Commentary

Commentary on Terry *et al.*, 10-Year Performance of Four Models of Breast Cancer Risk: A Validation Study. Lancet Oncol. 2019;20(4):504-17

Jack Cuzick *, Adam Brentnall

Wolfson Institute of Preventive Medicine, Queen Mary University of London, London EC1M 6BQ, UK

* Correspondence: Jack Cuzick, Email: j.cuzick@qmul.ac.uk.

Terry and colleagues [1] provide a useful analysis of some of the models currently being employed for the assessment of breast cancer risk. One of the early uses of these models was to identify women at sufficiently high risk to offer preventive therapy. This was particularly true for the International Breast Cancer Intervention Study (IBIS) (Tyrer-Cuzick) model [2], which was developed to guide entry into the IBIS-I breast cancer prevention trial with tamoxifen, and is recommended by the U.S. Preventive Services Task Force [3]. Subsequently there has been a great deal of interest in developing "risk-adapted screening", where the choice of the screening interval, and in high-risk cases decisions to use Magnetic Resonance Imaging (MRI) and other new technologies to augment mammography are made on an individual basis (such as using the IBIS model as recommended by the American Cancer Society [4]). These require good estimates of 10-year risk, and ideally all women at or before their first attendance at screening would be offered a risk assessment to personalise their screening programme.

The various models have focused on different populations. The BRCAT model was developed in a screening population for average risk women and based on minimal information on risk factors. While easy-to-use, the analysis by Terry *et al.* [1] and some others [5,6] has shown that it has less predictive value than models which use more extensive risk information. At the other extreme the BRCAPRO and Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) models were focused on women with a strong family history, and collect detailed information on both breast and ovarian (and other) cancer in an extensive pedigree, but place no emphasis at all on more common risk factors which are important in the general population. The IBIS model lies somewhere in between, and is particularly useful for women with a moderate family history or other risk factors to determine their suitability for preventive therapy [3]. It has now been evaluated both in women with a family history of breast cancer and large cohorts of women at average risk who completed a risk assessment when attending for screening [6–8]. The

Received: 03 April 2019
Accepted: 12 April 2019
Published: 26 April 2019

analysis by Terry *et al.* [1] confirms its good calibration and a predictive accuracy at least as good as other models in women with a family history of the disease. Their analysis also found little practical difference between the polygenic and "unknown" dominant gene statistical models that respectively the BOADICEA and IBIS models use to account for residual clustering within families that is not explained by *BRCA* mutations (see Supplemental Table 3 in [1]).

The importance of including breast density into these models has become more apparent in recent years. Almost half a century ago Wolfe [9] showed that it was a strong risk factor for breast cancer, which has subsequently been validated in hundreds of studies [10,11]. Breast density emerges as one of the most predictive variable in terms of population attributable risk, and very importantly, is provides information for risk that is largely independent of all the other known risk factors [12]. In studies of women attending routine breast cancer screening it contributes at least as much information as all other factors combined, so that including it essentially doubles the predictive value of the model [8,12]. There probably is more information to be extracted on risk from the mammogram, as experienced readers using a visual assessment of the percent density are able to provide more discrimination than objective computer programmes or less experienced readers [13]. It seems likely that artificial intelligence methods will be able to extract at least some of this added information, and make analysis of the mammogram even more important in risk assessment [14].

A third dimension for risk assessment is the use of single nucleotide polymorphisms (SNPs) via a polygenic risk score. Some early work used 18 SNPs [15,16], and several new models are now using more than 50 [17]. At last count more than 170 independent genome-wide significant SNPs had been identified [18], with an indication that more than 3000 might be informative for risk assessment [19]. However, more recent SNPs carry less risk information than the earlier ones, and we may be reaching a point of diminishing returns. Somewhat surprisingly the SNP score appears to be largely independent of classical questionnaire based risk factors, including family history, and of approximately similar or greater predictive value to them and mammographic density [15]—thus providing a third equally powerful component in risk assessment.

The most recent version of the IBIS (Tyrer-Cuzick) model (v8) includes mammographic density (which can be measured in a range of ways needing separate calibration), and a generic SNP based relative risk score, which can be used with any collection of independent SNPs. Recent studies [6,8,12,15–17] have confirmed this new version provides a substantial increase in power over methods using questionnaire data only, such as examined by Terry *et al.* [1].

Personalised screening will require risk assessment in all women at or before their first screen, with a possible need for repeat testing to update information and look at changes in breast density. This will stimulate

continued development of better models. One challenge that is currently unmet is to predict the risk of different types of breast cancer—e.g., oestrogen receptor positive versus negative disease for which different preventive therapies are needed, and aggressive and potentially fatal breast cancer for which early detection by increased screening is a particular need.

CONFLICTS OF INTEREST

The IBIS model is licensed by Cancer Research UK for commercial use and J Cuzick and Adam Brentnall receive a percentage of the royalty from them for this.

