abbreviations

AUC = area under the receiver operating characteristic curve, CI = confidence interval, HR = hazard ratio, KARMA = Karolinska Mammography Project for Risk Prediction of Breast Cancer, OR = odds ratio, PRS = polygenic risk score

Summary

A short-term risk model based on three mammographic features, with optional lifestyle factors and a polygenic risk score, identified women at high risk of breast cancer who need supplemental screening.

Key Results

- The full risk model for predicting breast cancer reached an area under the receiver operating characteristic curve of 0.77.
- There was an eight-fold relative difference in risk between the women at high risk and those at general risk.
- High-risk women were more likely to be diagnosed with stage II cancers and with tumors 20 mm or larger and were less likely to have stage I and estrogen receptor–positive tumors.

radiologists in identifying women with a negative screening result who are potential candidates for supplemental screening, more frequent screening, or risk-reducing medication.

Materials and Methods

All women in the Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) case-cohort provided written informed consent, and the ethics review board at Karolinska Institutet approved the study (diary number 2010/958–31/1). The Cohort of Screen-Age Women study was approved by the ethics board at Karolinska Institutet (diary number 2016/2600–31), and the Malmö Breast Tomosynthesis Screening Trial was approved by the ethics board at Lund University (diary number 2009/770).

Study Cohort

Women visiting mammography screening units at four hospitals in Sweden were recruited to the KARMA cohort between 2011 and 2013 (11). In Sweden, women aged 40–74 years are screened at 18–24-month intervals. Between 2011 and 2017, participants diagnosed with incident breast cancers after having entered the KARMA cohort and a random selection of 9376 healthy breast cancer–free women from the entire KARMA cohort formed the case-cohort. The mean follow-up time was 4.9 years, and the mean time from the last screening examination to diagnosis for interval cancers was 1.2 years.

Risk Factors

Information on age, body mass index, family history of breast cancer, use of hormone replacement therapy, use of tobacco and alcohol, and menopausal status was retrieved from self-reported questionnaires at study entry. Information on tumor characteristics, immunohistochemistry markers, and clinical-pathologic variables was added through linkage to the Swedish nationwide breast cancer registry (12). Full-field for-presentation digital mammograms in mediolateral oblique and craniocaudal views, obtained with machines from multiple vendors, were retrieved (11). Mammographic density was measured by using the area-based Stratus method (13). Suspicious microcalcifications and masses with malignant potential were identified with software (iCAD version 2.0; iCAD, Nashua, NH) (14,15). DNA for patients with breast cancer and healthy individuals was extracted from whole blood and genotyped by using the OncoArray genotyping chip (Illumina, San Diego, Calif) (16). PRSs, including 313 single nucleotide polymorphisms, were calculated for each individual as described elsewhere (17). Appendix E1 (online) presents a detailed definition of the risk factors (12,14,17–20).

Statistical Analysis

Baseline characteristics are presented based on descriptive statistics in the KARMA cohort. Differences between women with breast cancer and healthy women were calculated by using the Student *t* test, Wilcoxon rank sum, and χ^2 test for variable means, medians, and percentages, respectively.

Risk models were developed to predict the development of breast cancer up to 2 years after a negative screening mammogram on the basis of the risk factors. Negative screening mammograms obtained 3 months to 2 years before diagnosis were used for patients with cancer, along with mammograms in healthy women from the corresponding time period.

Three risk models were developed by using conditional logistic regression stratified according to age at the last negative mammographic examination before diagnosis. Model 1 included averages and differences in the left and right breasts with regard to mammographic density, microcalcifications, masses, and age; model 2 combined variables in model 1 with lifestyle factors and family history of breast cancer; and model 3 added the PRS to the variables in model 2. A detailed description of how the models were generated is shown in Appendix E2 (online) (21) and is available at *github.com/imikeclassic/KRisk.* The risk results were presented to radiologists as secondary capture images on workstations in the screening workflow as described in Appendix E3 (online).

Absolute risks were calculated on the basis of the estimated relative risks, Swedish national incidence rates of breast cancer and competing mortality risks, and risk factor exposure prevalence from the KARMA cohort (10). The absolute risks were categorized on the basis of the guidelines of the U.K. National Institute for Health and Care Excellence (22). The 10-year risk cutoffs used for women aged 40–50 years with general, moderate, and high risk were divided by 5 to calculate 2-year risk cutoffs. This corresponded to the 2-year risk categories of less than 0.6% (general risk), 0.6% to less than 1.6% (moderate risk), and 1.6% or greater (high risk). Because the group with less than 0.6% risk included the majority of the women, the group was further divided to include a low-risk group (2-year risk $<0.15\%$).

