29 Breast Cancer Risk Assessment and Genetic Testing

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29.1 Introduction

Breast cancer is a heterogeneous disorder and is the most common cancer in women all over the world [1], and its incidence has increased in the last few decades. According to the 2012 statistics [2], almost 1.7 million new breast cancer cases were diagnosed which account for approximately 12% of all new cancer cases. Thirty percent of all new cancer cases in women have been reported due to breast cancer [3]. Of all the causes of death from cancer, this is the fifth most common cause of death. The reasons contributing to its increased incidence are timely detection due to the rapid improvement in the screening strategies all over the world. The factor increasing the prevalence of this cancer is the advancement in the treatment protocols all over the world that have helped in improving the survival rate after the diagnosis. The 5-year survival rate has improved to 90% as compared to 75% in 1975 [4].

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29.2 Risk Factors

The most important risk factors for breast cancer are increasing age and female sex. Other risk factors are mentioned in Table 29.1.

29.2.1 Gender/Sex

Breast cancer is primarily seen in women with 99% of cases diagnosed in women and approximately 1% of breast malignancy in men. The risk factor for breast cancer in men includes obesity, Klinefelter syndrome, heavy alcohol use, family

Table 29.1 Risk factors for breast cancer

Female sex
Advancing age
Pathogenic germline mutations
Family history: breast, ovary, pancreas or prostate cancer (features of HBOC)
Ethnic origins: Ashkenazi Jewish population
Reproductive factors: nulliparity, early age at menarche, delayed menopause
Hormonal factors
Modifiable risk factors: obesity, alcohol, smoking, inadequate physical activity
Previous biopsy results: atypical hyperplasia, LCIS
Radiation exposure between 10 and 30 years

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history, previous estrogenic hormonal therapy, and previous radiation exposure to chest.

29.2.2 Age

This is the strongest factor known to affect the breast cancer risk. The risk increases with increasing age. It is seen most commonly in the postmenopausal age group when the risk doubles with every decade till 80 years of life [5]. After that, there is a decrease in the incidence of breast cancer which could be because of inadequate screening. In men, the risk of breast cancer also increases with increasing age.

29.2.3 Race and Socioeconomic Status

Risk of breast cancer is highest in Caucasian women, followed by Hispanics and African-American population. It is seen lowest in Asian women [5]. It is seen more commonly in women in the higher socioeconomic status which could be due to the change in lifestyle and reproductive factors [6].

29.2.4 Radiation Exposure

Therapeutic chest radiation increases the risk of breast cancer. This risk correlates with the doses received, the age at which there has been exposure to the radiation, and the time elapsed since the exposure [7]. Effect of ionizing radiation is most pronounced at the time of puberty, even at low doses [8].

29.2.5 Family History

Breast cancer has a familial predilection. If there is a family history of breast cancer, especially in the first-degree relative, the risk of developing cancer almost becomes twice the population-based risk [9].

29.2.6 Hereditary Breast Cancers

There is an earlier onset of breast cancer in women (and men) in syndrome-associated familial breast cancers. About 2–5% of all breast cancers are inherited [10]. Approximately, 4–5% of breast cancer is thought to be inherited with autosomal dominant predisposing gene mutation [11]. The most common genes searched after gene linkage analysis are BRCA1 and BRCA2. They are associated with hereditary breast and ovarian cancer (HBOC). In a study by Lalloo et al., almost 20% of breast cancer patients less than or equal to 30 years were caused by well-known genes, BRCA1, BRCA2, and TP53 [12]. The types of pathogenic variants of BRCA gene are described along with their cancer risk in Table 29.2.

BRCA 1 and BRCA 2: BRCA1 (on chromosome 17) and BRCA2 (on chromosome 13) are tumor suppressor genes with multitudinous cell functions, such as transcription, regulation of cell cycle, genomic stability, and DNA repair [24]. Its prevalence in the general population (excluding Ashkenazi Jewish population) is approximately 1:400 to 1:500 [25, 26].

The modes of inheritance for these genes are autosomal dominant. The various other genes associated with inherited breast cancer are enumerated along with their breast cancer risk in Table 29.3.

