

Chapter 2

Familial Breast Cancer and Genetic Predisposition in Breast Cancer

Vighnesh Walavalkar, Ashraf Khan and Dina Kandil

Introduction

Breast cancer is the most common non-dermatologic malignancy in women and it is estimated that approximately one in nine women will develop breast cancer over their lifetimes. In the United States, more than 200,000 new cases of breast cancer were reported in 2010 and breast cancer was responsible for approximately 40,000 deaths (15 % of all cancer deaths) in the same calendar year [1]. The etiology behind developing breast cancer is multifactorial, with many risk factors including diet, lifestyle, reproductive factors and hormonal status. However, a very important risk factor is a genetic predisposition and a positive family history. A genetic influence on mammary carcinogenesis has long been implicated and it is estimated that approximately 10 % of breast cancer patients are carriers of gene mutations susceptible for the development of breast cancer [2]. Of these genes, perhaps the most extensively studied are breast cancer 1, early onset (BRCA1), breast cancer 2, early onset (BRCA2) and Tumor protein p53 (TP53) genes. These are associated with a high risk of developing breast cancer in carriers and hence they are referred to as high-penetrance genes. It should be noted, however, that among breast cancer patients with a strong family history; only 40 % have cancers that are thought to be caused by the above-mentioned three genes [3]. This suggests that in the remaining 60 % of cases, apart from sporadic breast cancers, other genetic pathways are likely involved.

V. Walavalkar · A. Khan · D. Kandil (✉)

Department of Pathology, University of Massachusetts Medical School,
UMassMemorial Medical Center, Three Biotech, One Innovation Drive,
Worcester, MA 01605, USA
e-mail: dina.kandil@umassmemorial.org

Ataxia Telangiectasia Mutated Gene (ATM), CHEK2, BRIP1, PALB2, RAD50, PTEN, CDH1, STK11, etc. are examples of genes that are thought to play important roles in breast cancer pathways. In fact, it has now been shown that these moderate penetrance genes along with many low penetrance single nucleotide polymorphisms (SNPs) [4] interact with one another as well as influence pathways involving BRCA1 and BRCA2. Studies have suggested that these genes are involved in complex genetic pathways, some of which are closely related and ultimately are associated with the development of breast cancer. This chapter gives an overview of some of these genes along with the clinicopathologic features of the cancers associated with them. This will be summarized in Table 2.1. We will also briefly touch upon clinical syndromes associated with breast cancer, genetic testing, preventive strategies and certain aspects of management of familial breast cancer in the United States. A summary of these clinical syndromes are presented in Table 2.2.

Genetics of Breast Cancer

High-Penetrance Genes

Breast Cancer 1, Early Onset (BRCA1)

BRCA1 is a large gene located on the long (q) arm of chromosome 17 at position 21 (17q21). BRCA1 is a tumor suppressor gene, which is expressed in response to genomic instability and is influenced by estrogen. Its main function is related to DNA repair including homologous recombination, nucleotide excision repair, and spindle regulation. It also acts as a gatekeeper of cell-cycle progression mainly through checkpoint control [5]. Recent studies have described complex and innovative mechanisms for the localization of BRCA1 to DNA-breaks, including an emerging ubiquitylation-dependent cascade and an association with BRCA2 and genes in the Fanconi anemia pathway [6]. Thus, BRCA1 acts as a regulator of genome stability and its main function is to respond to various types of DNA damage via a complex interaction with BRCA2 and other genes.

Numerous mutations in BRCA1 have been described. The majority of which are point mutations and small insertions/deletions leading to truncated forms of the BRCA1 protein [7]. Large genomic deletions including whole exon deletions have also been detected using more sophisticated methods such as multiplex ligation-dependent probe amplification (MLPA) [8]. Some mutations appear to be more common in certain ethnic groups (founder mutations). The most commonly described is the c.5266dupC mutation (also known as 5382insC or 185delAG), which is seen in up to 2 % of the Ashkenazi Jewish population. However, recent studies have suggested that this mutation may be prevalent in some other ethnic groups where genetic screening of BRCA1 is not routinely performed [9].

Approximately 1 in 1000 individuals in the female population carries a pathogenic mutation in BRCA1. BRCA1 cancers account for approximately 10 %

Table 2.1 A summary of genes associated with the development of breast cancer

Gene	Chromosomal location	Function	Mode of inheritance	Lifetime risk of developing breast cancer	Other major cancer risk	Clinical syndrome association
TP53	17p13.1	Regulates expression of many genes by anti-proliferative mechanisms inducing cell cycle arrest and apoptosis	Autosomal dominant	85–90 %	Soft tissue (sarcomas), bone (osteosarcoma), CNS tumors (choroid plexus tumors), adrenal gland ^a	Li-Fraumeni syndrome, Li-Fraumeni-like syndrome
ATM	11q22-q23	Upstream regulator of proteins involved in double-stranded DNA repair, including BRCA1, TP53, and CHEK2	Autosomal dominant and recessive	~20 % or less	Lymphoproliferative disorders	Ataxia-telangiectasia
CHEK2	22q12.1	Encodes for a threonine/serine kinase that prevents cell proliferation by phosphorylation of proteins involved in checkpoint control	Autosomal dominant and recessive	~20 % or less	Colorectal, prostate	–
BRIP1	17q22.2	Encodes for a DNA helicase that performs BRCA1-dependent DNA repair and checkpoint control	Autosomal dominant and recessive	~20 % or less	Ovary, cervix	Fanconi anemia
PALB2	16p12.2	Acts as a functional bridging molecule linking the DNA repair functions of BRCA1 and BRCA2	Autosomal dominant and recessive	~20 % or less	Pancreas	Fanconi anemia