External validation was performed by using three cohorts: Cohort of Screen-Age Women, Malmö Breast Tomosynthesis Screening Trial cohort, and a separate subset of KARMA participants not used for training. The cohorts are described in Appendix E4 (online) (23).

Absolute risks were calculated and areas under the receiver operating characteristic curve (AUCs) were estimated with the

well-known Gail, Tyrer-Cuzick, and polygenic risk models for model comparisons by using the KARMA cohort where the required risk factors were available.

Statistical analyses were performed with software (SAS version 9.4 [SAS Institute, Cary, NC] and R version 3.3 [R Foundation for Statistical Computing, Vienna, Austria]). A two-sided $P = .05$ was indicative of a statistically significant difference.

Results

Characteristics of the Study Cohort

Of 70 877 participants recruited to the KARMA cohort between 2011 and 2017, a total of 974 participants were diagnosed with incident breast cancers after entering the cohort (mean age, 58 years ± 9 [standard deviation]). Together with a random selection of 9376 healthy women without breast cancer (mean age, 54 years ± 10) from the entire KARMA cohort, these participants formed the case-cohort of 10 350 women. Characteristics of women with breast cancer and the control population are shown in Table 1.

Model Performance

The discrimination performance of the KARMA risk tool (AUC) was 0.73 (95% confidence interval [CI]: 0.71, 0.74) for the image-based model (model 1); 0.74 (95% CI: 0.72, 0.75) for model 2, which included the image features, family history, and lifestyle factors; and 0.77 (95% CI: 0.75, 0.79) for the full model with image features, family history, lifestyle factors, and the PRS (model 3) (Table 2). The Hosmer-Lemeshow model fit statistic showed good model fit, with $P > .05$ for all models. The risk score based on image features (model 1) was validated in the external Malmö Breast Tomosynthesis Screening Trial and Cohort of Screen-Age Women cohorts and the external validation data set in KARMA. AUCs were 0.71 (95% CI: 0.67, 0.75), 0.73 (95% CI: 0.71, 0.76), and 0.73 (0.69, 0.77), respectively. The contributions of the different risk factors to the models described in Table 2 are shown in Table E1 (online). Notably, microcalcifications showed a risk association of odds ratio (OR) 1.88 (95% CI: 1.66, 2.14) in premenopausal women and OR 1.63 (95% CI: 1.50, 1.78) in postmenopausal women. Mammographic density showed risk associations of OR 1.49 (95% CI: 1.31, 1.70) in premenopausal women and OR 1.35 (95% CI: 1.24, 1.47) in postmenopausal women. The presence of masses was the strongest factor associated with breast cancer, with an OR of 2.03 (95% CI: 1.76, 2.34) in premenopausal women and an OR of 2.00 (95% CI: 1.83, 2.19) in postmenopausal women. Left-right difference in microcalcifications added OR 1.46 (95% CI: 1.30, 1.65) and OR 1.28 (95% CI: 1.17, 1.36) to the risk association in premenopausal and postmenopausal women, respectively. Left-right difference in masses added OR 1.64 (95% CI: 1.44, 1.87) and OR 1.79 (95% CI: 1.64, 1.96) to the risk association in premenopausal and postmenopausal women. The PRS showed associations of OR 1.62 (95% CI: 1.43, 1.83) and OR 1.43 (95% CI: 1.31, 1.56) in premenopausal and postmenopausal women, respectively.

In comparison with the KARMA risk score, the AUC for the 313 single nucleotide polymorphism PRS model alone reached 0.64 in the KARMA case-cohort. Similar results were seen in other prospective studies from different populations included in the study by Mavaddat et al (20). The AUCs of the Tyrer-Cuzick and Gail models were 0.62 and 0.61, respectively, after the addition of mammographic density (Table 3) (13,17,24,25). The PRS, Tyrer-Cuzick, and Gail risk scores showed lower AUCs compared with all KARMA risk models (model 1: AUC, 0.73 [95% CI: 0.71, 0.72]; $P < .01$ for all models). The PRS, Tyrer-Cuzick, and Gail models have been reported with similar AUCs previously (23,26).

