Should volumetric breast density be included in breast cancer prediction models? Proposal of an integrated quantitative and reproducible approach

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Purpose

Breast cancer is the most commonly diagnosed cancer among women in the western country, accounting for a third of all female cancer cases, and the second most common cause of cancer death. (1) Mammographic density is a strong risk factor for breast cancer, but its potential application in risk management is not clear, partly due to uncertainties about its interaction with other breast cancer risk factors. We aimed to analyze the relationship between volumetric breast density (VBD) and risk for breast cancer as estimated by prediction models (Tyrer Cuzick). To do this preliminary study we have selected:

1) the Tyrer Cuzick questionnaire and scoring which is the most accurate reliable risk model and has the most elevate AUC performance

2) the Volpara software for the automated and three dimensional measurements of the density which is the most reliable and repeatable method to assess breast density as we are going to illustrate in the rationale that follows.

RATIONALE

The forest behind the trees in choosing a risk assessment model i.e why we used the Tyrer Cuzick model.


Women who are at high risk of breast cancer can be offered more intensive surveillance or prophylactic measures, such as surgery or chemoprevention. Central to decisions regarding the level of prevention is accurate and individualized risk assessment. Over the past two decades, a number of statistical models have been designed and validated to assess breast cancer risk in both populations and individuals. For health-care policy-makers or insurers, models that have been calibrated to accurately estimate population risk are sufficient because they can be used for cost-benefit analyses. However, for clinicians, it is imperative that a risk assessment tool has a good ability to assess individual risks so that appropriate preventative treatment can be individually tailored. For such a tool to provide accurate individualized risk assessment, it must achieve a good balance between sensitivity and specificity. In statistical terms, receiver operating characteristic curves best represent this balance, with the area under the receiver
operating characteristic curve (AUC; also known as the c-statistic) quantifying a model's discriminatory accuracy.

An AUC of 0.5 identifies a model whose discriminatory accuracy is no better than a flip of a coin, whereas an AUC of 1.0 identifies a model with perfect discriminatory accuracy. Realistically, however, an AUC of 0.7 or 0.8 is consistent with good discriminatory accuracy. It is therefore important when assessing any model's performance that the setting for its use is known. All risk assessment models have limitations: Adoption, small family size [or "limited family structure" (2)], and lack of information about family history reduce the usefulness of all models to some degree. It is known that because of the reluctance of people to discuss their medical conditions, particularly those involving cancer, generations of family medical history are lost to present-day patients who are receiving care in the era of genetic testing (3). Of additional concern is the mistaken assumption that a paternal family history of breast or ovarian cancer is not relevant to risk for cancer (4). Furthermore, it is known from the noncancer (6) and cancer (6) literature that the reporting of parental medical history by offspring can be inaccurate. There is therefore a need to improve methods for collecting and acknowledging family history even while risk models continue to have their accuracy improved.

Risk Factors

Risk factors are summarized in table I

**Family History of Breast Cancer.** A good quality family history of breast cancer requires the following information: the age at onset of breast cancer, unilateral vs bilateral disease, the degree of relationship (first or greater), whether there are multiple cases in the family (particularly on the maternal or paternal side), other related early-onset tumors (eg, ovary, sarcoma), and the number of unaffected individuals (large families with many unaffected relatives will be less likely to harbor a high-risk gene mutation). Compared with women with no affected relatives, women with one affected first-degree relative have twice the risk of breast cancer, those with two first-degree relatives have thrice the risk, and those with three or more first-degree relatives have quadruple the risk (7). A younger age at breast cancer diagnosis in a family member is associated with an increased risk of breast cancer. However, this increase in risk appears to only affect first-degree relatives. For example, compared with a first-degree relative diagnosed with breast cancer after the age of 65 years, women who have a first-degree relative who was diagnosed with breast cancer before age 40 years have approximately thrice the risk of breast cancer, women with a first-degree relative who was diagnosed with breast cancer between age 40 and 50 years have twice the risk, and those with a first-degree relative diagnosed
between age 50 and 65 years have approximately 1.5 times the risk. There appears to be little increase in risk associated with having a single first-degree relative who was diagnosed after age 65 years unless there are multiple first-degree relatives in this age group (7). A relative with bilateral breast cancer can be counted as two affected relatives for the purposes of these calculations. Reproductive factors have long been recognized to be important in the development of breast cancer. Prolonged exposure to endogenous estrogens resulting from early menarche (age <12 years) and/or late menopause (age >55 years) is associated with an increased risk of breast cancer (8-9). Early age at menarche is associated with a 4% per-year increase in the relative risk of breast cancer, whereas late menopause is associated with a 3% per-year increase (7). Use of the oral contraceptive pill is also associated with an increased risk of breast cancer. In addition, the latest data from the Million Women Study showed that the use of hormone replacement therapy was associated with a 5% per-year increase in the risk of breast cancer but only in current users; the risk returned to baseline within a year of stopping hormone use (64-10). Furthermore, long-term combined hormone replacement therapy treatment (ie, estrogen plus progestin for >5 years) after menopause is associated with a statistically significant increase in risk (10). However, shorter times of treatment may also be associated with an increased risk of breast cancer for those with a family history of the disease (11). In a large meta-analysis of population-based studies, the risk of breast cancer appeared to increase cumulatively by 1%-2% per year with hormone replacement therapy but disappeared within 5 years of stopping treatment (63-9). The risk associated with estrogen-only hormone replacement therapy appears to be much less than that associated with combined estrogen and progestin and may be negligible (12-13). Another meta-analysis suggested a 24% increase in the risk of breast cancer during current use of the combined oral contraceptive and for 10 years after discontinuation (8).

