

Review

Establishing a Program for Individuals at High Risk for Breast Cancer

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Abstract

Our need to create a program for individuals at high risk for breast cancer development led us to research the available data on such programs. In this paper, we summarize our findings and our thinking process as we developed our own program.

Breast cancer incidence is increasing worldwide. Even though there are known risk factors for breast cancer development, approximately 60% of patients with breast cancer have no known risk factor, although this situation will probably change with further research, especially in genetics. For patients with risk factors based on personal or family history, different models are available for assessing and quantifying risk. Assignment of risk levels permits tailored screening and risk reduction strategies. Potential benefits of specialized programs for women with high breast cancer risk include more cost-effective interventions as a result of patient stratification on the basis of risk; generation of valuable data to advance science; and differentiation of breast programs from other breast cancer units, which can result in increased revenue that can be directed to further improvements in patient care.

Guidelines for care of patients at high risk for breast cancer are available from various groups. However, running a high-risk breast program involves much more than applying a guideline. Each high-risk program needs to be designed by its institution with consideration of local resources and country legislation, especially related to genetic issues. Development of a successful high-risk program includes identifying strengths, weaknesses, opportunities, and threats; developing a promotion plan; choosing a risk assessment tool; defining "high risk"; and planning screening and risk reduction strategies for the specific population served by the program. The information in this article may be useful for other institutions considering creation of programs for patients with high breast cancer risk.

Key words: Breast cancer, genetic counseling, BRCA, preventive therapy, prophylactic surgery.

Introduction

Since 2000, Clinica Alemana, located in Santiago, Chile, has been treating patients with breast cancer using a multidisciplinary approach. In 2011, the clinic directors decided to establish a clinic for patients at high risk for breast cancer based on current evidence

showing that high-risk individuals require different screening and risk reduction strategies from those deployed for the population at large. Fundamentally, the decision to establish a multidisciplinary program for individuals at high risk for breast cancer was mo-

tivated by the strong belief that all breast cancer centers should offer tailored prevention, screening, and risk reduction strategies. In fact, in 2004, the American College of Surgeons added genetic counseling and testing as a supportive service to the Commission on Cancer Program Standards (1).

In designing the Clinica Alemana high-risk clinic, the clinic directors drew in part on the experience of The University of Texas MD Anderson Cancer Center. Clinica Alemana is a member of MD Anderson's Sister Institution Network, administered by MD Anderson's Global Academic Programs. MD Anderson established a clinic for individuals at high risk for cancer in the late 1990s. In 2006, MD Anderson moved to a decentralized model, in which genetic counseling and medical risk assessment, together with tailored screening and risk reduction strategies, are offered in the care centers where patients with different kinds of cancers are treated rather than in one central clinic. In 2006, MD Anderson's Clinical Cancer Genetics Program reported 1500 patients visits; in 2011, the program reported 3400 visits.

In this article, we summarize key factors that were considered in designing the Clinica Alemana clinic for high-risk individuals and outline factors that should be considered in the design of any clinic for individuals at high risk for breast cancer. The advice presented herein is based on review of the literature, the Clinica Alemana experience of establishing a high-risk clinic, and the MD Anderson experience of operating a high-risk clinic. This article may be useful for other institutions considering creation of a high-risk program.

Rationale for Specialized Programs for Individuals at High Risk for Breast Cancer

Breast cancer is the most common cancer in the world, with an estimated incidence of 1.4 million cases per year (2).

In the United States, breast cancer accounts for 25% of cancers among women, and in 2011, approximately 230,480 new cases of invasive breast cancer and 57,650 cases of in situ carcinoma were diagnosed (3). The lifetime risk of breast cancer for an American woman is 12%, or 1 in 8 women. Wrongly interpreted, this fact may lead to the assumption that every American woman is at "high risk" for breast cancer development. However, this is not the case: in fact, an individual woman's risk of breast cancer development over the next 10 years will never be greater than 1 in 25 (3).

Worldwide, breast cancer incidence is increasing in both developed and developing countries per-

haps secondary to dietary and reproductive changes. There is also evidence that BRCA mutations are being detected more often worldwide; however, because of their low prevalence, they are not expected to contribute substantially to the total number of breast cancer cases (4-8).

It is now known that certain women are not "average" with respect to risk of breast cancer but rather have identifiable factors that modestly or greatly increase their risk. Screening strategies have been developed for the general population, but high-risk women need special screening, along with counseling regarding strategies for reducing the risk of breast cancer.

Studies have shown that breast cancer risk-reduction strategies have a higher impact in high-risk women than in the general population (9,10). Thus, if we desire to optimally distribute resources to achieve the greatest reductions in breast-cancer related morbidity and mortality, special attention should be paid to high-risk women.

In Chile, to our knowledge, before establishment of the Clinica Alemana program, there was only one program for individuals at high risk for breast cancer opened in 2009.

