

Modeling risk assessment for breast cancer in symptomatic women: a Saudi Arabian study

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Background: Despite the continuing increase in the breast cancer incidence rate among Saudi Arabian women, no breast cancer risk-prediction model is available in this population. The aim of this research was to develop a risk-assessment tool to distinguish between high risk and low risk of breast cancer in a sample of Saudi women who were screened for breast cancer.

Methods: A retrospective chart review was conducted on symptomatic women who underwent breast mass biopsies between September 8, 2015 and November 8, 2017 at King Abdulaziz Medical City, Riyadh, Saudi Arabia.

Results: A total of 404 (63.8%) malignant breast biopsies and 229 (36.2%) benign breast biopsies were analyzed. Women ≥ 40 years old (aOR: 6.202, CI 3.497–11.001, $P=0.001$), hormone-replacement therapy (aOR 24.365, 95% CI 8.606–68.987, $P=0.001$), postmenopausal (aOR 3.058, 95% CI 1.861–5.024, $P=0.001$), and with a family history of breast cancer (aOR 2.307, 95% CI 1.142–4.658, $P=0.020$) were independently associated with an increased risk of breast cancer. This model showed an acceptable fit and had area under the receiver-operating characteristic curve of 0.877 (95% CI 0.851–0.903), with optimism-corrected area under the curve of 0.865.

Conclusion: The prediction model developed in this study has a high ability in predicting increased breast cancer risk in our facility. Combining information on age, use of hormone therapy, postmenopausal status, and family history of breast cancer improved the degree of discriminatory accuracy of breast cancer prediction. Our risk model may assist in initiating population-screening programs and prompt clinical decision making to manage cases and prevent unfavorable outcomes.

Keywords: breast cancer management, risk assessment, modeling, patient stratification, predictive tool

Introduction

The incidence of breast cancer is increasing in Saudi Arabia and is currently the most common cancer among women,¹ accounting for 28.7% of all cancers reported among females in the country.² According to the Saudi Cancer Registry, the age-standardized incidence in 2001 was 11.8 per 100,000 females,³ which increased to 22.7 in 2014.² A Saudi Arabian study in 2008 reported that the incidence of breast cancer was expected to increase by 350% in 2025.⁴ The apparent increase in breast cancer incidence is possibly attributable to genetic, environmental, and dietary factors.¹

Breast cancer remains the major cause of death among women in Saudi Arabia.¹ This poor prognosis could be due to diagnosis at an advanced stage.⁵ Early detection of breast cancer is known to improve patients' survival and clinical outcomes.⁶ Also,

early detection can be aided by applying risk-assessment tools to stratify patients with greater risk of breast cancer.⁷ This may aid the screening process to improve individual clinical decision making. Numerous breast cancer risk-prediction models have been developed and validated in various female populations to aid diagnosis decision making and improve accuracy.^{8–10}

Gene expressions for breast cancer in Saudi Arabia are different from those in the North American population.¹¹ As such, the generalizability of the current existing models may be suitable for specific populations where they have been validated, but may not be suitable to project the risk of breast cancer in women in Saudi Arabia. To our knowledge, there is a great need to develop and validate a risk-prediction model in Saudi Arabia to stratify patients at high risk effectively and achieve better understanding of existing risk-prediction models.

The aim of this study was to develop a risk-assessment tool to distinguish between high risk and low risk of breast cancer in a sample of women screened for breast cancer at King Abdulaziz Medical City, Riyadh (KAMC-RD), Ministry of National Guard – Health Affairs (MNG-HA), Saudi Arabia. The model assessed the contribution of demographic, clinical, and reproductive factors and breast-imaging findings in predicting breast cancer. We hypothesized that a number of factors would be associated with increased risk of breast cancer in women who had undergone a biopsy of breast mass at KAMC-RD, MNG-HA.

Methods

A single center retrospective chart review was conducted on 637 symptomatic women who underwent a biopsy of breast mass between September 8, 2015, and November 8, 2017, at KAMC-RD, MNG-HA. The study received ethical approval from the institutional review board at the MNG-HA (SP17/027/R). Due to the study design, patient consent to review their medical records was not required as per the institutional review board.

