Breast Cancer Genetics for Plastic Surgeons

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Summary: Multidisciplinary genetic clinics offer counseling and testing to those who meet criteria for familial breast cancer, and plastic surgeons become integral to this process when risk-reducing surgery and postmastectomy reconstruction are deemed appropriate. As reconstructive surgeons, it is important that plastic surgeons are aware of the risks and issues associated with the genetic variants that cause patients to present for prophylactic or therapeutic surgery. (*Plast. Reconstr. Surg.* 140: 455, 2017.)

Genetic screening has evolved from the discovery of breast and ovarian cancer syndrome in 1971, to the present where specific genes can be analyzed to identify which members of cancer-prone families have an increased risk of developing breast cancer.[1] Multidisciplinary genetic clinics offer counseling and testing to those who meet criteria for familial breast cancer (Table 1).[2] This assessment allows stratification of risk so that appropriate counseling, screening, and/or risk-reducing interventions can be offered. Plastic surgeons are integral to postmastectomy reconstruction, often working as part of a multidisciplinary team that includes a clinical geneticist. It is therefore important for plastic surgeons to have an understanding of the genetic-related issues faced by these patients.

BRCA1 or *BRCA2* mutation carriers have a greater than 80 percent lifetime risk of breast cancer and, if diagnosed, a 40 percent risk of a contralateral breast cancer.[3–5] The identification of a *BRCA* mutation gives the carrier the option of bilateral prophylactic mastectomy that confers at least an 87 percent risk reduction of breast cancer, whereas contralateral mastectomy in the presence of breast cancer reduces the risk of a subsequent cancer by 97 percent.[5–7]

Rates of immediate reconstruction following prophylactic mastectomy vary.[8] An international study of 1635 patients found a rate of immediate reconstruction of 69.5 percent.[9] Of these 1137 immediate reconstructions, 73 percent had implants, 21 percent had an autologous procedure, and 6 percent had a combination implant and autologous procedure. The mean age of undergoing prophylactic surgery was 42.5 years (range, 20 to 75 years). A significant difference exists between age groups, with those undergoing surgery older than 45 years being 65 percent less likely to have immediate reconstruction compared with those younger than 35 years.[9] Geographic variation exists in the uptake of immediate reconstruction, with estimates of 71.9 percent in the United States, 66.9 percent in Canada, and 68.2 percent in Europe. These age and geographic differences in immediate reconstruction rates highlight the importance of breast reconstruction awareness initiatives, so that patients may better understand their options.

In addition to the *BRCA* genes, other high-risk syndromes and moderate-risk genetic mutations may lead to referrals for risk evaluation, preventative surgery, and breast reconstruction. We aim to give an overview of the genetic conditions that commonly lead to plastic surgery referral because of impending risk-reducing surgery, and high-risk familial syndromes and less common genetic variants.

FAMILIAL BREAST CANCER

Family history as a risk factor for breast cancer was first reported in Roman times.[10] First-degree relatives of an affected individual have an approximately two-fold increased likelihood of developing breast cancer.[11] This risk is increased with the number of affected relatives and is greater for women with relatives affected at a young age, bilateral disease, or a history of benign breast disease.[12,13]

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Table 1. Consideration of Familial Breast Cancer*

Three or more cases of breast and/or ovarian cancer are present in a family
Two breast cancer cases in a close relative with one diagnosed younger than 50 yr
Two breast cancer cases in a family diagnosed younger than 40 yr
Male breast cancer associated with a family history of early breast cancer or ovarian cancer
A history of breast and ovarian cancer in the same patient and finally in those of Ashkenazi Jewish heritage, particularly with triple-negative breast cancer diagnosed younger than 60 yr

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The lifetime risk of breast cancer in American women is estimated at 12.4 percent. This risk varies with age, and 10-year risk can be calculated from age 30 to 70 (Table 2).[14] The impact of genetic variants on this risk is central to the decision-making process when considering risk-reducing interventions. Three reasonably well-defined classes of breast cancer susceptibility alleles have been identified and have been categorized with regard to the risk they confer (Fig. 1).