Potential Benefits of a High risk Program

A high-risk program may promote awareness of the different risk levels among women. In addition, creation of a high-risk program may facilitate development of educational presentations and materials. Stratifying patients by risk level will allow screening and prevention programs based on personal risk, making such programs cost-effective (11-15). Finally, a high-risk program can help promote primary prevention measures for all patients, such as healthy lifestyle and diet.

At the level of the individual, a formal risk assessment may reassure the individual and aid her or him in taking the appropriate actions based on individual risk. Even though few patients carry a deleterious mutation, this group will benefit the most from risk reduction interventions.

From the perspective of science, a high-risk clinic will generate valuable data, providing the opportunity for research, publications, and alliances with academic institutions in areas such as genetics, screening, risk assessment, and prevention. Quantitative risk-assessment results have been used in prevention research and studies evaluating biomarkers of breast cancer risk (16-18). A perfect example of this type of contribution is studies that have shown the higher prevalence of BRCA mutations among patients with triple-negative breast cancer, which led to changes in guidelines regarding risk assessment and

genetic testing for patients with this breast cancer subtype (19).

Finally, adding a high-risk program to a breast unit will differentiate that unit from others. The availability of expertise on evaluation and management of high-risk patients may attract more patients and thereby increase revenue for the institution that can then be utilized for further improvements in patient care.

Defining the Goals of a High Risk Program

A program for patients at high risk for breast cancer needs to be developed according to the current legislation and health care conditions in the country where the program will be located and local decisions regarding what is wanted or needed. Regardless of where the program is developed, it may be useful to consider the excellent list of goals outlined by MacDonald (20) (Table 1).

MacDonald notes, "The goals of a genetic service are to minimize cancer incidence, morbidity and mortality" (20). These are long-term goals. It is also important to establish short-term goals that can be achieved in the process of reducing morbidity and mortality. Probably the first measureable results from a high-risk program will be changes in screening frequency, types of imaging, frequency of imaging, number and types of prophylactic surgeries, and number of patients and types of chemoprevention prescriptions in the enrolled patients. Once a breast cancer risk reduction strategy is applied, a long time may pass before measurable results are seen, which is very different from the situation with other preventive interventions, such as those for hypertension or dyslipidemia.

Table 1. Goals of a cancer genetics service (a).

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- Identify individuals at high risk for cancer and genetic mutation carriage
 - Stratify patients according to risk and tailor screening and management according to risk
 - Promote a healthy lifestyle as a primary preventive intervention
 - Provide genetic counseling regarding cancer risk
 - Protect patient privacy and confidentiality
 - Provide education about factors that confer a high risk of breast cancer to clinicians and the community
 - Establish research collaborations
 - Publish your actions and the results of your interventions
 - Promote your initiative and encourage the development of new programs for patients at high risk
 - Create a cost-effective breast program
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a Based on the goals proposed by MacDonald (20).

Developing the Program

Analysis of Strengths, Weaknesses, Opportunities, and Threats

A SWOT (strength, weaknesses, opportunities, and threats) analysis is useful at the outset of program development. Results of the SWOT analysis made for the Clinica Alemana high-risk program are shown in Table 2. This type of analysis may allow physicians and institutions to develop a program in a way that takes advantage of strengths and opportunities and overcomes or avoids threats and weaknesses that will be encountered in different possible scenarios.

Published experiences in the establishment of high-risk programs can also teach us aspects that need to be considered, such as having a feedback system in place to alert clinic leadership about failures and changes needed to keep the program functioning and successful (21). The cultural and social background of the patients attending the clinic should be considered (22). Finally, even with ideal conditions, difficulties such as an overcrowded system, lack of adherence to treatment, need for continuous medical education, and genetic testing implications may be encountered (23).

Develop a Promotion Plan

Along with a promotional plan, a simple referral guide should be created for distribution to physicians. Ideally, the guide should be kept visible in the clinics that may refer patients. Patients with relatives diagnosed with breast cancer frequently overestimate their own risk and may be interested in having a formal risk assessment. A program of this nature should also be promoted in the community encouraging patients to ask their physician for a referral.

Establish Institutional Support and Relationships with Health Insurance Providers

For any high-risk program, institutional support will be needed in terms of financing and time to develop the program.

The program will need to be marketed along with other ongoing prevention programs. It can be introduced to the whole institution at educational events where a program director describes the essential need for and importance of the program, the program's short-and long-term goals and the plans for accomplishing them, the program's expected benefits, and referral criteria. Institutional staff should be encouraged to participate. A clinic director should meet individually with the groups that will refer most of the patients, such as internal medicine, gynecology, and surgery, to foster relationships and develop a

feedback system to make these groups part of the program.

Table 2. Results of a strengths, weaknesses, opportunities, and threats (SWOT) analysis conducted as a first step in development of a clinic for individuals at high risk for breast cancer at Clinica Alemana Chile.

