

Assessing Women at High Risk of Breast Cancer: A Review of Risk Assessment Models

Eitan Amir, Orit C. Freedman, Bostjan Seruga, D. Gareth Evans

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Correspondence to: Eitan Amir, MB ChB, Division of Medical Oncology and Hematology, Princess Margaret Hospital, 610 University Ave, Toronto, ON, Canada M5G 2M9 (e-mail: eitan.amir@uhn.on.ca).

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. This review aims to distill the diverse literature and provide practicing clinicians with an overview of the available risk assessment methods. Risk assessments fall into two groups: the risk of carrying a mutation in a high-risk gene such as *BRCA1* or *BRCA2* and the risk of developing breast cancer with or without such a mutation. Knowledge of breast cancer risks, taken together with the risks and benefits of the intervention, is needed to choose an appropriate disease management strategy. A number of models have been developed for assessing these risks, but independent validation of such models has produced variable results. Some models are able to predict both mutation carriage risks and breast cancer risk; however, to date, all are limited by only moderate discriminatory accuracy. Further improvements in the knowledge of how to best integrate both new risk factors and newly discovered genetic variants into these models will allow clinicians to more accurately determine which women are most likely to develop breast cancer. These steady and incremental improvements in models will need to undergo revalidation.

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Genetic and familial factors can substantially increase the lifetime risk of developing breast cancer and are associated with the development of cancer at a young age. However, despite the fact that high-risk genes contribute to less than 5% of new breast cancer diagnoses (1), many health-care systems screen patients for high-risk genes before decisions regarding surveillance, prevention, or therapeutic strategies are made. In fact, many so-called family history clinics have been implemented in this setting so that patients who are considered to be at high risk of breast cancer can be adequately assessed and managed (2). In this setting, an accurate assessment of individualized risk is of paramount importance. Here, we review the various tools that are available for the assessment of this risk.

Overview of Breast Cancer Risk

Although the widely quoted general population risk of being diagnosed with breast cancer—one in eight to one in 12—is a lifetime risk, the 10-year risk in any given decade of life is never greater than one in 25 (see Figure 1) (3). In addition to this population risk of breast cancer, other risk factors, such as family history, endocrine factors, and host factors including breast density and history of benign proliferative breast disorders, can substantially modify the risk of developing breast cancer.

Other than age, the presence of a substantial family history of breast cancer is probably the most important risk factor for the development of this disease. Consequently, the search for specific

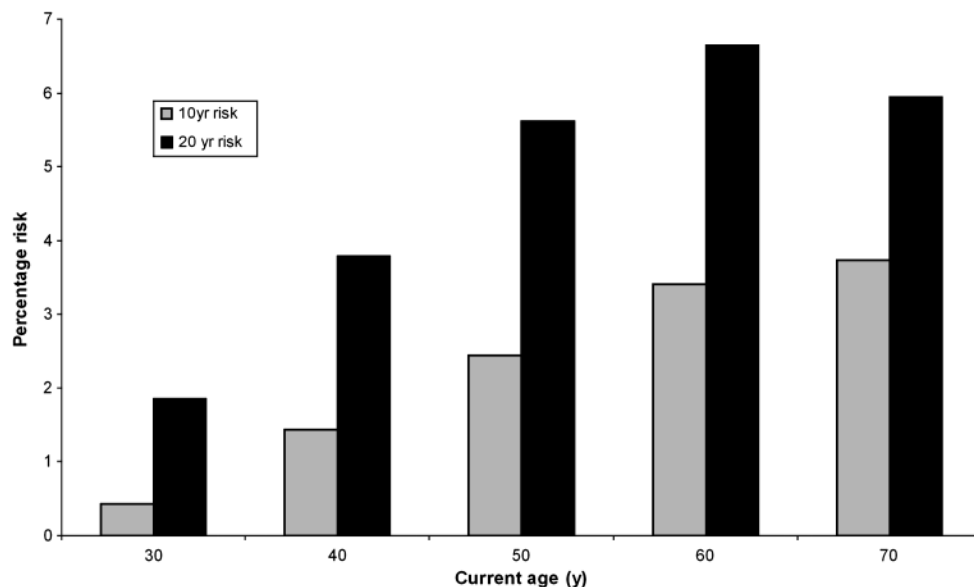
germline genetic susceptibility factors, such as mutations in the *BRCA* family of tumor suppressor genes, is of utmost importance in risk assessment. Hereditary factors are virtually certain to play a role in a high proportion of sporadic breast cancer; however, these factors are harder to evaluate, and it is hoped that genome-wide association studies will unravel them in the future (4).

Importance of Risk Assessment

Breast cancer remains a major global problem. Despite a steady reduction in the mortality rates from breast cancer in many Western countries, with the exception of the United States (5), the incidence of breast cancer continues to increase (6). Although this increase in incidence is likely to be related predominantly to changes in dietary and reproductive patterns, evidence from genetic studies has also shown an increase in incidence in patients with *BRCA1* and *BRCA2* mutations (7–9).