(continued)

Table 2.1 (continued)

Gene	Chromosomal location	Function	Mode of inheritance	Lifetime risk of developing breast cancer	Other major cancer risk	Clinical syndrome association
CDH1	16q22.1	Encodes for a cell adhesion molecule called E-cadherin	Autosomal dominant	50–60 %	Stomach	Hereditary diffuse gastric cancer syndrome
PTEN	10q23.3	Down-regulates the phosphatidylinositol-3-kinase (PI3K) signal transduction cascade and acts as a tumor suppressor and growth regulator	Autosomal dominant	25–50 %	Thyroid (except medullary carcinoma), endometrium, colon, rectum	Cowden syndrome
STK11	19p13.3	Encodes for serine threonine kinase	Autosomal dominant	~30 %	Colorectal, gastric, pancreatic, ovary	Peutz-Jeghers syndrome
RAD50	5q31	Part of MRN complex along with MRE11 and NBS1, which facilitates double-strand DNA break repair	Unknown	Unknown	Unknown	Ataxia-telangiectasia-like disorder, Nijmegen breakage syndrome (NBS) and NBS-like disorder

^aAdditional risk in TP53 mutations include: gastrointestinal tract cancers (esophageal, gastric and colorectal), genitourinary cancers (renal, Wilms tumor, endometrial, ovarian, prostate), melanoma, thyroid, and lymphoproliferative disorders

Table 2.2 Clinical syndromes associated with breast cancer

	Gene(s) involved	Clinical manifestations	Cancer prevention strategy	Cancer management
Hereditary breast and ovarian cancer syndrome ^a	BRCA1, BRCA2	Early onset of breast and ovarian cancer. Also high risk for early onset prostate, pancreas, skin (melanoma), gastrointestinal tract cancers	<ul style="list-style-type: none">• Genetic counseling and standard genetic testing with full gene sequencing and large genomic alterations analysis• Patient awareness and routine monthly self breast exam from 18 years of age onwards• Biannual clinical breast exam from 25 years of age onward• Annual bilateral mammogram and MRI starting at age 25• Discuss ovarian cancer screening (transvaginal ultrasound and serum CA125 testing every 6 months)• Discuss risks and benefits of chemoprevention• Risk-reducing mastectomies and salpingoophorectomies• Prostate cancer screening in men after age 40	<ul style="list-style-type: none">• Individualized chemotherapeutic regimen with poly(ADP-ribose) polymerase inhibitors ± platinum or other combination therapy• Bilateral mastectomies and salpingoophorectomy
Li-Fraumeni and Li-Fraumeni-like syndrome ^a	TP53	Autosomal dominant cancer predisposition syndrome associated with early onset of breast cancer, choroid plexus carcinomas, adrenocortical carcinoma, soft tissue sarcoma and osteosarcomas. Also high risk for many other visceral malignancies and lymphoproliferative disorders	<ul style="list-style-type: none">• Genetic counseling and testing• Patient awareness and routine monthly self breast exam from 18 years of age onwards• Biannual clinical breast exam from 25 years of age (or as early as 18 years) onward• Annual bilateral mammogram and MRI from 25 years of age (or as early as 18 years) onward• Colonoscopy every 2–5 years starting 25 years of age onward• Annual skin and neurologic exam	<ul style="list-style-type: none">• Surgical management preferred ± individualized chemotherapeutic regimen• Radiation therapy often used as last option as there is a questionable risk for therapy induced secondary malignancy

(continued)

Table 2.2 (continued)

	Gene(s) involved	Clinical manifestations	Cancer prevention strategy	Cancer management
Cowden syndrome ^a	PTEN	Autosomal dominant cancer predisposition syndrome with early onset of breast, thyroid, endometrium, and colorectal cancers. Also characterized by multiple hamartomas, facial trichilemmomas, acral keratoses and oral papillomatous papules	<ul style="list-style-type: none">• Genetic counseling and testing• Patient awareness and monthly breast exams• Discuss annual mammography ± MRI• Discuss increased surveillance for endometrial, thyroid, and colorectal cancers, although there is no consensus screen strategy• Discuss prophylactic mastectomies and hysterectomy	<ul style="list-style-type: none">• Individualized treatment strategy
Peutz-Jeghers syndrome	STK11	Rare autosomal dominant condition characterized by hamartomatous polyps in the GI tract, mucocutaneous pigmentation and increased risk for breast, colorectal, gastric, pancreatic, and ovarian cancer	<ul style="list-style-type: none">• Patient awareness, genetic counseling and testing• No established guidelines on cancer prevention, patients may be followed on an individualized basis	<ul style="list-style-type: none">• Individualized treatment strategy
Ataxia-telangiectasia (AT), AT-like disorder, Nijmegen breakage syndrome (NBS) and NBS-like disorder	ATM, RAD50, NBS1, MRE11 and MRN complex	AT is an autosomal recessive disorder characterized by progressive neurologic impairment, cerebellar ataxia, ocular telangiectasia, variable immunodeficiency, defective organogenesis and an increased risk of developing visceral malignancies and lymphoproliferative disorders	<ul style="list-style-type: none">• Patient awareness, genetic counseling, and testing• No established guidelines on cancer prevention, patients may be followed on an individualized basis	<ul style="list-style-type: none">• Individualized treatment strategy

