Genetic and Genomic Factors in Breast Cancer

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Introduction

Breast cancer is the result of a complex interaction of genetic, genomic, and environmental factors that result in the initiation and progression of malignancy. While certain germline (germinal) inherited genes have been identified that, when altered or mutated, predispose that individual to develop breast cancer and other associated malignancies such as ovarian epithelial cancer (OEC), the majority of breast cancer cases, even those occurring in women with multiple affected family members, are not associated with mutations of genes currently linked to cancer predisposition syndromes. Of interest is that women who develop breast cancer and have identified germinal gene mutations generally do not have a vastly different disease course or prognosis than those who develop sporadic breast cancer and have no detectable gene mutations. However, specific alterations of the somatic genome (i.e., the genome of the actual tumor tissue as opposed to the germinal genome found in all the nucleated cells of an individual) have been identified that better predict prognosis and the relative success or failure of specific therapeutic interventions.

Risk assessment for breast cancer in unaffected women continues to rely on a careful and detailed assessment of personal and family histories within a risk assessment algorithm with the offering of genetic testing to women (and some men) who are found to have an increased likelihood of being a carrier of a deleterious mutation in a cancer susceptibility gene. Accordingly, genetics and genomics have become a central aspect of clinical breast cancer, from risk assessment to prognosis and management. In this chapter, our current understanding of genetic and genomic factors in the assessment of breast cancer risk and prognosis will be presented, recognizing the central role of genetic counseling in cancer risk assessment and the expanding capabilities of genetic and genomic analyses to better delineate risk for developing breast cancer, assess prognosis in affected individuals, and identify more effective preventative and therapeutic interventions.

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Heritable Breast Cancer

The increased risk for developing cancer in women with mutations in cancer susceptibility genes invariably begins with the inheritance of a germline mutation from either parent. While gynecologic malignancies can only occur in females and the vast majority of breast cancers occur in women, genes that predispose to the development of gynecologic malignancies are mostly autosomal in nature and thus readily inheritable from either parent. This concept is critical when obtaining family history information as both parents can transmit gene mutations; accordingly, obtaining careful and detailed family histories of an individual's maternal and paternal families is vital to estimating accurate risk for cancer development in an individual.

By definition, a germline mutation is present at conception; every cell of the individual will have the gene mutation, a fact that is likely associated with the involvement of multiple organs in many cancer susceptibility syndromes. However, the inheritance of a mutated cancer susceptibility allele is only the *first* step in promoting the development of a malignancy and does not guarantee that an individual will go on to develop a particular malignancy. The development of a heritable cancer, as well as most other cancers, is postulated to be dependent on the occurrence of a second genomic alteration [1]. That an individual has inherited the first "step" serves to explain why such individuals have a considerably higher risk for developing cancer than the general population, as well as why cancer predisposition syndromes are characterized by cancer development at an earlier age and a higher rate of bilaterality than what is observed in the general population.

However, cancer is ultimately a disease of somatic cells; if two (or more) independent events are needed for the cells to become malignant, then inheriting the first step, as opposed to waiting for it to occur through some random events causing a somatic alteration, will surely increase the likelihood of it occurring compared to those individuals who do not inherit such mutations. The second (and any subsequent) step is invariably somatic in nature, also explaining why not everyone who inherits a susceptibility gene develops the malignancy. Molecular studies of cancers in individuals with malignancies arising from hereditary cancer syndromes frequently show a loss of heterozygosity at the genomic position of the tumor suppressor gene in tumor tissue. This loss of heterozygosity is the "second step" in the development of cancer in individuals who have inherited mutated cancer susceptibility genes. Sections describing germinal and somatic mutations that either predispose to or characterize breast cancer will be found later in this chapter; they represent the more current molecular definitions of the first and second "steps" described by Knudson in the early 1970s [2].

There are numerous mechanisms that likely lead to this loss of heterozygosity and the inactivation of the tumor suppressing gene. While such cellular and nuclear events are common and are mostly random processes by which genes and chromosomes are altered, deleted, replaced, or rearranged and not typically associated with organic pathology, such changes in the presence of an inherited mutation in a tumor suppressor gene can lead to the alteration or inactivation of tumor-suppressing gene function and predispose that organ to undergo malignant transformation. This process is known as monoallelic inheritance of a gene mutation with subsequent inactivation of the wild-type allele and loss of heterozygosity. However, it is now recognized that some individuals can inherit mutations in both alleles (either homozygous or compound heterozygous), an uncommon occurrence known as inherited biallelic mutations, which tend to present with a different clinical phenotype, including childhood cancers, to that usually observed with monoallelic (dominant) inheritance of mutations [3].

It is interesting to note that while most hereditary cancer syndromes, including hereditary breast and ovarian cancer syndrome, are mostly transmitted in and present as a classic autosomal dominant inherited condition, the requirement of a second step that inactivates both alleles (biallelic inactivation) makes the *cellular* mechanism necessary for the promotion of carcino-

Table 2.1 Cancer predisposition genes associated with breast cancer

Gene (chromosome)	Penetrance	Clinical features
BRCA1 (17q21)	High	Breast and epithelial ovarian cancers
BRCA2 (13q12-13)	High	Breast and epithelial ovarian cancers
PTEN (10q23.3)	High	Cowden syndrome
TP53 (17q13.1)	High	Li-Fraumeni syndrome
RAD51C (17q23)	High (?)	Breast and epithelial ovarian cancers; Fanconi anemia (subtype-O; biallelic mutation)
CDH1 (16q22.1)	Moderate	Gastric cancer and lobular breast cancer
ATM (11q22.3)	Moderate	Ataxia-teleangectasia (biallelic mutation)
CHEK2 (22q12.1)	Low	Some association with Li-Fraumeni syndrome
BRIP1 (17q22)	Low	Fanconi anemia (biallelic mutation)
PALB2 (16q12)	Low	Fanconi anemia (biallelic mutation)
KRAS-variant (12p12.1)	Unknown	Breast cancer, epithelial ovarian, lung cancer, head and neck cancers, GI cancer

genesis to be recessive in nature. However, the different phenotypes associated with biallelic inheritance compared to monoallelic inheritance bespeak a difference in the molecular biology of these two disease inheritance patterns, and may eventually provide valuable insight into the molecular mechanisms of cancer development.

Nonetheless, most breast cancers, even those associated with considerable family histories, are not associated with germline mutations of known cancer predisposition genes. Accordingly, an alternative mechanism is likely to be responsible for the development of the considerably more cases of cancer than those currently associated with germline mutations of cancer predisposition genes. Fasching et al. proposed that cancer susceptibility may be influenced by relatively common low penetrant genetic polymorphisms, similar to those associated with common adult diseases such as diabetes [4]. It is clear that while the delineation of deleterious mutations in cancer susceptibility genes was a great leap forward in the molecular and clinical delineation of cancer development, we require further investigations into the molecular processes and clinical characteristics of cancer in order to develop more effective screening and diagnostic algorithms and therapeutic interventions that are applicable to more malignancies and considerably more people than are currently impacted by the identification of individuals at high risk for the development of heritable malignancies.

