

What are the reasons to use the Gail risk assessment model?

Robin Seitzman, PhD, MPH, and Wendie Berg, MD, PhD

Question

Which of the following is not an appropriate reason to use the Gail risk model?

CHOOSE ONE:

- A. Predict lifetime risk of developing invasive breast cancer
- B. Identify women who meet high-risk criteria for MRI screening
- C. Identify women who may benefit from risk-reducing medications such as tamoxifen
- D. Predict 5-year risk of developing invasive breast cancer
- E. None of the above; these are all correct reasons to use the Gail risk model

Quiz developed
in collaboration with



Dr. Seitzman is Director of Education and Epidemiology Research, DenseBreast-info.org.

Dr. Berg is Professor of Radiology, University of Pittsburgh School of Medicine, Magee-Womens Hospital of the University of Pittsburgh Medical Center. She is also Chief Scientific Advisor, DenseBreast-info.org.

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Answer

B. The Gail risk model¹⁻³ is used to predict 5-year and lifetime risks of developing invasive breast cancer, and to identify women who may benefit from risk-reducing medications such as tamoxifen. The Gail model should not be used to determine risk for purposes of screening magnetic resonance imaging (MRI)⁴ (or genetic testing).

Breast cancer risk models are used to stratify patients into risk categories to facilitate personalized screening and surveillance plans for clinical management. Several breast cancer risk assessment tools have been developed that include different combinations of known risk factors and are used for the following purposes:

1. To identify women who may benefit from risk-reducing medications. The Gail model is used to determine risk for purposes of advising on use of risk-reducing medications. Any woman with a 5-year risk $\geq 1.67\%$ by the Gail model may be considered for treatment with tamoxifen (pre or postmenopausal), raloxifene (postmenopausal), or aromatase inhibitors (postmenopausal).⁵

In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P1 study,⁶ women at increased risk for breast cancer were defined as follows:

- age 35 to 59 years with at least a 1.66% 5-year risk for developing breast cancer by the Gail model
- personal history of lobular carcinoma in situ (LCIS)
- age over 60 years.

More than 13,000 such women were randomly assigned to receive tamoxifen or placebo daily for 5 years. Tamoxifen reduced the risk of invasive breast cancer by 49% and reduced the risk of noninvasive cancer by 50% compared with placebo. The reduced risk of breast cancer was only seen for estrogen-receptor-expressing tumors. There was a 2.5-fold increase in risk of endometrial cancer in women taking tamoxifen and a decrease in hip and spine fracture risk. Blood clots causing stroke and deep vein thrombosis are increased in women taking tamoxifen.^{7,8}

2. To identify women who may carry a pathogenic mutation in *BRCA1* or *BRCA2*. Some models (eg, Tyrer-Cuzick [IBIS],⁹ Penn II,¹⁰ BOADICEA,¹¹ and BRCAPRO¹²) estimate the probability of a *BRCA1/2* mutation; however, most testing guidelines are now criterion based (eg, National Comprehensive Cancer Network [NCCN]) as opposed to probability based. In practical terms, clinical decision making around genetic testing is rarely based on *a priori* probabilities.

3. To identify women who meet criteria for high-risk screening MRI. Current American Cancer Society (ACS) guidelines⁴ recommend annual screening MRI, in addition to mammography, beginning by age 25 to 30 in women who have a lifetime risk of breast cancer $\geq 20\%$. Any of the models used to predict risk of a pathogenic mutation (Tyrer-Cuzick [IBIS], Penn II, BOADICEA, BRCAPRO), or the Claus model,¹³ but **not the Gail model**, can be used to estimate lifetime risk for purposes of screening MRI guidelines. The ACS and NCCN guidelines specifically recommend against using the Gail model to determine risk for purposes of MRI screening or risk of pathogenic mutation, as it does not include detailed family history such as age at diagnosis or second-degree relatives.

ACS and NCCN guidelines also recommend annual screening MRI beginning by age 25, with the addition of mammography beginning at age 30, in women who are known to carry pathogenic mutations in *BRCA1* or *BRCA2* (unless the woman has had bilateral mastectomy), and in women who are first-degree relatives of known mutation carriers but who are themselves untested.¹⁴

Women who are known to carry or are first-degree untested relatives of individuals with less common disease-causing mutations (such as those associated with Li-Fraumeni syndrome, Bannayan-Riley-Ruvalcaba syndrome, hereditary diffuse gastric cancer, Peutz-Jeghers syndrome, Cowden syndrome, Neurofibromatosis type 1, or Fanconi anemia) are also recommended for annual screening MRI beginning between ages 20-35, depending on the mutation.¹⁴ Women

with known pathogenic mutations in *ATM*, *CHEK2*, or *NBN* should consider annual MRI starting at age 40 or 5-10 years before the earliest known breast cancer in the family (whichever comes first).

Finally, women with prior chest radiation therapy (such as for Hodgkin disease) between ages 10 and 30 are at high risk for developing breast cancer,^{4,15,16} with risk similar in magnitude to pathogenic *BRCA1* or *BRCA2* carriers. These women are also recommended for annual screening MRI starting at age 25 or 8 years after the chest radiation therapy, whichever is later.

Currently the Tyrer-Cuzick Model (IBIS) version 8¹⁷ and the Breast Cancer Surveillance Consortium (BCSC) models¹⁸ include breast density in risk calculations; the Gail, Penn II, and Claus models do not include breast density.

Adding polygenic risk scores based on single nucleotide polymorphisms to traditional comprehensive risk models such as the Tyrer-Cuzick model has been shown to improve model performance.¹⁹ In addition, artificial intelligence is being used to identify textural and other findings beyond breast density on mammograms that predict increased risk. Such information, which is complementary to the Tyrer-Cuzick model (v.8),²⁰ has more accurately identified high-risk

patients than the Tyrer-Cuzick v8 risk model and prior deep learning models.²¹

In a study from the Karolinska Institute, a model that included computer-aided detection of microcalcifications and masses in addition to other traditional risk factors (including breast density) successfully identified women who would develop interval or advanced cancer in the 2 years after a normal mammogram and improved short-term (2-to-3-year) risk assessment over Tyrer-Cuzick (v.7) or Gail models.²² This model proved more accurate than traditional risk models and can augment genetic/family history to help identify women who should and, importantly, who should not, have supplemental screening after 2D mammography. Risk models that include detailed family history should be used rather than the Gail model to identify women who meet high risk criteria for MRI screening. Research also supports the benefits of MRI in women with dense breasts who are not otherwise considered “high risk,” and while not widely available, lower cost, abbreviated MRI protocols have been validated for all women with dense breasts.²³ For more details on risk models, including a risk models table with live links to commonly used breast cancer risk assessment tools, visit <https://densebreast-info.org/for-providers/risk-model-tutorial/>. ●

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