(continued)

Table 2.2 (continued)

	Gene(s) involved	Clinical manifestations	Cancer prevention strategy	Cancer management
Fanconi anemia	BRIP1, PALB2, BRCA2 and other FANC group of genes	X-linked recessive disorder characterized by bone marrow failure, developmental abnormalities, and increased risk for ovarian, prostate, pancreas, skin gastrointestinal tract, and cervix cancers. Clinical features include skin pigmentation, short stature, upper limb, and eye malformations	<ul style="list-style-type: none">• Patient awareness, genetic counseling and testing• No established guidelines on cancer prevention, patients may be followed on an individualized basis	<ul style="list-style-type: none">• Individualized treatment strategy• Cells with mutated FANC genes show profound sensitivity to DNA interstrand cross-linking agents (cisplatin and mitomycin C)• Radiation and PARP inhibitors may play a role
Hereditary diffuse gastric cancer syndrome	CDH1	Autosomal dominant cancer predisposition syndrome with increased risk for developing breast and gastric cancers	<ul style="list-style-type: none">• Patient awareness, genetic counseling, and testing• No established guidelines on cancer prevention, patients may be followed on an individualized basis	<ul style="list-style-type: none">• Individualized treatment strategy

^aNCCN Guidelines Version 1.2014: breast and/or ovarian cancer genetic assessment

of all familial cancers; [10–12] and a mutation in BRCA1 confers a 70–85 % lifetime risk of developing breast cancer [11–13]. BRCA1 mutations also are associated with a 50 % increased risk of developing ovarian cancer, especially high-grade serous carcinoma [14]. The risk for developing both breast and ovarian cancer in BRCA1 patients is age dependant, and the age at which these cancers present is much younger than that of the general population [11, 14]. Tumors developing in patients with BRCA1 mutations are usually triple-negative (negative for ER, PR, and HER2), high-grade invasive ductal carcinomas. However, approximately 5–25 % of BRCA1 breast carcinomas can be ER positive and a small percentage can show low-grade nuclear histology. Gene expression profiling studies show that BRCA1 associated breast carcinomas tend to cluster with sporadic triple-negative cancers [15–18]. BRCA1 breast cancers share many morphologic features with medullary-like carcinoma and basal-like carcinoma, with pushing margins, a prominent lymphocytic infiltrate, high-grade nuclear atypia and brisk mitosis (see Chap. 11) [15, 16]. Further, immunohistochemical expression of basal cytokeratins such Cytokeratin (CK) 5/6, CK14, CK17 and epidermal growth factor receptor (EGFR) which define BLBC are also identified in many BRCA1 related tumors [19]. BRCA1 carcinomas also tend to show high expression of cell proliferation marker Ki-67 as well as p53 and p16 positivity as compared to sporadic cancers [20].

Breast Cancer 2, Early Onset (BRCA2)

BRCA2 is a large gene located on the long (q) arm of chromosome 13 at position 12.3 (13q12.3). BRCA2 belongs to a family of genes involved in the Fanconi anemia pathway; which also includes partner and localizer of BRCA2 (PALB2) and BRCA1 interacting protein C-terminal helicase 1 (BRIP1) which are discussed later in the chapter.

As in BRCA1, BRCA2 is also involved in DNA repair. Its role however is not as well understood as that of BRCA1. It is now thought that BRCA2 facilitates homologous recombination and double-strand break repair through its interaction with RAD51. The BRCA2 protein forms a stable complex with the RAD51 protein and directs it to sites of DNA damage [21]. BRCA2 also plays a role in the Fanconi anemia pathway of breast cancer through its interaction with other FANC (Fanconi anemia, complementation groups) genes such as BRIP1 and PALB2. A defect in any one of the proteins along the Fanconi anemia pathway prevents cancer cells from repairing interstrand crosslinks, predisposing them to chromosomal instability. It is suggested that BRCA2 protein helps to prevent these interstrand crosslinks by its ability to facilitate homologous recombination [22, 23].

Similar to BRCA1, hundreds of mutations have been described in BRCA2, the majority being point mutations leading to frameshifts and production of an abnormally truncated BRCA2 protein. Founder mutations in BRCA2 have been described in certain ethnic groups such as the c.5946delT (6174delT) mutation in the Ashkenazi Jewish population [3, 11].

