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Abstract

Background: Tools that can predict breast cancer risk in women will have a significant impact on women and healthcare systems in low- and middle-income countries.

Aims: We compared the performances of the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model, the International Breast Cancer Intervention Study (IBIS) model, and the Gail model in predicting breast cancer risk among women in Cyprus.

Methods: We recruited 655 women from Dr Burhan Nalbantoglu Devlet Hastanesi Hospital in Lefkosa: 318 had breast cancer and 337 did not have breast cancer (hospital-based controls). We collected retrospective data from the hospital's medical records and interviews with the women after informed consent. Data collected included: age, age at diagnosis, age at menarche, menopausal status, presence of benign breast disease, breast cancer in relatives, BRCA-1 and BRCA-2 mutations, history of hormone replacement therapy, and breast density. We calculated the 5-year risk of breast cancer and the risk values were used to plot receiver operating curves.

Results: For the area under the curve (95% confidence interval, CI), sensitivity and specificity for the models were: BOADICEA 0.81 (95% CI: 0.77–0.84), 26.4% and 98.8%; IBIS 0.80 (95% CI: 0.77–0.84), 19.4% and 97.3%; and Gail 0.76 (95% CI: 0.73–0.80), 17.3% and 98.5%.

Conclusions: The breast cancer risk prediction models performed similarly although on closer appraisal, the BOADICEA and IBIS models performed slightly better. These models are simple, appropriate, cost-effective, and non-invasive tools for identifying high-risk women in low- and middle-income countries who could benefit from mammography screening.

Keywords: breast cancer, mammography, risk prediction models, low- and middle-income countries; Cyprus.

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Introduction

Breast cancer has remained the leading cause of death among women worldwide (1). In 2018, more than 2 million women were diagnosed with breast cancer in 140 of 184 nations (2). Breast cancer incidence and deaths occur mostly in low- and middle-income countries (3): one half of all breast cancer cases are in low-and middle-income countries, with 62% of the world's breast cancer deaths (4). In contrast, in the United States, about 249 260 new cases of breast cancer are diagnosed each year and the mortality rate is decreasing (5), with a 5-year survival rate of 89.7% (6). This shows inequality in the global health standards. Globally, the incidence of breast cancer varies from 19.3 cases per 100 000 women in eastern Africa to 89.7 per 100 000 in western Europe, with incidence lower than 40 per 100 000 in most developing countries (7).

Cyprus can be regarded as a middle-income society. It is small and enclosed and hence ideal for epidemiological research. Cyprus has a typical western Mediterranean lifestyle with living conditions and diets that should favour good health (8). A previous study on the prevalence of cancer in the north of Cyprus compared to different European countries between 1990 and 2004 showed that breast cancer was the most common cancer among women and that it was

diagnosed at a lower average age than in northern and southern Europe (9). A later study between 2007 and 2012 found that breast cancer was the most common cancer type among women (10).

Despite the fact that mammography screening is supported for the early detection of breast cancer, it is not cost-effective and feasible for developing countries because of the large population of women, underfunding, and a lack of infrastructure and expertise (11–13).

Developing countries can benefit from cost-effective and efficient risk assessment screening methods that do not depend on tertiary or specialized health care. A number of cost-effective methods that can be used for breast cancer early detection, prevention, and care have been explored (14). Risk prediction models are an additional simple, cost-effective and non-invasive method for identifying high-risk women who could benefit from mammography and preventive treatments. Currently, several comprehensive breast cancer risk assessment tools exist that incorporate various risk factors for the calculation of breast cancer risk (1). Demographic and biomedical information, including breast cancer gene (BRCA)-1 and BRCA-2 mutation (15) and breast density (16), have been used as input variables in risk assessment models. Breast cancer risk can only be affected modestly by each risk factor alone, but the risk level can change significantly in combination with family history and genetic factors (11).