BRCA GENES

Disease-causing mutations in *BRCA1* and *BRCA2*, located on chromosomes 17 and 13, respectively, account for approximately 16 percent of the familial risk of breast cancer.[15,16] *BRCA1* was first implicated in breast cancer susceptibility in 1990, with *BRCA2* first identified in 1994.[17,18] Mutations in *BRCA1* or *BRCA2* inactivates repair of double-stranded DNA breaks, leaving DNA unrepaired, which leads to unrestricted mutations and tumor development.[19]

Mutations within *BRCA1* and *BRCA2* are highly penetrant with regard to breast cancer susceptibility, with varying estimates of the level of risk conferred. Studies of large breast cancer families propose that the risk of developing breast cancer by age 70 is 87 percent for *BRCA1* carriers and 84 percent for *BRCA2* carriers.[3,4] The risks were lower in population studies with samples unselected for family history, 65 percent for *BRCA1* and 45 percent for *BRCA2*.[20] *BRCA1* carriers have an increased incidence compared with *BRCA2* carriers and experience cancer at younger ages (38 percent versus 16 percent by 50 years of age). This is attributable to a steep rise in incidence between ages 40 and 49 years in *BRCA1* carriers followed by a relative constant rise thereafter. This is compared to *BRCA2* carriers, who exhibit a similar age pattern of incidence compared to the general population but at a magnitude 10 times greater.[20] The prevalence of *BRCA1* and *BRCA2* mutations is approximately one in 300. The contribution of causative mutations in these genes to the excess familial risk of breast cancer is estimated to be 15 to 25 percent.[21–23]

Table 2. Risk Stratification Depending on Age, Estimated for the Whole Population, Independent of Modifiable Risk Factors or Family History

Age	10-Yr Risk of Breast Cancer (%)
30 years	1 in 227 (0.44)
40 years	1 in 68 (1.47)
50 years	1 in 42 (2.38)
60 years	1 in 28 (3.56)
70 years	1 in 26 (3.82)

These genes are also highly penetrant for ovarian cancer, with *BRCA1* demonstrating higher penetrance compared with *BRCA2*. A meta-analysis of 22 studies estimated that the risk of developing ovarian cancer by the age of 70 is 33 percent in *BRCA1* mutation carriers and 11 percent in *BRCA2* mutation carriers.[20] *BRCA1* shows a sharp rise in incidence of ovarian cancer between 40 and 50 years to 1 to 2 percent per annum, whereas *BRCA2* demonstrates very low penetrance until 50 years and increases sharply thereafter.[20]

BRCA1 mutations have implications with regard to tumor pathology compared with *BRCA2* tumors. *BRCA1* tumors are characteristically high-grade invasive ductal carcinomas that are predominately triple-negative (estrogen, progesterone, and human epidermal growth factor receptor 2 receptors all staining negative).[24,25] Tumors identified in carriers of *BRCA1* mutations also show an increased incidence of medullary carcinoma compared with controls and *BRCA2* carriers, which fits with the distinctive basal phenotype.[24,26] *BRCA2* tumors have no definite characteristics but are typically estrogen and progesterone receptor positive. Male breast cancer is responsible for approximately 1 percent of all breast cancer cases. Although the risk for male breast cancer is elevated for carriers of mutations in both genes, it is most noticeable with *BRCA2*.[27]

For *BRCA1* and *BRCA2* gene carriers, breast awareness and self-examination counseling should begin from the age of 18. Some controversy exists with regard to the most appropriate screening strategy, but clinical assessment and imaging

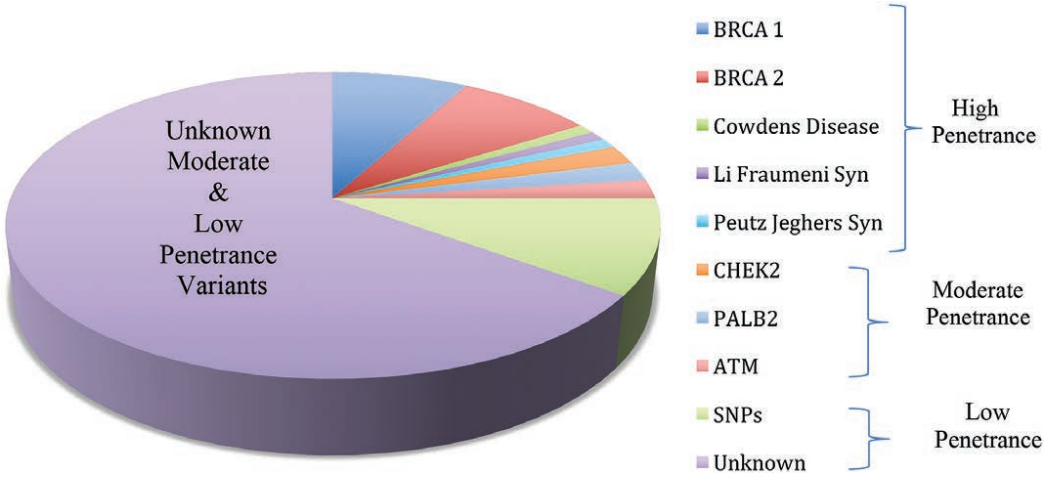

Fig. 1. Estimated spectrum of breast cancer susceptibility variants.