Data were retrieved on women's age at biopsy of breast mass, body-mass index (kg/m^2), diabetes, hypertension, asthma, lung disease, hyperlipidemia, use of oral contraceptives, use of hormone-replacement therapy (HRT) to treat signs and symptoms, change in size or skin of breast, family history of breast cancer, and history of genital disease. These data were recorded as yes/no. Breast cancer in Saudi Arabia predominantly impacts women who are over 40 years of age.¹² Women's age at biopsy was classified into two groups: <40 years and 40 years or more. This cutoff value was defined by the Youden index, as it produced sensitivity of 93% and

specificity of 57.2%. In accordance with the World Health Organization, a body-mass index $\geq 30 \text{ kg}/\text{m}^2$ was used to define obesity.¹³

Data were extracted on postmenopausal status (yes/no) from medical charts and age ≥ 50 years was used as a cutoff to define postmenopausal status in cases of unavailable data on postmenopausal status. This cutoff was used because two previous reports estimated mean age at menopause to be around 50 years among women in Saudi Arabia.^{14,15} Data were retrieved on imaging tests used to screen for breast cancer, including breast ultrasound, mammography, and magnetic resonance imaging (MRI). A positive screening for breast cancer on mammography, ultrasound, or MRI was classified as abnormal diagnostic imaging. A total of 637 symptomatic women underwent breast biopsy during the study period. Data were excluded for four women, because they had no available breast-biopsy findings on their records.

Informed consent

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Due to the study design, patient consent to review their medical records was not required as per the institutional review board at the Ministry of National Guard – Health Affairs.

Statistical analysis

Data were analyzed using STATA version 12 (StataCorp, College Station, TX, USA). An overall summary of sample characteristics and across-group analyses is presented in Table 1.

P-values of χ^2 /independent-sample *t*-tests and unadjusted OR were reported to test whether specific sample characteristics were associated with breast cancer. Accuracy was evaluated for each predictor alone in identifying breast cancer by area under the receiver-operating characteristic (ROC) curve (AUC) analysis and 95% CI (Table 2).

Development of a risk-prediction model to classify breast cancer risk was undertaken using the stepwise logistic regression model (Table 3). The model evaluated 14 potential factors that could be associated with increased risk of breast cancer, and were evaluated at $\alpha \leq 0.05$. The Hosmer–Lemeshow test was used to assess the goodness of fit of the final model, with $P > 0.05$, suggesting that the final model fit the data well.

The overall performance of the final model was evaluated by AUC and compared with the individual predictors in

Table 1 Women's characteristics

| | | n | % |
|---|-----|-----|------|
| Age ≥40 years | No | 159 | 25.3 |
| | Yes | 469 | 74.7 |
| Obesity | No | 291 | 49.7 |
| | Yes | 295 | 50.3 |
| Diabetes | No | 473 | 74.7 |
| | Yes | 160 | 25.3 |
| Hypertension | No | 432 | 68.2 |
| | Yes | 201 | 31.8 |
| Asthma | No | 583 | 92.1 |
| | Yes | 50 | 7.9 |
| Lung disease | No | 585 | 92.4 |
| | Yes | 48 | 7.6 |
| Hyperlipidemia | No | 444 | 70.1 |
| | Yes | 189 | 29.9 |
| Postmenopausal | No | 298 | 47.1 |
| | Yes | 335 | 52.9 |
| Oral contraceptive usage | No | 592 | 93.5 |
| | Yes | 41 | 6.5 |
| Hormone use | No | 454 | 71.8 |
| | Yes | 178 | 28.2 |
| Change in the size or skin of a breast | No | 525 | 82.9 |
| | Yes | 108 | 17.1 |
| Family history of breast cancer | No | 550 | 86.9 |
| | Yes | 83 | 13.1 |
| History of genital disease | No | 583 | 92.1 |
| | Yes | 50 | 7.9 |
| Abnormal diagnostic imaging | No | 32 | 5.5 |
| | Yes | 545 | 94.5 |
| Breast cancer | No | 229 | 36.2 |
| | Yes | 404 | 63.8 |

the final model (Figure 1). The AUC of the final model was internally corrected using a bootstrap resampling approach by generating 100 random samples drawn with replacements from the original sample (n=633). This was performed to validate the AUC result on 100 replicates. Average optimism and SD were calculated. A risk-probability calculator was developed to predict the risk of developing breast cancer, which is a function of the important selected factors.