Strengths

- Breast cancer is the main cancer treated in our clinic
- Multidisciplinary breast cancer team working since 2000, with weekly meetings
- Highly trained radiologist with experience in breast magnetic resonance imaging
- Availability of genetic counseling
- First breast cancer unit in Chile to show a series of patients undergoing contralateral prophylactic mastectomy
- Institutional support

Weaknesses

- Physicians are unaware of other programs for individuals at high risk for breast cancer
- There are no risk assessment models specially designed for Latin populations
- Private system of health care with high costs for appointments, examinations, and surgeries

Opportunities

- Expand breast health program
- Tailored screening and treatments for patients
- Advance science and advance understanding of breast cancer
- Create referral links with physicians from other areas
- Involve the community

Threats

- Implementation of a new program with unfamiliar processes for patients and referring physicians
 - Lack of national legislation in genetics and risk assessment
 - Because program will be established in a private institution, program will depend on referral of patients from other physicians
 - Will be difficult to demonstrate benefits from our actions in a short period of time
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Having health insurance support may allow for access to a large number of patients. To get health insurance companies to cover the services provided in the high-risk program, it should be explained that an economic benefit is expected from promoting prevention, screening, chemoprevention, and prophylactic surgeries, allowing resources to be focused where they are needed the most. Promotion of prevention as a cornerstone of breast cancer care may result in a larger number of patients attending the clinic. In the long term, a clinic for patients at high risk for breast cancer should produce a reduction in breast-cancer-related morbidity and mortality, which may be an interesting issue for insurance companies and the institution (24,25).

Identify Staffing Needs and Physical Location

The medical staff necessary and the location where patients will be seen should be decided on the basis of available resources and the current number of breast cancers treated per year. Development and adjustments of the program will be easier if the program starts small and grows gradually.

The staff should include genetic counselors, nurses, physicians, psychologists, social workers, secretaries, and a data manager. A medical director is needed to assist with development and monitor achievements and opportunities for improving the program.

In some high-risk programs, breast cancer screening and prevention services for high-risk individuals are offered in a centralized high-risk clinic located in a different area from the breast cancer unit. Other high-risk programs offer their services in the clinic where breast cancer patients are treated. In this arrangement, the high-risk team interacts with the oncology team, sharing examination rooms and clinics, allowing continuous feedback. In 2006, MD Anderson adopted a decentralized model for its clinical cancer genetics service, with genetic counseling services offered in the clinics where patients with that type of cancer are treated (e.g., gynecologic cancers, gastrointestinal cancers). Since then, the MD Anderson program has experienced tremendous growth in the number of patients treated and the interactions among medical staff. Adoption of the decentralized model has been described as a primary driver of this growth.

Probably both centralized and decentralized systems have strengths and weaknesses. Defining which is a better fit for an individual program may be crucial. The clinic will have patients at different risk levels such as those diagnosed with deleterious mutations creating a "genetic clinics" and other group of patients that have a higher risk based on "high risk breast lesions", personal or family history of cancer or a elevated risk assessment model score. That group may be the majority creating a "sporadic high risk clinic". Both groups do have a higher risk but the screening and risk reduction strategies may be different involving a multidisciplinary team. At the beginning the volume of patients may be small allowing to have all patients together but as the clinic grows a categorization based on risk level may be consider. Having a defined risk assessment model and strategies to treat ADH/ALH/LCIS will allow a better categorization and management of the clinic.

Establish General Clinic Procedures

The duration of appointments may be longer than the usual for patients being treated for cancer (20,21,24,25) as both the patient and any companion attending the clinic may have many questions. Having a good scheduler and being realistic about appointment duration is critical to allow each patient to be counseled appropriately without compromising the time allotted to other patients.

Specific patient information will be required, such as pathology reports and extensive family history data, including dates and causes of death. Such data may be collected through online data submission, a written questionnaire given to the patient prior to the appointment, or a PC tablet computer given to the patient in the waiting room. Because the personal data collected, such as data on genetic mutations, may have serious extramedical implications, confidentiality is essential. A flexible system should be created that allows collection of data during both the first appointment and follow-up visits.

A weekly conference should be established for discussing new patients, reviewing the results of risk assessment for these patients, and developing corresponding proposals for managing the patients risk. Referring physicians should be invited. At the beginning of each weekly conference, presentations related to high risk can be given, which will accomplish the task of continuing medical education. Such an initiative may encourage teamwork by keeping referring physicians informed and allowing the people in charge of the program to verify that data are being stored for future publications and monitoring of the results of actions taken.

Selecting a Risk Assessment Model

When one chooses a risk assessment model, it is important to consider that each model's assessment of risk is based on epidemiologic data from a specific population and that models yield different results when applied to other populations. There is no risk assessment model specifically designed for Hispanic populations. A high-risk program should select the model that best fits the population that it will serve. The Gail model, which once applied only to white patients, has been updated to apply to other races/ethnicities, making it more suitable for different populations (26).

Risk assessment models use personal and family data to estimate the risk of developing breast cancer or having a deleterious mutation. There are two general types of models, empirical and Mendelian, and it is important to understand how they perform and to whom and when they should be applied.