should commence at age 25. Imaging consists of either annual magnetic resonance imaging and alternating digital mammography starting at age 25 or annual magnetic resonance imaging with alternating digital mammography commencing at age 30.[28] Risk-reducing bilateral mastectomy decreases breast cancer risk by 90 percent, increasing to 95 percent if prior or concurrent oophorectomy has been performed.[6] Consideration of risk-reducing salpingo-oophorectomy is given by age 35 to 40 years.[29] This limits the risk of ovarian cancer to peritoneal disease and premenopausal women.[29]

FAMILIAL SYNDROMES

Li-Fraumeni Syndrome

Li-Fraumeni syndrome is caused by a germline mutation in *TP53* on chromosome 17, which encodes *p53*, a tumor suppressor gene.[30] Inheritance is autosomal dominant and gives rise to early-onset breast cancer, sarcoma, leukemia, adrenocortical tumors, and brain tumors.[31,32] Mutations in *TP53* account for less than 1 percent of breast cancer in those diagnosed younger than 40 years and is thus a rare cause of familial breast cancer.[33] Mutations within *TP53* have 100 percent penetrance with regard to breast cancer, and screening may be considered in patients who are *BRCA*-negative, diagnosed at younger than 35 years.[34,35]

Cowden Syndrome

Cowden syndrome is caused by a mutation in the tumor suppressor gene *PTEN* that leads to multiple hamartomas and an increased risk of a number of cancers, including breast cancer. Inheritance is autosomal dominant and is caused by a mutation at a single locus at 10q23.[36] Estimates of lifetime risk vary from 25 to 85 percent, typically occurring early in life and often bilaterally.[37]

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome is an autosomal dominant disorder characterized by mucocutaneous melanocytic macules of the lips, buccal mucosa, and digits in association with intestinal hamartomatous polyps. It is caused by a germline mutation of the *STK11/LKB1* (serine/threonine kinase) gene in most cases, which is located on chromosome 19.[38] Estimates vary, but a 6-fold increased risk of breast cancer has been proposed, translating into a 45 percent risk by the age of 70.[39]

MODERATE PENETRANCE VARIANTS

Despite the advances in our understanding brought about by the identification of these high-penetrance variants (in particular, *BRCA1/2*), it is still thought unlikely that these account for more than 20 percent of the familial aggregation of breast cancer.[12,40] Efforts at identifying further high penetrance breast cancer susceptibility genes using genomewide linkage analyses have thus far been unsuccessful.[41] The remaining approximately 80 percent of familial breast cancer susceptibility is thought to be polygenic in nature, consisting of a large number of moderate and low-penetrance variants each contributing in varying degrees to this risk.[42] *PALB2*, *CHEK2*, and *ATM* are the most noteworthy.

PALB2 (partner and localizer of *BRCA2*) is a gene located on chromosome 16 that acts as a tumor suppressor gene. It maintains the integrity of *BRCA2*, as the protein it encodes is involved in

the stable nuclear localization of *BRCA2* in addition to repair of double-stranded DNA breakages and homologous recombination.[43] In addition to its known association with Fanconi anemia, it was initially estimated to have a 2.3-fold relative increased risk of breast cancer.[44] The risk is now estimated to be 34 percent by age 70 years, increasing to 58 percent if two affected relatives younger than 50 years exist.[45]

CHEK2 is located on chromosome 22 and encodes a checkpoint kinase that is implicated in tumor suppression because of its function in the regulation of DNA repair by phosphorylating *BRCA1* and *p53*.[46,47] Causative mutations in this gene have been identified in breast cancer and Li-Fraumeni syndrome.[46–48] *CHEK2* is more prevalent in those with a younger age at diagnosis and a positive family history. It confers an increased risk of 2.3 to 7.[49,50] This is estimated to translate to a 20 percent lifetime risk in patients with no family history, 34 percent in those with an affected first-degree relative, and 40 percent if both first- and second-degree relatives are affected.[50] Screening with a positive family history for a *CHEK2* mutation has a potential role in the future, as these patients are candidates for magnetic resonance imaging screening and chemoprevention.

