By Prof Jack Cuzick & Dr Adam Brentnall

# Models for Assessment of Breast Cancer Risk

The so-called Tyrer-Cuzick (or IBIS) model was developed to predict the risk of developing breast cancer, initially for women with an elevated risk [1,2]. It is widely used and has now been validated in several studies, including with women at average risk attending routine breast screening [3,4]. The computer program of the model displays a chart to show a woman's risk of breast cancer until age 85 in comparison with the risk for a typical woman of the same age, together with estimates of the 10-year and lifetime risks. The risk factors that have been used to make this estimate are also recorded in a printable summary. The latest software is freely available for non-commercial research use from the website *www.ems-trials.org/riskevaluator*.

The model works by using a novel hybrid of a segregation model for familial risk and a proportional hazards model. The segregation model is used to estimate the chance that the woman carries a mutation in two high risk genes (*BRCA1* and *BRCA2*) and an unknown gene. The unknown gene is included to account for further inheritable genetic factors. The segregation model is combined with age and other risk factors through a proportional hazards model.

The risk factors chosen for the model were those most supported by the literature. They include age, a detailed family history of breast and ovarian cancer in first and second degree relatives with age at onset, prior proliferative benign breast disease or atypical hyperplasia, hormone replacement therapy use, height, weight age at menopause and parity including age at first child birth. Examples of lifetime risks associated with risk factors for a woman aged 50 are shown in Table 1 along with information on their prevalence. A useful feature to simplify data entry is that population average values are used if a factor is not known or not entered for any reason.

## ADDITIONAL FACTORS PLANNED FOR THE NEXT SOFTWARE UPDATE (V8)

Various improvements are planned for the next version of the program (version 8). The most important of these is the inclusion of mammographic density. Previous research indicates that this is the single most important factor and has a high population attributable fraction for breast cancer, particularly younger women [5]. This is because of the strong impact on risk (roughly fourfold between dense and fatty breasts) and the fact that dense breasts are not uncommon in the general population. Introduction of this factor was delayed because of the large number of ways in which density can be measured, and the different resultant scales on which it can be reported.

In the end we decided to not require one specific method, but will accept one of three standard methods and calibrate the risk according to the method cited.

These are:

(1) a visual analogue scale [3];

(2) BI-RADS density categories (4th edition) [6];

(3) Volpara density [7].

Of these methods number (2), the BI-RADS density classification (fourth edition) is widely used, especially in the United States and has four categories: fatty (0-25% dense), scattered (25-50%), heterogeneous (50-75%) and extremely dense (75-100%) [5]. The third density method to be included in the next update (v8) of our software is a volumetric measure of percent density based on the Volpara algorithm [7] which has the advantage of being fully automated and objective. The best results appear to be obtained by using percent density adjusted for age and BMI. The Volpara method has been predictive of risk in high-risk and average risk women in several studies, but despite better reproducibility than visually-assessed density from an expert radiologist, its relationship with risk does not appear to be any stronger [8].

Perhaps the most noticeable density method omitted is CUMULUS [5]. This is a semi-automated method, but it still has a subjective component due to the way in which thresholds for dense and total breast tissue are chosen. It has mainly been used in a research setting, but appears to be less often used now, partly because it is very labour intensive.

Another variable which appears to be useful, but is currently mostly used only in research circumstances, is a risk score given from a panel of genetic alterations, or single nucleotide polymorphisms (SNPs) [9]. Panels with between 7 and 94 SNPs have been investigated and shown to improve the performance of risk models based on phenotypic factors. The Tyrer-Cuzick model will be updated to accommodate such panels that provide a relative risk compared to a women of average risk of the same age.

Future extensions beyond v8 will explore the value of including additional lifestyle factors such as alcohol consumption and physical activity. A common problem


## THE AUTHORS

**By Prof Jack Cuzick & Dr Adam Brentnall**

Centre for Cancer Prevention

Wolfson Institute of Preventive Medicine

Queen Mary University of London

Charterhouse Square

London EC1M 6BQ, UK

email: j.cuzick@qmul.ac.uk

| Risk factor<br>*Nominal value and prevalence of high/low risk subgroup* | Specific Category | Residual Lifetime risk |
|---|---|---|
| **Average risk woman** | | 11.4% |
| **No family history** | | 9.9% |
| **Parity and age at first child** | | |
| *Median age: 24y* | First child aged 20y | 8.1% |
| *14% nulliparous* | Nulliparous | 12.1% |
| **Menarche** | | |
| *Median age 13y* | Age 15y | 9.2% |
| *14% 11y or younger; 20% 15y+* | Age 11y | 10.5% |
| **Height and weight** | | |
| *Mean BMI: 28 kg/m²*<br>*33% BMI<25 kg/m²* | 1.6m, 64kg (BMI 25.0) | 8.8% |
| *29% BMI>30 kg/m²* | 1.7m, 87kg (BMI 30.1) | 11.7% |
| **Menopause** | | |
| *Median age 50y*<br>*3 in 4 aged 45-54y* | Postmenopausal at 50y, but exact age unknown | 8.7% |
| | Postmenopausal, at age 49y | 9.7% |
| | Premenopausal at age 50y | 10.7% |
| **HRT (previous use 2yr)** | | |
| *4% current users* [3] | Estrogen only (intend 2yrs more) | 11.1% |
| | Combination (intend 2yrs more) | 11.5% |
| | Combination (intend 5yrs more) | 12.2% |
| **Family history** | | |
| *12% with 1+ affected first degree-relative* [3] | Mother (age 55y) | 19.8% |
| | Mother and Sister (both age 55y) | 24.7% |
| | Mother (bilateral age 55y) | 24.8% |
| **Benign disease** | | |
| *At least 2% proliferative disease in screening sample* [11] | Normal *vs* Hyperplasia | 18.0% |
| | Atypical Hyperplasia | 39.9% |
| **Mammographic density (BI-RADS 4th edition)** | | |
| *Approx. 82% screening-age women BI-RADS 2/3* [10] | 1 (fatty, 0-25%),9% | 5.2% |
| | 2 (scattered, 25-50%), 44% | 8.1% |
| | 3 (heterogeneous, 50-75%), 38% | 12.5% |
| | 4 (extremely dense, 75-100%), 9% | 19.0% |

**Table 1.** Lifetime risks for a woman aged 50y with only the risk factors stated (and no family history) entered into the Tyrer-Cuzick model (v8, UK rates). The prevalence statistics are from those used in the model, unless an alternative source is indicated.

with these is to obtain accurate reporting as alcohol consumption tends to be under-reported and physical activity over-reported. They are also more difficult to accurately code since alcohol consumption needs to be extracted from the type of alcoholic beverage consumed and physical activity depends both on the duration and the vigourousness of the exercise, which is complex to report in a simple manner.

## CONCLUSION

In summary, accurate estimation of increased risk is important for determining the need for additional screening - either by shortening intervals between mammograms or more expensive modalities such as MRI. They also may be used for identifying women at a lower risk of breast cancer, where screening intervals might usefully be lengthened or screening even avoided altogether. Breast screening is an attractive time to counsel woman about breast cancer prevention and to advise them on their risk both in absolute and relative terms.

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