Risk Assessment: Pros and Cons

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Disclosure

• Hologic, Inc. Shareholder and research agreement
• Volpara Solutions, Ltd. Shareholder and research agreement
Why Measure Risk?

• Identify women to undergo genetic testing
• Identify women at very high lifetime risk
• General screening population for educated decision making about screening
Risk Assessment

• Risk/Risk models
• Assessing risk of BRCA mutation
• Identifying women at high risk
• Use in general population
Risk Assessment

• Risk/Risk models
• Assessing risk of BRCA mutation
• Identifying women at high risk
• Use in general population
Breast Cancer Risk Factors

- Age
- Female gender
- Race/ethnicity
- Ashkenazi Jewish ancestry
- Socioeconomic status
- Age at menarche
- Age at menopause
- Age at first live birth
- Age at subsequent births
- Birth index
- Alcohol consumption
- Parity
- Physical activity
- Postmenopausal obesity
- Bone Density
- Breastfeeding

- Contraceptive use
- Menopausal hormone use
- Serum estradiol level
- Urine estrogen metabolites
- Surgical menopause
- Number of breast biopsies
- ADH/LCIS/ALH
- Breast density
- Radiation exposure
- Family history of breast cancer
- FH ovarian CA
- FH other cancers
- Genetic mutations (BRCA, etc)
Breast Cancer Risk Factors

Personal/Hormonal
- Parity
- Age at menarche
- Age at menopause
- Hormone therapy
- Obesity
- Alcohol use
- Exercise
- Urine estrogen metabolites

Breast Disease
- LCIS
- ALH
- ADH
- DCIS
- # Breast biopsies
- Breast density
- Radiation exposure

Hereditary
- Family history breast cancer
- FH ovarian CA
- Mutation carrier
Risk Prediction Model

- A statistical tool for estimating the probability that a currently healthy individual with specific risk factors (e.g. age, menopausal status) will develop a future condition (e.g. breast cancer) within a specific time period (5 or 10 years, lifetime)

Meads C. Br Cancer Res Treat, 2011
What Models Report

• Risk of BRCA 1 or 2 mutation
• Risk of breast cancer
  – Invasive
  – Invasive + DCIS
  – ER/PR +
• Timeframe of risk
  – 5 or 10 year
  – Lifetime
Breast Cancer Risk Factors

**Personal/Hormonal**
- Parity
- Age at menarche
- Age at menopause
- Hormone therapy
- Obesity

**Breast Disease**
- LCIS
- ALH
- ADH
- DCIS
- Breast density
- Radiation exposure

**Hereditary**
- Family
- Claus
- BRCA Pro
- BOADICEA
- Myriad

**Tyrer-Cuzick (IBIS) Model**

Gail
BCRAT
Rosner-Colditz
Gail Model (1989)

- 2,852 cases: 3,146 controls
- Breast Cancer Detection Demonstration Project (BCDDP)
- Six variables
- 10 validation studies
- 2 subpopulation studies

Gail MH. JNCI, 1989
Breast Cancer Risk Assessment Tool (BCRAT)

- Modified Gail Model (Gail 2)
- Projects risk in Asian population (2008)
- Validated using WHI data

Gail MH. JNCI, 2007
The Breast Cancer Risk Assessment Tool is an interactive tool designed by scientists at the National Cancer Institute (NCI) and the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate a woman's risk of developing invasive breast cancer. The tool has been updated for African American women based on the Contraceptive and Reproductive Experiences (CARE) Study, and for Asian and Pacific Islander women in the United States based on the Asian American Breast Cancer Study (AABC). See About the Tool for more information.

Before using the tool, please note the following:

1. The Breast Cancer Risk Assessment Tool was designed for use by health professionals. If you are not a health professional, you are encouraged to discuss the results and your personal risk of breast cancer with your doctor.

2. Although the tool may accurately estimate a woman's risk of developing breast cancer, these risk estimates do not allow one to say precisely which women will develop breast cancer. In fact, the distribution of risk estimates for women who develop breast cancer overlaps the estimates of risk for women who do not.