Results

A total of 633 women who underwent breast biopsy were analyzed, which included 404 (63.8%) who had had a malignant breast biopsy and 229 (36.2%) who had had a benign breast biopsy. The mean age was 49.3±15.6 years, ranging 16–97 years. The majority (94.5%) of our sample had at least one abnormal imaging examination. Table 1 presents the sample characteristics.

The unadjusted risk (Table 2) of being diagnosed with breast cancer tended to increase with age ≥40 years, obesity, diabetes, hypertension, asthma, lung disease, hyperlipidemia, postmenopause, use of HRT, changes in size or skin of breast, family history of breast cancer, and history of genital disease ($P \leq 0.05$). ROC-curve analyses were used to quantify discriminatory accuracy of individual predictors for classifying the risk of breast cancer (Table 3). AUC ranged between 0.509 (abnormal diagnostic imaging) to 0.751 (age ≥40 years). Age

Table 2 Bivariate analysis: factors associated with increased breast cancer risk

| | Breast cancer | | | | | | | |
|---|---------------|------|-----|------|--------------------|--------|--------|---------|
| | No | | Yes | | P | OR | 95% CI | |
| | n | % | n | % | | | Lower | Upper |
| Age ≥40 years | 98 | 42.8 | 371 | 93.0 | 0.001 ^a | 17.712 | 11.127 | 28.193 |
| Obesity (BMI ≥30 kg/m²) | 70 | 34.1 | 225 | 59.1 | 0.001 ^a | 2.782 | 1.953 | 3.961 |
| Diabetes | 24 | 10.5 | 136 | 33.7 | 0.001 ^a | 4.335 | 2.708 | 6.939 |
| Hypertension | 38 | 16.6 | 163 | 40.3 | 0.001 ^a | 3.400 | 2.277 | 5.076 |
| Asthma | 13 | 5.7 | 37 | 9.2 | 0.122 | 1.675 | 0.871 | 3.221 |
| Lung disease | 7 | 3.1 | 41 | 10.1 | 0.002 ^a | 3.582 | 1.580 | 8.123 |
| Hyperlipidemia | 40 | 17.5 | 149 | 36.9 | 0.001 ^a | 2.761 | 1.857 | 4.104 |
| Postmenopausal | 50 | 21.8 | 285 | 70.5 | 0.001 ^a | 8.573 | 5.866 | 12.532 |
| Oral contraceptive usage | 12 | 5.2 | 29 | 7.2 | 0.343 | 1.398 | 0.699 | 2.797 |
| HRT | 4 | 1.8 | 174 | 43.1 | 0.001 ^a | 42.365 | 15.459 | 116.099 |
| Change in size or skin of breast | 27 | 11.8 | 81 | 20.0 | 0.009 ^a | 1.876 | 1.173 | 3.001 |
| Family history of breast cancer | 18 | 7.9 | 65 | 16.1 | 0.004 ^a | 2.248 | 1.297 | 3.894 |
| History of genital disease | 11 | 4.8 | 39 | 9.7 | 0.033 ^a | 2.118 | 1.062 | 4.221 |
| Abnormal diagnostic imaging | 195 | 93.3 | 350 | 95.1 | 0.364 | 1.396 | 0.679 | 2.868 |