Except in very rare cases such as Cowden syndrome (10), a hereditary disorder caused by germline mutations in the *PTEN* tumor suppressor that is characterized by macrocephaly, slowly progressive cerebellar ataxia, multiple tumor-like growths, and an increased risk of certain forms of cancer including breast cancer, there are no phenotypic clues that help to identify people who carry pathogenic mutations that increase the risk of breast cancer. Consequently, a family history evaluation is necessary to assess the likelihood of predisposing genes for breast cancer in a family. Many family history clinics use a two-pronged approach to assess

Figure 1. Risk of developing breast cancer by age. Percentage risk refers to chance of developing breast cancer over the following 10 or 20 years. For example, a 60-year-old woman would have a 3.4% risk of breast cancer over the following 10 years and a 6.7% risk over the following 20 years.



breast cancer risk. First, they identify those patients who are at risk of carrying a germline mutation and offer them formal genetic testing. Second, for those who do not meet the criteria for genetic testing or who test negative for germline mutations, there is a need to quantify the risk of developing cancer over a specified length of time. With the resulting information, surveillance, lifestyle, pharmacological, or surgical interventions can be instituted to improve a patient's risk profile (Figure 2). It should be noted, however, that among breast cancer patients with a substantial family history of cancer who test negative (wild type) for *BRCA1* and *BRCA2*, approximately 12% can be expected to carry a large genomic deletion or duplication in one of these genes, and approximately 5% can be expected to carry a mutation in other breast cancer-predisposing genes (11). Effective methods for identifying these mutations should also be made available to these women.

Risk Assessment Modeling

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.

Individualized risk assessment is a crucial component in the effective assessment of women at high risk of breast cancer. In this review, we focus on individualized risk estimation for carrying specific breast cancer predisposing genes and for the development of breast cancer over a specified timeframe. We aim to distill the diverse literature and provide practicing clinicians with an overview of the available risk assessment methods.

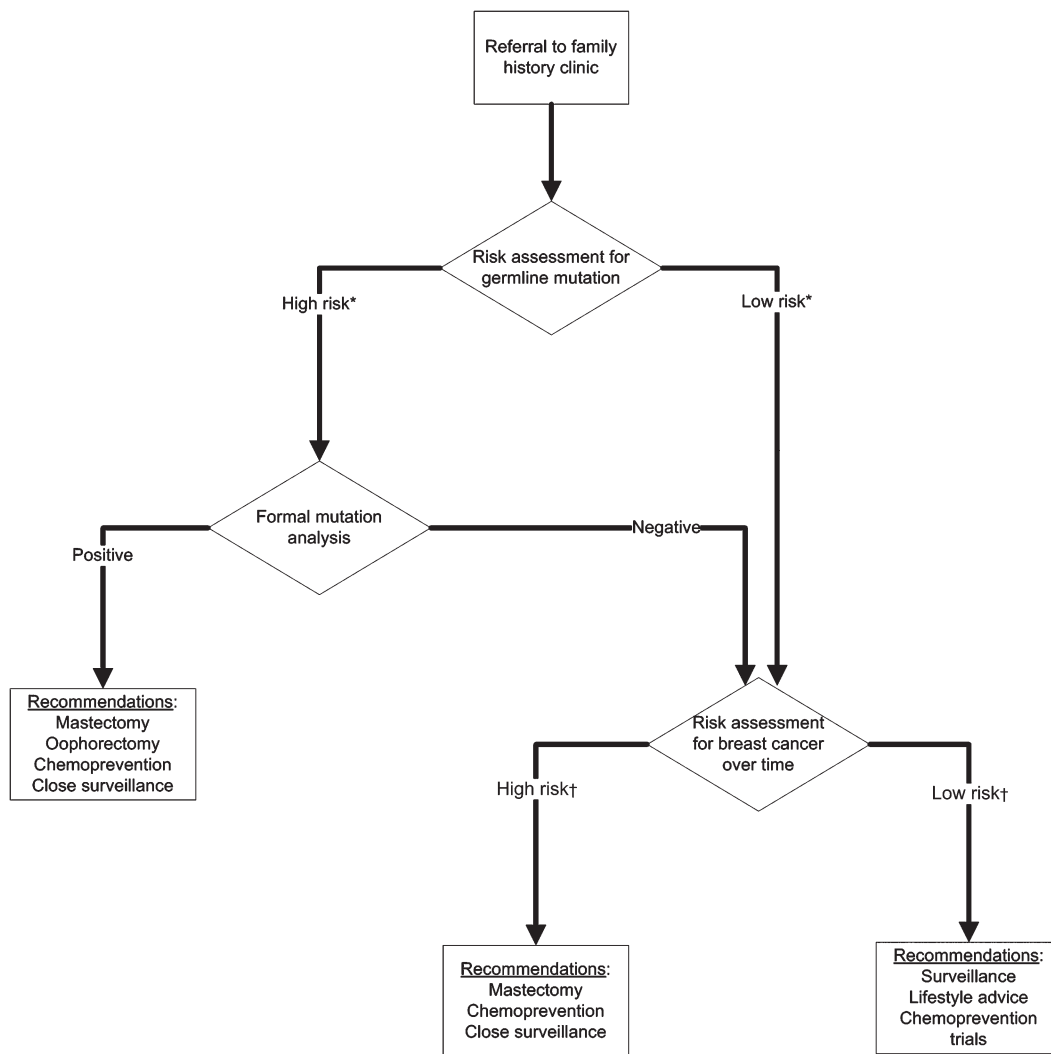
Assessing the Risk of Carrying a Germline Mutation