3. The tool should not be used to calculate breast cancer risk for women who have already had a diagnosis of breast cancer, lobular carcinoma in situ (LCIS), or ductal carcinoma in situ (DCIS).

4. The BCRA risk calculator may be updated periodically as new data or research become available.

5. Although the tool has been used with success in clinics for women with strong family histories of breast cancer, more specific methods of estimating risk are appropriate for women known to have breast cancer-producing mutations in the BRCA1 or BRCA2 genes.

6. Other factors may also affect risk and are not accounted for by the tool. These factors include previous radiation therapy to the chest for the treatment of Hodgkin lymphoma or women who have recently immigrated to the United States from certain regions of Asia where breast cancer risk is low. Further, the tool may not be appropriate for women living outside the United States. The tool's risk calculations assume that a woman is screened for breast cancer as in the general U.S. population. A woman who does not have mammograms will thereby be underestimating the risk of breast cancer.

http://www.cancer.gov/bcrisktool/
Other Modified Gail Models

• Tice (2005). SF Mammography Registry. Included breast density.
• Chen (2006). Added breast density and weight, removed age at menarche.
• Decarli (2006). Italian. Changed biopsy Y/N to #.
• Chlebowski (2007). Added breast feeding, smoking, alcohol, physical activity, MHT
• Tice (2008). BCSC. Kept only age, FH breast cancer, breast biopsy. Added breast density and race.
“Breast Tissue Aging” (M Pike, 1983)
  - Breast tissue most susceptible to DNA damage between puberty and first birth
  - Younger age at first birth associated with fewer mutations
  - Later age associated with proliferation of mutations
  - Late parity > Nulliparity > Early parity

- Included current age, age at first live birth, age at subsequent births, age at menopause
- Validated using Nurses Health Study ~ 90,000 women
- Modified Model (2000)
Genetic Risk Models

- Claus (1993)
- BRCAPro
- BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm)
- Tyrer-Cuzick (IBIS)
- Myriad
Tyrer-Cuzick Model (2004)

- International Breast Intervention Study (IBIS) and UK National Cancer Statistics
- Includes pedigree for FH breast and ovarian cancer
- Risk of BRCA 1 or BRCA 2 mutation
- Risk of breast cancer: 10 yr and lifetime

Tyrer J. Stat Med 2004
Tyrer-Cuzick Model

http://www.ems-trials.org/riskevaluator/
Model Validation

• Independent testing of the model
  – Same population (internal validation) or different population(s) (external validation)
  – Adjustments may lead to a modified model (change beta weights)
  – Performance may vary by population
• Calibration- performance overall in a population
• Discrimination- performance at individual level
Calibration

• How well a model predicts risk overall in a population
• Compares Expected number to Observed number of events ($E/O$ statistic)
• A well fitting model should have $E/O$ close to 1
  – < 1 underestimates
  – > 1 overestimates
• Presented as deciles of risk
Model Calibration

Meads C. Br Cancer Res Treat, 2012
Discrimination

• How well a model predicts risk at the individual level
• Proportion of randomly chosen pairs (with and without the condition) from the sample where the person with the condition has a higher predicted risk than the one without.
• $C$ statistic
  – 1.0 Perfect discrimination
  – 0.5 Random chance, no discrimination
  – AUC
### Discrimination (C-Statistic)

<table>
<thead>
<tr>
<th>Study</th>
<th>AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosner &amp; Colditz (1996)</td>
<td>0.64</td>
</tr>
<tr>
<td>Modified Rosner &amp; Colditz (2000)</td>
<td>0.64</td>
</tr>
<tr>
<td>Boyle (2004)</td>
<td>0.58</td>
</tr>
<tr>
<td>Tice (2005)</td>
<td>0.68</td>
</tr>
<tr>
<td>Chen (2006)</td>
<td>0.64</td>
</tr>
<tr>
<td>Decarli (2006)</td>
<td>0.59</td>
</tr>
<tr>
<td>Barlow (2006)</td>
<td>0.63</td>
</tr>
<tr>
<td>Chlebowski (2007)</td>
<td>0.61</td>
</tr>
<tr>
<td>Tice (2008)</td>
<td>0.66</td>
</tr>
<tr>
<td>Tyrer-Cuzick (2004)</td>
<td>0.76</td>
</tr>
</tbody>
</table>
Risk Assessment