Molecular Biology of Cancer Predisposition Genes

While most breast malignancies are not associated with an identified germinal mutation, a review of the literature confirms the identification and confirmation of five uncommon but highly penetrant genes (*BRCA1*, *BRCA2*, *PTEN*, *TP53*, *CDH1*) and four rare but moderately penetrant genes (*CHEK2*, ataxia teleangectasia mutated [*ATM*], *BRIP1*, *PALB2*), along with an expanding list of low penetrant genes and putative genes that contribute to the risk of developing breast cancer (Table 2.1). Most of the low penetrant genes have been discovered in genome-wide association studies (GWAS), which are extensive studies of DNA obtained from a large cohort of individuals with a particular condition or disease in search for common genes or genomic sequences that may be associated with development of the disease in question or its prognosis [5]. GWAS studies are becoming an increasingly important tool in identifying cancer- and disease-predisposing germinal genes; however, such studies account for the identification of genes and genomic sequences that account for less than 1/3 of inherited cases of

breast cancer [6]. Such studies have also been applied to the detection of somatic gene mutations and genomic sequences in cancer tissue that are associated with disease prognosis and the development of more effective therapeutic interventions.

Highly Penetrant Susceptibility Cancer Genes

As with other cancer susceptibility genes, those that predispose women and men to develop breast cancer are also likely to increase the risk for developing other cancers in affected individuals. Which organs other than the breast that may be at risk for undergoing malignant transformation resulting from a mutation in a cancer predisposition gene depends on a wide variety of molecular and environmental factors including the specific function(s) of the gene products (RNA, proteins), individual lifestyle issues (e.g., obesity, smoking), and the specific molecular pathway(s) by which the gene mutation increases the likelihood of breast cancer, among other epigenetic and acquired factors. The following genes presented here represent those that convey the highest risk for developing breast cancer as a result of inheriting a deleterious mutation in the specific gene. Inheritance of the gene mutations that result in cancer predisposition syndromes occurs in an autosomal dominant fashion.

Mechanism of Breast Cancer Susceptibility: Fanconi Anemia (FA) and BRCA Pathway (FA-BRCA)

Mutations of *BRCA1* and *BRCA2* make up the majority of currently detectable germinal mutations associated with a predisposition to breast cancer, with the general mechanism by which this increased risk for breast and ovarian cancer is conferred is believed to be a disruption in the repair of double-stranded DNA resulting from endogenous or exogenous factors. It may be surprising that many of the genes associated with a predisposition to hereditary breast cancer are associated with Fanconi anemia (FA), a rare (approximately 1/350,000 live births), autosomal recessive condition characterized by congenital abnormalities (e.g., short stature, hyperpigmented skin), bone marrow failure, and a predisposition to leukemia (AML) along with solid tumors including vulvar, esophageal, and head and neck malignancies [7, 8].

Fifteen genes currently comprise the FA family of genes with biallelic mutation of these genes resulting in the FA phenotype, as would be expected in any autosomal recessive Mendelian disorder. Not surprisingly, monoallelic mutation of some of these 15 genes results in a different phenotype, one that is characterized by a predisposition to breast cancer and, in some cases, other malignancies such as OEC [9]. In addition to the association of these 15 genes with FA, they also play important roles in the repair of DNA interstrand crosslinks (ICLs) and have come to be characterized as the FA-BRCA pathway. Indeed, it is this repair function that links these genes to an increased risk of breast and other cancers. Adverse affects on DNA repair and homologous recombination, a process which maintains genomic integrity by repairing endogenous and exogenous DNA double strand breaks, are the mechanisms by which *BRCA1*/*BRCA2* mutations, as well as mutations of other cancer predisposition genes such as *ATM*, *BRIP1*, and *PALB2* (all of which are either directly or indirectly associated with the FA-BRCA pathway), are believed to increase the risk for breast and other malignancies [10].

The FA-BRCA pathway provides a strong pathophysiological basis for the delineation of molecular mechanisms associated with the development of breast cancer and associated malignancies. While not all genes in the FA-BRCA pathway are associated with an increased risk for hereditary breast cancer, the study of the FA-BRCA pathway provides important information concerning potential mechanisms of tumorigenesis. Mutations of the genes associated with the multistep mismatch repair (MMR) pathway are associated with Lynch syndrome, a cancer predisposition syndrome not typically associated with a considerable increased risk

for breast cancer. However, Williams et al. showed that FANCD2, one of the 15 FA genes, interacts with two of the MMR proteins (MSH2 and MLH1) [8]. With an earlier demonstration of the interaction of *BRIP1* (*FANCJ*) with the MMR complex MutLα, these findings suggest an important role for MMR proteins in the activation of the FA-BRCA pathway and the repair of ICLs, all of which are integral to the process that prevents or predisposes an individual to hereditary breast cancer. With regard to somatic changes associated with the FA-BRCA pathway, a study by Rudland et al. found that the absence of the FA protein FANCD2 was strongly associated with malignant breast cancer specimens, with negative staining being strongly correlated with the presence of metastatic-inducing proteins such as S100A4, S100P, osteopontin, and AGR2 [11]. Such information will be critical for the development of novel and effective therapies that will utilize molecular and protein information from FA-BRCA pathway for the development of effective screening algorithms and therapeutic interventions.

BRCA1/BRCA2

BRCA1 and *BRCA2* are two separate and distinct tumor suppressor genes that account for approximately 5% of all breast cancer cases [12] and 85% of all cases of hereditary breast and OEC [13], although these two genes account for a smaller percentage of isolated familial breast cancer cases in the absence of EOC [14]. In addition to breast and OECs, individuals with mutations in *BRCA1/2* also demonstrate an increased risk for other cancers including pancreas, stomach, prostate, and colon [15].

BRCA1 is located on chromosome 17q21, contains 22 coding exons, and spans 80 kb DNA while *BRCA2* is located on chromosome 13q12-13, contains 26 coding exons, and spans 70 kb DNA [16]. These disparate genes are part of the DNA breakage repair pathway and function as tumor-suppressor genes, with mutations resulting in a highly penetrant susceptibility to the development of breast cancer and EOC. Both genes are involved in DNA repair by activating the repair of double strand breaks and initiating homologous recombination [12]. *BRCA1* is a gatekeeper of genomic integrity with multiple roles including homologous repair, checkpoint control, spindle regulation, and transcriptional regulation [17]. *BRCA2* appears to have a more singular role in the DNA repair process through its strict interaction with RAD51 filament formation, which likely serves as a regulatory step in recombination repair [12].