In addition to increasing the risks of breast and ovarian cancers, germline mutations in *BRCA1* and *BRCA2* are associated with an increased risk of prostate cancer and *BRCA2* mutations are associated with increased risks of pancreatic and gastric cancers and melanoma (12). *BRCA* mutations tend to cluster within certain ethnic groups, such as Ashkenazi Jews (13–15), and in some populations, such as those in the Netherlands (16), Iceland (17,18), and Sweden (19). Germline mutations that are associated with familial breast cancer have been identified in other genes, including *TP53*, *PTEN*, *ATM*, *CHEK2*, *NBS1*, *RAD50*, *BRIP1*, and *PALB2*, and others are suspected (20,21).

There is evidence that strategies to reduce the risk of cancer in populations that carry such mutations are effective (22). Therefore, identifying individuals who should undergo genetic testing for mutations is very important. Although formal mutational analysis on all patients is possible, it would be a laborious and expensive process: Full sequencing of *BRCA1* and *BRCA2* costs approximately US \$3000 in North America but is cheaper in Europe because of the absence of substantial patent rights. Therefore, most family history clinics have been offering such testing to patients who have high-risk features, such as early-onset breast cancers or a family history consistent with germline mutations.

There are two main approaches to identify patients for whom formal genetic testing would be beneficial. These approaches, which involve the use of family history patterns and the use of statistical models to predict the likelihood of carrying a mutation, are not mutually exclusive and are often used in conjunction. The

Figure 2. Flowchart of the management of women who are referred to family history clinics. *High risk usually defined as more than 10% risk of harboring mutation, and low risk usually defined as 10% or lower risk. †High risk usually defined as a 5-year risk of developing breast cancer more than 1.67%, and low risk usually defined as a 5-year risk of developing breast cancer 1.67% or lower.



US Preventative Services Task Force (23) published specific guidelines for referring a patient for *BRCA* mutation testing. These guidelines include two first-degree relatives with breast cancer, with one diagnosed at or before age 50 years; three or more first- or second-degree relatives with breast cancer regardless of age at diagnosis; a combination of both breast and ovarian cancers among first- and second-degree relatives; a first-degree relative with bilateral breast cancer; two or more first- or second-degree relatives with ovarian cancer regardless of age at diagnosis; a first- or second-degree relative with both breast and ovarian cancers at any age; a history of breast cancer in a male relative; or a woman of Ashkenazi Jewish heritage with any first-degree relative (or any two second-degree relatives) with breast or ovarian cancer. Similar guidelines have been published elsewhere, including in the United Kingdom by the National Institute for Clinical Excellence (24).

A number of models and scoring systems have been derived to assess the probability of the presence of a *BRCA1* mutation or a *BRCA2* mutation in a given individual based on family history. These models fall into two general groups: the empirical models and the genetic risk prediction models.

Empirical Models

Empirical models estimate the probability that genetic testing will detect a *BRCA1* or *BRCA2* mutation and do not make explicit assumptions about the underlying genetic risks (eg, penetrance, mutation frequencies, and method of inheritance). The empirical models include some of the early models, such as the Shattuck-Eidens model (also known as the Myriad I model) (25) and the Couch model (also known as the UPenn or Penn Model) (26), which were derived before the widespread use of genetic testing. The Couch model was recently updated as the Penn II model (27) and now includes more comprehensive personal and family cancer histories. However, although this model is available online (27), the details of its development and validation have not yet been published. Other empirical models include tabular scoring systems that were derived from the Myriad Genetic Laboratories genetic testing program (28,29), of which the second scoring system, Myriad II (also known as the Frank model), was based on testing in more than 10 000 individuals (29). In an attempt to simplify the use of these models, which can be time-consuming, two similar models were developed, both of which use scoring systems and

cutoff values to define patients who are at risk of carrying a germline mutation. These include the family history assessment tool (30) and the Manchester model (31), the latter of which was developed and validated in two independent datasets and was shown to perform well compared with other established models. Another group of empirical models that use regression analysis to generate risk estimates include the Australian LAMBDA model (32) and the National Cancer Institute (NCI) model (33), both of which were developed for use in Ashkenazi Jewish women, as well as models that were derived from data from Spanish (34) and Finnish (35) populations. A comparison of these scoring system models and the Myriad II model in a Spanish dataset showed that all models had similar discriminatory power and concluded that models that are targeted to specific populations did not have improved discriminatory accuracy compared with those that are not targeted to specific populations and, therefore, may not be necessary in all cases (36).

Genetic Risk Prediction Models

Genetic risk prediction models make explicit assumptions about the number of susceptibility genes involved, the allele frequencies in the general population, and the cancer risks that are conferred by these alleles. These models use pedigree analysis methods, which are based on information about the exact relationships among individuals within a family. The main advantage of genetic risk prediction models is that they can, in principle, compute cancer risks and mutation carrier probabilities regardless of the family structure and disease pattern. However, their accuracy depends on their underlying assumptions. At best, the current genetic risk prediction models give approximate risk estimates because not all breast cancer susceptibility genes have been identified (37). These models include the most widely used and validated model, BRCAPRO (38–40), as well as the Yale University model (41), the International Breast Cancer Intervention Study (IBIS) model (also known as the Tyrer–Cuzick model) (42), and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (43).