Approximately 1 in 800 individuals in the female population carry a pathogenic mutation in BRCA2. Similar to BRCA1, BRCA2 cancers account for approximately

10 % of familial cancers; [10–12] and a mutation in BRCA2 confers a 50–85 % lifetime risk of developing breast cancer [11–13]. There is an approximate 30 % risk for BRCA2 patients to develop ovarian cancer [14]. Males who are carriers of germline mutations in BRCA2 have an increased risk of developing breast cancer, approximately 10 % greater than men in the general population [24]. BRCA2 also confers an increased risk for the development of other cancers. Compared to non-carriers, men with BRCA2 mutations have a three-fold risk of developing prostate cancer and; according to recent studies; these tumors are often of a higher grade (Gleason score >7) and have an increased risk of recurrence [25]. Germline BRCA2 gene mutations are also responsible for approximately 5–20 % of familial pancreatic cancers [26, 27]. Additionally, there is some evidence for an increased risk of gastrointestinal tract cancers, melanomas, bone tumors and even rarely pharyngeal carcinomas in BRCA2 families [28, 29]. BRCA2 associated breast cancers are generally heterogeneous and unlike BRCA1, there is no specific phenotype that has proven to be predictive of BRCA2 status. Clinical features of BRCA1 and BRCA 2 genes and their associated cancers are compared in Table 2.3.

Table 2.3 Comparison of BRCA1 and BRCA2

Gene	BRCA1	BRCA2
Chromosomal location	17q21	13q12.3
Function	DNA repair including homologous recombination, nucleotide excision repair, and spindle regulation	Homologous recombination and double-strand break repair through its interaction with RAD51
Mode of inheritance	Autosomal dominant	Autosomal dominant
Lifetime risk of developing breast cancer	70–85 %	50–85 %
Other major cancer risk	Ovary	Ovary, male breast, prostate, pancreas, skin (melanoma), gastrointestinal tract
Clinical syndrome association	Hereditary breast and ovarian cancer syndrome	Hereditary breast and ovarian cancer syndrome, Fanconi anemia
Typical phenotype	High-grade ductal carcinomas, often with ‘basal phenotype’ (medullary appearance, pushing edges, lymphocytic infiltrate, high nuclear grade, and brisk mitotic activity). Tumors are often triple negative	No specific phenotype, ductal carcinoma NOS
Cancer management	Individualized chemotherapeutic regimen with poly (ADP-ribose) polymerase (PARP) inhibitors ± platinum-based therapy. Bilateral mastectomies and salpingoophorectomy	Individualized chemotherapeutic regimen with poly (ADP-ribose) polymerase (PARP) inhibitors ± platinum-based therapy. Bilateral mastectomies and salpingoophorectomy

Tumor Protein P53 (TP53)

TP53 is a tumor suppressor gene located on the short (p) arm of chromosome 17 at position 13.1 (17p13.1). It is the most commonly altered gene in human cancer; being mutated in more than 50 % of all cancers.

TP53 encodes a transcription factor which responds to numerous cellular mechanisms to regulate expression of target genes, and does so primarily by anti-proliferative mechanisms inducing cell cycle arrest and apoptosis.

Thousands of mutations in TP53 have been described in a variety of human cancers. The majority of which are missense substitutions; and other alterations include frameshift insertions and deletions, nonsense mutations, and silent mutations [30]. An exhaustive and comprehensive list of over 25,000 germline, somatic and experimentally induced mutations in TP53 along with information on the functional impact of mutant p53 proteins is available online at the International Agency for Research on Cancer (IARC) TP53 Database [31].

Rare germline mutations in TP53 cause Li-Fraumeni and Li-Fraumeni-like syndrome, which are autosomal dominant genetic disorders characterized by an increased likelihood of developing a number of different malignancies. Somatic mutations in tumors are very common and occur in more than 50 % of all human cancers. In patients with a TP53 mutation, the lifetime risk for developing any cancer is almost 100 %. This risk is age dependant, with approximately 35–50 % developing by age 30, and 80–90 % by age 60 [32]. The majority of cancers seen in affected families are breast cancer (most common), soft tissue sarcomas, osteosarcomas, central nervous system tumors (especially choroid plexus tumors) and adrenocortical carcinomas. Other cancers seen in patients with TP53 mutations are gastrointestinal malignancies (esophageal, gastric, and colorectal), genitourinary malignancies (bladder, renal, Wilms tumor, endometrial, ovarian, germ cell tumors, prostate), melanoma, thyroid cancers, and lymphoproliferative disorders. Due to its general low prevalence, TP53 mutations account for less than 1 % of familial breast cancers [10]. There is no specific phenotype seen in TP53 mutated breast cancers.

Moderate Penetrance Genes

Ataxia Telangiectasia Mutated Gene (ATM)

The ATM gene is located on the long (q) arm of chromosome 1, between positions 22 and 23 (11q22-q23). A large number of mutations involving the ATM gene have been identified, which are responsible for approximately 2 % of familial breast cancers [33].

The ATM protein acts as an important upstream regulator of proteins involved in double-stranded DNA repair, including BRCA1, TP53, and CHEK2. ATM mediates checkpoint regulation and homologous repair by phosphorylation of

these proteins. Most mutations in this gene lead to truncated forms of the ATM protein which increases the susceptibility for developing genomic instability, especially during exposure to ionizing radiation [34]. Mutations in ATM lead to ataxia-telangiectasia, an autosomal recessive disorder characterized by progressive neurologic impairment, cerebellar ataxia, ocular telangiectasia, variable immunodeficiency, defective organogenesis and an increased risk of developing visceral malignancies, and lymphoproliferative disorders. A link between ATM mutations and breast cancer has been suspected for many years. Recent studies of patients with ataxia-telangiectasia have suggested that female relatives have a two to five fold increase in risk of developing breast cancer [35–37]. There are no known histologic phenotypes of breast cancer that predict an ATM mutation, and the clinical usefulness of testing for ATM mutations in breast cancer patients is uncertain at this time.

