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Review Article

Contemporary Clinical Issues And Recent Inclinations In Hereditary Breast And Ovarian Cancer Syndrome

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ABSTRACT

Breast cancer (BC) is the most common malignancy among women worldwide. A major advance in the understanding of the genetic etiology of BC was the discovery of BRCA1 and BRCA2 (BRCA1/2) genes, which are considered high-penetrance BC genes. In non-carriers of BRCA1/2 mutations, disease susceptibility may be explained of a small number of mutations in BRCA1/2 and a much higher proportion of mutations in ethnicity-specific moderate- and/or low-penetrance genes. However, the carriers of mutations in the major predisposition genes represent only approximately 25% of cases among high-risk BC patients. Numerous candidate predisposing genes for breast and other cancers have recently been identified. The risk of cancer development associated with alterations in these genes is lower, and there is a considerable population variability in different regions worldwide. Mutations in BRCA genes cannot account for all cases of HBOC, indicating that the remaining cases can be attributed to the involvement of constitutive epimutations or other cancer susceptibility genes, which include Fanconi anemia (FA) cluster (FANCD2, FANCA and FANCC), mismatch repair (MMR) cluster (MLH1, MSH2, PMS1, PMS2 and MSH6), DNA repair cluster (ATM, ATR and CHK1/2), and tumor suppressor cluster (TP53, SKT11 and PTEN). Sporadic breast cancers with TP53 mutations or epigenetic silencing (hypermethylation), ER- and PgR-negative status, an earlier age of onset and high tumor grade resemble phenotypically BRCA1 mutated cancers termed 'BRCAness', those with no BRCA mutations but with a dysfunction of the DNA repair system

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INTRODUCTION

BRCA1- and BRCA2-associated hereditary breast and ovarian cancer syndrome (HBOC) is characterized by an increased risk for female and male breast cancer, ovarian cancer (includes fallopian tube and primary peritoneal cancers), and to a lesser extent other cancer such as prostate cancer, pancreatic cancer, and melanoma primarily in individuals with a BRCA2 pathogenic variant[1-2]. The exact cancer risks differ slightly depending on whether HBOC is caused by a BRCA1 or BRCA2 pathogenic variant. The diagnosis of BRCA1 and BRCA2 HBOC is established in a proband by identification of a heterozygous germline pathogenic variant in BRCA1 or BRCA2 on molecular genetic testing. HBOC syndrome is an autosomal dominantly inherited disease characterized by a young age of onset, more than one synchronous or metachronous tumor, and a family history of first- and second-degree relatives with similar cancers.[3] Mainly HBOC syndrome results from germline mutations in breast cancer genes BRCA1 or BRCA2. Other genes or low penetrance alleles might be associated with the HBOC phenotype[4]. There is an increasing understanding that the interrelationship between BRCA gene cluster and Fanconi anemia (FA), mismatch repair (MMR) and DNA repair gene status plays a key role in the pathogenesis of cancer predisposition syndromes. We reviewed the HBOC syndrome and current knowledge of inherited susceptibility genes.[5]

Surveillance

Breast cancer screening in women relies on a combination of monthly breast self-examination, annual or semiannual clinical breast examination, annual mammography, and breast MRI. Annual transvaginal ultrasound and CA-125 concentration beginning at age 35 years may be considered for ovarian cancer screening. However, this screening has not been effective in detecting early-stage ovarian cancer, either in high-risk or average-risk women. For men, breast cancer screening includes breast self-examination education and training and annual clinical breast examination beginning at age 35. Annual prostate cancer screening should begin at age 45. Screening for melanoma should be individualized based on the family history.[6] Screening of asymptomatic individuals for pancreatic cancer is not generally recommended.

Genetic counseling.

Germline pathogenic variants in BRCA1 and BRCA2 are inherited in an autosomal dominant manner. The vast majority of individuals with a BRCA1 or BRCA2 pathogenic variant have inherited it from a parent. However, because of incomplete penetrance, variable age of cancer development, cancer risk reduction resulting from prophylactic surgery, or early death, not all individuals with a BRCA1 or BRCA2 pathogenic variant have a parent affected with cancer.

Offspring of an individual with a BRCA1 or BRCA2 germline pathogenic variant have a 50% chance of inheriting the variant[7]. Prenatal testing is possible for pregnancies at increased risk if the cancer-predisposing variant in the family is known; however, requests for prenatal diagnosis of adult-onset diseases are uncommon and require careful genetic counseling.

At-risk asymptomatic adult relatives.

In general, relatives of an individual who has a *BRCA1* or *BRCA2* germline pathogenic variant should be counselled regarding their risk of having inherited the same variant, their options for molecular genetic testing, their cancer risk, and recommendations for cancer screening and prophylactic surgery.