Mutations of *BRCA1* and *BRCA2* associated with the development of breast and associated malignancies are found throughout the coding regions and at splice sites, with most of these mutations being small insertions or deletions that lead to frameshift mutations, nonsense mutations, or splice site alterations. All of these genetic alterations invariably lead to premature protein termination and altered or absent proteins that result in reduced or absent DNA repair and the elimination of suppression of the development of malignancies in breast and ovarian epithelial tissues. In addition to these mutations and some missense mutations, large deletions and rearrangements not detectable by standard PCR have been identified and are now part of the molecular testing provided to those undergoing genetic testing for BRCA mutations. Palma et al. reported that genomic rearrangements, detected by an analysis separate from conventional gene sequencing and aimed at detecting large gene rearrangements not amenable to detection by conventional analyses (e.g., BART analysis), accounted for 18% of *BRCA1/2* mutations in non-Ashkenazi Jewish probands with no such rearrangements being detected in Ashkenazi Jewish probands [18].

The frequency of *BRCA1* and *BRCA2* mutations in the general population is estimated to be 1/300 to 1/800 [19], though a study by Risch et al. in Canada suggests that these frequencies may be considerably higher at 1/140 to 1/300 [20]. However, some populations and communities have a higher frequency of certain *BRCA1/2* mutations than the general population. In the United States, *BRCA1/2* mutations are found in approximately 1 of every 40 individuals of

Eastern European (Ashkenazi) Jewish ancestry. What also distinguishes this community is that three mutations (185delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*) account for approximately 98% of all mutations detected [21]. In Iceland, the 999del5 mutation in *BRCA2* accounts for approximately 7% of all cases of epithelial ovarian cancer occurring in Icelanders [22]. These mutations are known as "founder mutations," so named because in certain populations begun by a small ancestral group isolated by societal behavior or geography, certain genes in the original "founders" of a community or population can become far more common in succeeding generations than would be expected to occur in the general population because of that geographical or social isolation. The identification of founder mutations allows for more facile screening of individuals of those groups associated with these mutations. As such, evaluating individuals of Eastern European Jewish ancestry at increased risk for a *BRCA1* or *BRCA2* mutation based on family history is now accomplished by first determining the presence of one of these three mutations unless analysis of an affected relative shows that the *BRCA1/2* mutation in the family is not one of these three mutations. Evaluating for these three mutations in high-risk members of the Ashkenazi Jewish community is not only easier than gene sequencing but also less costly. However, even in some clinical scenarios in which a single putative *BRCA1/2* mutation is of interest in the risk assessment process, a "single site" analysis would potentially be augmented with a founder mutation analysis or even full gene sequencing if the family history indicates that another mutation may be present, possibly from the other parental lineage. For individuals from populations associated with founder mutations who are at increased risk for *BRCA1/2* mutations based on family history and found not to have one of the founder mutations, gene sequencing and rearrangement analysis can be offered after a "negative" founder mutation result in order to provide a complete and thorough molecular evaluation [16].

While the clinical aspects of *BRCA1/BRCA2* germinal mutations are well described, there are clinical implications of the somatic changes associated with *BRCA1/BRCA2* breast and ovarian cancers that impact prognosis and the use of certain therapeutic interventions that go beyond the considerable increased risk for developing cancer among those women and men who inherited such mutations. These advancements are associated with use of poly(ADP-ribose) polymerase 1 (PARP1) inhibitors, which provide a new approach to therapies for women and men with *BRCA1/BRCA2*-related cancers by impacting the DNA repair mechanism that is adversely affected in *BRCA1/BRCA2*-related malignancies. A more detailed description will be provided in the section "Somatic Genes."

Cowden Syndrome

Cowden syndrome, or multiple hamartoma syndrome, is an autosomal dominant condition characterized by the formation of multiple hamartomas in any organ of the body and an increased risk for certain malignancies. Pathognomonic features of Cowden syndrome include facial trichilemmomas, acralkeratoses, and oral papillomatous papules Individuals with Cowden syndrome are at increased risk for developing a variety of benign and malignant conditions, with over 90% of individuals demonstrating mucocutaneous lesions [23]. Germline mutations in PTEN (*P*hosphatase and *TEN*sin homologue deleted on chromosome *TEN*), located at 10q23.3, have been found in 85% of individuals with Cowden syndrome as well as in people with other rare and unrelated conditions such as Bannayan-Riley-Ruvalcaba syndrome and Proteus syndrome. However, these syndromes do share some common phenotypic features that have led to the characterization of these conditions under the common classification of PHTS (PTEN hamartoma tumor syndrome) [24].

In addition to the hamartomas and dermatological conditions, Cowden syndrome is associated with an increased risk of a variety of malignancies. Lifetime risk for nonmedullary thyroid cancer is approximately 10%, with benign thyroid conditions also markedly increased in

prevalence among affected individuals. Lhermitte-Duclos disease (dysplastic gangliocytoma of the cerebellum) and renal cell carcinoma have also been reported to be components of Cowden syndrome, although the exact frequency of these two conditions among individuals with Cowden syndrome has yet to be well delineated.

An increased risk of breast cancer has been reported among men with Cowden syndrome, with women with Cowden syndrome having an approximate 75% risk for benign breast disease such as fibromas, fibroadenomas, and fibrocystic changes, as well as an over 50% lifetime risk for breast cancer [25]. In addition, women with Cowden syndrome have a 5–10% lifetime risk of endometrial cancer and an increased risk of developing uterine fibroids [26].

Diagnosis of Cowden syndrome is achieved by demonstrating major and minor criteria as put forth in the International Cowden Syndrome Consortium Operational Criteria for the Diagnosis of Cowden Syndrome [27]. Approximately 80% of individuals who meet the diagnostic criteria are found to have mutations in *PTEN*. Because of the considerable and varied increased risk for cancer development in individuals with Cowden syndrome, surveillance should be undertaken to detect malignancies at an earlier and more treatable stage. Such screening may include a baseline thyroid examination and ultrasound assessment at 18-years-old with an annual thyroid exam thereafter. A family history of renal cancer should prompt an annual urinalysis and urine cytology along with a renal ultrasound. Women with Cowden syndrome should begin annual clinical breast exams at age 18 with semiannual exams beginning at age 25. Mammography should be offered at approximately 25–30 years of age, or 10 years earlier than the youngest affected female in the family. In addition, women with Cowden syndrome should be offered an annual breast MRI upon initiation of annual mammographic exams. Men with Cowden syndrome should have annual clinical breast exams starting at age 25–30, with further evaluation based on the finding of palpable lesions. Annual endometrial biopsies should be performed starting at age 35–40, or 10 years earlier than the youngest affected individual in the family. This can also be augmented by an annual endovaginal ultrasound examination in postmenopausal women [23]. Endometrial cancer is amenable to risk reduction, and conservative approaches to prevention (e.g., copper T 380A, levonorgestrel intrauterine system, oral contraceptives) should be discussed with affected women during their reproductive years. Definitive preventative measures for endometrial cancer, such as hysterectomy, should also be discussed, but should be reserved for women who have completed their childbearing as conservative preventative measures such as combination oral contraceptive and intrauterine contraceptive devices are highly effective in preventing endometrial cancer [28].