Measuring Model Performance

The performance of risk assessment models can be measured with the C statistic, which is the same as area under the curve. The C statistic expresses the ability to identify which particular individuals in a group have a condition predisposing to a higher risk. A C statistic value of 1 indicates perfect discrimination; a C statistic value of 0.5 indicates no better than chance. The C statistic calculated for commonly used risk assessment models ranges from 0.55 to 0.68 (27,28). This may seem disappointing, but it is important to remember that risk assessment models only complement clinical evaluation by quantifying the risk assessment.

Another measure used to describe the performance of risk assessment models is the calibration score, which is the ability to accurately predict breast cancer incidence. The calibration score compares the expected number of events to the observed number of events. If the model performs perfectly, the result is 1; a number lower than 1 means that the model underestimates risk, and a number higher than 1 indicates that the model overestimates risk.

Types of Risk Assessment Models

Empirical models use specific observational data that are applied to a logistic regression model to obtain a quantitative assessment of risk for breast cancer development in a defined period of time. Empirical models assess mutation carriage probability by using "tabular scoring systems" assigning values to certain variables, giving a quantitative score correlated with a threshold value for being a mutation carrier (29). The Gail model is an empirical model with reported calibration scores from 0.93 to 1.03 (30,31) but C statistic values from 0.47 to 0.63 (32,33). This is an example of a good population assessment model with limitations in clinical practice.

Mendelian models are based on Mendelian rules of inheritance; they use observational data to estimate the allelic frequency and penetrance of the genes of interest, giving estimates of the probability of genetic mutation carriage and the probability of cancer development. Comparisons of the seven most commonly used Mendelian models showed that all of them had a C statistic near 0.8; the best result was seen for the BRCAPRO model, which had a C statistic of 0.82 (34). If more information is added to the BRCAPRO model, its discrimination may improve (35).

Genetic risk prediction models estimate cancer risk and the probability of being a genetic mutation carrier regardless of the family structure and disease pattern. To assess risk, they rely on pedigree analysis,

making assumptions about gene and allelic involvement and how that will affect risk. The assumptions made may affect the accuracy of the calculation (36).

There are no big differences in accuracy between different models used to predict the mutation carriage probability, only slight differences in sensitivity and specificity when the same model is applied to different populations or when different models are applied to the same population (34,35,37,42). Analysis of frequently used risk assessment models for deleterious mutation in the United Kingdom showed C statistics ranging from 0.72 to 0.77 (43).

Threshold values used to indicate the need for genetic testing vary. In the United States and most of Europe, the threshold will be a 10% risk of being a

genetic mutation carrier; in the United Kingdom, the cut-off is 20% (44). Different cut-off values have an impact on the sensitivity and specificity of risk assessment models.

Defining the “High Risk Patient”: Risk Factors and Risk Categories

Breast cancer risk factors and their impact on breast cancer risk (45-89) are outlined in Table 3. Among breast cancer patients, 5-10% will have a germline mutation related to breast cancer, 15-20% will have a family history of breast cancer, and 60% will not have a known risk factor (90-92).

Table 3. Breast cancer risk factors.

Not Modifiable

Genetic mutation: 2-3% absolute risk per year; relative risk (RR) 10-20 (46-52).

Early menarche: 4% increase in RR per year earlier than the median age at menarche (53).

Age over 60 years: 0.33% absolute risk per year; RR 10 compared to risk of a 30-year-old patient (45).

Race/ethnicity (populations with known predisposition to be carriers of mutations that increase their risk of developing cancer).

Late menopause: 3% increase in RR per year later than the median age at menopause (53).

Previous chest irradiation: Cumulative risk by age 55 years, 29.0% (95% CI, 20.2-40.1%); RR 5-20 (45,54).

Family history: One first-degree relative with postmenopausal breast cancer, RR 1.8; one first-degree relative with premenopausal breast cancer, RR 3.3; two first degree relatives with breast cancer, RR 3.6; one second-degree relative with breast cancer, RR 1.5; three or more relatives with breast cancer, RR up to 4 (55,56).

Personal history of breast cancer: RR 1.7-4.5; if patient < 40 years old when cancer diagnosed, RR up to 8.0 (57).

Potentially Modifiable

Age at first birth: First birth after 30 years of age confers double the risk compared with first birth before 20 years of age (58). The protective effects of early birth and parity are less for breast cancer diagnosed before 40 years of age than for breast cancer diagnosed at older ages. Also, there is a transient increase in absolute risk after birth because of a mitogenic effect (59-61).

Breastfeeding: 4.3% reduction in relative risk per year of breast feeding (62).

Preneoplastic lesion: 1-2% absolute risk per year; RR 2-10 depending on the type of lesion (63).

Modifiable

Diet and exercise: Healthy lifestyle including exercise and a balanced diet may reduce risk (64).

Overweight and obesity: Obesity may increase risk by about 20% (47,65-67). Weight gain after a breast cancer diagnosis confers an increase in all-cause mortality and breast-cancer-specific mortality (68-70). High body mass index could be protective for breast cancer in premenopausal women (71).