• Risk/Risk models
• Assessing risk of BRCA mutation
• Identifying women at high risk
• Use in general population
Identify women to undergo genetic testing

- Use pedigree based models (BOADICEA, BRCA Pro, Tyrer-Cuzick)
- Risk of BRCA mutation >10%, consider genetic testing (NCCN guidelines)
- If BRCA mutation carrier, then apply risk reduction strategies: chemoprevention, prophylactic surgery, intensive screening
Discrimination for BRCA mutations

<table>
<thead>
<tr>
<th>Model</th>
<th>AUC (C-Statistic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BODICEA</td>
<td>0.77</td>
</tr>
<tr>
<td>BRCAPro</td>
<td>0.76</td>
</tr>
<tr>
<td>IBIS</td>
<td>0.74</td>
</tr>
<tr>
<td>Myriad II</td>
<td>0.75</td>
</tr>
</tbody>
</table>

Meads C. Br Can Res Treat; 2012
Genetic Risk Models

- Claus
  - Must have affected first degree relative
- BRCAPro
  - Assumes risk only due to BRCA gene mutation
- BOADICEA
  - Allows for familial transmission not accounted for by BRCA 1 or 2 mutations
- Tyrer-Cuzick
- Myriad
Myriad BRCA Risk Calculator

The BRCA Risk Calculator is based on data, which will be updated periodically, that represent observations of deleterious mutations by Myriad Genetic Laboratories through its clinical testing service. Data obtained through testing performed under specific research protocols is not included. The data were obtained from a routine laboratory requisition form and have not been independently verified by Myriad Genetic Laboratories. Patients for whom relevant information was not provided were not included in this tabulation. The data on individuals with Ashkenazi Jewish ancestry are for patients tested only for three prevalent founder mutations as well as patients tested by full sequence analysis. The method used to develop the prevalence tables has been published in Frank TS et al: Clinical Characteristics of Individuals With Germline Mutations in BRCA1 and BRCA2: Analysis of 10,000 Individuals. Please contact cliniresearch@myriad.com or call 1-800-469-7423 with any questions or comments.
Modeled Risk of BRCA Mutation Declines with Age
Risk Assessment

• Risk/Risk models
• Assessing risk of BRCA mutation
• Identifying women at high risk
• Use in general population
Identifying High Risk Women

• Goal: identify women who may benefit from risk reduction strategies
• Use pedigree based model
  – BOADICEA, BRCA Pro, Tyrer-Cuzick
  – TC if multiple risk factors
• >20-25% lifetime risk
• Lifetime risk is projected and poorly validated
Percent of Women High Risk Varies by Model

Lifetime breast cancer risk 20% or greater by model

Tyrer-Cuzick = 330
(5.6%)

Adjusted BRCAPRO
61 (1%)

Claus = 54 (0.9%)

Ozzane EM. CEBP; 2013
Tyrer-Cuzick Model, Version 7

- Accounts for increasing incidence of breast cancer and greater longevity of women
  - Higher number of women at >20% lifetime risk
  - Consider using 25% lifetime risk as cut-off if using V.7

- Next version will include BI-RADS and automated density
10 year vs. Lifetime Risk

• 35 yo woman
  – Mother breast cancer age 58
  – Sister, breast cancer age 45
  • Tyrer-Cuzick
    – 10 y risk 2.8%
    – Lifetime risk 25.2%
• 65 yo woman
  – Mother breast cancer age 58
  – Sister, breast cancer age 45
  • Tyrer-Cuzick
    – 10 y risk 6.4%
    – Lifetime risk 9.9%

Lifetime Risk Declines with Age
Woman with FH Mother, 1 Mat Aunt
Risk Assessment

• Risk/Risk models
• Assessing risk of BRCA mutation
• Identifying women at high risk
• Use in general population
Use of Models in General Population

