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REVIEW

Recent developments in the ability to predict and modify breast cancer risk

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Summary The identification of women at higher risk for breast cancer is a matter of public health and anyone who participates in any treatment modality of this condition (this includes the plastic surgeon) should be aware of the tools and predictive models of breast cancer. Screening for breast cancer in the community, and probably during the daily plastic surgery consultation, until recently, was limited to decisions about when to initiate a mammography study. New developments that predict and modify breast cancer risk must be clearly understood by our specialty through identification of women at higher risk for breast cancer and be familiar with the current issues related to screening and risk-reduction measures. In this review, we discuss current knowledge regarding the recent data of breast cancer risk, screening strategies for high-risk women and medical and surgical approaches to reduce breast cancer risk. Patients with breast cancer belong to one of three groups:

- a. Sporadic breast cancer (75%)—patients without family history or those who have a breast biopsy with proliferative changes.
- b. Genetic mutation breast cancer (5%)—women who have a genetic predisposition, and most of these are attributable to mutations in the breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2).
- c. Cluster family breast cancer (20%)—seen in women with a relevant history of breast cancer in the family and breast biopsy with proliferative breast changes with no association with mutations. Those at high risk for breast cancer should investigate the family history with genetic testing consideration, clinical history, including prior breast biopsies and evaluation of mammographic density.

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Tools for breast cancer risk assessment include the Gail and Claus model, genetic screening, BRCAPRO and others that are evaluated in this review.

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This is a review and update that intends to put together what is known about prediction and modification of breast cancer risk. We discuss the current knowledge regarding screening strategies for high-risk women and medical and surgical approaches to reduce breast cancer risk.

The identification of women at higher risk for breast cancer is a matter of public health, and participants in any treatment modality of this condition (including plastic surgeons) should be aware of the tools and predictive models of this type of cancer.

Until recently, screening for breast cancer in the community has been limited to decisions such as when to initiate a mammography.¹

New developments that predict and modify breast cancer risk must be clearly known and understood by our specialty through identification of women at higher risk for breast cancer and be familiar with the current issues related to screening and risk-reduction measures.

The facts

1. The average risk of breast cancer is 12% and also expressed as one in eight women, whereas the chance that a woman will never have a breast cancer is 87.3% or seven in eight women. This risk is greater after the sixth decade of life.²
2. The three most important risk factors for breast cancer are gender, ageing and family history.²
3. Mammography remains the gold standard screening tool and most women, older than 40 years, should participate in this exam.¹
4. Patients with breast cancer belong to one of three groups:
 - a. Sporadic breast cancer (75%)—Patients without family history or those who have a breast biopsy with proliferative changes.
 - b. Cluster family breast cancer (20%) — Relevant history of breast cancer in the family and breast biopsy with proliferative breast changes with no association with mutations.
 - c. Genetic mutation breast cancer (5%) — Women with a genetic predisposition and related to mutations in the breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2).

The assessment of women at high risk for breast cancer should include:

- I. Family history with genetic testing;
- II. Clinical history, including prior breast biopsies; and
- III. Evaluation of mammographic density.

Family history

Many women have a family history of breast cancer, but risks do not increase substantially; there is at the most, doubling of the lifetime risk. Inheritance of an autosomal

dominance is seen in only 1–2% of breast cancer cases; it is a high-penetrance gene, conferring up to an 85% lifetime risk of breast cancer. In some families, there is also a high risk of ovarian cancer.^{3–5}

Features of family history suggesting that cancer may be caused by a high-penetrance gene are:

1. Current age, race, age at menarche, age at first live birth and lactation,
2. Two or more first-degree (parent, sibling or child) or second-degree (grandmother, granddaughter, aunt, niece and half-sibling) relatives with breast or ovarian cancer,
3. Breast cancer occurring before the age of 50 (premenopausal) in a close relative,
3. Family history of bilateral breast and ovarian cancer.
4. One or more relatives with two cancers (breast and ovarian cancer or two independent breast cancers),
5. Male relatives with breast cancer,
6. Presence of BRCA1 and BRCA2, and
7. Number of previous breast biopsy examinations and presence of atypical hyperplasia.