Smoking: Data on firsthand smoking and breast cancer are consistent with causality and data on secondhand smoking and breast cancer may be consistent with causality among young premenopausal women (72).

Alcohol: Regular consumption of alcohol may increase risk in premenopausal and postmenopausal women (64,70). However, a recent German review did not find an increase in risk due to alcohol consumption (73).

Hormonal replacement therapy (HRT): One report showed a 5% per year increase in RR in current users with RR returning to baseline within 1 year of discontinuation of HRT; patients who received HRT for more than 5 years significantly increased their risk (74). Another report showed an absolute 1-2% risk per year of therapy with risk returning to baseline within 5 years of discontinuation of HRT (75). Estrogen-only HRT has not been proven to increase risk (76).

Reproductive history: Recent studies suggest that reproductive and hormonal factors increase the risk mainly of estrogen-receptor-positive breast cancer subtypes (77).

Contraceptives: Data are contradictory. Some data show that current use of contraceptives does not confer a higher risk, even in BRCA mutation carriers, whereas other data show that current use of contraceptives increases risk of premenopausal breast cancer (78-85).

Vitamin D deficiency: The Institute of Medicine released a consensus statement on vitamin D concluding that there is not enough evidence to support a relationship between vitamin D and cancer risk (89). A recent meta-analysis supports this conclusion (86-89).

a Throughout the table, risk and RR refer to risk of breast cancer.

It is important to assess an individual's risk as patients may overestimate their risk for developing breast cancer based on personal or familiar history, leading to erroneous decisions in screening and treatment (93,94). A system to select the patients who require further evaluation should be created to optimize resources and acceptability (22).

Knowledge of risk factors will help clinicians develop risk levels and make clinical decisions. Risk factors that confer at least double the risk of average-risk women are considered major, and risk factors that confer less than double the risk of average-risk women are considered minor.

Definitions of "high risk" for breast cancer and definitions of breast cancer risk levels differ among medical societies. It may be appropriate to define risk differently for different populations and for countries with different resource levels. Such tailored risk definitions along with adoption of management guidelines created by local medical societies may result in the best approach for each program.

The American Cancer Society (95) defines high risk as a lifetime risk of 20% or more, moderate risk as a lifetime risk of 15-20%, and normal risk as a lifetime risk of less than 15%.

The NICE UK (96) risk definitions are as follows: low, 10-year risk of less than 3% for women aged 40-49 years or lifetime risk of less than 17%; moderate, 10-year risk of 3-8% for women aged 40-49 years or lifetime risk of 17-29%; and high, 10 year risk of more than 8% for women aged 40-49 years or lifetime risk of greater than 30%. Patients with a 20% or greater chance of carrying a BRCA1, BRCA2, or TP53 mutation are also classified as high risk.

In 2007, the International Consensus Conference on Breast Cancer Risk, Genetics, and Risk Management was held. The recommendations from that conference (45) are suitable for different practice settings because they suggest the use of locally tailored screening programs. The risk categories from the consensus conference are as follows:

- Average risk: Follow country-specific cancer screening recommendations. Hormonal replacement therapy (HRT) may be used in women with symptoms related to menopause for up to 5-10 years.
- Moderate risk: RR less than 5. Follow country-specific cancer screenings recommendations. Chemoprevention may be used. If HRT is needed, use the lowest dose for the shortest possible period of time.
- High risk: RR 5-10. Consider use of digital mammography. If lifetime risk is greater than 20%, the use of magnetic resonance imaging (MRI) is suggested, and semiannual clinical

breast examination is recommended. Consider use of chemoprevention. Risk reduction surgery is not usually indicated.

- Very high risk: RR greater than 10. Screen with annual MRI alternating at 6 months with mammography starting at age 25 years. Perform semiannual clinical examination and monthly breast self-examination. Chemoprevention must be discussed with patients. Risk reduction surgeries should be discussed.

Evaluating Risk and Communicating Results

If patients are to be expected to comply with recommended risk-reduction interventions, they need to understand their risk and the potential benefits from actions taken to reduce it. Unfortunately, there exists a situation, described by Gigerenzer et al. as "collective statistical illiteracy", in which many doctors, patients, journalists, and politicians are unable to understand health-related statistics and do not recognize that they are unable to understand them (97). Thus, great care must be taken to present risks in a manner that patients are most likely to understand.

As Vázquez Caruncho said in a very interesting paper, "When giving information to the patient, consider that the relative risks are not informative if they are not attached to their respective absolute risks. The most common error is to present the benefits of a strategy in terms of the reduction in the relative risk and the disadvantages or side effects in terms of the absolute risk. This leads to a misperception by exacerbating the benefits of an intervention and minimizing its complications" (translated from the original Spanish) (98).