REFERENCES

1. Terry MB, Liao Y, Whittemore AS, Leoce N, Buchsbaum R, Zeinomar N, et al. 10-year performance of four models of breast cancer risk: a validation study. Lancet Oncol. 2019;20(4):504-17. doi: 10.1016/S1470-2045(18)30902-1
2. Tyrer J, Duffy SW, Cuzick J. A breast cancer prediction model incorporating familial and personal risk factors. Stat Med. 2004;23(7):1111-30. doi: 10.1002/sim.1668
3. U.S. Preventive Services Task Force. Breast Cancer: Medications for Risk Reduction. Available from: https://www.uspreventiveservicestaskforce.org/Page/Document/RecommendationStatementFinal/breast-cancer-medications-for-risk-reduction. Accessed 2018 Apr 1.
4. Saslow D, Boetes C, Burke W, Harms S, Leach MO, Lehman CD, et al.; American Cancer Society Breast Cancer Advisory Group. American cancer society guidelines for breast screening with MRI as an adjunct to mammography. CA Cancer J Clin. 2007;57:75-89.
5. Cintolo-Gonzalez J, Braun D, Blackford A, Mazzola E, Acar A, Plichta J, et al. Breast cancer risk models: a comprehensive overview of existing models, validation, and clinical applications. Breast Cancer Res Treat. 2017;164(2):263-84. doi: 10.1007/s10549-017-4247-z
6. Evans DG, Astley S, Stavrinos P, Harkness E, Donnelly LS, Dawe S, et al. Improvement in risk prediction, early detection and prevention of breast cancer in the NHS breast screening programme and family history clinics: a dual cohort study. Programme Grants Appl Res. 2016;4(11):1-210. doi: 10.3310/pgfar04110
7. Evans DG, Thomas S, Caunt J, Burch A, Brentnall AR, Roberts L, et al. Final results of the prospective FH02 mammographic surveillance study of women aged 35–39 at increased familial risk of breast cancer. EClinicalMedicine. 2019;7:39-46. doi: 10.1016/j.eclinm.2019.01.005
8. Brentnall AR, Cuzick J, Buist DS, Bowles EJ. Long-term accuracy of breast cancer risk assessment combining classic risk factors and breast density. JAMA Oncol. 2018;4(9):e180174. doi: 10.1001/jamaoncol.2018.0174
9. Wolfe JN. Breast patterns as an index of risk for developing breast cancer. AJR Am J Roentgenol. 1976;126(6):1130-37.

10. McCormack VA, dos Santos Silva I. Breast density and parenchymal patterns as markers of breast cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev. 2006;15(6):1159-69.
11. Assi V, Warwick J, Cuzick J, Duffy SW. Clinical and epidemiological issues in mammographic density. Nat Rev Clin Oncol. 2011;9(1):33-40. doi: 10.1038/nrclinonc.2011.173
12. Brentnall AR, Harkness EF, Astley SM, Donnelly LS, Stavrinos P, Sampson S, et al. Mammographic density adds accuracy to both the Tyrer-Cuzick and Gail breast cancer risk models in a prospective UK screening cohort. Breast Cancer Res. 2015;17(1):147. doi: 10.1186/s13058-015-0653-5
13. Astley SM, Harkness EF, Sergeant JC, Warwick J, Stavrinos P, Warren R, et al. A comparison of five methods of measuring mammographic density: a case-control study. Breast Cancer Res. 2018;20(1):10. doi: 10.1186/s13058-018-0932-z
14. Wang C, Brentnall AR, Cuzick J, Harkness EF, Evans DG, Astley S. A novel and fully automated mammographic texture analysis for risk prediction: results from two case-control studies. Breast Cancer Res. 2017;19(1):114. doi: 10.1186/s13058-017-0906-6
15. van Veen EM, Brentnall AR, Byers H, Harkness EF, Astley SM, Sampson S, et al. Use of Single-Nucleotide polymorphisms and mammographic density plus classic risk factors for breast cancer risk prediction. JAMA Oncol. 2018;4(4):476-82. doi: 10.1001/jamaoncol.2017.4881
16. Evans DG, Brentnall A, Byers H, Harkness E, Stavrinos P, Howell A, et al. The impact of a panel of 18 SNPs on breast cancer risk in women attending a UK familial screening clinic: A case-control study. J Med Genet. 2017;54(2):111-3. doi: 10.1136/jmedgenet-2016-104125
17. Cuzick J, Brentnall AR, Segal C, Byers H, Reuter C, Detre S, et al. Impact of a panel of 88 single nucleotide polymorphisms on the risk of breast cancer in High-Risk women: Results from two randomized tamoxifen prevention trials. J Clin Oncol. 2017;35(7):743-50. doi: 10.1200/JCO.2016.69.8944
18. Michailidou K, Lindström S, Dennis J, Beesley J, Hui S, Kar S, et al. Association analysis identifies 65 new breast cancer risk loci. Nature. 2017;551(7678):92-4. doi: 10.1038/nature24284
19. Mavaddat N, Michailidou K, Dennis J, Lush M, Fachal L, Lee A, et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. Am J Hum Genet. 2019;104(1):21-34. doi: 10.1016/j.ajhg.2018.11.002

How to cite this article:
Cuzick J, Brentnall A. Commentary on Terry *et al.*, 10-Year Performance of Four Models of Breast Cancer Risk: A Validation Study. Lancet Oncol. 2019;20(4):504-17. Med One. 2019;4:e190006. https://doi.org/10.20900/mo.20190006