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare cancer predisposition syndrome estimated to account for approximately 1% of hereditary breast cancer cases. Mutations in *TP53*, a tumor suppressor gene located on 17p13.1, are the primary cause of LFS, which is transmitted in an autosomal dominant fashion. In addition, families with classic LFS phenotypes have also been found to have mutations in the *CHEK2* gene, found on 22q12.2. Unlike *TP53*, *CHEK2* encodes for a serine/threonine protein kinase that phosphorylates p53, leading to cessation of mitosis and allowing DNA repair; *CHEK2* mutations thus promote the development of malignancy by inhibiting DNA repair, similar to the MMR genes associated with Lynch syndrome.

LFS is characterized by early-onset breast cancer, soft-tissue sarcomas, adrenocortical tumors, brain tumors, and leukemias. In some families with LFS, brain tumors, adrenocortical tumors, and sarcomas may present in childhood. Additional tumors reported in LFS families include ovary, pancreas, lung, stomach, melanoma, and Wilms' tumor [23]. Similar to other cancer susceptibility conditions, LFS appears to increase the risk of early development of cancer, with a 50% risk of cancer by age 40 and a 90% risk of cancer by age 60 [29]. Screening and

management of patients at risk for LFS is challenging given the variety of early-onset malignancies associated with this condition. In women, annual clinical breast examinations, including MRI and mammography, should start at age 20, and consideration of oral contraception use is warranted to reduce the risk of ovarian cancer, along with an annual pelvic and abdominal ultrasound examination. However, there are no published guidelines for screening LFS patients; clinicians should strongly consider genetic counseling and testing (*TP53* and *CHEK2*) for individuals and family members with a considerable history of sarcomas and early-onset cancers.

Hereditary Diffuse Gastric Cancer

Gastric cancer is a common cause of cancer worldwide and estimated to become the tenth leading cause of mortality by the year 2030 [30]. As with breast and ovarian cancers, the vast majority of gastric cancers occur sporadically, with only 1–3% of gastric cancers being associated with an inherited cancer predisposition syndrome. Such cases are referred to as hereditary diffuse gastric cancer (HDGC) [31]; with approximately 1/3 of families fulfilling criteria for HDGC will have a mutation in *CDH1* (E-cadherin; 16q22). Mutations in *CDH1* are highly penetrant, resulting in an 80% lifetime risk for developing gastric cancer, similar to the risk of developing breast cancer in women with *BRCA1/2* mutations [31].

Inheriting a mutation in *CDH1* is also associated with a high risk for developing lobular breast cancer in women, with *CDH1* mutations conveying an approximate lifetime risk of 60%. The *CDH1* locus (16q22) is frequently associated with a loss of heterozygosity in breast cancers and is associated with a poor clinical prognosis. Accordingly, inheriting a mutation in *CDH1* ("first step") would markedly increase the likelihood of breast cancer by increasing the likelihood of a loss of heterozygosity if the "second step" occurs. The molecular mechanism by which this occurs appears to be associated with aberrant promoter hypermethylation, an event observed in cancers and in this clinical situation, associated with a loss of expression and function of E-cadherin, a protein related to tissue integrity [32, 33]. Accordingly, the striking increase in breast cancer risk among women who carry a *CDH1* mutation is associated with a loss of heterozygosity that prevents the normal production of E-cadherin which serves to maintain tissue integrity and suppress the development of breast cancer.

Other Susceptibility Genes in Breast Cancer

Similar to the aforementioned genes, other genes predispose to the development of breast cancers and other malignancies by similar mechanisms; specifically, an altered gene that essentially reduces or removes the inhibition of abnormal cell growth and development in breast tissue and other organs. What differentiates these genes from the others previously described is that these genes are not as highly penetrant; that is, inheriting the gene by an individual does not increase the likelihood of breast cancer development to the same degree as that associated with more highly penetrant genes. The likely reason for this is that there are other genes or epigenetic factors, thus far unidentified, which are required to initiate the development of breast and extramammary malignancies. The epidemiological impact of mutations in the *CHEK2* gene (see below) may be an example of a gene that when mutated can present with a novel phenotype associated with other cancer predisposing genes (*TP53*). Perhaps the actual mechanism affected by the gene mutation (i.e., *CHEK2* mutations apparently inhibit DNA repair similar to the MMR genes of Lynch syndrome) determines whether the gene mutation has a singular clinical impact, as with *BRCA1/2* mutations, or rather functions more like a modifier gene that exerts a deleterious effect only in the presence of other genetic, genomic, or epigenetic factors.

RAD51C

Germline mutations in genes involved in homologous recombination have been associated with a

variety of human genetic disorders and malignancies. Homologous recombination maintains genomic integrity by repairing endogenous and exogenous DNA double strand breaks, failure of which can lead to aberrant genetic rearrangements and a variety of chromosomal structural alterations associated with Mendelian syndromes (e.g., Fanconi anemia, Bloom syndrome) and a predisposition to the development of a number of malignancies [34]. With the recognition that *BRCA1* and *BRCA2* are known to regulate homologous recombination, other genes that adversely affect homologous recombination can be associated with an increased likelihood of genetic disorders and cancer development.

An apparently highly penetrant gene for breast and ovarian cancer, *RAD51C*, has recently been identified and is found on chromosome 17q23. RAD51C is involved in two specific complexes and has multiple functions in DNA damage response and the maintenance of genomic stability [35, 36]. Similar to *PRIB1* and *PALB2*, biallelic mutations of *RAD51C* are associated with Fanconi anemia (subtype-O), whereas monoallelic mutations are associated with a predisposition to hereditary breast cancer. RAD51 function appears to be regulated by both BRCA1 and BRCA2, although BRCA2 has regions that directly interact with RAD51 for the mobilization of RAD51 in response to DNA damage.

Initial studies have demonstrated that *RAD51C* may be mutated in 1.5–4.0% of all families predisposed to breast and ovarian cancer [37]. Despite the initial scientific and clinical support for *RAD51C* as a cancer susceptibility gene, others have not found a high prevalence of *RAD51C* mutations in at-risk breast-ovarian cancer cohorts [38] or may not be as highly penetrant as has been demonstrated in some studies [39]. As the actual frequency of *RAD51C* has not yet been precisely delineated as well as the effect of the various identified germline mutations on the risk of breast and ovarian cancers in women and men carrying such mutations, further studies are needed in order to determine whether *RAD51C* should be included in a universal or targeted genetic screening panel for women with family histories of breast and ovarian cancer. Further studies of the mechanism of *RAD51C* mutations in the initiation and development of breast and ovarian cancers, especially its molecular interaction with *BRCA2*, will help determine the precise role of *RAD51C* in risk and prognosis determination for breast and ovarian cancers in low- and high-risk populations.