Absolute and Relative Risks

Figure 1 shows the distribution of 2-year absolute risk in patients and control participants in the KARMA case-cohort. Approximately 8% of the women (810 of 10 350) fell into the highest risk category (women with 2-year risk >1.6%) (10, 26). In contrast, 27% of woman had a risk below 0.15%. The absolute median risk of breast cancer in the low-risk group was 0.09%, corresponding to approximately one woman per 1000 diagnosed with breast cancer within 2 years. For the high-risk group, the corresponding values were 2.70%, corresponding to one woman per 35 diagnosed with breast cancer within 2 years. The relative risks of the high- and low-risk groups compared with the reference general-risk group were 9.4 and 0.3, respectively, corresponding to a 30-fold relative risk between high-risk and low-risk women.

Tumor Characteristics in Women at High Risk versus General Risk

Figure 2 describes the tumor characteristics in women at high risk (8% of the KARMA women) compared with women at general risk according to the image-based model 1, the lifestyle and familial extended model 2, and the full model 3. The overall hazard ratio (HR) in comparing the high-risk group with the general-risk group was 8.5 (95% CI: 7.1, 10.2) for model 1, 7.9 (95% CI: 5.8, 10.7) for model 2, and 7.6 (95% CI: 5.6, 10.3) for model 3. Forest plots show the HRs for tumor characteristics in the high-risk group compared with those in the general-risk group in relation to the overall HR. With model 1, women in the high-risk group were more likely to have tumors measuring 20 mm or greater (HR, 1.34; 95% CI: 1.18, 1.52) and stage II tumors (HR, 1.54; 95% CI: 1.29, 1.83) compared with the general-risk group. High-risk patients were also less likely to be diagnosed with stage I tumors (HR, 0.90; 95% CI: 0.86, 0.93) and estrogen receptor–positive tumors (HR, 0.96; 95% CI: 0.94, 0.98). Models 2 and 3 predicted tumor characteristics with similar estimates as model 1 except for estrogen receptor–negative tumors (HR, 0.74 [95% CI: 0.56, 0.98] and 0.65 [95% CI: 0.46, 0.92] for models 2 and 3, respectively).

Risk for Interval Cancer

With regard to the risks for interval cancer, the HR was 7.9 (95% CI: 5.8, 10.8) for model 1, 7.9 (95% CI: 5.8, 10.7) for model 2, and 7.6 (95% CI: 5.6, 10.3) for models 3.

Table 1: Baseline Characteristics of 974 Women with Breast Cancer and 9376 Healthy Women in the KARMA Case-Cohort Study

Characteristic	Women with Breast Cancer	Healthy Women	*P* Value*
No. of women	974	9376	…
Age at baseline (y)	58 ± 9	54 ± 10	<.001
Invasive breast cancer†	824 (85)	…	…
Age at breast cancer diagnosis (y)	60.5 ± 9.2	…	…
Screening-detected breast cancer†	690 (72)	…	…
Body mass index	25.6 ± 4.2	25.2 ± 4.3	.004
Age at menarche (y)	13.1 ± 1.5	13.1 ± 1.5	.20
Parity†	843 (87)	8098 (87)	.84
Age at first birth (y)	27.1 ± 5.2	27.1 ± 5.3	.67
Current use of hormone replacement therapy†	67 (7)	365 (4)	<.001
Regular smoking during previous year†	119 (12)	1128 (12)	.88
Regular alcohol drinking during previous year†	807 (83)	7624 (81)	.26
Postmenopausal†	673 (69)	5067 (54)	<.001
Breast cancer in family†	220 (23)	1295 (14)	<.001
Onset of breast cancer in family, age ≤50 y†	52 (5)	281 (3)	<.001
Mammographic density (%)	25.6 ± 18.4	20.0 ± 19.3	.34
Microcalcifications (probability)	0.21 ± 0.24	0.09 ± 0.13	<.001
Masses (probability)	0.26 ± 0.27	0.16 ± 0.19	<.001
Left-right difference in mammographic density (%)	6.0 ± 6.1	5.7 ± 6.1	.10
Left-right difference in microcalcifications (probability)	0.06 ± 0.09	0.02 ± 0.04	<.001
Left-right difference in masses (probability)	0.08 ± 0.09	0.04 ± 0.05	<.001

Note.—Except where indicated, data are means ± standard deviations. KARMA = Karolinska Mammography Project for Risk Prediction of Breast Cancer.

* *P* values for means were calculated by using the Student *t* test, and *P* values for percentages were calculated with the χ^2 test.

† Numbers are numbers of women, with percentages in parentheses.