Younger age at first pregnancy is associated with a decrease in the relative risk of breast cancer because pregnancy transforms breast parenchymal cells into a more stable state, potentially resulting in less cell proliferation in the second half of the menstrual cycle. As a result, women who give birth to their first child after age 30 years have double the risk of breast cancer as women who give birth to their first child before age 20 years (14). Breast feeding appears to be associated with a reduced risk of breast cancer. The latest estimates show a 4.3% relative reduction in risk for every year of breast feeding (15); therefore, a number of years of breast feeding would be necessary to have a substantial impact on risk.

Incorporation of Risk Factors Into Risk Assessment Models

Current risk prediction models are based on combinations of risk factors, and in general, their outputs include a breast cancer risk estimate over a specific time and/or over the lifetime of the patient. A number of models have been designed for this purpose. All of these models have important limitations, foremost of which is their reliance on known risk factors.
factors, despite data that show that up to 60% of breast cancers can arise in the absence of any known risk factors (16). Furthermore, at present, many of the known risk factors that are unrelated to family history are not included in these risk models. In particular, mammographic density, perhaps the most important risk factor apart from age, is not included in any mainstream model.

**IBIS or Tyrer-Cuzick Model.** No single model has to our knowledge integrated family history, surrogate measures of endogenous estrogen exposure, and benign breast disease in a comprehensive fashion. The IBIS model (17), also known as the Tyrer-Cuzick model, which was based in part on a dataset acquired from the International Breast Intervention Study and other epidemiological data, has attempted to address these deficiencies by including the most comprehensive set of variables of all the models. Furthermore, unlike the Claus and BRCAPRO models, the IBIS model allows for the presence of multiple genes of differing penetrance. The IBIS model is similar to the Jonker model, in that its algorithm includes the likelihood of *BRCA1* and *BRCA2* mutations while allowing for a lower penetrance of *BRCAu*.

**Comparisons of Model Accuracy**

The accuracy of the models for individual patients was evaluated using receiver operating characteristic curves: The AUC was 0.735 for the Gail model, 0.716 for the BRCAPRO (Claus) model, 0.737 for the BRCAPRO (Ford) model, and 0.762 for the IBIS model. It was therefore concluded that the IBIS model was the most consistently accurate model for predicting the risk of breast cancer.

**Mammographic density i.e. why we used Volpara automated software.**

**Mammographic Density.** Mammographic density is perhaps the single most important risk factor that is assessable and that may also have a substantial heritable component (8). It remains unclear whether this variable can truly be considered hormonal or whether its etiology is more diverse. Mammographic density is generally quantified as the proportion of the breast tissue on a mammogram that appears dense. Approximately 5% of the white female population worldwide has mammographic density covering more than 75% of the breast (19). These women have a fivefold increased risk of breast cancer.
compared with women with mammographic breast density of less than 10%. The increase in relative risk for women with 50%-75% mammographic breast density is approximately twice that of women with mammographic breast density of less than 10%, and these women comprise approximately 14% of white women (19). Breast density can be rapidly and reliably measured from mammograms, and such mammographic data have yielded good risk prediction accuracy (20).

Breast density has been shown to reduce the sensitivity of mammography and increase a women's risk of developing breast cancer. Accurate methods for measuring breast density are, therefore, essential to optimize the breast cancer screening process and enhance objective clinical decisions regarding supplemental imaging. Radiologists typically judge breast density visually by assessing the area of dense tissue from a 2D mammogram, an imprecise and subjective method known to suffer from both inter- and intra-reader variability.