Table 29.2 Risk of various types of malignancies in individuals of BRCA1/BRCA2 pathogenic variants [13–23]

Cancer	Population risk	BRCA1	BRCA2
Breast	12%	46–87%	38–84%
Second primary breast	2% in 5 years	21.1% in 10 years	10.8% in 10 years
Ovarian	1–2%	39–63%	16.5–27%
Male breast cancer	0.1%	1.2%	8.9%
Prostate	6% by 69 years	8.6% by 65 years	15% by 65 years, 29% by lifetime
Pancreatic	0.5%	1–3%	2–7%
Melanoma	1.6%		Increased risk

Table 29.3 Various cancer-specific syndromes and their breast cancer risk

Cancer-specific syndrome	Gene	Inheritance	Breast cancer risk	Associated tumors
Li–Fraumeni syndrome [27]	TP53	AD	≤79% (premenopausal)	Soft tissue sarcoma, osteosarcoma, brain tumors, adrenocortical cancer, leukemias •Occur in childhood or young adulthood
Cowden syndrome [28]	PTEN	AD	25–50%	Thyroid cancer Renal cell carcinoma Endometrial carcinoma Colorectal cancer Hamartomas Trichilemmomas Papillomatous papules •Present some features by 20 years
Hereditary diffuse gastric cancer [29]	CDH1	AD	39–52%	Diffuse gastric cancer •Present before 40 years
CHEK2 [30]	CHEK	AD	25–39%	Prostate cancer Stomach cancer Sarcoma Kidney cancer
ATM heterozygotes [31]	*ATM*	AD	17–52%	
PALB2 [32]	PALB2	AD	≤58%	Male breast cancer Pancreatic cancer
Peutz–Jeghers syndrome [27]	SKT11	AD	32–54%	Gastrointestinal malignancies Ovary, cervix, uterus, pancreas Sertoli cell testicular and lung cancer Gastrointestinal polyposis
Bloom syndrome	BLM	AR	Increased risk	Epithelial carcinoma Lymphoma, leukemia Severe pre- and postnatal growth deficiency, sparse subcutaneous fat tissue, short stature, sun-sensitive, erythematous skin lesion of the face
Werner syndrome [33]	WRN	AR	Increased risk	Sarcomas Melanoma Thyroid cancer Hematologic malignancies

29.2.7 Reproductive Factors

These are early menarche, late menopause, nulliparity, longer interval between menarche and first pregnancy, and decreased breastfeeding. All these reflect the risks arising from the hormonal changes in estrogen and progesterone in the life of a woman. These factors mainly carry risks for hormone receptor-positive cancer.

29.2.7.1 Early Menarche and Late Menopause

The risk of developing breast cancer decreases by almost 5% with increase in every 1 year of decreased age of menarche [34]. The increased age at the menopause, on the other hand, increases the breast cancer risk.

29.2.7.2 Parity and Breastfeeding

In comparison to nulliparous females, the parous females have almost 17–41% lower risk of developing breast cancer [34]. The risk with each added pregnancy is reduced by approximately 7% [35], and with each year of breastfeeding, the relative risk of developing breast cancer decreases by 4.3%. With the hormonal milieu during pregnancy and breastfeeding, the breast epithelial cells become time and again well differentiated

saving them from the damage that is bound to happen because of DNA damage during the reproductive period [36].

29.2.7.3 Age at the First Birth

Apart from the number of pregnancies, the age at the first pregnancy becomes an important determining factor of breast cancer. This could be attributed to the advantage provided by the early onset of the final terminal duct maturation of the breast [37]. If a woman has the first pregnancy at or after 35 years of age, her risk of having breast cancer is 60% more as compared to women with the first pregnancy at 18 years of age [34].

29.2.8 Hormonal Therapy

29.2.8.1 Oral Contraceptive Pills (OCPs)

The association between the use of OCP and breast cancer is well established with an overall 20% increased risk among women currently using OCP as compared to women who have never used [38]. Mørch et al. [39], in a recently published large prospective study in women younger than 50 years, observed a 20% higher risk of breast cancer among women who were currently using or had recently used hormonal contraceptives, and the risk increased with the duration of contraceptive used. This relative risk increased from 1.09 with less than 1 year of use to 1.38 with more than 10 years of use. Every different formulation of birth control pill as well as the intrauterine device (IUD) that releases the hormone levonorgestrel (a progestin) was associated with a higher risk of breast cancer.

Increased risk with the use of hormonal contraceptive in women at higher risk for developing breast cancer due to strong family history or due to the presence of *BRCA1* or *BRCA2* mutation is controversial till date. A meta-analysis looking at the increased risk of breast cancer in such population suggested that associations between ever use of OCPs and breast cancer among women who are *BRCA1* or *BRCA2* mutation carriers are similar to those reported for the general population [40].