The proposal of the aforementioned International Consensus Conference on Breast Cancer Risk, Genetics, and Risk Management is that risk should be expressed in absolute terms compared to the risk of an average woman in the patient's age group (45). Relative risks can be misleading and may not be well understood by patients and their families. For example, suppose a physician tells a patient that by taking tamoxifen she is likely to reduce her risk of breast cancer development by 50%. For a patient with a BRCA mutation, the absolute lifetime risk of breast cancer could be as high as 60%, and in such case the absolute risk reduction would be 30%; however, a patient without any identifiable risk factors could have an absolute lifetime predicted risk as low as 8%, and thus her absolute risk reduction would be only 4%.

Another important issue is communication with colleagues who refer patients from other institutions, cities, or countries. Using consistent and clearly understandable terminology to communicate risk may

help colleagues understand genetic testing results and proposed risk management strategies, which would allow those colleagues to make recommendations for follow-up and long-term management of high-risk patients without patients having to come to the multidisciplinary high-risk clinic all the time.

Legal Issues and Confidentiality

Legal issues must be addressed by every high-risk program. Depending on the country, there may be important issues related to the lack of laws about genetic syndromes and risk assessment. The information that is going to be generated must be managed confidentially; disclosure of such information to insurance companies and health care providers may be threatening for patients if there is no legislation that protects patients.

High-risk programs should obtain approval from patients and institutions to share very sensitive information and should create an information-sharing system that protects patient privacy (99). Such a system is particularly important in the case of referral or assessment of patients who live outside the city or country where the high-risk program is located.

Risk Reduction Strategies for All Patients

Regardless of their level of breast cancer risk, all patients should maintain a normal body mass index (18.5-24.9 kg/m²), exercise regularly (at least 150 minutes per week of moderate-intensity activity or 75 minutes per week of vigorous activity), eat five servings of fruits and vegetables per day, and limit consumption of processed meat, red meat, refined grains, and alcohol (64).

Offering these recommendations to all patients is a simple and noninvasive primary prevention intervention that can have a huge positive impact on the population regardless of individuals' risk of breast cancer.

Screening and Surveillance

Mammography is the only screening strategy that has been proven to reduce mortality from breast cancer (100-102). The reported sensitivity of mammography in the detection of breast cancer ranges from 69% to 90%, and the reported specificity ranges from 10% to 40% (103). Ultrasonography is not included in the National Comprehensive Cancer Network (NCCN) breast cancer screening guidelines. However, ultrasonography may be useful to complement MRI or mammography.

The American College of Radiologists has stated that MRI is the ideal screening method for women with a lifetime breast cancer risk of 22-25% or greater. The NCCN guidelines suggest MRI alternating with

mammography for patients with a lifetime risk of 20% or greater (100). MRI may detect 37% of breast cancers that were missed by mammography and clinical evaluation (103,104).

The sensitivity of the combination of mammography, ultrasonography, and MRI in the detection of breast cancer is approximately 95%; the sensitivity of mammography plus physical examination is 45% (103,104). Currently, there is no evidence that MRI reduces breast cancer mortality, but MRI may lead to earlier diagnosis and thereby have an impact in terms of reducing mortality (105-110). The false-positive rate of MRI is controversial; the false-positive rate may be similar to that of mammography, but the rate is highly dependent on the experience of the radiology team (100,111-113). In major trials comparing MRI and mammography, the specificity of MRI is 81-97% and that of mammography is 93-100% (109,114-117).

There are interesting reports indicating that in the screening of very high risk patients, breast MRI alternating every 6 months with mammography leads to earlier diagnosis (118). With Monte Carlo models comparing combined screening with MRI and mammography versus prophylactic surgery in BRCA mutation carriers, the results in terms of overall survival were similar (119).

At Clinica Alemana, we suggest surveillance with breast MRI alternating with mammography and ultrasonography every 6 months in patients with at least a 20% lifetime risk of breast cancer. The frequency and types of images are as suggested by the NCCN guidelines.

Prevention Therapy (Chemoprevention)

Recently, it was proposed that the term chemoprevention be changed to preventive therapy to have better acceptability (120). Preventive therapy is defined as "the use of pharmacological or natural agents to inhibit the development of invasive cancer either by blocking the DNA damage that initiates the carcinogenesis or by arresting or reversing the progression of pre-malignant cells in which such damage has already occurred" (121). Preventive therapy may be applied to healthy people at high risk for development of a disease to prevent that disease, to patients with premalignant conditions to reduce the probability of development of invasive cancer, and to patients already treated for cancer to prevent a recurrence (122).

Drugs used in prevention should have benefits that outweigh by far the potential complications. The Food and Drug Administration has defined the group of patients eligible for breast cancer preventive therapy as those with a Gail model risk assessment of a greater than 1.66% risk of breast cancer development within 5 years. Breast cancer preventive therapies

need a long period to show results. Adherence to treatment and pharmacological interactions may affect the results, and sadly, there is no test yet available to assure efficacy during treatment. This “uncertainty” about the benefits of preventive therapy, along with the potential side effects, may affect patient compliance with treatment.