CHEK2 (Checkpoint Kinase 2 Gene)

The CHEK2 gene is located on the long (q) arm of chromosome 22 at position 12.1 (22q12.1). CHEK2 is a tumor suppressor gene, and mutations in this gene have been identified in a number of human malignancies including breast, prostate, and colon cancers [38].

CHEK2 encodes a threonine/serine kinase involved in the same pathways as TP53 and BRCA1. In response to DNA damage, this protein prevents cell proliferation by phosphorylation of proteins involved in checkpoint control, thus blocking cellular entry into mitosis [39]. Mutations in CHEK2 were originally investigated as a cause of Li-Fraumeni like syndrome [40], however, many subsequent studies have shown that CHEK2 mutations are directly associated with the development of breast cancer. Although numerous mutations in CHEK2 have been described, perhaps the most important is a founder mutation, 1100delC, discovered in people of North European descent. The 1100delC mutation is present in ~1 % of European families and in up to 5 % of breast cancer families of North European descent. Individuals heterozygous for this mutation have a two to three fold increased risk of developing breast cancer [41, 42]. In women with estrogen receptor-positive breast cancer, 1100delC heterozygosity is also associated with a three to four fold risk of developing a second breast cancer [43]. Many more CHEK2 mutations have been described, but their clinical significance are still unknown.

BRCA1 Interacting Protein C-Terminal Helicase 1 (BRIP1)

The BRIP1 gene is located on the long (q) arm of chromosome 17 at position 22.2 (17q22.2). BRIP1 belongs to the Fanconi anemia pathway of genes, which also includes PALB2 (discussed ahead) and BRCA2.

BRIP1 encodes for a DNA helicase that interacts with BRCA1 and has BRCA1-dependent DNA repair and checkpoint functions. Biallelic mutations in

BRIP1 result in the chromosome instability disorder Fanconi anemia, while heterozygous inactivating mutations have been reported to confer an increased susceptibility to breast cancer in monoallelic carriers [44, 45]. These account for less than 0.5 % of all breast cancers. Patients with BRIP1 mutations have approximately a 20 % lifetime risk of developing breast cancer. Frameshift mutations in BRIP1 have been described which may be associated with an increased risk of developing ovarian cancers in some European populations [46]. Most recently, BRIP1 has been implicated in the genetic susceptibility for developing cervical cancer [47].

Partner and Localizer of BRCA2 Gene (PALB2)

The PALB2 gene is located on the short (p) arm of chromosome 16 at position 12.2 (16p12.2). As discussed above, PALB2 belongs to the FANC group of genes in the Fanconi anemia pathway of breast cancer.

PALB2 encodes for a protein that is involved in double-stranded DNA break repair. Studies have suggested that PALB2 acts as a functional bridging molecule linking the DNA repair functions of BRCA1 and BRCA2; as well as stimulating the recombinant functions of RAD51, and hence is critical in the maintenance of genomic stability [48–50]. PALB2 mutations account for a minority of breast cancer (less than 0.5 %). Similar to BRIP1 mutations, PALB2 mutations confer an approximate 20 % overall lifetime risk of developing breast cancer. Recently, PALB2 germline truncating mutations have also been implicated in the development of pancreatic cancer [51].

Other Genetic Mutations Conferring an Increased Risk of Developing Breast Cancer

Germline mutations of **CDH1 [cadherin 1, type 1, E-cadherin (epithelial) located at 16q22.1]** are associated with Hereditary Diffuse Gastric Cancer, which is an autosomal dominant cancer predisposition syndrome. CDH1 encodes for a cell adhesion molecule called E-cadherin. Patients with germline CDH1 mutations have a very high risk of developing gastric cancer but are also at an increased risk of developing breast cancer including both ductal and lobular carcinomas [52, 53]. Lobular carcinomas that arise in CDH1 mutation carriers as well as sporadic cases show similar phenotypes; i.e., both are characterized by a loss of E-cadherin expression at the cell membrane which can be demonstrated by immunohistochemistry. CDH1 mutations account for a small fraction of familial breast cancers (<2 %); and female carriers have an approximate 50 % lifetime risk of developing breast cancer [54]. Studies have estimated the cumulative risk of developing gastric cancer by age 80 years to be ~65 % for men and ~80 % for women [55].

STK11 (serine/threonine kinase 11, located at 19p13.3) mutations lead to Peutz-Jeghers syndrome, a rare autosomal dominant condition associated with the development of hamartomatous polyps throughout the gastrointestinal tract and mucocutaneous pigmentation. These patients are at increased risk of developing gastrointestinal as well as breast cancers. Women who are STK11 mutation carriers have an approximate 30 % lifetime risk of developing breast cancer. These tumors are often bilateral and sometimes develop at an early age [56].