29.2.8.2 Postmenopausal Hormone Therapy

Long-term estrogen replacement (more than 5 years) post menopause has been shown to increase the risk of breast cancer; however, it has not been seen when used for short term to treat menopausal symptoms. On the contrary, combined short-term estrogen-progestin use has shown increased risk [41]. Estrogen antagonists (selective estrogen receptor modulators) on the contrary have shown a protective effect on breast cancer incidence [42].

29.2.9 Benign Breast Disorders

Women with histological diagnosis of atypical ductal/lobular hyperplasia and lobular carcinoma in situ on biopsy specimens from suspected benign breast lesions have a four times higher risk of developing breast cancer [43]. The various histological types of benign breast disorder that are seen associated with breast cancer risks [44] are tabulated with their relative risks in Table 29.4.

The relative risks differ with the menopausal status [45]. It is 5.9 (95% CI, 2.9–13.2) in premenopausal group with atypical hyperplasia, whereas in the postmenopausal age group, it is less 2.3 (95% CI, 0.9–5.9). The type of histology also affects the breast cancer risk, with lobular hyperplasia having a fivefold increase in cancer risk as compared to ductal hyperplasia (2.4-fold increase). Both have a higher risk when compared to women with nonproliferative breast lesions [46].

Table 29.4 The pathological types of benign breast diseases and their breast cancer risks [42]

Breast disease	Breast cancer risk	OR (95% CI)
Benign disease without hyperplasia	1.5-fold	1.5 (1.3–1.9)
Hyperplasia with atypia	2.6-fold	2.6 (1.6–4.1)
Hyperplasia without atypia	1.8-fold	1.8 (1.1–2.5)
Fibroadenoma	1.7-fold	1.7 (1.1–2.5)

29.2.9.1 Density of the Breast

Women with higher breast density have a higher risk of development of breast cancer [47]. Also, there is difficulty in detecting cancer in dense breasts. Among women with more than 75% breast density, the risk of breast cancer is more than four times that of women with much less dense breasts [48]. The density of the breast is measured by the amount of radiodense areas. This represents the epithelial tissue and the stroma [49]. It correlates with epithelial proliferation and stromal fibrosis.

Table 29.5 Relative risk of known breast cancer risk factors

Relative risk <2	Relative risk 2–4	Relative risk >4
Early menarche	One first-degree relative with breast cancer	Mutation *BRCA1* or *BRCA2*
Late menopause		LCIS
Nulliparity	*CHEK2* mutation	Atypical hyperplasia
Hormone replacement therapy	Age >35 years for the first birth	Radiation exposure before 30
Alcohol use	Proliferative breast disease	
Postmenopausal obesity		

29.3 Modifiable Risk Factors

29.3.1 Obesity and Physical Activity

Increasing body mass index (BMI) especially at adult onset has been associated with an increased risk for breast cancer in postmenopausal women, while this association is not seen in premenopausal women [50]. However, an increased BMI becomes a protective factor for young adolescent girls. This could be explained by the early age for menarche with obesity in these girls. Physical activity decreases the breast cancer risk in postmenopausal women; however, it has not been proven for premenopausal women [51].

29.3.2 Alcohol

Intake of alcohol at any age is considered a risk factor for breast cancer. The risk with alcohol is usually dose-dependent, and it increases to around 7.1% for every 10 g of alcohol consumed each day [52]. This alcohol-related risk can be attributed to the effects of alcohol on folate metabolism which is required for the action of the hormones [53].