The main drugs used for breast cancer chemoprevention are tamoxifen and raloxifene, both of which are selective estrogen receptor modulators. Tamoxifen reduces the probability of invasive breast cancer by 50%, in situ cancer by 49%, and atypical ductal hyperplasia by 89% (123).

A recent update of STAR trial, which compared tamoxifen to raloxifene for breast cancer prevention, showed that the raloxifene group had a 24% higher incidence of invasive breast cancer than the tamoxifen group. The prevention of in situ cancers was also worse with raloxifene, but the difference between tamoxifen and raloxifene in the prevention of in situ cancers was less than in the original report. However, raloxifene has a better safety profile than tamoxifen and might be suitable for some patients (124).

Approximately 2 million women are eligible for chemoprevention with tamoxifen in the United States, but only 4% of them accepted such treatment when it was offered. Subgroup analysis revealed that a minority of eligible women aged 40-79 years accepted use of tamoxifen (125-127).

Aromatase inhibitors have been shown to be effective in preventing breast cancer and to be less toxic than tamoxifen, in trials such as IBIS II (anastrozole 1 mg/day for 5 years versus placebo for postmenopausal women at high risk) and MAP 3 (exemestane 25 mg/day for 5 years versus exemestane 25 mg/day for 5 years plus celecoxib 200 mg/day for 3 years versus placebo for postmenopausal women at high risk for breast cancer or diagnosed with ductal carcinoma in situ and treated with mastectomy). An estimated risk reduction of 65% has been designed to assess its efficacy in prevention. Final conclusions from the IBIS II study are pending.

The MAP 3 trial showed a 65% reduction in the risk of invasive breast cancer and also a reduction in the risk of in situ breast cancer among the exemestane users, and there were no significant differences in toxic effects and adverse effects between the treatment and placebo groups (120,128-130).

Research on breast cancer risk reduction with other selective estrogen receptor modulators, aspirin, bisphosphonates, statins, nonsteroidal antiinflammatory drugs, and fenretinide seeks to aid patients with triple-negative breast cancer, for whom current options do not work, and uncover preventive strategies that could be offered after the usual 5 year duration of

current preventive therapy (120).

Management guidelines such as the NCCN guidelines give information about patient eligibility for preventive therapy, recommended dosage, and recommended duration of use of preventive therapy (131).

At Clinica Alemana, we cannot follow the Food and Drug Administration’s guideline of prescribing chemopreventive therapy to women with a greater than 1.66% risk of breast cancer development within 5 years because the Gail model was designed for a population different from our patient population. To determine whether to prescribe chemoprevention, we consider the pros and cons for each patient. Patient eligibility, dosage, and duration of use of preventive therapy are the main issues suggested by the NCCN and the Proceedings of the International Consensus Conference on Breast Cancer Risk, Genetics, and Risk Management 2007 (45,131).

Risk Reduction Surgery

Risk reduction surgery, including bilateral risk reduction breast surgery and bilateral risk reduction salpingo-oophorectomy, may be performed in healthy people with a high risk of cancer development. Risk reduction surgery may also be performed in patients who have already been treated for or diagnosed with breast cancer, in which case the prophylactic procedure is done in the contralateral breast with or without salpingo-oophorectomy.

A study published in the Cochrane Database indicated that most women undergoing prophylactic mastectomies (bilateral and contralateral) will not experience a benefit in terms of overall survival, especially the ones choosing risk-reducing contralateral mastectomy (132). However, the data from that study regarding contralateral mastectomy for risk reduction have since been challenged by at least five publications that have shown a survival benefit from the procedure in selected groups of patients (133-137). Overall, all studies to date show a benefit in terms of reducing the risk of breast cancer development, but whether there is an overall survival benefit remains controversial (134). The rate of complications after contralateral prophylactic mastectomy and reconstruction is 15-20%, and complications may delay adjuvant therapy (138,139).

When informing a patient about her breast cancer risk before any decision is made about prophylactic surgery, it is important to keep in mind that the risk of development of breast cancer or contralateral breast cancer differs according to whether or not a BRCA mutation is present (139-146) (table 4).

Table 4. Breast cancer risk and recurrence rates among BRCA mutation carriers and individuals without BRCA mutations.

Type of patient	Probability of Breast Cancer over lifetime	Probability of contralateral breast cancer	Probability of synchronous contralateral breast cancer
BRCA mutation carriers	BRCA 1 mutation: 57-65% BRCA 2 mutation: 45-69% (140-143)	40% within 10 years after initial diagnosis of breast cancer (140-143)	3-5% (139,144)
Individuals without BRCA mutation	12.2% (145)	6% within 10 years after initial diagnosis of breast cancer (146)	3-5% (139,14)

There was an impressive 150% increase in the number of patients undergoing contralateral prophylactic mastectomy in the United States between 1995 and 2005 (147-150). This is a worldwide trend, but fewer procedures per capita are performed in Europe than in the United States; ethnicity and cultural factors may influence decisions regarding prophylactic surgery (151-153). A Cochrane review of six observational studies concluded that contralateral prophylactic mastectomy reduces the risk of contralateral cancer but does not improve survival (132). This finding challenged the findings of several previously mentioned studies (133-137).