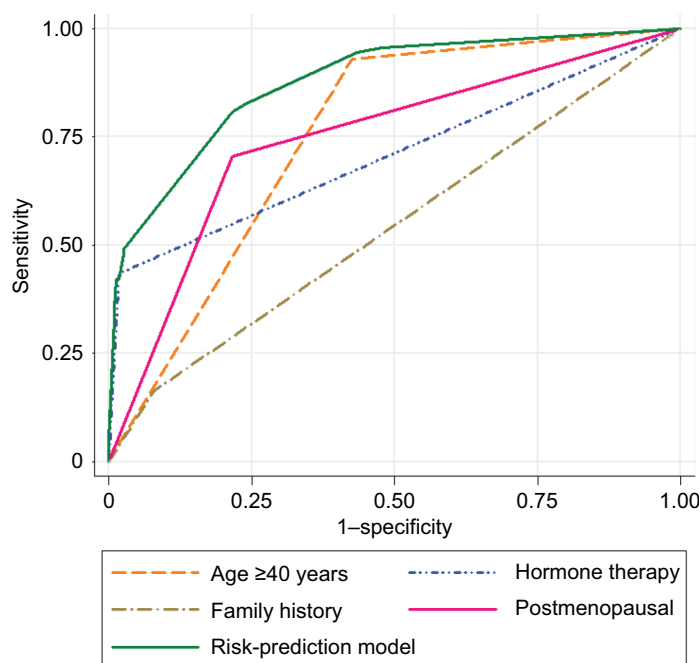
Note: ^a $\alpha=0.05$.

Abbreviation: HRT, hormone-replacement therapy.

Table 3 ROC analysis: accuracy of individual factors

| | AUC | SE | 95% CI | |
|--|-------|-------|--------|-------|
| | | | Lower | Upper |
| Age ≥ 40 years | 0.751 | 0.018 | 0.716 | 0.785 |
| Obesity (BMI ≥ 30 kg/m ²) | 0.625 | 0.021 | 0.584 | 0.665 |
| Diabetes | 0.616 | 0.016 | 0.585 | 0.646 |
| Hypertension | 0.619 | 0.017 | 0.585 | 0.653 |
| Asthma | 0.517 | 0.011 | 0.497 | 0.538 |
| Lung disease | 0.536 | 0.009 | 0.517 | 0.554 |
| Hyperlipidemia | 0.597 | 0.017 | 0.563 | 0.631 |
| Postmenopausal | 0.744 | 0.018 | 0.709 | 0.778 |
| Oral contraceptive use | 0.510 | 0.010 | 0.491 | 0.529 |
| HRT | 0.707 | 0.013 | 0.681 | 0.732 |
| Change in size or skin of breast | 0.541 | 0.015 | 0.513 | 0.570 |
| Family history of breast cancer | 0.541 | 0.013 | 0.516 | 0.566 |
| History of genital disease | 0.524 | 0.010 | 0.504 | 0.544 |
| Abnormal diagnostic imaging | 0.509 | 0.010 | 0.489 | 0.529 |

Abbreviations: HRT, hormone-replacement therapy; ROC, receiver-operating characteristic; SE, standard error.

**Figure 1** ROC curves of individual factors and breast cancer risk prediction model.

≥ 40 years, postmenopause, and use of menopausal hormone therapy showed higher discriminatory accuracy (AUC > 0.7) compared with other individual predictors (Table 3). A prediction model that combines various patients' information to increase the discriminatory accuracy for classifying the risk of breast cancer was used.

From a total of 14 predictive factors, four significant independent risk factors (Table 4) were identified to predict high risk of breast cancer. These were age ≥ 40 years, HRT,

postmenopause, and family history of breast cancer. We noted that women > 40 years had higher odds of developing breast cancer (aOR 6.202, CI 3.497–11.001; $P=0.001$). Women who used menopausal hormone therapy had 24.365 times the odds of breast cancer than women who did not use menopausal hormone therapy (aOR 24.365, 95% CI 8.606–68.987; $P=0.001$). Women who had a family history of breast cancer were twice as likely to develop breast cancer as those who had no had family history of breast cancer (aOR 2.307, 95%