These are responsible for approximately 40% of cases of inherited breast cancer. In patients with BRCA1 mutations, the average cumulative risk of developing cancer by the age of 70 ranges between 55% and 85% for breast cancer and between 16% and 60% for ovarian cancer. In BRCA 2 mutation, the risks range between 37% and 85% for breast cancer and between 11% and 27% for ovarian cancer.

Clinical history

Clinical features to be aware of are:

1. Radiation treatment

There is a higher risk in young survivors after radiation treatment. Among women with Hodgkin's disease who received radiation, the risk of breast cancer increases significantly from 15 years to 30 years after radiation therapy.⁶
2. Premalignant lesions

These are:

- a. Atypical ductal hyperplasia (ADH),
- b. Atypical lobular hyperplasia (ALH) and
- c. Lobular carcinoma *in situ* (LCIS).

LCIS and ALH are both described as lobular neoplasia, and are associated with increased risk of breast cancer, with lifetime risk estimate ranging from 10% to 20%. ADH is part of ductal proliferative breast diseases, ranging from usual ductal hyperplasia to ductal carcinoma *in situ* (DCIS).⁷ Once thought to be a precursor to invasive carcinoma, LCIS is now

considered to be a marker of increased risk for breast cancer in either breast. In most cases, it is multifocal and bilateral. More than 50% of patients with LCIS have multiple lesions in the ipsilateral breast, and approximately 30% have LCIS in the contralateral breast. On the other hand, DCIS represents the stage of breast cancer development in which most of the molecular changes that characterise invasive breast cancer are already present, even though the lesion has not assumed a fully malignant phenotype.^{8–10} The presence of ADH confers a risk of about 1% per year and is similar to LCIS. The risk is for both lobular and ductal cancers bilaterally.

This is important for the plastic surgeon who receives a pathology report informing about this condition after a reduction mammoplasty.

Mammographic density

Extensive mammographic density is strongly associated with the risk of breast cancer. A meta-analysis of 42 studies showed that women in the highest quartile of mammographic density have a risk of breast cancer that is approximately 4–6 times higher than that of women of similar age in the lowest quartile.¹¹

Breast density is not currently used routinely when assessing breast cancer risk. In the future, measures of mammographic density could be useful in assessing the risk of breast cancer and in guiding measures to prevent breast cancer.¹²

Tools for breast cancer risk assessment

The discussion and evaluation of risk is a good way to engage patients in a reminder of factors that may contribute to their increased risk. These models incorporate family history, previous abnormal breast biopsies and reproductive history. Women at high risk should be referred to genetic counselling and a more definitive assessment of risk. The National Cancer Institute and the National Surgical Adjuvant Breast and Bowel Project (NSABP) have developed an interactive tool to estimate a woman's risk of developing invasive breast cancer. This is available on the National Cancer Institute's Website (<http://www.cancer.gov/bcrisktool>). This tool evolved from the original Gail model and includes the following risk factors: current age, race, age at menarche, age at first live birth, the number of first-degree relatives with breast cancer, the number of previous breast biopsy examinations and presence of atypical hyperplasia. It predicts a woman's likelihood of having a breast cancer diagnosis within the next 5 years and within her lifetime (up to the age of 90). Although this prediction model has been validated in large populations, it has limitations because it is not good at predicting individual risk.^{13,14} In addition, it does not take into consideration the paternal family history, second-degree relatives or the age at onset in affected relatives. Both of these factors are significant in predicting hereditary breast cancer risk.¹⁵ The effect of ADH on risk assessment has been found to be underestimated by the Gail model.¹⁴

The Claus model (<http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp>) estimates the probability that a woman will develop breast cancer based on her

family history of cancer, incorporates more extensive data but excludes other risk factors. Risk tables of this model are able to calculate lifetime probabilities of developing cancer or an estimated risk that a woman will develop cancer over 10-year intervals. It should be emphasised that the Claus model may be used only for women with at least one female first- or second-degree relative with breast cancer. The model does not take into account other risk factors that have been associated with breast cancer, such as age of menarche, age at first live birth or a family history of ovarian cancer.