When advising a patient considering contralateral mastectomy after an initial diagnosis of breast cancer, it is important to keep in mind that she may substantially overestimate her risk of contralateral breast cancer and recurrence, which might influence her decision (154-157). The initial breast cancer is normally what determines overall survival; in most cases, metachronous contralateral breast cancers are detected at an early stage.

The number of women opting for bilateral prophylactic surgery is also increasing, but not as much as the number of women opting for contralateral prophylactic mastectomy (158). A reduction in risk of 90-95% has been reported for all types of patients undergoing bilateral prophylactic mastectomy, but the overall survival impact is not clear. Patients who choose this procedure still need follow-up and must understand that the risk reduction is not 100% (159). It is supposed that the majority of patients opting for bilateral prophylactic mastectomy will be BRCA mutation carriers because even under intensive surveillance, the incidence of contralateral invasive breast cancer development in BRCA mutation carriers is 33-40% (160,161).

Not only mutation carriers are having contralateral prophylactic surgeries, though, as indicated by a report by Stucky et al. showing a 20% increase in the number of patients undergoing this procedure between 2000 and 2008 in a population studied in Phoenix, Arizona, with only 0.79% of the patients be-

ing diagnosed with a BRCA mutation (162).

There was also a 148% increase in the use of contralateral prophylactic surgery among patients with in situ cancers between 1998 and 2005, which does not seem to make sense considering the excellent overall survival in this group with standard treatments (163).

The Society of Surgical Oncology statement about breast risk reduction surgeries, which outlines potential indications and recommendations for these procedures, may aid in decision making about prophylactic surgery (164). Also, there is an online computerized model for comparing the benefits of risk reduction strategies in patients with BRCA mutations (165,166).

Bilateral salpingo-oophorectomy reduces the risk of ovarian cancer (hazard ratio [HR] = 0.21, 95% CI, 0.12-0.39) and breast cancer (HR = 0.49, 95% CI, 0.370.65) and also may have an impact on overall survival if performed before 40 years of age. If bilateral mastectomy is performed at the same time as bilateral salpingo-oophorectomy, a 95% reduction in breast cancer risk may be achieved (167-169).

With clear information, patients may choose among the different management strategies, considering the pros and cons of each alternative. This is a particularly difficult area in which the patient's preference may outweigh the medical criteria. Health care professionals should strive to ensure that whatever decisions patients ultimately make about risk reduction surgery, those decisions are informed decisions.

At Clinica Alemana, we evaluate in a standing multidisciplinary conference each patient for whom a prophylactic mastectomy is being considered. If the patient has not been diagnosed with cancer, the Society of Surgical Oncology recommendations are used as a guideline. If the patient has been diagnosed with breast cancer and is considering a contralateral prophylactic mastectomy, the decision whether or not to recommend the surgery is based on the index cancer prognosis, the patient's age, and the tumor hormone receptor status, and we clarify for the patient the benefits, limitations, and potential complications

related to physical, psychological, and quality-of-life aspects.

Final Thoughts

Groups considering the implementation of a program for individuals at high risk for breast cancer should keep in mind that successful projects have common purposes and objectives. Performing a SWOT analysis may allow groups to capitalize on strengths and opportunities while being better prepared to overcome potential threats. In the creation of a high-risk program, groups may engage with people whose involvement may not necessarily be continuous or long term, like administrative staff of the institution or an external physician with experience in running a high-risk clinic. In Table 5, we have summarized the steps necessary to develop a multidisciplinary high-risk program. The recommendations in the table are based on the information gathered during the development of this paper. The risk assessment tools, patient data collection system, and risks levels are issues that need to be addressed by each new high-risk program.

Table 5. Proposed steps in the organization of a multidisciplinary program for individuals at high risk for breast cancer.

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- Submit your idea to your institution and get their approval and support.
 - Establish business relationships with health care insurance companies.
 - Define the number of staff members needed for the program and the competences they require.
 - Define the physical space and resources needed.
 - Define short-term and long-term goals, define how will you monitor progress toward these goals and create measures to evaluate the project.
 - At the beginning, base your referral criteria, screening strategies, and risk reduction strategies on validated international guidelines. With time, you will be able to develop local guidelines.
 - Choose a risk assessment tool that is suitable for your population and useful in clinical practice. Probably a combination of two or more risk assessment tools is the better option.
 - Define your different groups on the basis of previously described groups and if necessary, modify the definition of risk groups to fit the reality for your patient population
 - Promote continuous education for the health care team and the community. Create committees or conferences open to referring physicians and other interested health care providers. PowerPoint presentations and written documents may be used for continuing medical education (CME) activities.
 - Publish your results and compare them with results from other high-risk breast cancer programs.
 - Try to develop a formal association with an established multidisciplinary program for individuals at high risk for breast cancer.
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Competing Interests

The authors have declared that no competing interest exists.

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