PTEN (phosphatase and tensin homolog), located at 10q23.3) mutations are associated with the development of the autosomal dominant Cowden syndrome, characterized by multiple hamartomas in different organs, increased risk of cancers, facial trichilemmomas, acral keratoses and oral papillomatous papules. PTEN functions by down-regulating the phosphatidylinositol-3-kinase (PI3K) signal transduction cascade and acts as a tumor suppressor and growth regulator [57]. Many types of mutations in the PTEN gene have been identified in patients with Cowden syndrome. Breast cancer is the most common cancer seen in Cowden syndrome and females who carry mutations in the PTEN gene have a 25–50 % lifetime risk of developing breast cancer [58]. Cowden syndrome is responsible for less than 1 % of familial breast cancers. Other cancers seen in patients with PTEN mutations include thyroid cancers (non-medullary), colon, rectal, and endometrial carcinomas.

RAD50 (RAD50 homolog gene, located at 5q31) is a gene that has been implicated in the development of breast cancer. RAD50 interacts with two other genes, **MRE11 (meiotic recombination 11, located at 11q21)** and **NBS1 [Nijmegen breakage syndrome 1 (also called Nibrin), located at 8q21]**, to form the **MRN complex** which acts as the primary sensor of double-stranded DNA breaks. The MRN complex facilitates double-strand DNA break repair by activating ATM kinase (discussed above). Mutations of MRE11, NBS1, and RAD50 give rise to cancer predisposition syndromes: ataxia-telangiectasia-like disorder, Nijmegen breakage syndrome (NBS) and NBS-like disorder, respectively [59, 60]. A founder mutation in RAD50 (687delT) has been discovered in breast cancer families of Finnish descent, but as this mutation is rare and has not been discovered in non-familial populations, its actual role in breast cancer development is still under scrutiny [61].

The risk of breast cancer in **Lynch Syndrome** (Hereditary Non-Polyposis Colorectal Cancer Syndrome) is uncertain due to conflicting data, and currently the National Comprehensive Cancer Network (NCCN) has no guidelines on risk assessment or screening for breast cancer in patients with Lynch Syndrome [62].

In recent years, well-validated studies have implicated a number of **SNPs** in various genes (e.g.,: **FGFR2**, **TOX3/TNRC9**, **MRPS30**, **MAP3K1**, **NOTCH2**, **RAD51L1** etc.) to be associated with a slightly increased or decreased risk of developing breast cancer [4, 63–70]. SNPs in these genes are considered to be of low penetrance in the development of familial breast cancer and their clinical significance is currently uncertain. These genes are however important in understanding the biology of breast cancer development and may play a key role in discovering potential therapeutic targets in the future.

Clinical testing for moderate penetrance genes is difficult and controversial due to the rarity of these mutations and the lack of clinical data on how to manage patients with positive results. There is obvious clinical concern that patients who test positive for one of these genetic mutations may seek unnecessary treatment; and that those who test negative may be left with a false sense of security which may preclude routine preventive strategies. Many studies suggest that these genes, along with other low-penetrant alleles implicated in the development of breast cancer, act in interrelated pathways and therefore testing for these mutations in patients with a strong family histories may be justified [4, 5, 71]. Genetic surveillance of patients in the correct clinical context, (appropriate ethnic background and those with significant family histories), may help to stratify patients into a high-risk group that may benefit from increased radiographic surveillance, chemoprevention, or risk-reducing surgery. Genetic testing for rare mutations that have not been proven to be pathogenic or of clinical utility should be discouraged as their true significance is still unknown. Clinical features of the genes implicated in breast cancer and their associated cancer predisposition syndromes are summarized in Tables 2.2 and 2.3.

Genetic Testing and Management of Familial Breast Cancer in the United States

Guidelines for Genetic Testing in the United States

Strong family history, early onset of breast cancer, ethnic background, and possibly histologic phenotype, are important criteria determining the need for genetic testing. In the United States, there are two main regulatory groups that have established guidelines for genetic testing in breast cancer patient; the NCCN and the United States Task Force Preventive Services (USTFPS), both of which have similar recommendations [72, 73]. The NCCN recommends referral to a cancer genetics professional if: an individual with breast cancer has a family member with a known mutation in a breast cancer susceptibility gene, an early onset of breast cancer, a triple-negative breast cancer, a male breast cancer, two breast primaries in the same individual; or in an unaffected individual who has a history of a first or second degree relative with cancers that are known to be associated with familial cancer syndromes. If the patient meets criteria for screening, then the NCCN recommends full sequencing of BRCA1 and BRCA2 for point mutations along with further testing for large genomic alterations. If the patient has a known family mutation, then it is appropriate to screen for that mutation in lieu of full sequencing. If a patient is suspected to have Li-Fraumeni or Li-Fraumeni-like syndrome and meets criteria for Classic Li-Fraumeni syndrome [74] or fulfills modified Chompret Criteria for Germline TP53 Mutation Screening, [75] then full sequencing of TP53 along with deletion/duplication analysis is recommended.