Comparison of Germline Mutation Risk Prediction Models

There have been many attempts to validate and compare these *BRCA1* and *BRCA2* risk estimation models (38–40,44–47). A number of these models were also independently compared and validated in a 2007 study, which showed that no one type of model is best (48). However, the authors noted that although both empirical and genetic models are able to discriminate well between mutation carriers and noncarriers, the sensitivity and specificity varied among the models and test populations (48). More recently (49), data from six genetics clinics in the United Kingdom were used to compare the most commonly used models in that country, namely BOADICEA, BRCAPRO, IBIS, the Myriad II model, and the Manchester model. Of the five models, only BOADICEA accurately predicted the overall observed number of mutations that were detected. BOADICEA also provided the best discrimination between mutation carriers and noncarriers and was statistically significantly better than all of the other models except BRCAPRO (AUC: BOADICEA = 0.77, BRCAPRO = 0.76, IBIS = 0.74, Manchester = 0.75, and Myriad II = 0.72). All of the models underestimated the number of *BRCA1* and *BRCA2* mutations in a popu-

lation with a low estimated risk of carrying *BRCA1* or *BRCA2* mutations (49). A single-institution study from Toronto, Canada, compared the BRCAPRO, Myriad II, Couch, family history assessment tool, Manchester, Penn II, IBIS, and BOADICEA models and showed that the BRCAPRO, Penn II, Myriad II, family history assessment tool, and BOADICEA models had similarly good discriminatory accuracy (all AUCs were approximately 0.75), whereas the Manchester and IBIS models had somewhat lower discriminatory accuracy (AUCs were 0.68 and 0.47, respectively) (50). Of interest, when assessing the probability of carrying a mutation at which a patient is eligible for testing, the Penn II model achieved higher sensitivity at the 10% testing threshold compared with the other models.

Perhaps the most useful aspect of work that has assessed thresholds for genetic testing referral has been the development of a cutoff at the 10% or 20% level. Because genetic testing for *BRCA1* and *BRCA2* mutations costs approximately \$3000, insurance companies and health-care systems require a mutation carrier probability threshold for test use. In the United Kingdom, this threshold is set at a mutation carrier probability of 20% (24); in most of the rest of Europe and North America, the threshold is 10%. Although these cutoffs are helpful in the clinical context, the quantitative choice of cutoff has a number of limitations that need to be addressed. For example, in high-risk populations, a referral threshold of 10% results in relatively high sensitivity but a very low specificity, whereas in population-based cohorts, the specificity is high but the sensitivity is low, and the 10% threshold misses a large proportion of patients who have *BRCA1* and/or *BRCA2* mutations (48). However, in the context of family history clinics, which select for high-risk patients on the basis of their referral criteria, these scoring systems can be beneficial.

Practical Limitations of Risk Models

Although simple tabular or scoring systems are easy to use and can generate mutation carrier probabilities in as little as 1–2 minutes, computer-based programs can take up to 15 minutes to input all the relevant data. Nonetheless, computer-based programs can be carried out in clinics to generate pedigrees and store family information.

All risk assessment models have limitations: Adoption, small family size [or “limited family structure” (51)], 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 (52). Of additional concern is the mistaken assumption that a paternal family history of breast or ovarian cancer is not relevant to risk for cancer (53). Furthermore, it is known from the noncancer (54) and cancer (55) 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.

Other important weaknesses of the available genetic risk assessment models include the fact that they incorporate information only about first- or second-degree relatives of the person who is

being assessed. Such practice may underestimate cancer risk if there are many third-degree or higher relatives with breast or ovarian cancer. Some models do not include a family history of other types of cancer, such as prostate cancer and pancreatic cancer, which are known to be influenced by *BRCA1* or *BRCA2* mutations (12). These models can be further improved by incorporating population-specific risks, mutation prevalence, or tumor-specific characteristics. For example, *BRCA1* mutations are associated with triple-negative grade 3 breast cancer histology [reviewed in (56)]. Therefore, the presence of this phenotype should allow for an increase in the estimated risk of carrying a *BRCA1* mutation. These pathological correlates are increasingly being added to the established models described above and have resulted in improved discriminatory accuracy (57,58).

In view of the current weaknesses in the collection of data needed for these models and the inherent limitations of the model algorithms themselves, it has been recommended that the use of these model-based predictions should only occur in conjunction with clinical judgment (59).

Assessing the Risk of Breast Cancer Over Time

To assess breast cancer risks over time as accurately as possible, it is important to assess as many risk factors for breast cancer as possible. A number of risk factors for breast cancer have been identified and quantified. These are summarized below.

Risk Factors

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 (60). 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 (60). A relative with bilateral breast cancer can be counted as two affected relatives for the purposes of these calculations.

Hormonal and Reproductive Risk Factors. Hormonal and 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 (61–63). 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 (60). Use of the oral combined 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). 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 (64). 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 (62). 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). 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 (65,66). 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 (61).

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 (67). 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 (68); therefore, a number of years of breast feeding would be necessary to have a substantial impact on risk.