29.3.3 Smoking

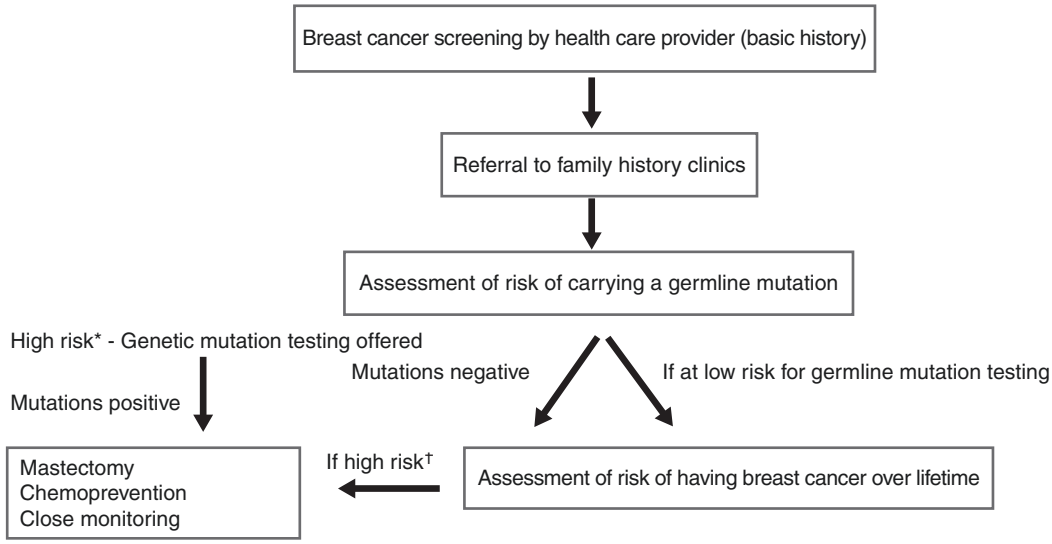
There have been multiple studies on association of smoking with breast cancer; however, the results have been inconclusive. A meta-analysis by Gaudet et al. that included 15 prospective cohort studies till 2013 on association of smoking with breast cancer showed that smoking any time in life whether current or former increases the breast cancer risk [54]. In a recent study by Catsburg et al., it was concluded that women with history of smoking for more than 40 cigarettes in a day for over 40 years are at the highest risk of breast cancer [55].

The relative risk for breast cancer associated with various risk factors is shown in Table 29.5.

29.4 Breast Cancer Risk Assessment

As detailed, the breast cancer risk is based on the combination of the above risk factors (see Table 29.2). In the initial history taking, it is important to include the reproductive factors, hormone use, BMI, radiation exposure, and any specific family history of breast and other cancers, i.e., ovarian, pancreatic, colon, prostate, and other types of germline cancers in first-, second-, and third-degree relative. The biopsy reports should also be reviewed for the type of lesions diagnosed earlier.

With respect to family history, it is also important to take into consideration the age of the affected family member at the time of diagnosis. The incidence of bilateral breast cancer in the affected relative is important. It can be counted as



*High risk is labelled as with greater than 10% risk of carrying the pathological mutation and low risk as 10% or less. †High risk usually defined as a 5-year risk of developing breast cancer more than 1.67%, and low risk usually defined as a 5-year risk of developing breast cancer 1.67% or lower. Reproduced from Amir et al. [57]. By permission of Oxford University Press

Fig. 29.1 Breast cancer screening and mutation testing.

two affected relatives for the calculation of the overall risk. The number of members affected particularly on one side is another aspect of risk calculation. The frequency of unaffected members should also be taken into account as with big families and few affected individuals, the chances of a germline predisposing gene would be less.

The family history of breast cancer is very important to look for the predisposing gene in the family since, apart from BRCA1/BRCA2 dominantly inherited genes, hereditary factors are also important in association with sporadic cancers but at present are difficult to be evaluated, and more genome-wide studies are required in the future [56].

The factors like early age at the diagnosis of cancers and more than one cancer in a single individual in the pedigree give a clue toward the possibility of germline mutations in the family. The risk calculated varies with the age of onset in a family member in relation to the degree of relationship. For instance, if we compare with respect to the age group, the risk is three times if a first-degree relative has been affected at less than 40 years of age in comparison to the age group of greater than 65 years. Again, this becomes two times, if the age group is between 40 and 50 years and is one and half times if the age group is 50–65 years. All these are the risks calculated for the first-degree family members affected [9].

Women who become positive with any of these risk factors should be further assessed by any of the web tools for breast cancer risk assessment like Gail, BRCAPRO, Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm, International Breast Cancer Intervention Studies, or Claus model. Figure 29.1 describes the breast cancer screening and mutation testing algorithm in low- and high-risk women [57].

Types of risk assessment—two groups [57]:

1. The risk of carrying a mutation in a known high-risk gene such as BRCA1 or BRCA2
2. Chances of developing breast cancer over a given life span in the presence or absence of such mutation

Different online tools take into consideration either one of or both these aspects. However, it is very important to assess all known risk

contributors to evaluate the breast cancer risks over a time period.

There are two types of risk assessment models [57]:

1. Empirical model
2. Genetic risk prediction model

The first type (empirical) calculates the probability of detecting BRCA mutations without any explicit assumption of the underlying genetic risks like the type of inheritance, the frequency of mutations, or the penetrance, whereas the genetic risk prediction models make these assumptions regarding the number of susceptible genes involved and the frequency of alleles in the population along with their cancer risks.