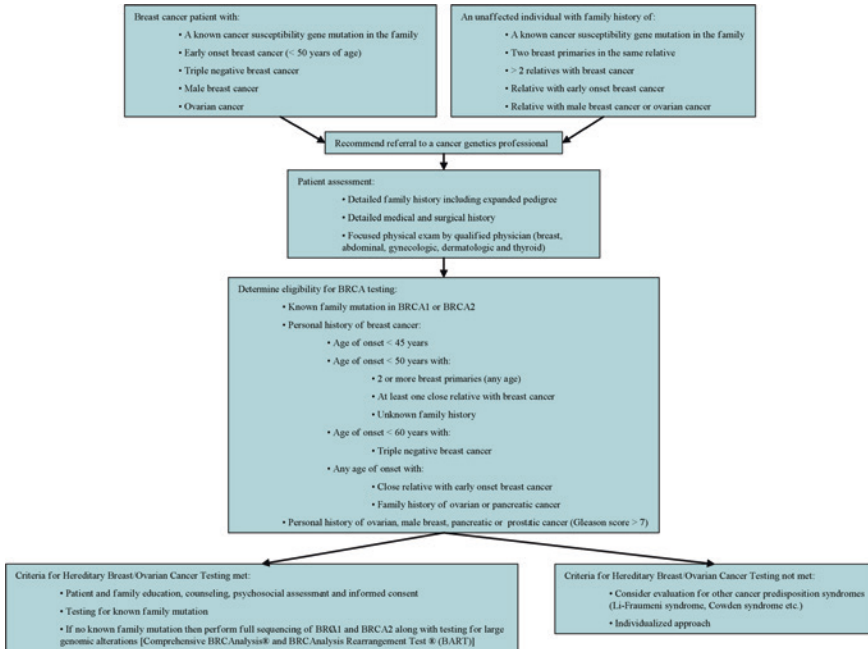


Fig. 2.1 Summary of recommendations regarding genetic testing for BRCA1 and 2

Again, if the patient has a known family mutation [31], then it is appropriate to screen for that mutation first. Patients who meet criteria for Cowden syndrome [76] should have full sequencing of the PTEN gene including deletion/duplication and promoter analysis. Studies have shown that genetic counseling by a cancer genetics professional reduces patient stress, improves the estimation, and likelihood of actual cancer risk as well as reduces unintentional or unnecessary testing [73]. The NCCN does not have specific recommendation for other rare familial cancer predisposition syndromes and recommends an individualized multidisciplinary approach in the management of these patients. Guidelines for genetic testing for BRCA mutations are summarized in Fig. 2.1.

Modality of BRCA Testing

There are several predictive models based on statistical methods, pedigree, and outcome data that are used by genetic counselors to determine the likelihood or risk of mutations in BRCA1 or BRCA2. These models include BRCAPRO, Myriad, the Finnish, the National Cancer Institute, the University of Pennsylvania, and Yale University models. Recent studies have shown these models have equal

efficacy in predicting the likelihood of a BRCA mutation when applied in the proper context [77]. If these models are incorrectly interpreted, varied results and false risk assessment for BRCA mutations may result. Therefore, it is imperative to ensure that qualified healthcare professionals with experience in genetics are included in the multidisciplinary approach to make decisions on whether BRCA testing is needed. As discussed above, the majority of BRCA1 and BRCA2 mutations are point mutations which can be routinely detected by traditional DNA sequencing methodologies (e.g.,: Sanger sequencing). Apart from these point mutations, <1 % of BRCA mutations can be due to large genomic deletions and duplications, especially in BRCA1 [8]. These larger genomic alterations cannot be detected by traditional sequencing methods and require more complex testing modalities (e.g.,: MLPA, and potentially next generation sequencing).

For the last two decades, because of gene-patent issues, BRCA testing in the United States has been done through commercially available tests from one genetic laboratory, namely Myriad Genetics Inc. (Myriad Genetics, Salt Lake City, UT). A blood or oral sample from a patient is sent to their central reference laboratory and results are reported back to the consulting healthcare provider. Myriad now provides the Comprehensive BRCAnalysis® test, which includes full sequence analysis for certain regions of BRCA1 and BRCA2 along with large genomic rearrangement testing for five commonly occurring large genomic rearrangements of the BRCA1 gene. Testing for a few commonly occurring point mutations is also available (e.g.,: 187delAG and 5385insC in BRCA1; 6174delT in BRCA2). In an effort to identify other large genomic alterations not detected by Comprehensive BRCAnalysis®, Myriad has offered a test called the BRCAnalysis Rearrangement Test (BART)® in 2006. BART allows assessment of all coding exons, flanking intron regions and their promoters in BRCA1 and BRCA 2, either by quantitative endpoint polymerase chain reaction (PCR) analysis or microarray comparative genomic hybridization analysis (microarray-CGH) [78, 79]. Therefore, patients who were tested before 2006 by Comprehensive BRCAnalysis® only and had subsequent negative results may benefit from repeat testing along with BART to ensure large genomic alterations are not missed [72].

The Gene-patent controversy surrounding Myriad, who in association with others, located and sequenced BRCA1 and BRCA2 almost 20 years ago, has ended in June 2013 when a landmark decision in gene patenting was reached in response to a case filed by the Association of Molecular Pathology. The Supreme Court upheld that, “A naturally occurring DNA segment is a product of nature and is not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring.” thus possibly ending the monopoly of Myriad Genetics in the field of BRCA testing [80, 81]. Since then, several companies (Gene by Gene, Ltd.; Counsyl, Inc.; Quest Diagnostics; gnostics; GeneDx; Invitae Corporation; Laboratory Corporation of America Holdings; etc.) have announced plans of developing a commercially available BRCA test in the United States and other countries.