- Identify women that may be at high risk
- Educate women about their risk
- Risk based screening
Perceptions of Risk

- Telephone survey of 1024 Virginia women age 35-70, June-October 2013 (one year after effective date of VA Density Notification Law)

- Compared to the average woman, do you feel that their risk of getting breast cancer is:
  - a little more or much more - 13.3%
  - the same as the average woman- 46.4%
  - a little less or much less than average- 28.9%
  - don’t know- 9.6%
“As a percentage, what do you think your chance is of developing breast cancer in your lifetime?”
Risk Based Screening

• Pros
  – Identify high risk women
  – May prompt women to comply with annual screening if above average risk
  – May be most cost effective if resources are limited

• Cons
  – Risk models only have moderate discrimination
  – Women may decrease screening if perceived to be of lower than average risk
  – Risk alone does not predict who may benefit from ancillary screening
Which Would You Choose?

Risk Calculator

1. Does the woman have a medical history of any breast cancer or ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS)?

2. What is the woman’s age? This tool only calculates risk for women 35 years of age or older.

3. What was the woman’s age at the time of her first menstrual period?

4. What was the woman’s age at the time of her first live birth of a child?

5. How many of the woman’s first-degree relatives - mother, sisters, daughters - have had breast cancer?

6. Has the woman ever had a breast biopsy?

6a. How many breast biopsies (positive or negative) has the woman had?

6b. Has the woman had at least one breast biopsy with abnormal findings?

7. What is the woman’s race/ethnicity?

7a. What is the subrace/ethnicity?

[Calculate Risk]
Risk Assessment can be Automated

<table>
<thead>
<tr>
<th>NCI Risk</th>
<th>Patient</th>
<th>Average Woman</th>
</tr>
</thead>
<tbody>
<tr>
<td>within 5 years</td>
<td>1.6 %</td>
<td>1.9 %</td>
</tr>
<tr>
<td>within lifetime</td>
<td>7.3 %</td>
<td>8.6 %</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tyrer-Cuzick Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Person life-time probability</td>
<td>4.4 %</td>
<td></td>
</tr>
<tr>
<td>BRCA1 probability</td>
<td>0.1 %</td>
<td></td>
</tr>
<tr>
<td>BRCA2 probability</td>
<td>0.1 %</td>
<td></td>
</tr>
</tbody>
</table>
Including Risk Information in Reports

• What to Include?
  – BRCA risk
  – Lifetime risk
  – 5/10 year risk
Risk in Reports

- Context is important

  “Based on the Tyrer-Cuzick (IBIS) model, this patient's lifetime risk for developing breast cancer is 4.4%.”

The American Cancer Society considers women with a greater than 20% lifetime risk as high risk, and 15-19% as moderate risk. Women at high risk for breast cancer may benefit from additional screening using MRI or other modalities. Formal risk assessment, genetic counseling, and risk reduction strategies are available through the UVa High Risk Breast and Ovarian Cancer Clinic.
Risk in Reports

• Context is important

“Based on the Tyrer-Cuzick (IBIS) model, this patient's lifetime risk for developing breast cancer is 4.4%. Population risk for this age is 2.0%”

The American Cancer Society considers women with a greater than 20% lifetime risk as high risk, and 15-19% as moderate risk. Women at high risk for breast cancer may benefit from additional screening using MRI or other modalities. Formal risk assessment, genetic counseling, and risk reduction strategies are available through the UVa High Risk Breast and Ovarian Cancer Clinic.
Woman with FH Mother, 1 Mat Aunt
Risk in Reports

Based on the Tyrer-Cuzick (IBIS) model, this patient's lifetime risk for developing breast cancer is 4.4% (population risk for this age is 2.0%); 10 year risk is 7.5% (population risk 2.9%). The American Cancer Society considers women with a greater than 20% lifetime risk as high risk, and 15-19% as moderate risk. Women at high risk for breast cancer may benefit from additional screening using MRI or other modalities. Formal risk assessment, genetic counseling, and risk reduction strategies are available through the UVa High Risk Breast and Ovarian Cancer Clinic.
Based on the Tyrer-Cuzick (IBIS) model, your lifetime risk for developing breast cancer is 4.4% (population risk for this age is 2.0%); your risk of having breast cancer in the next 10 years is estimated to be 7.5% (population risk 2.9%).