Other Putative and Less Penetrant Cancer Susceptibility Genes

While there are likely highly penetrant genes that are responsible for the development of breast and other malignancies that have not yet been identified as a result of their very low frequency among women and families with breast and ovarian cancer, the presence of mild to moderately penetrant genes is likely responsible for a considerable percentage of breast and other organic malignancies. The following listing of genes is by no means exhaustive, but does represent some of the more commonly evaluated genes associated with cancer predisposition.

ATM

The ataxia teleangectasia mutated gene, or *ATM*, is located on chromosome 11q22.3 and encodes a checkpoint kinase intrinsic to DNA repair. Biallelic mutations of this gene are associated with the autosomal recessive disease known as ataxia-teleangectasia. Heterozygotes that carry a single mutation do not express the phenotype of ataxia-teleangectasia, but do have a 2–5-fold increase in the risk for breast cancer [12].

CHEK2

The checkpoint kinase-2 gene (*CHEK2*) is located on chromosome 22q12.1 and encodes a checkpoint kinase that is a key mediator in DNA damage response. Mutations of *CHEK2* were initially associated with LFS (see above); however, studies found some *CHEK2* germline variants (e.g., 1000delC, 1157T) were not associated

with LFS or an LFS-like syndrome but only with an increased risk for breast cancer [40]. *CHEK2* seems to be a low penetrant gene; the 1000delC variant incurs a twofold increase in the risk of breast cancer in women and a tenfold increase in men [12].

BRIP1 (BRCA1-Interacting Protein-Terminal Helicase 1)

BRIP1, also known as *FANCJ* or *BACH1*, is found on chromosome 17q22 and along with *PALB2* and *RAD51C*, encodes for proteins that participate in the FA pathway and are involved in the maintenance of DNA stability. Biallelic mutations in these genes are associated with FA phenotypes while monoallelic mutations of these genes are associated with a predisposition to hereditary breast cancer [41].

Cantor et al. first detected *BRIP1* mutations in two individuals with early onset breast cancer and family histories of breast cancer [42]. However, the exact mechanism by which *BRIP1* mutations may increase the risk for breast cancer, or whether or not all *BRIP1* mutations predispose to hereditary breast cancer, remains unclear. Seal et al. found that *BRIP1* mutations conferred a twofold increase in the risk for breast cancer among mutation carriers [43].

Indeed, the relationship between specific *BRIP1* and *BRCA1* mutations and their role in the development and progression of breast cancer remains unclear with further delineation of this genetic "relationship" potentially providing important information regarding tumorigenesis in *BRCA1* and *BRIP1* mutation carriers [10]. Until further clinical and molecular studies are undertaken, it is best to describe *BRIP1* as a low to moderately penetrant gene with an as yet undefined impact on the risk for breast cancer.

PALB2

As opposed to BRIP1, the literature concerning *PALB2* provides for a stronger association between mutations in this gene and a predisposition to hereditary breast cancer. In a small study from Australia, Wong et al. found that mutations in *PALB2* were responsible for 2.8% of hereditary breast cancer cases [41], a frequency comparable (1.1%) to that reported by Rahman et al. in a larger UK study in which there were no *PALB2* mutations detected among the 1,084 subjects in the comparator control group [9].

PALB2, which is derived from the phrase "partner and localizer of BRCA2," is located on 16p12. Because of its interaction with BRCA2, it is not surprising that biallelic mutations of *PALB2* result in a Fanconi anemia phenotype similar to that found in individuals with biallelic *BRCA2* mutations and different from the phenotype associated with biallelic mutations of the other FA genes. It is also not surprising that *PALB2* mutations are not only associated with an increase in the risk for breast cancer in women but also in men. To this end, Rahman et al. found that mutations in this gene conferred an increased risk of almost exclusively breast cancer and that the magnitude of the increase in women was 2.3-fold with an increased, though not specified, risk of breast cancer in men with *PALB2* mutations [9]. In all, *BRCA1*, *BRCA2*, and *TP53* account for approximately 15–20% of the familial risk for breast cancer; *PALB2* mutations are estimated to add an additional 2–3% to the characterization of familial risk for breast cancer. However, the mechanisms by which *PALB2* and the other FA-BRCA pathway gene mutations predispose women and men to breast cancer are complex and still not well delineated. *PALB2*, along with *BRCA2* and *BRIP1*, are all cancer susceptibility genes that are not part of the FA core complex but are the only FA genes that act downstream of FANCD2, a FA protein associated with an increased risk for sporadic breast cancer [44].

KRAS-Variant

While the aforementioned cancer susceptibility genes increase the risk of malignancy as a result of mutations of tumor suppressor genes, an oncogene may result in increased cancer susceptibility through a completely different pathway.

The *KRAS*-variant is a functional variant in a *let-7* microRNA (miRNA) complementary site in the 3′-untranslated region of the *KRAS* oncogene (rs61764370). miRNA are a class of approximately 22-nucleotide noncoding RNAs that are evolutionarily conserved and function by negatively regulating gene expression by binding to partially complementary sites in the 3′-untranslated regions (3′ UTR) of target mRNAs. miRNAs are aberrantly expressed in virtually all cancers, where they function as a novel class of oncogenes or tumor suppressors [45]. Because miRNAs are global gene regulators, even small aberrations in miRNA levels or their target sites can lead to important cellular changes. In support of this concept, emerging evidence shows that SNPs within miRNAs or miRNA binding sites can be functional and act as powerful biomarkers of cancer risk when one allele alters miRNA function or binding characteristics [46]. The variant is relatively uncommon with a minor allele frequency of about 7% in populations of European descent, is uncommon in Africans, and almost absent in East Asians and Native Americans [46, 47].

Ratner et al. reported the *KRAS*-variant to be associated with 28% of unselected cases of OEC and 61% of cases of HBOC syndrome not characterized by *BRCA1/2* mutations [46]. Another study found a significant increased association of the *KRAS*-variant among women with triple-negative (i.e., estrogen and progesterone receptor negative and HER2 negative) [48]. However, similar to *RAD51C* and other putative cancer predisposition genes, not all studies have found a significant or clinically relevant association of the *KRAS*-variant among women with ovarian cancer or a personal or family history of HBOC syndrome [49]. Nonetheless, a recent study by Cerne et al. may shed light on the novel attributes of the *KRAS*-variant and the risk of breast and ovarian cancer [50]. In this study from Slovenia, the authors found results similar to that of Pharoah et al. [49]; specifically, that among 530 sporadic cases of postmenopausal breast cancer and 165 cases of familial breast cancer cases, including 29 cases characterized by *BRCA1/2* mutations, there was no increased incidence of *KRAS*-variant when compared to 270 matched postmenopausal controls. However, they did find that among postmenopausal women using estrogen-based hormone therapy, the presence of the *KRAS*-variant was associated with HER2-positive tumors and tumors that were more poorly differentiated, both characteristics indicative of a poorer prognosis and suggestive of a potentially novel mechanism that may involve an estrogen pathway or receptor in the development and progress of breast cancer among women with *KRAS*-variant.