Table 4 Multivariate analysis: factors associated with increased breast cancer risk

| | β | SE | P | aOR | 95% CI | |
|---------------------------------|---------|-------|-------|--------|--------|--------|
| Age ≥ 40 years | 1.825 | 0.292 | 0.001 | 6.202 | 3.497 | 11.001 |
| HRT | 3.193 | 0.531 | 0.001 | 24.365 | 8.606 | 68.987 |
| Family history of breast cancer | 0.836 | 0.359 | 0.020 | 2.307 | 1.142 | 4.658 |
| Postmenopausal | 1.118 | 0.253 | 0.001 | 3.058 | 1.861 | 5.024 |
| Intercept | -1.844 | 0.229 | 0.001 | 0.158 | 0.101 | 0.248 |

Abbreviation: HRT, hormone-replacement therapy; SE, standard error.

CI 1.142–4.658, $P=0.020$). Postmenopausal women were associated with higher odds of developing breast cancer (aOR 3.058, 95% CI 1.861–5.024, $P=0.001$). According to the goodness-of-fit test, the model showed an acceptable fit (Hosmer–Lemeshow, $P=0.053$). The model showed substantial discriminatory accuracy for classifying the risk of breast cancer (AUC 0.877, 95% CI 0.851–0.903). In 100 bootstrap resamples, the overall accuracy of these samples was also high, with an AUC of 0.870 with mean optimism of 0.002 and SD 0.012. The corrected estimate of discriminatory accuracy was $0.877-0.012=0.865$. From these results, a breast cancer risk calculator was developed (Supplementary material).

A probability of 0.72 was defined as the optimal operating point to discriminate between high risk and low risk of breast cancer, with sensitivity, specificity, and Youden index of 80.7%, 78.5%, and 0.592, respectively (Table S1 and S2).

Discussion

This study proposes a breast cancer prediction model based on a retrospective cohort of 633 symptomatic women who underwent breast biopsy at KAMC-RD, MNG-HA, Saudi Arabia. The predictive accuracy of breast cancer risk classification into high risk and low risk has not been previously reported in the Saudi population. The developed model integrates four risk factors: age ≥ 40 years, postmenopausal status, HRT, and family history of breast cancer. The discriminatory accuracy of each factor alone was: 0.751, 0.744, 0.707, and 0.541 (AUC), respectively. However, combining information on age, HRT, postmenopausal status, and family history of breast cancer increased the degree of discriminatory accuracy of breast cancer prediction (0.877) with optimism-corrected AUC of 0.865.

Age ≥ 40 years was associated with increased risk of breast cancer. This is comparable to several previous existing risk-prediction models, where older women are much more likely than younger women to be diagnosed with breast cancer.^{7,16–20} Our findings are also in agreement with annual data reported by the Saudi Health Council, where the incidence of breast cancer was higher in women aged >40 years.^{2,3} Targeting and

monitoring women aged >40 years may improve early detection,^{7,21} and improve the survival rate from breast cancer.²²

HRT use was the strongest predictor and associated with the highest risk of breast cancer. This association was in agreement with a number of earlier studies.^{23–26} Barlow et al reported that the model could be improved by adding the use of HRT.²³ The use and duration of hormone therapy must be justified and monitored, as it can be used as part of preventive health strategies or as a modifiable factor to reduce the risk of developing breast cancer.

In agreement with several earlier studies,^{25–29} postmenopausal women have a higher risk of breast cancer. The results also show agreement with previous models,^{23,27,29} wherein family history of breast cancer was significantly associated with breast cancer. Breast cancer-screening strategies should target postmenopausal women and women with a family history of breast cancer to reduce risk. These study findings might become a prerequisite for a large prospective study, and then for the development of preventive health programs to reduce the high risk of breast cancer in these groups.