The American Cancer Society considers women with a greater than 20% lifetime risk as high risk, and 15-19% as moderate risk. Women at high risk for breast cancer may benefit from additional screening using MRI or other modalities. Formal risk assessment, genetic counseling, and risk reduction strategies are available through the UVa High Risk Breast and Ovarian Cancer Clinic.
Are Women Willing to Change?

- 942 UK women age 18-74 interviewed
- 65% supported idea of varying frequency by genetic risk
- 85% willing to have more screening if high risk
- Only 58% willing to reduce screening if low risk
- Ethnic minority less accepting of more screening (OR 0.40)

Meisel SF. Breast 2015
Clinical Use of Models

STAHLER.
THE COLUMBUS DISPATCH.
2003

YOU ARE SUFFERING FROM CONFUSING CANCER GUIDELINE SYMPTOMS.

WE DON'T NORMAL START TESTING FOR THAT UNTIL YOU'RE THIRTY.
## Models: When and Which to Use

<table>
<thead>
<tr>
<th>Model</th>
<th>Population Calibrated</th>
<th>Breast Cancer Outcome</th>
<th>Preclude Use</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCRAT</td>
<td>U.S.</td>
<td>Invasive</td>
<td>LCIS</td>
<td>Only model validated for African-American; Adjusts for Asian; validated in general population</td>
</tr>
<tr>
<td>Claus</td>
<td>U.S.</td>
<td>Invasive &amp; DCIS</td>
<td>No affected first degree relatives</td>
<td></td>
</tr>
<tr>
<td>BRCAPRO</td>
<td>U.S.</td>
<td>Invasive for non-carriers</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>IBIS</td>
<td>England &amp; Wales</td>
<td>Invasive &amp; DCIS</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>
## Suggested Use of Models

<table>
<thead>
<tr>
<th>Situation</th>
<th>Model(s) to consider</th>
</tr>
</thead>
<tbody>
<tr>
<td>Known or suspected BRCA mutations in family</td>
<td>BRCAPro, BODICEA; IBIS</td>
</tr>
<tr>
<td>Paternal FH Breast Cancer</td>
<td>BRCAPro, BODICEA; IBIS</td>
</tr>
<tr>
<td>FH Ovarian Cancer</td>
<td>Claus, BRCAPro, BOADICEA, IBIS</td>
</tr>
<tr>
<td>Hispanic or non-White</td>
<td>BCRAT</td>
</tr>
<tr>
<td>Prior breast biopsy</td>
<td>BCRAT</td>
</tr>
<tr>
<td>LCIS</td>
<td>IBIS</td>
</tr>
<tr>
<td>Multiple Risk Factors</td>
<td>IBIS</td>
</tr>
<tr>
<td>Under age 35</td>
<td>IBIS</td>
</tr>
<tr>
<td>Radiation Exposure at young age</td>
<td>No model</td>
</tr>
<tr>
<td>Suspected or known Li-Fraumeni, Cowden, or Bannayan-Riley-Ruvalcaba Syndrome</td>
<td>No model- Genetic counseling</td>
</tr>
</tbody>
</table>
Conclusion

• Breast cancer risk models all have relatively good calibration (prediction of risk to the population), but relatively modest discrimination (prediction of risk at individual level)

• Tyrer-Cuzick (IBIS) has best overall discrimination

• Using risk models in your practice depends upon your goal:
  – Identifying potential BRCA mutation carriers (BRCAPRO, BOADICEA, IBIS, Myriad)
  – Identify women at high risk for risk reduction strategies (Pedigree based model, TC if multiple risk factors)
  – Educate women about personal risk for decisions regarding screening (TC, BCRAT?)