29.4.1 Empirical Models

These are Shattuck–Eidens model (Myriad 1) and Couch model (UPenn or Penn). These were the earliest models developed even before the genetic testing evolved. Nowadays, these have been modified further with incorporation of risk factors including individual and family history. The Penn II model [58] now includes more comprehensive personal and family cancer histories. Furthermore, the scoring systems were developed, and cutoffs were defined to estimate the risk of carrying the germline mutation. These were used in the family history assessment tool [59] and the Manchester model [60]. Other examples are the Myriad II, National Cancer Institute, and the Australian LAMBDA models.

29.4.2 Genetic Risk Prediction Models

These can calculate the cancer risks and mutation carrier probability irrespective of family structure and the disease type. These specifically involve the use of family pedigree to extract the exact family relationships, and the cancer risks are computed. But, their calculations are merely based on the estimated assumptions. Also, since the cancer susceptibility genes are still under evaluation, these models can give only approximate risks. The various models under this subgroup are BRCAPRO model, Yale University model, International Breast Cancer Intervention Study (IBIS) model, and the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA).

29.4.3 Limitations of Various Models

The different models consume varying time intervals for the risk assessment depending upon the scoring systems and the computerized calculations.

The most important risk factor is family history apart from the age. Detailed family history is difficult to be reproduced as it is a retrospective data. Also, emotional and ethical issues with respect to adoption come into play. With the nuclear family concept [61], the knowledge about distant family is scarce. Patients are also reluctant to discuss the illness of their family sometimes due to social issues. It is a mistaken assumption to consider only maternal family history in cases of breast and ovarian cancer [62], and it has been reported in the literature [63, 64] that parental medical illness is not precisely reproduced and discussed by the offspring.

An important limitation is the incorporation of history of cancers of the breast and ovary only with respect to first- and second-degree relatives in different models. This can further underestimate the risks calculated. So despite continuous improvement in various types of models, the data collection is limited especially with respect to family history. In some models the family history of other BRCA-associated cancers like pancreatic and prostate is not evaluated [65]. In order to improve these algorithms, these models should consider including the population-specific risks, the prevalence of various genetic mutations, and/or the cancer-specific characteristics. The latest literature

has improved the accuracy of risk calculation by addition of pathological features of the various types of breast and ovarian cancer [66, 67].

The most commonly used models are discussed below.

29.4.3.1 Gail Model

It is the most frequently used method [68] and was developed by Dr. Mitchell Gail in 1989. A screening study (1973–1980) of 300,000 women aged between 35 and 74 years, as a part of the Breast Cancer Detection and Demonstration Project, was conducted to draft this online tool. Subsequently, it has been validated in the Nurses' Health Study [69], and modification was done in 1999 [70].

The modified model (NCI Gail model) differs from the original draft in three aspects. The original model considers both invasive and in situ cancers, whereas the modified version only incorporates the invasive cancers. The age-specific incidence rates have been gathered by the Surveillance, Epidemiology, and End Results database rather than from the Breast Cancer Detection and Demonstration Project in the modified tool. And lastly, the composite incidence rates for African-American patients have been incorporated in the modification.

It comprises of seven key factors: age; age at menarche; age at the first pregnancy; family history of breast cancer in mother, daughter, or sister; previous breast biopsy and their number; biopsy with atypical hyperplasia; and race/ethnicity. A 5-year risk of greater than or equal to 1.67% is defined as "high risk" and is an indication to start with risk-lowering drugs.

It is not appropriate to be used in women less than 35 years of age, women with family history of breast cancer on paternal side, and in second-degree relative, and it also doesn't take into account the history of other cancers related with germline mutations. Another important limitation of this model is that the biopsy results not with atypical hyperplasia are not included while calculating the risk. In such situations the other online models can be of appropriate use. Of the current available evidence, this is the only tool that has been validated in large population-based databases [69, 70]; however, it has limited discriminatory accuracy [71]. It can therefore not be used in higher-risk groups, for example, in the family history clinics [72].