Mammographic Density. Mammographic density is perhaps the single most important risk factor that is assessable and that may also have a substantial heritable component (69). 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 (70). 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 (70). Breast density can be rapidly and reliably measured from mammograms, and such mammographic data have yielded good risk prediction accuracy (71).

Benign Proliferative Breast Disease. Certain types of benign breast disease are associated with an increased risk of breast cancer. For example, lobular carcinoma in situ, unlike ductal carcinoma in situ, is a benign condition and is associated with a 10-fold increase in the relative risk of breast cancer (72). The presence of atypical ductal hyperplasia or lobular hyperplasia is associated with a four- to fivefold increase in the risk of breast cancer compared with normal breast parenchyma. Proliferative hyperplasia without atypia is associated with a doubling of the risk (72). Nonproliferative lesions, including fibroadenomata and cysts, have not been associated with an increased risk of breast cancer (73).

Other Risk Factors. A number of other risk factors for breast cancer are being further validated. Obesity, diet, and exercise are risk factors that are probably interlinked (74,75). Other risk factors such as alcohol intake and smoking history have a fairly small effect on breast cancer risk (76). More recently, attention has been paid to the possible link between vitamin D deficiency and breast cancer risk (77,78).

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, and commonly used ones are summarized in Table 1. All of these models have important limitations, foremost of which is their reliance on known risk factors, despite data that show that up to 60%

of breast cancers can arise in the absence of any known risk factors (80). 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 except for an adaptation of the Gail model (71).

Gail Model. The most widely known and most commonly used model for breast cancer risk assessment is the Gail model (81). This model was initially designed in 1989 using data that were collected as part of the Breast Cancer Detection and Demonstration Project, a nested case-control study of almost 300 000 women who were undergoing breast screening between 1973 and 1980. The model was then validated in the Nurses' Health Study (82). It was subsequently modified in 1999 (83). The modified model (occasionally called the NCI-Gail model) differs from the original model in three ways. First, the incidence rates in the modified model include only invasive cancers rather than both invasive and in situ cancers as in the original model. Second, the age-specific incidence rates in the modified model were obtained from the Surveillance, Epidemiology, and End Results database rather than from the Breast Cancer Detection and Demonstration Project. Finally, composite incidence rates for African American patients were added to the modified model. Both the original and the modified versions of the Gail model use six breast cancer risk factors, namely age, hormonal or reproductive history (age at menarche and age at first live birth), previous history of breast disease (number of breast biopsies and history of atypical hyperplasia), and family history (number of first-degree relatives with breast cancer).

Table 1. Known risk factors and their incorporation into existing risk models*

Variable	Relative risk at extremest†	Gail	Claus	BRCAPRO	IBIS	BOADICEA	Jonker
Personal information							
Age	30	Yes	Yes	Yes	Yes	Yes	Yes
Body mass index	2	No	No	No	Yes	No	No
Alcohol intake	1.24	No	No	No	No	No	No
Hormonal and reproductive factors							
Age at menarche	2	Yes	No	No	Yes	No	No
Age at first live birth	3	Yes	No	No	Yes	No	No
Age at menopause	4	No	No	No	Yes	No	No
Hormone replacement therapy use	2	No	No	No	Yes	No	No
Oral contraceptive pill use	1.24	No	No	No	No	No	No
Breast feeding	0.8	No	No	No	No	No	No
Plasma estrogen level	5	No	No	No	No	No	No
Personal history of breast disease							
Breast biopsies	2	Yes	No	No	Yes	No	No
Atypical ductal hyperplasia	3	Yes	No	No	Yes	No	No
Lobular carcinoma in situ	4	No	No	No	Yes	No	No
Breast density	6	No	No	No	No	No	No
Family history of breast and/or ovarian cancer							
First-degree relatives with breast cancer	3	Yes	Yes	Yes	Yes	Yes	Yes
Second-degree relatives with breast cancer	1.5	No	Yes	Yes	Yes	Yes	Yes
Third-degree relatives with breast cancer	1.3	No	No	No	No	Yes	No
Age of onset of breast cancer in a relative	3	No	Yes	Yes	Yes	Yes	Yes
Bilateral breast cancer in a relative	3	No	No	Yes	Yes	Yes	Yes
Ovarian cancer in a relative	1.5	No	No	Yes	Yes	Yes	Yes
Male breast cancer	3–5	No	No	Yes	No	Yes	Yes

* BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; IBIS = International Breast Cancer Intervention Study.

† Data from Evans and Howell (79).

The Gail model is the only model to our knowledge that has been validated in three large population-based databases (82–84). However, a recent systematic review (85) reported that although eight studies comprising almost 13 000 patients have shown that the Gail model is well calibrated, it has limited discriminatory accuracy. This limitation is the likely reason for the poor individualized risk assessment of the Gail model when it was tested in higher-risk populations, such as patients enrolled in family history clinics (86,87) or those with atypical hyperplasia (88).

Claus Model. Another model in widespread use is the Claus model (41). This model was developed using data from the Cancer and Steroid Hormone Study, a nested population-based case-control study conducted between 1980 and 1982 using breast cancer patients registered in eight Surveillance, Epidemiology, and End Results regions. The original model only included data on family history of breast cancer; the model was subsequently updated to include data on ovarian cancer as well (89). Unlike the Gail model, the Claus model only uses family history to estimate risk; however, it incorporates a substantially more comprehensive history than the Gail model and includes affected first- and second-degree relatives and the age at which cancers in those relatives were diagnosed. The Claus model also includes cancers in the paternal lineage. However, to our knowledge, the Claus model has never been validated in an independent dataset.