The use of the fully automated software eliminated intra- and inter-observer differences, correlated with BI-RADS categories ($r = 0.62$, $p < 0.01$) and can replace the semi-automated one (Bland-Altman statistics) (21).

This study demonstrates that automated estimation of breast density is feasible and eliminates subjectivity. Furthermore both the semi-automated and the fully automated density estimation are more accurate than BI-RADS quantitative evaluation and could also be used in the daily clinical practice.

To demonstrate that fully automated volumetric estimates as Volpara are accurate, several researchers have published validation studies comparing volumetric breast density estimated from FFDM, to volumetric measurements estimated from breast MRI.

Gubern-Mérida et al (22) compared VolparaDensity to MRI, an automated segmentation method for breast density evaluation VolparaDensity estimates were highly correlated with the MRI measurements ($r = 0.93$, 0.97 and 0.85, for volumetric breast density, breast volume, and fibroglandular volume, respectively).
<table>
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<tr>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Personal history for 2\textsuperscript{nd} primary</td>
<td>3-4X</td>
</tr>
<tr>
<td>2 or more family members</td>
<td>3X</td>
</tr>
<tr>
<td>Mother dx’d before age 50</td>
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**Fig. 1**: TABLE OF RISK FACTOR FOR BREAST CANCER

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Methods and materials

The study included 249 patients (fig 2) who underwent CR mammography in four views (RCC, LCC, RMLO, LMLO) between Jan 2014 and Jul 2014 self referring for screening. For each patient the individual risk profile was determined using the Tyrer-Cuzick model, counting for familial and personal factors. A VBD value was computed from each mammogram (Volpara software), and averaged among the four views to obtain the mean VBD per patient.

Differences in lifetime risk distributions for four groups of patients with increasing breast density single measurements (Fig 4) or classified in VG,1,2,3,4 (Fig 5) (VG1: 0% - 4.5 %; VG2: 4.5% - 7.5%; VG3: 7.5% - 15.5%; VG4 >15.5%) were compared .

The overall median VBD was 10.9%, ranging between 4.6% and 30%. There was no case in VG1, 58 cases in VG2 (median VBD: 6.0%), 135 cases in VG3 (median VBD: 10.35%), and 56 cases in VG4 (median VBD: 18.2%) (Fig 4).
## Fig. 1: TABLE OF RISK FACTOR FOR BREAST CANCER

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Study population

- 232 patients
- 4 views per patient (RCC, LCC, RMLO, LMLO)
- 928 images

Mean = (50.3 ± 10.9) y
Median = 45.5 y (range: 33-81)

**Fig. 2:** FIG 2

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**Fig. 4:** FIG 4

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Fig. 5: FIG 5

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Results

The median lifetime risk was 11.0% for VG2, 14.5% for VG3, and 15.6% for VG4. Differences in lifetime risk between patients in VG2 and patients in VG3 and VG4 were significant (P-values equal to 0.0011 and 0.0002, respectively), while risk was comparable for patients in VG3 and VG4 (P = 0.0931) (Fig6).
Fig. 6: FIG 6

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Conclusion

Lifetime risk increases with breast density. Volumetric mammographic density measure might be used with existing risk prediction models to identify high-risk women more precisely. Further studies with largest population and to compare women with BC vs thought without.

Two study (23-24) have been performed to evaluate relationships between mammographic density and Tyrer Cuzick risk assessment model, but both are limited from using a subjective optical or semiautomated methods which (as results from our rationale) are subjective and are not validated with other gold standard methods for breast density as MRI.

Our model overcomes subjectivity e repeatability of breast density estimate and may allow even more precisee identification of high risk women.

We present a case report of a 43 yrs old woman followed for multiple fibroadenomas (Fig. 7) since 2008 with US exams who developed a cancer in april 2014 (see image from 3D ultrasound in the Fig. 8). Mx were always negative (Fig 9). Ex post evaluation of the breast density (VG4) (Fig 10) and of the risk model (28% lifetime risk ) (Fig 11) would have included additional MRI imaging for early detection of BC (strain elastography was not informative and citology was not performed because she had several fibroadenomata unmodified since 5 years).
Images for this section:

**Fig. 7:** FIG 7

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Fig. 8: FIG 8

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**Fig. 9: FIG 9**

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**Fig. 10:** FIG 10

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Fig. 11: FIG 11

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