Somatic Genes

Breast cancer is a heterogeneous disease. Initially, prognosis for breast cancer was based on tumor size alone; however, this approach was not accurate given the novel and unique prognostic and therapeutic aspects attributable to breast malignancies regardless of tumor size. Later on, a histological classification system was developed, dividing breast cancer into groups distinguished by the histological appearance of the tumor. While this represented an improvement over the previous classification system, it too failed to provide an accurate assessment of prognosis. The most widely used classification system of breast cancer currently combines histomorphological information (such as histological subtype and grading) as well as TNM staging information [tumor size (T) together with lymph node (N) and distant metastasis occurrence (M)] [51, 52].

The aforementioned genes presented in this chapter characterize germline or heritable mutations that are found in each and every cell of an individual but increase the risk of malignancy in only specific organs. The development of cancer invariably results in a profound alteration of the genetic material in tumor cells when compared to similar cells that have not undergone malignant transformation. While many of these changes within the cancer genome are random and represent the disruptive effect of the malignant transformative process on the nuclear, cellular, and even mitochondrial functions within the cell, studies have shown that there are certain changes within the affected cellular genome, or somatic

changes, that occur in a nonrandom manner and may be representative of novel processes that are associated with malignant transformation. In this regard, analysis of the somatic nature of breast cancer tissue has been found to be very useful in providing for a more accurate estimation of prognosis and the development therapeutic interventions that target novel molecular pathways in the cancer tissue and provide for the development of more effective treatment modalities.

A more recent approach to better classify breast cancer subgroups is that of gene expression profiling which seeks to characterize the somatic changes within the tumor tissue. This molecular characterization of breast cancer tissue has become commonplace in cancer centers worldwide. Malignancies are now routinely characterized by the positivity or negativity of the molecular expression of estrogen (ER) and progesterone receptors (PR), as well as for the overexpression of the oncogene HER-2. The implication of the positivity or negativity of any of these three somatic findings is covered in greater detail elsewhere in this book. However, one particular result of these three assays deserves discussion in this chapter: triple negative breast cancer (TNBC). TNBC is defined as the absence of estrogen receptors (ER), progesterone receptors (PR), and the absence of HER-2 overexpression and accounts for approximately 15% of all breast cancer tumors, and occurs at a higher frequency among premenopausal women and women of African descent [53]. TNBC is also associated with obesity and high parity, instead of the low parity more commonly associated with other types of breast cancer [53]. Regardless of the demographic distribution of TNBC cancers, these malignancies are associated with a poorer prognosis than non-TNBC breast cancers, with a higher rate of metastatic spread to brain and lungs and early recurrence, with few effective therapeutic options available in cases of recurrence [17, 52, 54].

Sørlie et al. categorized breast cancers into five gene expression subtypes: Luminal A, Luminal B, HER-2 Enriched, Basal-like, and Normal-like, each of which have been associated with unique clinical characteristics [55]. TNBC tumors have a basal-like morphology, expressing myoepithelial-cell-type cytokeratins CK5, CK14, CK17, frequent mutations in *TP53*, cadherin, and epidermal growth factor receptor similar to that found in basal epithelial layer cells [56]. *BRCA1*-associated tumors are also frequently associated with basal-like morphology and commonly display a TNBC phenotype [54]. Somatic mutations in *BRCA1/2* rarely occur in cases of sporadic breast cancer, but a high incidence (20%) of *BRCA1/2* mutations are found in cases of TNBC. While not all basal-type tumors or *BRCA1*-associated tumors are triple negative malignancies, the molecular mechanisms associated with the development of breast cancer in women with *BRCA1* mutations clearly underlie the somatic changes found in sporadic TNBC cancers [17]. Of further interest is that among those cases of TNBC not associated with *BRCA1* mutations, there appears to be an inhibition of BRCA1 expression through other mechanisms including "gene silencing" in which methylation resulting from carcinogenesis effectively blocks expression of *BRCA*-related proteins and renders the cell to be similar to a *BRCA1/2* mutated cell without any of the germline mutations typically associated with the loss of *BRCA* gene expression [57]. These unique tumor characteristics have been described as "BRCAness" and represent the considerable similarities between *BRCA1*-related cancers and TNBC. However, the similarities described herein do not apply to *BRCA2*-related malignancies, which appear to be a far more heterogenous group of cancers than *BRCA1*-related cancers.

It is the spectrum of molecular and cellular similarities of TNBCs to *BRCA1*-related breast cancers that provides the potential for development of more effective therapeutic interventions for these more aggressive tumors. Inactivating mutations in genes involved in the DNA damage response pathways are associated with increased risk for cancer susceptibility and occur both as germline or somatic mutations with increasing evidence of epigenetic gene silencing as an additional cause of loss of protein function. Loss of function by any mechanism of the aforementioned gene products in a tumor cell

precursor clone leads to an accelerated mutation acquisition and underpins the initiation and development of the malignancy [58]. A potentially new strategy that has emerged for treatment of *BRCA1*- and *BRCA2*-related tumors is the use of poly(ADP-ribose) polymerase 1 (PARP1) inhibitors.

The human genome is continuously exposed to exogenous (e.g., exposure to genotoxic compounds) and endogenous (e.g., recombination aberrations) deleterious events that have the potential to destabilize the genome. It is the DNA repair pathways that serve to maintain genome stability and integrity, and as such have been found to be tumor suppressor in nature with mutations in the genes that make up these pathways being associated with cancer predisposition syndromes, as has been previously described with *BRCA1* and *BRCA2*, both of which are involved in DNA double strand break repair. There are currently 16 members of the PARP family of which only PARP1 and PARP2 are involved in DNA repair [59]. PARP is involved in base excision repair, a key pathway in the repair of DNA single strand break. PARP activity in cells is typically low, but is stimulated by DNA strand breaks. PARP1 and PARP2 form homodimers and heterodimers at DNA break sites and serve to recruit other needed proteins for the repair process as well as activating other necessary cellular processes needed for DNA repair. The absence of PARP leads to spontaneous single strand breaks that collapse replication forks into double strand breaks, triggering homologous recombination for repair. However, with the loss of functional BRCA1 or BRCA2, cells will be sensitized to inhibit PARP activity, apparently leading to the persistence of the DNA lesions which are usually repaired by homologous recombination. When both pathways are defective this will result in chromosomal instability, cell cycle arrest, and finally apoptosis. Cell survival assays show that cell lines lacking wildtype BRCA1 or BRCA2 were extremely sensitive to PARP inhibitors compared to heterozygous mutant or the wildtype cells [60]. These results suggest the potential use of PARP inhibitors in the treatment of *BRCA1*- and *BRCA2*-related breast and ovarian cancers with recent and ongoing clinical trials showing promising results and clinical outcomes [61].