ATM (ataxia telangiectasia mutated), located on chromosome 11, is a tumor suppressor gene. It is activated by DNA double-stranded breakages. It is involved in DNA repair of many proteins, including p53, BRCA1, and CHEK2. *ATM* is responsible for the autosomal disorder ataxia telangiectasia, and variants within this gene that cause ataxia telangiectasia have been shown to confer a 2- to 5-fold relative increased risk of breast cancer, especially in the setting of radiation therapy.[51–53] These initial results await replication, and a role for prophylactic surgery in these patients is not well defined.[53]

BILATERAL PROPHYLACTIC MASTECTOMY

This knowledge of breast cancer genetics allows us to ask the question, at what level of risk is a risk-reducing intervention indicated? Women who carry high-risk variants are obvious candidates. A threshold of risk where prophylactic mastectomy would maximize protection is not well defined. Offering surgery when risk approaches 2 percent annually in *BRCA* carriers would seem like a sensible approach, corresponding to age 25 years in *BRCA1* and 25 to 30 years in *BRCA2* carriers.[7]

Moderate risk variants are less so, with approximate relative risks of 2 or 4 equating to an absolute risk of 16 or 32 percent by the age of 80, respectively.[54] Factors that may influence the level of risk must be taken into account, such as family history, other genetic factors, and lifestyle. A strong family history increases the absolute risk of breast cancer in carriers of *BRCA1*, *BRCA2*, *PALB2*, and *CHEK2*.[20,55,56] For carriers of *CHEK2* or *PALB2* mutations, this may increase their risk to a level that makes prophylactic surgery justifiable.[50] A threshold of 5 percent would seem reasonable in this setting, which would indicate offering prophylactic surgery to those aged 35 to 40 years.[50,57] Referral for postmastectomy reconstruction in carriers of moderate-risk variants should therefore occur after in-depth consultation at a multidisciplinary genetic clinic (Table 3).

LOW-PENETRANCE VARIANTS

High-throughput genome-wide association studies have attempted to explain the unknown proportion of familial breast cancer by identifying several low-penetrance breast cancer susceptibility variants.[58] A single-nucleotide polymorphism is a DNA sequence variation that occurs when a single nucleotide in the genome sequence differs between paired chromosomes in an individual. Risk associated with heterozygotes and homozygotes for individual single-nucleotide polymorphisms is estimated at 1.26 and 1.65, respectively.[59] The multiplicative action of these variants on a person's risk has only recently become apparent. It is estimated that women carrying the 14 risk alleles from the seven known low-penetrance variants are at a 6-fold increased risk of developing breast cancer.[60] The single-nucleotide polymorphism profile of a *BRCA* gene carrier alters the absolute risk to the patient which, with further understanding, may allow single-nucleotide polymorphisms to play a role in clinical decision-making for high-risk individuals.[61]

Table 3. Risk Profiles of Causative Breast Cancer Genetic Mutations

Gene	Risk of Breast Cancer (%)	Increased Relative Risk	Age at Which Prophylactic Surgery Is Considered (yr)
BRCA1	>80	10	25
BRCA2	>80	10	25–30
PALB2	34–58	2–4	35–40
CHEK2	20–40	2–4	35–40
ATM	20–40	2–4	35–40

A panel of genes can now be tested, and this technology has gained attention with both media and the general population. However, the availability of gene panel sequencing, which includes low-penetrance variants, does not mean that it is clinically useful or appropriate. Each variant must have an established quantified risk, allowing the application of a management strategy with due regard to clinical significance of this risk.

CONCLUSIONS

Plastic surgeons should have an understanding of risk stratification for women with a genetic predisposition for breast cancer. *BRCA* mutation carriers are now commonly referred to breast reconstruction clinics, but it is expected that the less common genetic variants discussed above will be encountered more frequently as specialist clinics and our knowledge increase further. Although it will be the geneticists that will have a greater role in counseling and in disseminating information, it is beneficial for the reconstructive surgeon to have an understanding of the issues involved. In summary, we present a review of the breast cancer genetic variants that may lead to referral for postmastectomy reconstruction, discussing the risk stratification involved to enable plastic surgeons to have an informed and considered interaction with these patients.

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