Prevention Strategies and Clinical Management of Familial Breast Cancer

Patient awareness and education are of paramount importance in the overall management of familial breast cancer. A multidisciplinary approach in patient care including input from oncologists, surgeons, radiation oncologists, radiologists, pathologists, genetic counselors, and clinical psychologists is recommended. Women in breast cancer families should perform monthly self-breast exams starting from 18 years of age, and have biannual clinical breast exams by a physician starting from 25 years of age onward. Current NCCN guidelines suggest that annual mammograms along with magnetic resonance imaging (MRI) starting from the age of 25 are appropriate screening options in women with known mutations in breast cancer susceptibility genes [72]. Digital mammography (with or without tomosynthesis) and MRI can be performed at the same time, or as some studies have suggested are more accurate and cost-effective in detecting suspicious lesions when performed alternatively at 6 month intervals [82–84]. Since MRI is more sensitive in detecting architectural distortion in breast tissue as compared to conventional mammography, theoretic harms of intensive screening include: increased false-positive imaging studies (resulting in unnecessary biopsies); unnecessary additional imaging (e.g., targeted ultrasound after MRI); unnecessary surgical treatment; patient anxiety and increased financial burden on patients and hospitals. A recent large study showed significantly higher false-positive and lower false-negative rates for MRI compared with mammography [85]. Studies have shown that women who undergo intensive radiographic screening have no increased pain, discomfort, or anxiety when compared to women undergoing routine screening [85]. Studies looking at the clinical utility of extensive radiographic surveillance in familial breast cancer families are conflicting and therefore its role in preventing breast cancer is currently uncertain [73].

Breast cancer risk-reducing medications should also be discussed with patients who are BRCA mutation carriers. Chemoprevention of breast cancer with estrogen receptor antagonists and selective estrogen receptor modulators is not common in the United States owing to their well-known thromboembolic side effects. Tamoxifen and Raloxifene are two drugs that have been widely studied for their potential use in breast cancer prevention and are currently FDA approved for this use (for a period of up to 5 years). Since BRCA-associated cancers are usually hormone receptor-negative, there are no studies looking at the role of these drugs in BRCA mutation carriers specifically. However, there are large studies investigating their role in women with varied risks [73]. The National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (NSABP P-1) [86–88] demonstrated that tamoxifen reduced the risk of estrogen receptor positive breast cancers in the population studied. The benefits of tamoxifen chemoprevention were thought to outweigh the risks associated with its use. The main risks of tamoxifen use as mentioned above, were found to be thromboembolic events such as stroke and deep-vein thrombosis, as well as cataracts. There was also a

moderate increased risk of developing endometrial cancer reported with tamoxifen use but was not statistically significant. The NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 [89] trial compared tamoxifen to raloxifene in the prevention of invasive breast cancer and found that tamoxifen had a greater efficacy than raloxifene in reducing invasive breast cancer, but was associated with a higher risk of complications.

The NCCN also recommends discussing the option of risk-reducing surgery, i.e., prophylactic mastectomy and bilateral salpingo-oophorectomy, in patients who are at a high risk for developing breast cancer including those who are BRCA mutation carriers. Prophylactic mastectomies have been reported to reduce the overall risk of developing breast cancer by approximately 90 %, [90] and a significantly decreased rate of breast cancer specific death. In patients with breast cancers, risk-reducing salpingoophorectomies are associated with also an approximate 90 % reduction in breast cancer specific death and a very high reduction in the risk for gynecologic cancers [91]. In patients without breast cancer, risk-reducing salpingoophorectomies provide a significantly reduced risk of developing a primary breast cancer and this benefit is thought to be more so for BRCA2 mutation carriers as compared to BRCA1 mutation carriers.

The treatment of BRCA associated cancers is complex and difficult due to the relative rarity of these cancers. Knowing that the mechanism of carcinogenesis in cells that have BRCA mutations is related to defective homologous recombination DNA repair, the role of DNA cross-linking agents such as carboplatin, cisplatin, and mitomycin-C have been widely studied. These agents cause DNA damage, which would normally be repaired via an intact BRCA mediated process. Therefore, these agents may potentially cause irreversible fatal DNA damage and chromosomal instability in BRCA mutated cancers cells leading to suppression of tumor growth [92]. Poly(ADP-ribose) polymerase 1 (PARP) inhibitors are also currently being investigated for their potential role in the treatment of BRCA associated breast cancers. PARP is a nuclear protein which localizes to the site of DNA damage and initiates double-stranded DNA break repair by recruiting repair proteins. Therefore, PARP inhibitors such as iniparib may help to prevent DNA repair in BRCA mutated cancer cells leading to cell death. Studies are beginning to reveal that PARP inhibitors may also be potentially useful in other BRCA associated cancers such as ovarian and pancreatic cancers. Clinical trials using PARP inhibitors as a single agent or in combination therapy with other drugs are currently underway for many types of cancers (see Chap. 11).

Key Points

- Approximately 10 % of breast cancer patients are carriers of gene mutations susceptible for the development of breast cancer.
- BRCA1, BRCA2, and TP53 genes are associated with a high risk of developing breast cancer in carriers and hence are referred to as high-penetrance genes.

- ATM, CHEK2, BRIP1, PALB2, RAD50, PTEN, CDH1, STK11, etc. are examples of moderate penetrance genes, while SNPs are considered low penetrance.

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