Given the similarities of TNBC and *BRCA-1* related cancers, its stands that PARP inhibitors could have a similar beneficial effect on TNBC. Indeed, early studies showed promise with addition of iniparib to a chemotherapeutic regimen provided to women with TNBC. However, a more robust phase 3 trial recently showed no clinical benefit with iniparib in women with TNBC [62]. However, it should be noted that iniparib is different from other PARP inhibitors, so that the findings with iniparib should not necessarily be considered to be representative of all PARP inhibitors.

With our increasing understanding of the complex network that is the DNA damage response, pathways already recognized to be critical to the establishment of the cancer phenotype are thus gaining additional roles as controllers of DNA repair and subjects of clinical study as putative sites for therapeutic agents. The initial success with PARP-1 and PARP-2 in *BRCA1/2*-related cancers has been shown to target tumor deficiencies in DNA repair as well sensitizing to DNA damaging therapeutics such as radiation and chemotherapy. Further identification of relevant somatic changes and the implication of these changes in tumorigenesis will likely be the approach that we use to develop new and more effective diagnostic and therapeutic modalities.

Cancer Risk Assessment

The past two decades have witnessed the identification of several genes that have been associated with hereditable breast and gynecologic cancers, thereby promoting the development of and need for cancer genetic counseling. Similar to conventional genetic counseling for pediatric and prenatal conditions, cancer genetic counseling is geared to identifying individuals with mutated cancer predisposition genes as well as those family and personal histories that impact the overall risk for development of cancer. However, unlike conventional genetic counseling

in which most individuals or fetuses with a particular phenotype are likely to possess a deleterious gene or abnormal chromosome complement, most cases of cancer, even those associated with considerable family histories in individuals of high-risk ethnic and racial groups, are not associated with the inheritance of cancer predisposition genes. Indeed, no more than 10% of most types of cancer are associated with increased heritability [63]. Nonetheless, counseling has become a central part of the risk assessment process, provided not only to identify those individuals with mutations in cancer predisposition genes, but also to provide accurate information and emotional support to those individuals who have not inherited deleterious mutations found in parents or siblings as well as to those individuals who have not inherited specific mutations but still may be at an increased risk for developing cancer.

Cancer risk assessment is a process by which individuals are identified who are at increased risk for a hereditary or familial cancer and are offered a different approach to prevention and screening than that which is offered to individuals in the general population. Such altered interventions for high-risk individuals can range from an earlier initiation of screening, such as the initiation of mammography before the age of 40 in women with a *BRCA1/2* mutation, to the incorporation of screening protocols not offered to non-high risk individuals, such as the use of regular breast MRI examinations in women with *BRCA1/2* mutations. The detection of a deleterious mutation may also prompt a more novel or extreme approach to prevention, such as the consideration of prophylactic mastectomy to reduce the risk for breast cancer in women with *BRCA1/2* mutations. However, not all preventative measures offered to high-risk individuals are necessarily extreme or extirpative in nature; for example, women at increased risk for epithelial ovarian cancer are likely to be encouraged to breastfeed or consider bilateral tubal ligation once childbearing has been completed as a way to reduce the risk for EOC without increasing the risk for breast cancer [14, 64]. What is clear is that the identification of high-risk individuals, whether as a result of inheriting a deleterious mutation or because of an extensive family history of cancer, allows for the offering of risk reducing strategies that have been shown to prolong lives and improve quality-of-life for high-risk individuals [65].

Assessing risk for hereditable cancers involves a variety of tools and tests that a counselor can use depending on the personal and family history of the individual presenting for counseling and risk assessment. Nonetheless, obtaining medical records and pathology reports is critical to provide accurate counseling and risk assessment, as many individuals may not be aware of the actual information concerning their own medical history or that of family members. While genetic testing provides definitive information in individuals with deleterious mutations, most individuals at risk for a heritable cancer will not test positive for a deleterious mutation, which will most likely be the result if an individual is actually not at risk for the malignancy associated with the tested mutation as a result of an inaccurate family history.

Assuming one has provided accurate personal and family histories, counselors can use a variety of approaches to assess risk for developing heritable cancers. Qualitative and quantitative risk assessments are used to determine an individual's risk for possessing a deleterious mutation in a cancer susceptibility gene and for developing cancer. Qualitative risk assessment primarily uses family and personal histories to determine an individual's risk. Such risk analysis also incorporates a variety of other factors including, where applicable and not exclusively, environmental factors including exposure to toxic substances, use of medications, pathology reports, and lifestyle issues (e.g., number of pregnancies, length of time breastfeeding, etc.). An accurate qualitative assessment includes a detailed personal and family history, supported by corroborated details of the individual's personal and family history. Such details will include, but are not limited to, the age of patient and family members, reproductive histories, histories of genetic disorders and major illnesses, causes of death, and lifestyle issues (e.g., obesity, oral contraceptive use) that

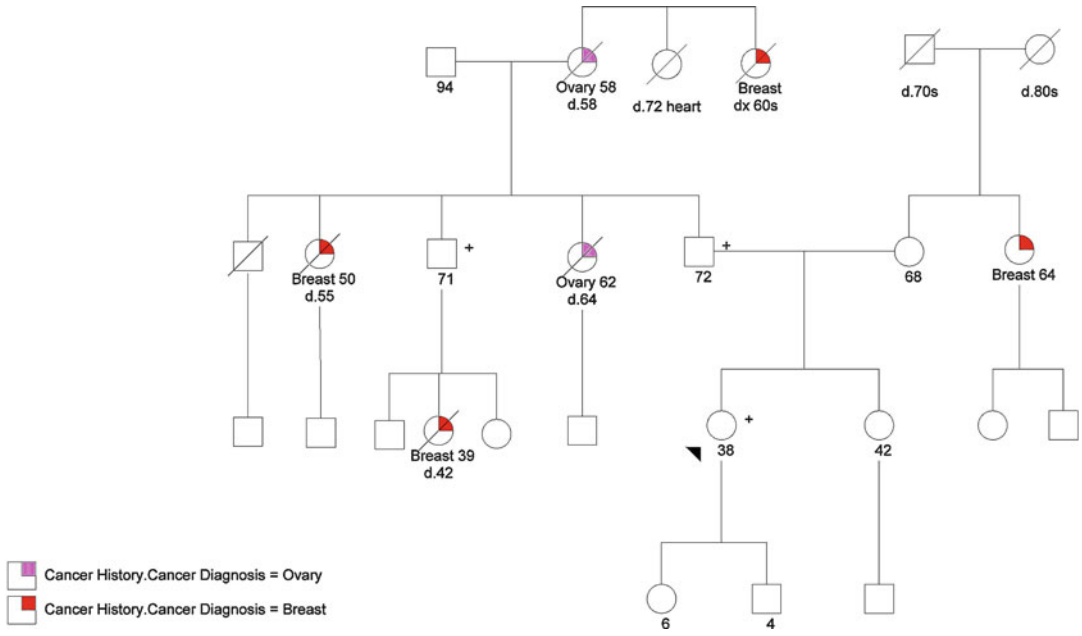


Fig. 2.1 Pedigree of woman with *BRCA2* mutation (6174delT; *arrowhead*). Transmission is through paternal side of family; paternal uncle was the individual initially tested and was found to carry the deleterious mutation. All individuals in the family with the mutation are denoted with a [+] symbol