Genetic testing

Women who carry mutations such as BRCA-1 and BRCA-2 are at very high risk for breast cancer. The information provided by genetic testing is invaluable when making informed decisions related to breast cancer risk management. Universal genetic testing has some major drawbacks such as high cost and the frequency of mutations of uncertain clinical significance. The American Society of Clinical Oncology has devised guidelines suggesting that it is reasonable to consider testing of women whose mutation probability is greater than 10%.¹⁶

The BRCAPRO (<http://www4.utsouthwestern.edu/breasthealth/cagene/default.asp>)¹⁷ program calculates the probability that a particular family member carries a germline mutation of the BRCA1 and BRCA2. The calculations are based on Bayes' rules of determination of the probability of a mutation, given family history. Women at high risk should be referred to genetic counselling for a more definitive risk assessment. Risk assessment tools are recommended as an adjuvant to genetic counselling. Genetic counselling is recommended before mutation testing. Data are not available to determine the optimal age for testing.

Screening strategies

Mammography has been proven to detect breast cancer at an early stage. However, for women with an increased risk of breast cancer, newer screening technologies are available for earlier detection, particularly in women younger than 40 years for whom mammography is less sensitive.¹ Contrast-enhanced magnetic resonance imaging (MRI) has been shown to have a high sensitivity (86–100%) for detecting breast cancer in high-risk asymptomatic and symptomatic women, although reports of specificity have been more variable (37–97%).^{18–22}

The American Cancer Society now recommends MRI screening in addition to mammograms for women who meet at least one of the following conditions²³:

1. BRCA1 or BRCA2 mutation;
2. First-degree relative (parent, sibling and child) with a BRCA1 or BRCA2 mutation (even if they have yet to be tested themselves);
3. Lifetime risk of breast cancer has been scored at 20–25% or greater (as defined by BRCAPRO or other accepted risk assessment tools that look at family history and other factors);
4. Radiation to the chest between the ages of 10 and 30; and

- Clinical syndromes that place them at high risk (Li–Fraumeni syndrome, Cowden syndrome or Bannayan–Riley–Ruvalcaba syndrome); or they may have one of these syndromes based on a history in a first-degree relative.

There is still not enough evidence for/or against recommending MRI screening in women who have²¹:

- Family history and other factors, demonstrating 15–20% lifetime risk of breast cancer based on one of several accepted risk assessment tools;
- LCIS or atypical lobular hyperplasia;
- ADH;
- Dense breasts or unevenly dense breasts on a mammogram; and
- Have already had breast cancer, including DCIS.

Screening MRIs are not recommended for women with a lifetime risk of breast cancer below 15%. Although an MRI is a more sensitive test, it may still miss some cancers that a mammogram would detect. An MRI should therefore be used in addition to, not instead of, a screening mammogram. For most high-risk women, screening with MRI and mammograms should begin at the age of 30 and continue for as long as the woman is in good health. This decision should be based on shared decision making between patients and their doctors, taking into account individual patient circumstances and preferences, because evidence is limited regarding the best age at which to start screening.^{21,22}

Other strategies to reduce breast cancer risks:

- Regular exercise may reduce breast cancer risk, although the mechanism is unknown.²⁴
- Reduction in body weight and decreasing or stopping alcohol consumption may reduce breast cancer risk in post-menopausal women.²⁵
- Dietary folate seems to protect against the increased risk of breast cancer caused by alcohol intake.^{26–28}
- Although not statistically significant, the Women's Health Initiative found that a low-fat diet was associated with a 9% reduction in the risk of breast cancer.²⁹
- Descriptive studies also suggest that vitamin D and calcium might be involved in the development of breast cancer. Of the 13 studies of breast cancer, nine reported a favourable association of vitamin D markers or sunlight with cancer risk, including one where the association was limited to premenopausal women; one study reported a favourable trend of borderline statistical significance and three found no association. None reported adverse effects. However, there are no data from randomised controlled trials indicating that adequate vitamin D intake could reduce the risk of breast cancer.³⁰ It is important to discuss these statements with patients, but they need to be aware that lifestyle changes alone should not be relied on as the only risk-reduction strategies.