To facilitate the use of the Claus model in the clinical setting, lifetime risk tables for most combinations of affected first-degree and second-degree relatives were subsequently published (90). Although these tables do not give risk estimates for some combinations of relatives (eg, it is not possible to estimate the combined risk of having an affected mother and maternal grandmother), an estimation of this risk can be extrapolated using other combinations, such as mother and maternal aunt.

The Claus model has three major drawbacks that limit its routine use. First, the model does not include any nonhereditary risk factors (eg, hormonal or reproductive factors). Second, the Claus lifetime risk tables reflect risks for North American women in the 1980s, which are known to be lower than the current incidence of breast cancer in North America and in most of Europe (5,6). Third, the published tables and computerized versions of the model appear to give different results (91): The tables give consistently higher risk figures than the computer model. A possible explanation for this discrepancy is that whereas the tables make no adjustments for unaffected relatives, the computerized version is able to reduce the likelihood of a germline mutation in an individual with an increasing number of unaffected women. It may also be possible that a population risk element is not added back into the calculation by the computer model or that the adjustment for unaffected relatives is made from the original averaged figure rather than from assuming that each family will have already had an “average” number of unaffected relatives. It is interesting that concordance of risk estimates between the Gail and Claus models has also been shown to be relatively poor. The greatest discrepancies in the risk estimate were seen in women with nulliparity, multiple benign breast biopsies, and a strong paternal or first-degree family history (92,93).

BRCAPRO Model. In addition to assessing the likelihood of carrying a *BRCA* gene mutation, the computerized BRCAPRO model (94) also includes an extension software package (95) that is able to calculate overall breast cancer risk based on the Bayes rules of determination of the probability of a mutation, given the family history. The model gives the option of using estimates of mutation frequencies from three independent populations: two unselected populations [using data from Claus et al. (96) and from Ford et al. (97)] and one Ashkenazi Jewish population [using data from Struewing et al. (13)].

An advantage of this model is that it includes information on both affected and unaffected relatives. However, this model has a number of limitations. For example, none of the nonhereditary risk factors have yet, to our knowledge, been incorporated into the model, and therefore, this model is likely to underestimate breast cancer risk in women who have nonhereditary risk factors. Furthermore, because no other “genetic” elements (eg, non-*BRCA* gene mutations) are incorporated into the model, it is likely that the model will underestimate risk in breast-cancer-only families.

Jonker Model. Jonker et al. (98) published a genetic model to predict breast cancer risk based on the family history of breast and ovarian cancers. In this model, which is essentially an extension of the Claus model combined with the BRCAPRO model, familial clustering of breast and ovarian cancers is explained by three genes: *BRCA1*, *BRCA2*, and a hypothetical third gene called BRCAu. The hypothetical gene was modeled to explain all familial clustering of breast cancer that was not accounted for by the *BRCA1* and *BRCA2* genes. The model parameters were estimated using published population incidence and relative risk estimates. The Jonker model does not include data on personal risk factors for breast cancer.

The Jonker model gave rise to a model that was validated and is known as the Claus extended model (99). This model was derived by linear regression of the independent variables on the predictions given by the Jonker model and, therefore, includes estimates of the risk of bilateral breast cancer, of ovarian cancer, and of having three or more affected relatives. The Claus extended model has been criticized (100) for two major limitations, namely its inability to estimate risk in women with complex family histories and its validation in individual families rather than in an independent series.

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 (42), 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.

BOADICEA Model. The BOADICEA model was designed with the use of segregation analysis in which susceptibility is explained by mutations in *BRCA1* and *BRCA2* as well as a polygenic component that reflects the multiplicative effect of multiple genes, which individually have small effects on breast cancer risk (43). This algorithm allowed predicted mutation probabilities and cancer risks in individuals with a family history to be estimated. Early validation studies of BOADICEA were carried out for the probability of germline mutation only (43); more recently, validation included cancer risk prediction over time (57).

Comparisons of Model Accuracy

To our knowledge, only one study has compared multiple cancer risk models in a prospective fashion (86). In this relatively small study of 1933 women enrolled in family history clinic, 52 cancers were observed. The Gail, BRCAPRO, and IBIS models were tested. The BRCAPRO model was calibrated to use the mutation prevalence estimates described by Claus (96) and by Ford (97), hereafter referred to as BRCAPRO (Claus) and BRCAPRO (Ford), respectively. Model inputs were derived from data collected over a mean follow-up of 5.27 years, and outputs of breast cancer risk estimate were obtained. The ratios of the expected to the observed numbers of breast cancers were 0.48 (95% confidence interval [CI] = 0.37 to 0.64) for the Gail model, 0.56 (95% CI = 0.43 to 0.75) for the BRCAPRO (Claus) model, 0.49 (95% CI = 0.37 to 0.65) for the BRCAPRO (Ford) model, and 0.81 (95% CI = 0.62 to 1.08) for the IBIS model. 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.