could impact morbidity and mortality as well as increasing or decreasing risk for cancer development. In addition, for family members with cancer, further detail is needed including age of diagnosis, staging and grading of tumor, and years of survival. Optimally, this information should be obtained from operative and pathology reports as well as medical records. All of this information can be included into a pedigree (Fig. 2.1) that provides an easy-to-access overview of the proband and his/her family. Such information is critical even in the absence of genetic testing outcomes.

Quantitative risk assessment employs risk assessment models to ascertain an individual's risk for developing cancer or for carrying a deleterious mutation in a cancer susceptibility gene. While risk assessment models are widely used to assess risk for certain cancers such as breast cancer, not all malignancies are amenable to risk assessment by a model [66]. As such, counselors usually use qualitative and quantitative approaches to determine an individual's risk for carrying a deleterious cancer susceptibility gene and provide nondirective counseling concerning the decision to undergo genetic testing or to initiate particular screening, diagnostic, or preventative measures.

Counselors also perform a psychosocial assessment of their patients, as patients frequently face emotional stress and psychological upset based on the findings of the counseling and genetic testing. Counselors should obtain information from patients prior to counseling and risk assessment concerning their expectations for the counseling session, the personal impact of the cancer(s) in question, the economic impact of undergoing counseling and testing and the potential clinical outcomes, their relationship with relatives and the ability to obtain information from those relatives as well as the desire to alter their lifestyle and initiate preventative measures in case an increased risk for cancer is determined. Equally important is the sense of the patient

concerning the personal and familial implications of positive or negative genetic testing results. Olaya et al. found that 50% of individuals at increased risk for carrying a *BRCA1/2* mutation chose not to undergo genetic testing, with insurance coverage playing little to no role in the decision to undergo or forego such testing [67]. In this study, the authors sought to develop counseling instruments that would better explain the benefits of testing to unaffected high-risk individuals and to target those with a high school level education as a strategy to improve testing rates. One should consider that those individuals who chose to forego genetic testing in this study did choose to undergo genetic counseling because of an increased risk for developing cancer. This study thus clearly demonstrates that a variety of psychosocial factors play a major role in determining not only decisions to obtain counseling and testing, but also specific choices in this informational process. Accordingly, counselors must be aware of and incorporate these psychosocial issues into their counseling process if they are to provide effective counseling and empower their patients to obtain all the information that they seek and to respect the patient's desire to not obtain certain information.

While testing an individual for an autosomal dominant deleterious mutation that occurs in a parent is a relatively straightforward process, the emotional implications of either a positive or negative results should be addressed prior to testing as the emotional impact of the testing outcomes may not necessarily be easy to predict. A good example of this is found in the movie "In The Family" (J. Rudnick, Producer, Kartemquin Films, 2008), a film that documents the life of a woman who carries a *BRCA1* mutation and details the lives of other individuals at risk for or with heritable breast and ovarian malignancies. In one scene, three daughters are finding out their *BRCA1* mutation status, having decided to get testing because their mother has a deleterious *BRCA1* mutation. Two daughters are found to have inherited the mutation while the other was found to not carry the gene. Surprisingly, it is the unaffected sibling who is most upset at the findings of the genetic testing. Genetic risk assessment and testing may provide qualitative and quantitative analysis to individuals at increased risk for developing cancer; however, the perception of that risk by patients is driven by emotional and psychological factors that are considerably impacted by the individual's experience with cancer. The delineation and acceptance of psychosocial factors such as coping mechanisms, behavior modifications, and emotional reactions to medical and nonmedical events can greatly assist the counselor in providing accurate information that is best used by the patient.

Finally, not everyone who undergoes genetic testing receives a definitive result indicating the presence or absence of a deleterious mutation. Of those undergoing testing for *BRCA1/2* mutations, approximately 5–10% are found to have a variant of uncertain clinical significance (VUS) [68]. VUS are usually missense or potential splice site changes that have not, as yet, been shown to be definitively associated with adverse clinical outcomes. More than 1,500 VUS have been identified and are frequently identified in individuals of minority ethnic population. Most VUS have only been reported in one to two individuals, making further analysis of the clinical impact of VUS challenging [69]. Once a VUS is identified, further analyses such as segregation analysis or study variants in multiple unrelated individuals are applied in an attempt to characterize the VUS as clinically relevant (favor deleterious) or irrelevant (favor polymorphism). However, small sibships and family sizes as well as few individuals with any particular VUS impede the mathematical estimation needed to better characterize the clinical impact of a specific VUS [69].

The finding of a VUS is obviously a difficult clinical outcome that can lead to considerable emotional distress and angst concerning the unknown clinical implication of the genetic test result. In such situations, counselors must use their skills to provide a clear and measured overview of the meaning and implication of the test and provide emotional support for a patient who may be distraught because of the inability to obtain a definitive assessment of her risk for developing cancer [70].

Conclusions

The recognition of the increasing role of genetics and genomics in the development, assessment, and treatment of cancer requires professionals to be able to integrate current scientific and clinical evidence with an ability to obtain critical information from patients so as to provide the necessary support to facilitate the process by which individuals at high risk are identified and offered appropriate screening, diagnostic, and preventative interventions to reduce the risk of cancer and improve overall clinical outcomes. As we learn more about the molecular mechanisms of cancer initiation, development, and metastasis, the assessment of the tumor genome and exome will not only better characterize the prognostic and therapeutic aspects of each malignancy, but allow for the development of targeted and more effective preventative and therapeutic interventions. Given the heterogeneity of breast cancer, it is unlikely that a single laboratory assay, imaging procedure or historical vignette will provide sufficient information to adequately screen the population. Accordingly, cancer risk assessment will remain our most important tool in assessing the risk of each individual woman to develop breast cancer and thus to determine the best approach to screening for that individual person.

For those found to be at high risk for developing breast cancer, counseling is the process by which high-risk women are provided with the information and emotional support needed to facilitate their decision-making process concerning further testing and preventative interventions. Although technological advances will likely alter the cancer genetic counseling process in the future, for now and the foreseeable future this is how patients will best be served in their search for answers concerning their risks for developing cancer, and in the delineation of improved interventions to prevent and treat breast cancer, a widespread cause of morbidity and mortality among all women regardless of race, ethnicity, or socioeconomic status.

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