Strength and limitations

We identified several limitations in the present study. Association does not necessarily indicate causation. Due to the nature of the study design, some potential risk factors for breast cancer were not available to be included in the model (eg, breast density, age at menarche, age at first pregnancy, number of children). Although it was a large retrospective cohort, validation was performed internally, rather than in a separate prospective cohort. The results of this prediction model may be suitable only for symptomatic women who were treated at KAMC-RD, MNG-HA and underwent breast-mass biopsy.

Despite these limitations, it appears promising that combining information on demographic, clinical, and reproductive factors, ie, age, hormone use, postmenopausal status, and family history of breast cancer, produced substantial improvement in the discriminative ability of the model com-

pared to individual factors. The model confirmed findings in other published risk-prediction models and may contribute to clinical decision making on the diagnostic pathway and prompt a screening program.

Conclusion

The prediction model developed in this study had a high ability to predict increased breast cancer risk in our facility. Risk assessment was improved by combining information on age, menopausal hormone therapy, being postmenopausal, and family history of breast cancer. This model can be used in risk assessment for identifying high-risk groups and improving the early-diagnosis process. Our risk model may assist in initiating population screening programs and prompt clinical decision-making to manage cases and prevent unfavorable outcomes. External validation is required to assess the effectiveness of the model in a prospective cohort and then develop primary preventive strategies for breast cancer in Saudi Arabia.

Abbreviations

MNG-HA, Ministry of National Guard-Health Affairs; KAMC-RD, King Abdulaziz Medical City, Riyadh; CI, confidence interval; ROC, receiver-operating characteristic; AUC, area under the ROC curve; MRI, magnetic resonance imaging; BMI, body-mass index.

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Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

Table S1 Breast cancer risk calculator

| Breast cancer risk calculator | | | | | | |
|---|---------------------------|-----------------------------------|----------------|---------------------------------|---------------------|-------------------|
| Ahmed et al, January 2019 | | | | | | |
| Probability-prediction model to calculate the potential risk of breast cancer | | | | | | |
| The following variables are used for calculating breast cancer risk: | | | | | | |
| Predictor | Label | | | | | |
| Women older than 40 years | Yes=1, No=0 | | | | | |
| Use of menopausal hormone therapy | Yes=1, No=0 | | | | | |
| Postmenopausal | Yes=1, No=0 | | | | | |
| Family history of breast cancer | Yes=1, No=0 | | | | | |
| Case | Women older than 40 years | Use of menopausal hormone therapy | Postmenopausal | Family history of breast cancer | Probability of MERS | High risk (>0.72) |
| 1* | 1 | 1 | 1 | 1 | 0.994 | Yes |
| 2* | 0 | 0 | 0 | 0 | 0.137 | No |

Note: *Randomly selected symptomatic women.

Table S2 Optimal operating point to discriminate between high risk and low risk of breast cancer

| Cutoff | Sensitivity | 1 - specificity | Specificity | Se+Sp-I | Max |
|----------------|--------------|-----------------|--------------|--------------|--------------|
| 0 | 1.000 | 1.000 | 0 | 0.000 | 0.592 |
| 0.20126 | 0.955 | 0.478 | 0.522 | 0.477 | |
| 0.29017 | 0.945 | 0.434 | 0.566 | 0.511 | |
| 0.41014 | 0.942 | 0.430 | 0.570 | 0.513 | |
| 0.60270 | 0.827 | 0.241 | 0.759 | 0.586 | |
| 0.72368 | 0.807 | 0.215 | 0.785 | 0.592 | |
| 0.77161 | 0.491 | 0.026 | 0.974 | 0.465 | |
| 0.83335 | 0.479 | 0.026 | 0.974 | 0.452 | |
| 0.89478 | 0.421 | 0.018 | 0.982 | 0.404 | |
| 0.94013 | 0.421 | 0.013 | 0.987 | 0.408 | |
| 0.97227 | 0.353 | 0.009 | 0.991 | 0.345 | |
| 0.98463 | 0.328 | 0.009 | 0.991 | 0.320 | |
| 0.99022 | 0.050 | 0 | 1.000 | 0.050 | |
| 1.00000 | 0.000 | 0 | 1.000 | 0 | |

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