Subgroup analyses (86) showed that the Gail, BRCAPRO (Claus), and BRCAPRO (Ford) models all underestimated the risk of breast cancer, particularly in women who had a single first-degree relative affected with breast cancer. The IBIS model was an accurate predictor of risk in this subgroup. Conversely, all of the models accurately predicted risk in women with two first-degree relatives or one first-degree relative plus two other relatives with breast cancer. These findings suggest that having a single affected first-degree relative influences risk more than was previously appreciated. It is not surprising that the BRCAPRO (Ford) and IBIS models—the only ones to include a woman's family history of ovarian cancer—were the only models to accurately predict breast cancer risk in women with a family history of ovarian cancer. This finding confirms that family history of ovarian cancer has a substantial effect on breast cancer risk. The Gail, BRCAPRO (Claus), and BRCAPRO (Ford) models all statistically significantly underestimated the risk of breast cancer in women who were nulliparous or whose first live birth occurred after age 30 years. A more recent retrospective study that included the Gail, Claus, Claus extended, Jonker, IBIS, and BOADICEA models also showed that the Gail, Claus, and Jonker models underestimated breast cancer risk. The authors concluded that for current clinical practice, the IBIS and BOADICEA models appeared to be the most accurate for assessing the risk of breast cancer (101).

It is clear that some models are better than others in certain circumstances. In Figure 3, we present a flowchart for selecting a breast cancer risk assessment model in the clinical setting. It should be noted, however, that the presence of only one prospective comparison of cancer risk models (86) is a major limitation to the formulation of guidelines for the choice of risk assessment model for breast cancer. Clearly, more prospective studies are necessary to gauge the accuracy of the existing, and newer, models.

Future Directions

Studies are in progress to examine whether inclusion of additional factors, such as mammographic density (102–104), weight gain (75), and serum steroid hormone measurements (105), into existing models will improve breast cancer risk prediction. Results of these studies reported thus far suggest that the addition of mammographic density data can improve the discriminatory accuracy of existing models that are based on classical factors (85). It should be noted, however, that variability in the approach for measuring mammographic density places substantial limitations on the impact that the addition of mammographic density has on overall model accuracy. First, current methods require that the mammogram is digitized and a trained operator makes decisions about how to define the dense and nondense areas. This approach, therefore, disregards all grayscale information from the image because each pixel is considered to be either black (nondense) or white (dense). Furthermore, this method is also liable to introduce operator-dependent variability. Second, mammography produces a two-dimensional image of a three-dimensional object. Obtaining a measure of the total dense volume of the breast or of the percentage of the breast volume that is dense may give a more precise and reproducible measure of density that might predict breast cancer more accurately than the current two-dimensional measure (106). Some of the breast cancer risk assessment models have been updated to include mammographic density but still require independent validation before they can replace the models that are currently available. Clearly, advances in breast imaging that focus on reproducible measures of breast density are needed before this variable is routinely included in risk assessment modeling.

Further genome-based research is also likely to yield new risk prediction methods. Thus far, only one common variant in the *CASP8* gene with a minor allele frequency greater than 5% has been found, by using the candidate gene approach, to be associated with breast cancer risk (107). Consequently, examinations of a range of high-risk genes as well as single-nucleotide polymorphisms (SNPs) in several genes that are associated with low risks of breast cancer have been conducted to potentially improve our understanding of cancer genetics. Genome-wide association studies have identified multiple, new, common genetic variants that are associated with breast cancer risk. The largest of these studies (4) genotyped 390 breast cancer patients with a family history of breast cancer and 364 control subjects in a multistage process. A total of 227876 SNPs were initially analyzed. Of these, 10405 SNPs of interest were assessed in a second-stage replication study. Finally, 30 SNPs were analyzed in a third stage that involved an independent validation set comprising more than 9000 subjects. Eventually, five chromosomal loci were identified as risk factors for breast