Breast cancer risk assessment models are empirical or genetic (17) such as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model (18), the International Breast Cancer Intervention Study (IBIS) model (19) and the National Cancer Institute's Breast Cancer Risk Assessment Tool (breast cancerRAT) also known as the Gail model (20). Although several other risk assessment models have been proposed, the selection of these models for our study was based on their performance and discriminatory accuracy (17). Their known performance in predicting high-risk women reassured us that these models could streamline candidates for mammography, and early identification of high-risk women would lead to early preventive interventions (21) that would save lives.

Predictions derived from the models are more frequently used in the development of guidelines and recommendations for clinical care, in which women with a higher predicted risk are advised to initiate earlier mammography screening and to consider chemoprevention. Therefore, in this study, we compared the performances of the BOADICEA, IBIS and Gail models in predicting the risk of breast cancer among women in the north of Cyprus.

Methods

Study setting

This study was conducted at the Dr Burhan Nalbantoglu Devlet Hastanesi Hospital in Lefkosa, Cyprus between April 2018 and December 2018. The hospital treats all breast cancer cases in the north of Cyprus

We recruited 655 women in the hospital: 318 women with confirmed breast cancer (case group) and 337 women without breast cancer (control group). Study participants with breast cancer were registered with the centre's database and diagnosed based on pathological reports according to the International Classification of Diseases for Oncology (22). Women with history of lobular or ductal carcinoma in-situ were excluded from the controls. Only participants aged 30-84 years were included. Informed consent to participate was obtained after the aim of the study had been explained to respondents by a medical professional.

Data collection

Retrospective medical and demographic information of both groups was collected from medical records; if the information was not available in the medical records, the women were interviewed one-on-one using a questionnaire to gather the data. The questionnaires included questions on: age, age at menarche, age at first delivery, menopausal status, presence or absence of benign breast disease, history of breast cancer in first-degree relatives or other relatives, BRCA-1 and BRCA-2 mutation, history of hormone replacement therapy (including estrogen/progestin) and breast density (those without breast density information in their medical records were excluded).

Retrospective data were used because of the long latency period to breast cancer manifestation and the changing nature of the population, which makes follow-up difficult.

Breast cancer risk assessment

The information collected was used in the models to predict the risk of breast cancer. Information on BRCA-1 and BRCA-2 mutation status could not be provided by the participants so it was excluded.

The IBIS model is a computer-based programme that provides a woman's overall risk of breast cancer by incorporating genetic determinants such as the BRCA-1 and BRCA-2 genes (19), and data about breast/ovarian cancer among family members, personal risk factors (such as age, body mass index, age at menarche, parity, age at first child, menopausal status, breast density, age at menopause) and benign breast disease (19). We did not collect information on parity.

The IBIS model accommodates residual familial correlation by incorporating a latent common autosomal dominant low-risk gene (23). We used the IBIS or Tyrer-Cuzick breast cancer risk evaluation tool version 8.0b (http://www.ems-trials.org/riskevaluator/). The performance of the IBIS model was measured by estimating the breast cancer risk for each individual. The 10-year risk was divided by two to obtain the 5-year risk. Although breast cancer risk increases with age, dividing the 10-year risk gave only an approximate value for the 5-year risk.

The BOADICEA model calculates 5-year risk of breast cancer among women based on their age, family history and BRCA-1 and BRCA-2 carrier probabilities. It includes a polygenic component that allows for the familial correlation which is not captured by mutations in BRCA-1 or BRCA-2. The BOADICEA risk calculation was carried out using BWAv3 (http://ccge.medschl.cam.ac.uk/boadicea/).

The National Cancer Institute's online version of the breast cancer risk assessment tool (breast cancerRAT or Gail model) is available at: http://www.cancer.gov/bcrisktool/. It assesses the 5-year breast cancer risk based on age, age at menarche, age at first live birth, first-degree relatives with breast cancer, previous breast biopsies with or without atypical hyperplasia, BRCA mutation and race. White race/ethnicity (Caucasian) variables were used to estimate the risk for all the women in this study. For the Gail model 5-year risk assessment, a rate of less than 1.67% was defined as low-risk while a rate of 1.67% or more was defined as high-risk (23).