Table 2: Discrimination Performance of Three Risk Models

Model	AUC
KARMA case-cohort (974 cancers, 9376 healthy women)	
Model 1: mammographic density, microcalcifications, masses, age	0.73 (0.71, 0.74)
Model 2: variables from model 1 + lifestyle and familial risk factors*	0.74 (0.72, 0.75)
Model 3: variables from model 2 + PRS†	0.77 (0.75, 0.79)
Malmö Breast Tomosynthesis Screening Trial cohort (104 cancers, 9745 healthy women), model 1	0.71 (0.67, 0.75)
Cohort of Screen-Age Women (613 cancers, 8489 healthy women), model 1	0.73 (0.71, 0.76)
KARMA external validation set (179 cancers, 9491 healthy women), model 1	0.73 (0.69, 0.77)

Note.—The model 1 2-year risk is compared with the three external validation data sets. The discrimination performances in subgroups of premenopausal and postmenopausal women in the KARMA cohort and in subgroups of women with invasive and in situ cancers were not significantly different from the average performances in the three models. Numbers in parentheses are 95% confidence intervals. AUC = area under the receiver operating characteristic curve, KARMA = Karolinska Mammography Project for Risk Prediction of Breast Cancer, PRS = polygenic risk score.

* The included lifestyle and familial risk factors were body mass index, menopausal status, current use of hormone replacement therapy, tobacco use, alcohol use, and family history of breast cancer.

† PRS including 313 single nucleotide polymorphisms (20).

Discussion

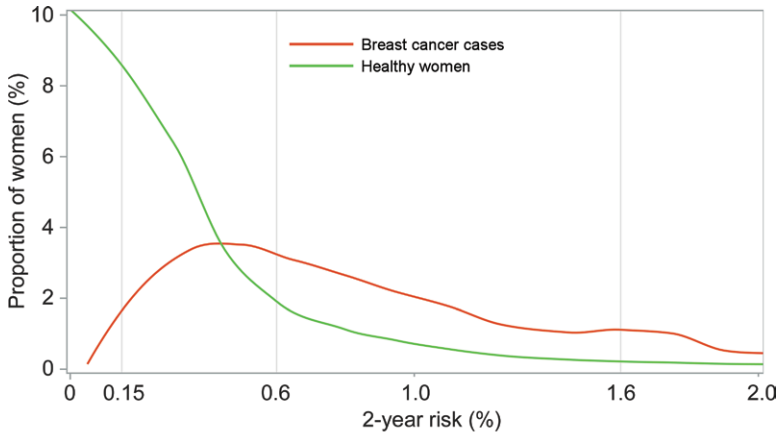
Mammography screening reduces breast cancer mortality, but a substantial proportion of breast cancers are missed and are detected at later stages or develop between screening intervals. The Karolinska Mammography Project for Risk Prediction of Breast Cancer (KARMA) risk tool amalgamates mammographic features, lifestyle factors, and a polygenic risk score to enable identification of women more likely to be diagnosed with a primary breast cancer before or at the next mammographic screening examination. The full model reached an area under the receiver operating characteristic curve of 0.77. When comparing women at highest risk with women at general risk, women at high risk had eight times higher relative risk of being diagnosed with breast cancer, corresponding to a 30-fold gradient when women in the highest and lowest risk groups were compared. Approximately 8% of the population was at high risk as defined by the guidelines of the National Institute for Health and Care Excellence (22). It is recommended that women in this risk category undergo increased surveillance and risk-reduction interventions. The corresponding number

for high risk according to the U.S. Preventive Services Task Force definition (3% 5-year risk cutoff) was 12% (27). In the high-risk group, one woman in 35 will be diagnosed with an interval cancer or a cancer at the next screening examination. The KARMA risk tool identifies women with more stage II tumors and tumors 20 mm or larger and with fewer stage I and estrogen receptor–positive tumors relative to the overall hazard ratio.