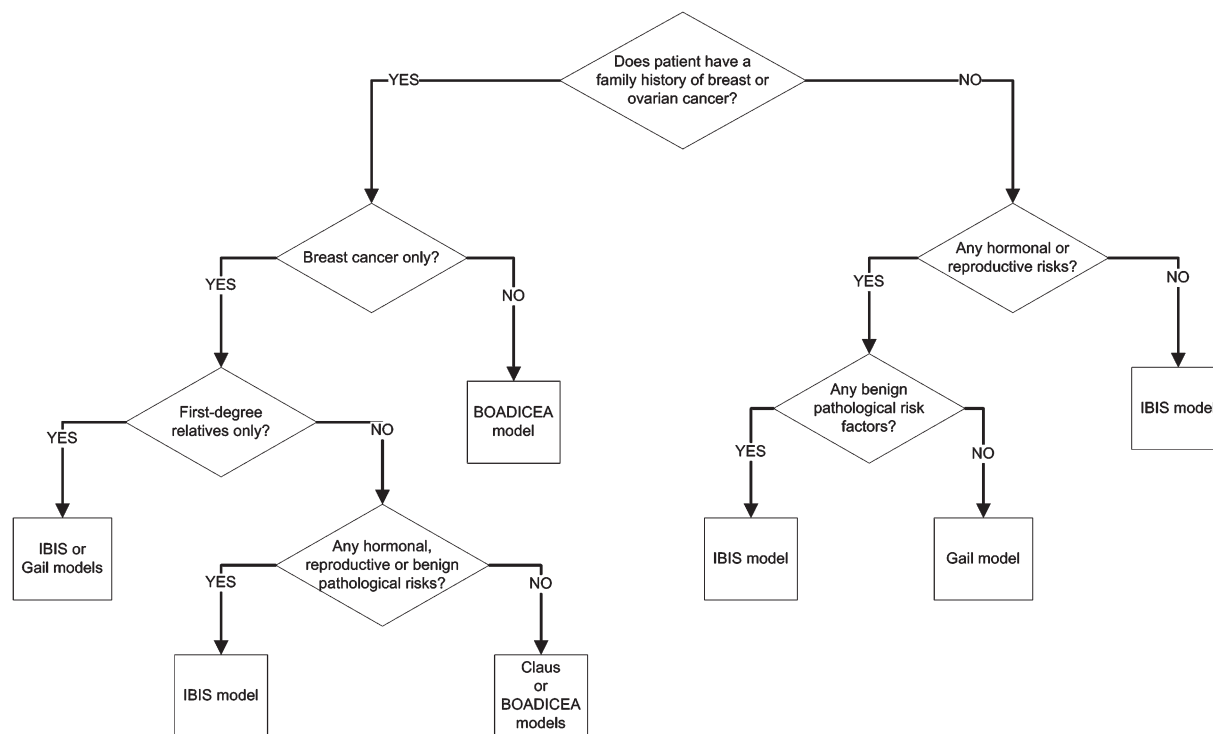


Figure 3. Flowchart for the choice of model for assessing risk of breast cancer over time. BOADICEA = Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm; IBIS = International Breast Cancer Intervention Study.

cancer: 10q26 (the site of *FGFR2*), 16q12.1 (*TOX3*), 5q11.2 (*MAP3K1*), 8q24, and 11p15.5 (*LSP1*). In another study that was conducted by the National Cancer Institute Cancer Genetic Markers of Susceptibility initiative, a SNP in intron 2 of *FGFR2* was found to be associated with the risk of breast cancer based on a follow-up of 10 SNPs from the stage I genome-wide association study (108). The same SNP in the *FGFR2* locus was subsequently confirmed to be associated with breast cancer risk in an Icelandic population, as was another locus at 2q35 that was associated with estrogen receptor-positive breast cancer (109). A combined analysis of a promising signal in the three published genome-wide association studies led to the identification of an additional locus on 5p12 that is associated with breast cancer risk (110). Most recently, a genome-wide association study has confirmed strong association signals for the genomic regions described above and has also identified new associations with genome-wide statistical significance for markers on chromosomes 1p11.2 and 14q24.1 (111). In addition, the authors confirmed that the two loci previously associated with genome-wide statistical significance, namely, 2p24.1 (*CASP8*) and 11p15.5 (*LSP1*), were again associated with a high risk of breast cancer. These data show that because of the variable presence of these SNPs in the general population, very large datasets are required to identify, at genome-wide statistical significance levels, loci with small estimated per-allele effect sizes.

At present, none of the breast cancer risk models described in the previous section incorporate any of the SNPs that were found in the genome-wide association studies of breast cancer into their risk calculations. Research on genetics, epigenetics, gene expression profiling, and, most recently, whole genome scans has already provided exciting findings that have led to the discovery of novel risk alleles.

However, because of the large number of low-risk alleles that are associated with breast cancer, these methods are both time-consuming and prohibitively expensive. Therefore, at present, these discoveries cannot be translated into personalized medicine. Ongoing efforts in developing innovative networking algorithms to understand, assess, and measure extremely complex gene-gene and gene-environment interactions may ultimately lead to improved individualized risk assessment and thereby allow for better targeting of breast cancer screening and chemoprevention strategies. Therefore, despite the excitement related to these methods and the expectation that they could be incorporated into prediction programs with other known risk factors, at present, there are insufficient data to support their routine inclusion in breast cancer risk estimation.

Conclusions

It is well established that the greatest benefit from breast cancer prevention strategies comes from treating women who are at high risk of the disease (112). Among high-risk women, such prevention strategies have been shown to potentially reduce the incidence of breast cancer by up to 1500 cases per 100 000, whereas among low-risk women, the reduction is at best 25 cases per 100 000 (113). Consequently, it is imperative that accurate and individualized risk assessment can be carried out so that appropriate women are selected for prevention strategies. A number of models are available to assess both breast cancer risk and the chances of identifying a *BRCA1* or *BRCA2* mutation. Some models perform both tasks, but to date, none are totally able to discriminate between families that do and do not have mutations or between women who will and will not develop breast cancer. Steady and incremental improvements in the models

are being made, but these changes require revalidation. The discovery of alleles that are associated with breast cancer risk will add a new layer of complexity to all of these models.

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Affiliations of authors: Division of Medical Oncology and Hematology, Princess Margaret Hospital, Toronto, ON, Canada (EA, OCF, BS); Medical Genetics Research Group and Regional Genetics Service, University of Manchester, Manchester, UK (DGE); Central Manchester Foundation Hospital NHS Trust, Manchester, UK (DGE).