Based on the 2016 National Comprehensive Cancer Network recommendation for prophylactic treatment for women, the cut-off value of 1.67% for 5-year risk was used for all the models to categorize high- and low-risk women (24).

Statistical analysis

Receiver operating characteristic (ROC) curves were plotted to measure the models' discriminative capacities. The concordance (C) statistic ranges from 0.5 (no discriminative ability) to 1.0 (perfect discrimination). This determines whether the models will yield a higher risk for breast cancer cases and lower risk for hospital-based controls. The predicted scores were used to distinguish between high-and low-risk. Sensitivities and specificities of the models were estimated for 5-year breast cancer risk at 1.67%. The sensitivity test can detect true positives and the specificity can detect true negatives.

The predictive accuracies of correctness and the Nagelkerke R2 of the models were analysed using logistic regression of the scores predicted by the models. In the logistic regression

analysis, the dependent variables were the breast cancer disease outcomes and the predictor variables were the calculated breast cancer risks. Predictive accuracy of correctness measures how well the models fit the samples. The Nagelkerke R2 is an adjusted version of the Cox and Snell R2 that adjusts the scale of the statistic to cover the full range from 0 to 1. A perfect model has a theoretical maximum value of less than 1. All statistical analysis was done using SPSS, version 24.0 analytical software.

Ethical considerations

Ethical approvals for the research were obtained from the Near East University scientific research evaluation ethics committee and the hospital's ethics committee. The relevant ethical guidelines and regulations on research involving humans of the Helsinki declaration were followed.

Results

Table 1 summarizes the baseline characteristics of the participants: 318 breast cancer cases and 337 hospital-based controls.

The performances of the models were evaluated as good overall. Using logistic regression analysis of the predicted scores, the BOADICEA, Gail and IBIS models displayed a Nagelkerke R2 of 0.32, 0.19 and 0.23, respectively. The predictive accuracies of correctness of the models were: BOADICEA 72.4%; IBIS 71.1%; and Gail 69.9%.

The ROC curves are shown in Figure 1 . The discriminatory capacities of the models were derived from the ROC curve and the area under the curve as shown in Table 2 . The BOADICEA model had an area under the curve of 0.81 (95% confidence interval (CI): 0.77–0.84), the IBIS model an area under the curve of 0.80 (95% CI: 0.77–0.84) and the Gail model an area under the curve of 0.76 (95% CI: 0.73–0.80.

At a cut-off point of about 1.67%, the sensitivities of the models in predicting a high-risk woman among the breast cancer cases were: BOADICEA 26.4%; IBIS 19.4%; and Gail 17.3%. (Table 3)

Discussion

Demographic and biomedical data of the participants were used to predict the risk of breast cancer by the models. We found that all the models performed well in predicting the risk of breast cancer among the women. Although the BOADICEA and IBIS models had slightly better predictive values, all the models showed a reasonable predictive accuracy. It is important for a risk prediction model to have a good predictive accuracy (25). The estimated risk of breast cancer varied between the risk models because each model uses different statistical calculations for the same variables and different risk factors for statistical calculation. The models used genetic factors such as family history in combination with other risk factors to enhance their stratification of breast cancer risk. Inherited factors explain about a quarter of breast cancer risk (26). Meta-analyses and pooled studies have demonstrated that breast cancer risk is about twice as high among women who have one first-degree relative with breast cancer than women who have no first-degree relatives with breast cancer. The risk increases with the number of affected first-degree relatives or relatives affected younger than 50 years (27). BRCA 1 and 2 mutations explain the molecular pathogenesis behind 15–20% of cases with first-degree family history (26,28). The remaining 80–85% can be a result of breast density, age, menopausal status, history of hormone replacement therapy and age at menarche. Breast density seems heritable (29), but the mechanism underlying the association between breast density and breast cancer is not yet understood. Although age and menopausal status affect breast density, younger and premenopausal women in general have denser breast (30). Women with an early age of menarche have a slightly increased risk of breast cancer, because they will have a longer time of exposure to estrogens, which increases breast cancer risk (31). The use of hormone replacement therapy is common among postmenopausal women and is linked to increased breast cancer risk (32). In comparison to a recent validation study (33), the sensitivities of the models examined in our study at 1.67% were low – 17.3% (Gail), 19.4% (IBIS) and 26.41% (BOADICEA) – but the specificities were similar (98.5%, 97.3% and 98.8%, respectively). The sensitivities can be improved by including information on genetic mutations such as BRCA 1 and BRCA 2, but our participants could not provide this.