29.4.3.2 Claus Model [11]

This has been developed using data from Cancer and Steroid Hormone Study, conducted from 1980 to 1982 in which the patients enrolled from eight Surveillance, Epidemiology, and End Results regions. It uses just the family history to estimate risk as compared to the abovementioned Gail model where many other factors are also considered. But the advantage over the Gail model is that the family history is taken extensively, and both first- and second-degree relatives are taken into account. Also, their age at the onset of breast cancer is included. Paternal family history is also incorporated in the pedigree. The family history of only breast cancer was initially asked, but recent modification also questions about the ovarian cancer history. The tables were further drafted giving the lifetime risks of first- and second-degree relatives [73].

Limitations of Claus Model

The first drawback is that only the hereditary factors are incorporated, so the individual hormonal and reproductive associated individual risks are not evaluated. The risks calculated are still based on the data collected from North American women in the 1980s. However, the current studies show that the incidence of breast cancer in the same population as well as in some European groups is higher as compared to the incidence rates collected for the model. Another very important limitation is the difference between the

published tables and the computerized versions [74]. The computerized risks are considerably lower than those calculated from the tables. This could be explained by the advantage of computerized adjustments due to the included unaffected family members. A large unaffected population definitely reduces the inherent risk of inheriting a germline mutation. It could also be due to noninclusion of population-based risks in the computerized model or because of the level at which the adjustments are done for the unaffected family members.

An important thing to consider is the huge differences in the risk calculation by the Claus and the NCI Gail model. This was largely seen in women with nulliparity, with multiple benign breast biopsies, or with paternal or first-degree family history [75, 76].

29.4.3.3 BRCAPRO Model

This online model was developed by Parmigiani et al. [77] at the Institute of Statistics and Decision Sciences, Duke University, USA. It is used to predict the probability of mutation in BRCA1 and BRCA2 genes in the individual. This model calculates the risk of breast cancer on the basis of Bayes rules of determining probability of a mutation, once the family history is provided. The mutation frequencies in the general population and in the Ashkenazi Jews give an estimate of the probability of the mutation in the studied subject, before checking the family history [78–80]. It includes the history of first- and second-degree relatives.

The main feature of this model is that family history of both affected and unaffected relatives is used for the risk calculation. It was initially validated only for female population but at present is used for both men and women.

Limitations: Just like the Claus model, only hereditary factors are taken into consideration without incorporating other individual risk factors.

29.4.3.4 Jonker Model [81]

This is a combination of features from the Claus and the BRCAPRO models. Family history of both breast and ovarian cancers is included. It is based upon the hypothesis that hereditary breast cancer can be due to three types of genes—BRCA1, BRCA2, and an unknown gene named as BRCAu. This can explain all non-BRCA germline mutation cancers. This also doesn't include non-hereditary risk factors and thereby can underestimate the overall risks.

29.4.3.5 IBIS Model

This is also known as the Tyrer–Cuzick model [82]. The main advantage of this model is that it includes the family history, reproductive risk factors, and also the history of benign breast disease. Data has been collected from the International Breast Intervention Study. This model includes the presence of multiple genes of differing penetrance.

29.4.3.6 BOADICEA Model

The concept of segregation analysis has been used here, which explains the mutation in BRCA genes along with polygenic inheritance, which defines the combined effect of multiple small genes [83]. Initial design calculated only the risk of carrying a germline mutation [83], but the latest validation also gives the risk of developing breast cancer over lifetime [66].

Even after extensive studies by various probability models, there is no clearly defined risk threshold that can be used in determining the appropriate use of genetic testing (American Society of Clinical Oncology 2003) [84]. However, the use of these models has somehow helped to discriminate which individuals are likely to have pathological variants of BRCA gene.

A comparison of various probability models is shown in Table 29.6.