Table 3: Discrimination Performance with Use of Comparison Risk Models

Model	AUC
PRS	0.64 (0.62, 0.66)
PRS + mammographic density	0.67 (0.65, 0.69)
Tyrer-Cuzick	0.58 (0.56, 0.60)
Tyrer-Cuzick + mammographic density	0.62 (0.60, 0.64)
Gail	0.56 (0.54, 0.58)
Gail + mammographic density	0.61 (0.60, 0.63)

Note.—Table shows the discrimination performance (AUC) of the PRS, Tyrer-Cuzick, and Gail risk scores with and without mammographic density in the Karolinska Mammography Project for Risk Prediction of Breast Cancer case-cohort. The PRS included 313 single nucleotide polymorphisms (20). Mammographic density (13) was adjusted for age and body mass index. The Tyrer-Cuzick model (23) includes risk factors regarding age, age at menarche, age at first child, menopause, height, weight, use of hormone replacement therapy, hyperplasia, atypical hyperplasia, lobular cancer in situ, and first- or second-degree family history of breast cancer. The Gail model (24) includes risk factors regarding age, age at menarche, age at first live birth, number of previous breast biopsies, atypical hyperplasia, and number of instances of first-degree family history of breast cancer. Numbers in parentheses are 95% confidence intervals. AUC = area under the receiver operating characteristic curve, PRS = polygenic risk score.



Risk groups[1]	Percent women at risk	Absolute 2-year risk (%)	Relative risk[2]
0-0.15 (low)	26.7	0.09	0.3
0.15-<0.6 (general)	48.2	0.29	1.0 (reference)
0.6-<1.6 (moderate)	17.3	0.87	3.0
≥1.6 (high)	7.8	2.70	9.4

Figure 1: Graph shows frequency distribution of 2-year absolute risks for developing breast cancer in women with breast cancer and healthy women in Karolinska Mammography Project for Risk Prediction of Breast Cancer case-cohort based on model 3. Model 3 includes mammographic density, microcalcifications, masses, age, lifestyle and familial risk factors, and polygenic risk score. *1*, Cutoffs for general-, moderate-, and high-risk groups are based on National Institute for Health and Care Excellence guidelines for 10-year risk in women aged 40–50 years (<3%, 3%–8%, and >8%, respectively) divided by 5. We added a fourth low-risk group with an absolute risk cutoff of 0.15. *2*, Relative risk was calculated as ratios of median risks in each absolute 2-year risk category. High-risk women had 30-fold higher risk compared with low-risk women.

There are several distinctive features of our 2-year risk model. It was generated by using a large prospective data set, it was designed to build on three mammographic features and left-right differences of these features, and it can be extended with lifestyle and familial factors and a PRS. Our tool for measuring mammographic density has been used in several studies (13). When measuring microcalcifications and masses, we used U.S. Food and Drug Administration–approved and established computer-aided detection software (14). A recent study showed similar discrimination results as ours, although the study aim was to use the model to reduce the need to review negative mammograms (28).

Most current risk models use established risk factors for breast cancer, such as number of children, age at first child's birth, family history of breast cancer, and previous benign breast disease, and generate a 5- or 10-year or lifetime risk (29). The few models in which mammographic features are added use the reader-dependent Breast Imaging Reporting and Data System score (30). Different genetic scores have been tested, but to our knowledge none are as comprehensive as the one we used (31).

Current risk models are designed for use in prevention and for referring high-risk women for more intense screening in early detection (32,33). The preclinical stage of a breast cancer is assumed to be 10 years, but a cancer is typically detectable only approximately 3 years before diagnosis (34–36). This suggests that an effective clinical risk model used for individualizing screening should be a short-term model. It could be argued that a short-term risk model merely picks up developing cancers and could be viewed as an expanded early-detection device. From a clinical perspective, with breast health as the main aim, the distinction between detection or risk estimation is of lesser importance. Our model identifies women in whom there is a high likelihood that they will be diagnosed with a cancer that was missed, masked, or fast growing.

A key question is whether a short-term model based on mammographic features—that is, model 1—is sufficient for identifying high-risk women or whether a more complex model should be used. Our results indicate that information on lifestyle, family history, and PRS improved the model. A scoring system based only on automated image analyses would be easier to implement.

The concept of breast cancer screening has been challenged during the past decades (5). Overdiagnosis of nonfatal cancers is a major problem. With the image-based model, when we compared the women at 8% highest risk with women at general risk, women in the high-risk group showed more