Despite the rise in breast cancer incidence among women in the north of Cyprus (10), there are no studies on the effectiveness of risk models for breast cancer screening.

These models can serve as suitable simple non-invasive alternative screening for the identification of high-risk women, thus streamlining the focus of the limited mammogram resources to the right group in low- and middle-income countries. Using these models will reduce unnecessary mammography and radiation exposure among potentially low-risk women. The use of the risk prediction model has additional advantages as it is not dependent on physical examination, is easy to use, is cost-effective and seems to enhance outcome and survival (17).

The risk assessment models can be incorporated into the mHealth features similar to the WHO

initiative in 2012, thus empowering women (34) and benefitting low-risk women in primary care.

While the models intend to ascertain the risk for an individual, the risk factors used depend on population risk from epidemiological investigations. Therefore, more studies need to be conducted among various populations of women to identify new lifestyle/environmental factors, biomarkers, genetic markers and incidence rates that are peculiar to that population. These factors can be incorporated into prospective risk models because the possibility of identifying those at high-risk would be enhanced by using a comprehensive risk model that integrates all known risk factors.

Our study has some limitations. First, it was based on retrospectively collected data. However, the data collection was done independently so it is unlikely to have altered the results and caused bias. Second, the area under the curve estimates would have been biased since our study was carried out on a case–control group, but this was minimized (35). Third, BRCA 1 and 2 information was not used because it is not a common test in the study setting and could not be provided by the participants. Therefore, a comprehensive family history of breast cancer, which explains the BRCA 1 and 2 mutation associations in about 20% of breast cancer cases, was used alongside other risk factors (26,28). Information about environmental risk factors was not collected because they were not considered risk predictors in the models and this may have created a gap in the awareness of interethnic risk factors in the studied population.

Despite these biases and limitations, the urgent need for for the use of these risk prediction models in breast cancer control in developing countries outweighs the shortfalls.

We recommend further prospective studies that will compare more risk models on a larger cohort of women in the north of Cyprus.

Conclusion

Our results suggest that breast cancer risk prediction models are suitable, simple, cost-effective, and non-invasive tools for the identification of high-risk women in low- and middle-income societies. By identifying low- and high-risk women, these model may reduce unnecessary mammography and radiation for low-risk women and thereby lower health care costs. Risk prediction models can be used in screening women who miss mammography because of limited facilities. Hence, these models need to be explored in developing regions where access to early detection, cancer care and mammography is limited. Although all the models performed similarly, the BOADICEA and IBIS models were slightly better.

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Conflict of interest statement: None declared.

Performance des modèles de prédiction du risque pour le dépistage du cancer du sein chez les femmes à Chypre

Résumé

Contexte : Les outils permettant de prédire le risque de cancer du sein chez les femmes auront un impact significatif sur les femmes et les systèmes de santé dans les pays à revenu faible et intermédiaire.

Objectifs : Nous avons comparé les performances des modèles d'évaluation du risque nommés BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), IBIS (International Breast Cancer Intervention Study) et Gail pour la prédiction du risque de cancer du sein chez les femmes à Chypre.