Table 29.6 Comparison of risk assessment models

Method	Empirical model (myriad prevalence tables) [58–60]	NCI Gail model [70]	BRCAPRO [77]	BOADICEA [83]	IBIS model [82]
Description	Calculates the probability of detecting BRCA mutations without any explicit assumption of the underlying genetic risks Uses only history (both self and family) documented in the forms	Statistical model, absolute risk is calculated for the next 5 years and over lifetime	Statistical model, assumption based on autosomal dominant inheritance of BRCA1/2	Statistical model, assumption based on polygenic risk	Statistical model, assumption based on autosomal dominant inheritance of BRCA1/2
	Tested individual (proband) may be affected or unaffected by breast or ovarian cancer	Tested individual is unaffected by breast cancer	Tested individual may be affected or unaffected by breast or ovarian cancer	Tested individual may be affected or unaffected by breast or ovarian cancer	Tested individual should be unaffected by breast or ovarian cancer
	Age at time of onset of breast cancer is taken as greater or less than 50 years		Exact age at the time of onset of breast cancer is incorporated	Exact age at the time of onset of breast cancer is incorporated	
	Family history significant only if ≥1 relative with breast cancer at age ≥50 years	Only first-degree relatives with breast cancer are considered	Includes all first- and second-degree family members with or without cancer	Includes all first- and second-degree family members with or without cancer	
		Age, reproductive history, and previous history of breast disease also considered			Reproductive history, BMI, and history of benign breast disease also considered
	Includes Ashkenazi Jewish ancestry		Includes Ashkenazi Jewish ancestry	Includes Ashkenazi Jewish ancestry	
Limitations	Simplified and easy to use		Requires computer software and time-consuming data entry	Requires computer software and time-consuming data entry	Requires computer software and time-consuming data entry
	Early age of breast cancer onset	Limited discriminatory accuracy, cannot be used in higher-risk groups	Risk factors other than the family history are not evaluated	Risk factors other than the family history are not evaluated	

29.5 Genetic Mutation Analysis

The various genes associated with breast cancer risk have been tabulated in Table 29.3 along with their mode of inheritance.

According to US Preventive Services Task Force [85] and NICE guidelines [86], women who have the following risk factors are further offered BRCA testing.

- More than one first-degree relative affected with breast cancer and one of them affected ≤50 years of age
- Greater than three first-degree relatives affected irrespective of their age of presentation
- Combination of both ovarian cancer and breast cancer in first- and second-degree relative
- Cancer affecting both breasts in any first-degree relative
- Greater than two first- or second-degree relatives with ovarian cancer irrespective of the age at presentation
- Breast cancer and ovarian cancer at any age in a first- or second-degree relative
- Any male relative affected with breast cancer
- Women with Ashkenazi Jewish heritage with first-degree relative (or two second-degree relatives) with breast/ovarian cancer

It is important to know that even after mutation analysis for BRCA genes in women with significant family history of breast cancer, results can come as negative. These are termed as a "wild type." Of these wild-type cases, around 12% can still have a large genomic deletion or duplication in one of these genes, and approximately 5% are likely to have a mutation in the rest of the breast cancer-predisposing genes [87].

According to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [88], there are some added scenarios in which genetic testing for Hereditary Breast and Ovarian Cancer can be offered.

- Triple-negative breast cancer, especially when diagnosed before age 60 years
- Individuals with pancreatic cancer and/or prostate cancer (Gleason score ≥7) along with breast cancer and/or ovarian cancer (any of these combinations)

29.5.1 Diagnosis

Molecular genetic testing is used to identify heterozygous germline pathogenic variants in BRCA1 or BRCA2 [89].

1. *Targeted analysis*. It is used for founder germline pathogenic variants—BRCA1 c.68_69delAG (BIC: 185delAG), BRCA1 c.5266dupC (BIC: 5382insC), and BRCA2 c.5946delT (BIC: 6174delT).
2. *BRCA1 and BRCA2 gene panel.* Both sequence analyses along with deletion/duplication analysis of BRCA1 and BRCA2 are done.
3. *Multigene panel.* This includes testing for other genes of interest along with BRCA1 and BRCA2. It is very important to understand what kind of testing should be preferred in different individuals.

For example, in individuals with Ashkenazi Jewish descent, the targeted analysis can be performed as there is a high population frequency of the three founder pathogenic variants. Also, coexistence of more than one of these three variants has been reported in few families. On the other hand, if there is a knowledge of BRCA1 or BRCA2 pathogenic variant on one side of the family along with the typical features of HBOC on the other side, sequence and deletion/duplication analysis of *BRCA1* and *BRCA2* can be performed.

The clinicians should also be aware of the various genes available in the multigene panel along with their sensitivities as this may vary from lab to lab and over time. All these options should be weighed according to the affording cost of the individual.

29.5.2 Interpretation of Results

Once an individual has been identified as positive for germline pathogenic variant in *BRCA1* or

BRCA2, proper counselling of available options of surveillance and prevention should be discussed.

The prevention strategies are prophylactic bilateral mastectomy, prophylactic bilateral oophorectomy, and chemoprevention.

29.5.3 Surveillance [88, 89]

In women:

- Self-examination of the breast every month.
- Annual or 6-monthly clinical breast examination starting at 25 years of age.
- Breast MRI yearly to be initiated at 25 years. It can be advised early if the onset of cancer in the family is at age less than 30 years.
- Yearly mammography starting at 30 years of age.
- Transvaginal sonography and serum CA 125 evaluation yearly ≥35 years.