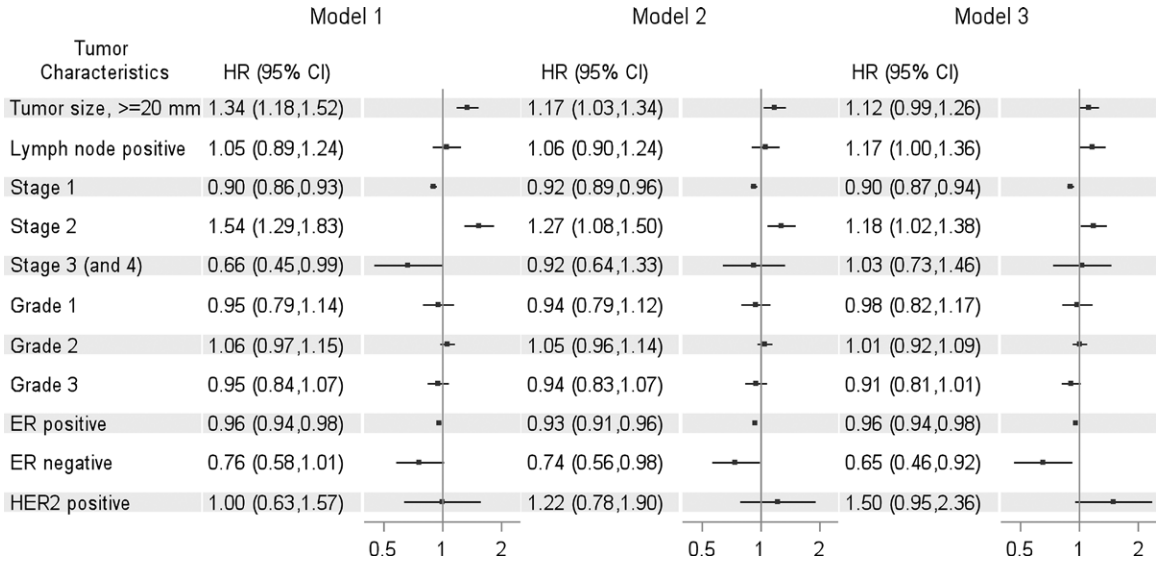


Figure 2: Plot shows hazard ratios (HRs) of tumor characteristics in patients with high risk relative to those in women with general risk by using overall HR as reference. Results were obtained with models 1, 2, and 3 in the Karolinska Mammography Project for Risk Prediction of Breast Cancer case-cohort. Horizontal bars represent nominal 95% confidence limits. Model 1 includes age, mammographic density, microcalcifications, and masses in breast. Model 2 includes variables in model 1 and lifestyle and familial factors. Model 3 includes variables in model 2 and polygenetic risk score. Overall reference risk was HR of 8.5 (95% confidence interval [CI]: 7.1, 10.2) for model 1, HR of 8.4 (95% CI: 7.1, 10.1) for model 2, and HR of 7.7 (95% CI: 6.4, 9.2) for model 3. Risk for interval cancer was HR of 7.9 (95% CI: 5.8, 10.8) for model 1, HR of 7.9 (95% CI: 5.8, 10.7) for model 2, and HR of 7.6 (95% CI: 5.6, 10.3) for model 3. ER = estrogen receptor, HER2 = human epidermal growth factor receptor 2.

stage II cancers and cancers 20 mm or larger and fewer stage I and estrogen receptor–positive cancers relative to the overall HR. This is in contrast to current risk models that identify less aggressive subtypes (37).

Not all high-risk women have dense breasts, and not all women with high breast density are at high risk. Approximately half of the high-risk women in our study had the equivalent of Breast Imaging Reporting and Data System A or B density (fatty breasts or breasts with scattered fibroglandular tissue), and their risk was influenced by microcalcifications, masses, left-right difference, and family history of breast cancer (data not shown). The Food and Drug Administration recently issued a press release on a policy change regarding mammography service, which described mammographic density as the only factor to report when notifying women of breast cancer risk and masking (38). Our results imply that such an approach is not necessarily the best advice.

Our study had limitations. We were able to externally validate only model 1 because we were not able to identify comprehensively phenotyped prospective screening cohorts. For the same reason, we were unable to validate the association with more stage II cancers and those 20 mm or larger and fewer stage I and estrogen receptor–positive cancers. Our model was developed by using a prospective screening cohort in which women were invited for 18–24-month screening examinations from ages 40 to 74 years. National screening programs differ with respect to age range for invitation, screening intervals, and screening modalities, but our model could be adopted to other screening routines and modalities.

In conclusion, we have shown that lifestyle factors and polygenic risk scores add to a short-term risk model built on in-depth analyses of three mammographic features and their differences. With a high discriminatory performance, the model has the potential to support the decision regarding which women should be recalled for supplemental screening or should undergo more frequent screening, or in whom risk-reducing medication should be recommended, thereby potentially improving overall prognosis of breast cancer and decreasing breast cancer incidence.

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