Méthodes : Nous avons recruté 655 femmes à l'hôpital Dr Burhan Nalbantoglu Devlet Hastanesi de Lefkosa : 318 avaient un cancer du sein et 337 n'en avaient pas (témoins hospitaliers). Nous avons collecté des données rétrospectives à partir des dossiers médicaux de l'hôpital et des entretiens avec les femmes après consentement éclairé. Les données recueillies comprenaient les éléments suivants : l'âge, l'âge lors du diagnostic, l'âge aux premières menstruations, le statut ménopausique, la présence d'une maladie bénigne du sein, le cancer du sein chez les parents, les mutations BRCA-1 et BRCA-2, les antécédents de traitement hormonal substitutif et la densité mammaire. Nous avons calculé le risque de cancer du sein à cinq ans et les valeurs de risque ont été utilisées pour tracer les courbes de la fonction d'efficacité du récepteur.

Résultats : Pour l'aire sous la courbe (intervalle de confiance [IC] à 95 %), la sensibilité et la spécificité des modèles étaient les suivantes : BOADICEA 0,81 (IC à 95 % : 0,77-0,84), 26,4 % et 98,8 % ; IBIS 0,80 (IC à 95 % : 0,77-0,84), 19,4 %

et 97,3 % ; et Gail 0,76 (IC à 95 % : 0,73-0,80), 17,3 % et 98,5 %.

Conclusions : Les modèles de prédiction du risque de cancer du sein ont obtenu des résultats similaires, bien qu'après une évaluation plus approfondie, les modèles BOADICEA et IBIS aient produit de meilleurs résultats. Ces modèles sont des outils simples, appropriés, non invasifs et d'un bon rapport coût-efficacité permettant d'identifier les femmes à haut risque dans les pays à revenu faible et intermédiaire qui pourraient bénéficier d'un dépistage par mammographie.

ع [illegible] ج [illegible] ع [illegible]

[illegible]

[illegible]

[illegible] : [illegible] (BOADICEA) [illegible] (IBIS) [illegible] (Gail) [illegible]

[illegible]: [illegible] 655 [illegible] 337 [illegible] 318 [illegible] .([illegible]) [illegible] 2-BRCA 1-BRCA [illegible]

WHO EMRO | Performance of risk prediction models in breast cancer screening among women in Cyprus

وكثافةَ الثدي . وكذلك حسبنا مخاطر الإصابة بسرطان الثدي على مدى 5 سنوات، واستُخدمت قيم المخاطر لرسم منحنيات فِعل المُسْتَقْبِلات .

: فيما يخصُّ المنطقة الواقعة تحت المنحنى (فاصل الثقة 95% ، CI) ، فإن حساسيةالنتائ ج : خوارزمية تحليل الثدي والمبيض لدى حالات مصابةكالتالي النماذج وخصوصيتها بالمرض وتقدير الناقل (BOADICEA) 0.81 (فاصل ثقة 95%: 0.77 – 0.84) ، 26.4% و98.8% ؛ ونموذج التدخل الدولي لمكافحة سرطان الثدي (IBIS) 0.80 (فاصل ثقة 95%: 0.77 – 0.84) ، 26.4% و98.8% ؛ ونموذج جايل (Gail) 0.80 (فاصل ثقة 95%: 0.73–0.80) ، 17.3% و98.5%.

: كان أداء نماذج التنبؤ بخطر الإصابة بسرطان الثدي متماثلًا، وإن كان قدالاستنتاجات تبين أن أداء نماذج خوارزمية تحليل الثدي والمبيض لدى حالات مصابة بالمرض وتقدير الناقل (BOADICEA) ونموذج التدخل الدولي لمكافحة سرطان الثدي (IBIS) أفضل قليلًا عند إجراء تقييم تدقيق . وهذه النماذج أدوات بسيطة ومناسبة وعالية المردود غير باضعة، لأجل تحديد النساء المعرضات لمخاطر عالية في البلدان ذات الدخل المنخفض والمتوسط، اللاتي يمكن أن يستفدن من فحص تصوير الثدي بالأشعة .

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