This is important if a woman has not opted for prophylactic mastectomy/oophorectomy.

In men:

- Self-breast examination of the breast every month after training starting at 35 years of age
- Yearly clinical breast examination at age 35.
- Annual screening for prostate cancer starting at age 45.

The prevention and treatment strategies are beyond the scope of this chapter.

29.6 Genetic Counselling for Breast Cancer Risk Assessment [90]

Genetic counselling is the process in which the individuals and families are provided information relevant to the nature, inheritance, and implications of genetic disorders in order to help them take medical and personal decisions.

As described in the beginning, the inheritance of most of the breast cancer predisposing genes is autosomal dominant. This implies that offspring of an individual identified as having a pathogenic gene variant have a 50% chance of inheriting the same and the risk that the sibling of an index case will inherit the same variant is 50%.

Though most of the individuals with pathogenic variants in BRCA1 or BRCA2 have got it from either of the parents, but due to incomplete penetrance, gender of the parent, varying age of onset of cancer, prophylactic surgeries, and early death, all individuals with such pathological variants may not have a parent with the diagnosis of cancer.

Once an individual is tested positive for BRCA1/BRCA2 pathogenic variants, both parents should be offered molecular testing so as to identify the side of the family is at risk. In most of the cases, the pedigree analysis representing the cancers in the family of the proband gives us the information as to which parent is tested first.

Rarely, when neither of the parents come as positive for any of these variants, it can be of a de novo origin; it has been reported as less than 5% only [91–93]. Also, before attributing the negative testing of both parents to de novo origin, alternate paternity or maternity and adoption should be ruled out. Due to the rapid advancement in prenatal and preconception counselling, many young couples may come up to clinicians for genetic counselling regarding breast cancer issues. The best time to offer such counselling is before planning of pregnancy.

It is definitely important to discuss potential risks to the offspring and provide the available reproductive options to the affected couples or who are found to be at risk as part of the same pedigree. The position of the particular individual in that pedigree will help the geneticist to identify the risks and offer further counselling.

Prenatal testing can be discussed, but ethical and legal issues vary with the country of origin as it would lead to the termination of pregnancy rather than the need for early testing of the offspring. Still, these issues should be discussed specially in the current scenario.

29.6.1 Genetic Evaluation of Younger Age Group

According to the available recommendations by the American College of Medical Genetics and the American Society of Human Genetics, it is not advisable to offer genetic testing at less than 18 years of age. Genetic testing for HBOC is not recommended for at-risk individuals younger than age 18 years. However, it can be done if required for medical management in certain cases. Since the management of such inherited cancers begins at 25 years of age, one should ideally wait for an individual to be capable of making independent decisions.

29.6.2 Pros and Cons of Genetic Testing for Inherited Breast Cancers

1. The proband once identified as a carrier for the pathogenic germline variant gets an advantage of early detection by screening at a younger age and can opt for the preventive strategies for cancer reduction.
2. Those that have been identified as negative for these mutations along with their offspring have the benefit of cost reduction over various expensive screening strategies. This also decreases the level of anxiety and stress for the development of breast cancer.
3. The decision of genetic testing by one member in the family and the final results can have implications to the rest of the family [94].

Genetic testing is also performed once diagnosis of cancer is made in the patient for the surveillance post therapy and to calculate the probability of other organs being affected in the lifetime. And here, it is a very mixed psychological feeling when one receives inconclusive results despite significant family history. This could imply that even if they are negative for the known mutant genes, they have no assurance that they are not at any risk for hereditary cancers in self or the offspring. In such cases, further testing the patient and the family becomes important, and there is a possibility of genes other than the known BRCA1 and BRCA2 variants to be involved.

Key Points

- Breast cancer contributes to 30% of all new cancers identified in women.
- Risk assessment is based on the interplay of multiple risk factors.
- Clinicians and health workers should evaluate the risk factors and distinguish between the average-risk and high-risk population by the available and most appropriate models for risk assessment.
- Family history must be taken in detail, and referral can be made to family history clinics.
- If there is high risk based on the family history, genetic mutation testing should be offered.
- An appropriate gene panel should be offered for the genetic testing keeping in mind the affordability.
- Once declared as positive on mutation testing, adequate counselling by the genetic counsellor should be offered.

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