Hormonal interventions

The identification of the oestrogen receptor provided a successful target for the treatment and prevention of

breast cancer. Selective Estrogen Receptor Modulators (SERMs), which antagonise oestrogens in some tissues and mimic their action in others, play a key role in chemoprevention. Tamoxifen acts as an oestrogen antagonist in breast tissue and as an oestrogen agonist in the endometrium. Conversely, raloxifene behaves as an oestrogen antagonist in both the breast and the endometrium. Differences in their molecular and three-dimensional structures affect the transcriptional activity of the activated oestrogen receptor. The NSABP P-1 Breast Cancer Prevention Trial evaluated the use of tamoxifen for the prevention of breast cancer in high-risk women who were either pre- or post-menopausal. The study found that tamoxifen, when given for 5 years, decreased the risk for developing invasive breast cancer by 49% in women, who were at an increased risk for developing breast cancer. Those with atypical hyperplasia derived the largest risk reduction: 85%. Significant adverse effects are associated with tamoxifen, including hot flashes, endometrial cancer and venous thrombo-embolism. Women may perceive these risks as outweighing the potential benefits and may choose not to take tamoxifen, which was the first drug approved for chemoprevention of breast cancer. Recent evidence suggests a similar magnitude of benefit from the related drug raloxifene. In the NSABP P-2 study of tamoxifen and raloxifene trial, both had equivalent effects in reducing risk of invasive breast cancer in all high-risk post-menopausal women examined, including women with a history of atypical hyperplasia or LCIS, who had the highest annual rates of invasive breast cancer. There were fewer noninvasive cancers in the women who took tamoxifen, although this was not statistically significant. Comparisons of raloxifene with tamoxifen show equal efficacy as a chemopreventive agent for breast cancer, but there were fewer thrombo-embolic disorders, endometrial cancers, hysterectomies, cataracts and cataract surgeries in women taking raloxifene that was approved for the prevention of invasive breast cancer in high-risk post-menopausal women in 2007. Women should be offered chemoprevention with SERMs only after a shared decision-making process that involves careful consideration of the risks and benefits. Data are currently needed regarding the optimal time to initiate chemoprevention in women identified as high risk.^{31–33}

Aromatase inhibitors

The aromatase enzyme is required for the last step in oestrogen biosynthesis. The third-generation aromatase inhibitors, which include exemestane, anastrozole and letrozole, are potent and selective inhibitors of aromatase activity. The effect of aromatase inhibitors, as measured by the degree of aromatase inhibition, is approximately 98% for each of the third-generation agents.³⁴ Interest in the use of the drugs for chemoprevention developed from the findings of the anastrozole and tamoxifen alone and in a combination trial. Post-menopausal women with early-stage breast cancer, who were using anastrozole alone, had a 58% reduction in contralateral invasive breast cancer. The second International Breast Cancer Intervention prevention trial began in 2003 and compares anastrozole to placebo in

6000 post-menopausal women with an increased risk of breast cancer as well as women with mammographic density covering at least 50% of the breast.^{34,35}

Prophylactic mastectomy

Prophylactic mastectomy can reduce the risk of breast cancer by up to 90%³⁸ and, if combined with simultaneous breast reconstruction, is an option of treatment for some high-risk women. The procedure and rationale of prophylactic mastectomy is controversial because there are no randomised controlled trials to demonstrate the potential benefits (effects on risk reduction) or harms (concerning the patient's quality of life) of this irreversible operation. The procedure should be discussed extensively with the patient, because there is no way to verify that all breast tissue has been removed. The discussion and care pathway for patients opting for mastectomy and breast reconstruction must depend on a team of experts in breast pathology (a multidisciplinary team, including a plastic and general surgeon, medical oncologist, pathologist, genetic counsellor, gynaecologist, psychiatrist and nurse) and patients should be informed of the consequences, current evidence of benefits, limitations and alternatives. The patient should choose this procedure after a discussion with the experts, where topics such as reconstructive procedures, realistic cosmetic results, complications and extra costs predominate. The cosmetic outcome is of great importance because it is a prophylactic operation, even if it is still less important to the patient than risk reduction. In a patient who has no evidence of breast cancer but who is at high risk, bilateral mastectomy is an option for risk reduction, and is reported to reduce breast cancer incidence in more than 95%.^{36–39}

A recent position statement made by the American Society of Surgical Oncology,⁴⁰ suggests potential indications for bilateral prophylactic mastectomy, and that this operation may be considered in the following patients without a cancer diagnosis, but who are at high risk:

1. BRCA mutations or other genetic susceptibility genes;
2. A strong family history of breast cancer with no demonstrable mutation; cancer in multiple first-degree relatives and/or multiple successive generations of family members with breast and/or ovarian cancer.
3. Histologic risk factors: ADH, ALH or LCIS confirmed on biopsy (these changes are especially significant if they are present in a patient with a strong family history of breast cancer); and
4. Difficult surveillance; a clinically and mammographically dense breast may make surveillance difficult.

There is no evidence at this time to recommend routine sentinel lymph node (SLN) biopsy for patients undergoing prophylactic mastectomy. However, this may be considered since high-risk patients may have an unsuspected cancer and axillary staging would be difficult after mastectomy.^{36,39}

Potential indications for prophylactic contralateral mastectomy in patients with current or previous diagnosis of breast cancer are⁴⁰:

1. Risk reduction
Women overestimate their risk of developing a second cancer and it is a fact to be considered when planning a contralateral prophylactic mastectomy. Furthermore, an individual's risk of a contralateral breast cancer, the lack of impact of prophylactic mastectomy on mortality from the index cancer and the significant benefit of endocrine therapy in reducing the risk of contralateral cancer should be included in the discussion of prophylactic mastectomy in this circumstance.
2. Difficult surveillance
This includes patients with clinically and mammographically dense breast tissue or diffuse indeterminate microcalcifications in the contralateral breast. Stereotactic core biopsy of any suspicious cluster should be performed in this situation to rule out carcinoma. However, diffuse and/or indeterminate calcifications in some situations may make subsequent surveillance difficult.
3. Plastic surgery breast reconstruction
It is difficult to reasonably match these patients' breasts with reconstructive techniques, and a contralateral mastectomy with reconstruction may be indicated to maintain symmetry and balance in patients who have a large and/or ptotic contralateral breast or a disproportionately sized contralateral breast.

Prophylactic salpingo-oophorectomy

Bilateral prophylactic salpingo-oophorectomy is widely used for cancer risk reduction in pre-menopausal women with BRCA1/2 mutations. This procedure significantly reduces breast cancer risk by approximately 50% and ovarian cancer risk by 80–95%, but may be accompanied by menopausal symptoms, increased cardiovascular risk, impaired quality of life and accelerated bone loss. Therefore, decisions regarding the timing of bilateral prophylactic salpingo-oophorectomy and the use of hormone replacement therapy after bilateral prophylactic salpingo-oophorectomy should be made only after consultation with the multidisciplinary team.^{41–43}

Discussion

This is a review on the subject of the evaluation and management of women at high risk of breast cancer. Therefore, it would be useful as an update for those not necessarily working in the field. New tools that predict and modify breast cancer risk are discussed. Every plastic surgeon should be informed of which women are at higher risk for breast cancer and be familiar with these issues related to screening and risk-reduction measures. Thus, routine application of tools that have the ability to study breast cancer risk should be integrated to plastic and reconstructive surgery protocols in order to maintain our hierarchy in the breast onco-plastic multidisciplinary team.

Disclosure

No conflicts of interest and nothing to disclose.

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