At-risk adult relatives who have not inherited the cancer-predisposing germline variant identified in the proband are presumed to be at or above the general population risk of developing cancer, depending on personal risk factors. For example, a female at-risk relative who does not have the family-specific BRCA1 or BRCA2 pathogenic variant may still be at an elevated risk for breast cancer based on a breast

biopsy history that revealed atypical ductal hyperplasia.[8]

For family members determined to be at general population risk of developing cancer, appropriate cancer screening such as that recommended by the American Cancer Society or the National Comprehensive Cancer Network (NCCN) for individuals of average risk is recommended. Note: This presumption cannot apply to individuals who did not have an identifiable *BRCA1* or *BRCA2* germline patho genic variant if the affected individual in the family either has not undergone molecular genetic testing of *BRCA1* or *BRCA2* or did not have an identified BRCA1 or BRCA2 pathogenic variant.

Establishing the Diagnosis

The diagnosis of BRCA1- and BRCA2-associated hereditary breast and ovarian cancer (HBOC) is established in a proband by identification of a heterozygous germline pathogenic variant in BRCA1 or BRCA2 on molecular genetic testing (see Table 1).

Table:1 Molecular Genetic Testing Used in BRCA1 and BRCA2 Associated HBOC

Gene	Proportion of *BRCA1/BRCA2* Associated HBOC Attributed to Pathogenic Variants in This Gene	Proportion of Pathogenic Variants 2Detected by Test Method	
		Sequence analysis	Gene-targeted deletion/duplication analysis
BRCA1	66%	>80% 5	~10% 5
BRCA2	34%	>80% 5	~10% 5

Molecular testing is most likely to be informative in an individual with a BRCA1/2-associated cancer (e.g., breast cancer at age <50 years, ovarian cancer) and is often referred to as the "best test candidate." Thus, molecular genetic testing ideally should be performed initially on the "best test candidate" as opposed to a family member who may have an unrelated cancer or who may not have a personal history of cancer[9]. If the "best test candidate" is not available, molecular testing may be performed on another individual, without a cancer history, with the understanding that failure to detect a pathogenic variant does not eliminate the possibility of a BRCA1 or BRCA2 pathogenic variant being present in the family.

Molecular testing approaches can include a BRCA1 and BRCA2 gene panel and use of a multigene panel: BRCA1 and BRCA2 gene panel. Sequence analysis of BRCA1 and BRCA2 is performed concurrently with deletion/duplication analysis.[10]

Targeted analysis can be considered in individuals of Ashkenazi Jewish ancestry by starting with targeted testing for three BRCA1 and BRCA2 pathogenic founder variants: BRCA1 c.68_69delAG (BIC: 185delAG) BRCA1 c.5266dupC (BIC: 5382insC), and BRCA2 c.5946delT (BIC: 6174delT), which together account for up to 99% of pathogenic variants identified in individuals of Ashkenazi Jewish ancestry. If no pathogenic variant is identified by targeted analysis, it may be appropriate to proceed with sequence and deletion/duplication analyses of BRCA1 and BRCA2 or a multigene panel.

In a family known to have a BRCA1 or BRCA2 germline pathogenic variant, at-risk adults may be tested for the family-specific germline pathogenic variant. In most cases, relatives at risk need only be tested for the family-specific germline pathogenic variant, except in the following situations: Individuals of Ashkenazi Jewish heritage should consider testing for all three-founder germline pathogenic variants because of the high population frequency of these founder pathogenic variants as well as reports of the coexistence of more than one founder germline pathogenic variant in some families.[11]

Individuals with a familial BRCA1 or BRACA2 pathogenic variant on one side of the family and characteristics of HBOC on the other side of the family may consider sequence analysis and deletion/duplication analysis of BRCA1 and BRCA2, which would detect the familial germline pathogenic variant if present and also address whether a germline pathogenic variant is present on the other side of the family (Table 2).

The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and over time. Some multigene panels may include genes not associated with the condition discussed in this Gene Review; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition at the most reasonable cost while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician.[12] Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

Table:2 Risk of Malignancy in Individuals with a Germline BRCA1 or BRCA2-Pathogenic Variant.

Cancer Type	General Population Risk	Risk for Malignancy 1	
		BRCA1	*BRCA2*
Breast	12%	46%-87%	38%-84%
Second primary breast	2% within 5 years	21.1% within 10 yrs	10.8% within 10 yrs
		83% by age 70	62% by age 70
Ovarian	1%-2%	39%-63%	16.5%-27%
Male breast	0.10%	1.20%	Up to 8.9%
Prostate	6% through age 69	8.6% by age 65	15% by age 65
			20% lifetime
Pancreatic	0.50%	1%-3%	2%-7%
Melanoma (cutaneous & ocular)	1.60%		Elevated Risk

Table 3.Disorders to Consider in the Differential Diagnosis of BRCA1- and BRCA2-Associated HBOC

Cancer Susceptibility Syndrome / Gene	Gene(s)	MOI	Lifetime Breast Cancer Risk & Other Associated Cancers	Other Distinguishing Features
Li-Fraumeni syndrome	*TP53*	AD	Breast cancer ≤79% 1	Cancers often occur in childhood or young adulthood.
			(often pre-menopausal)	Survivors are at increased risk for multiple primary cancers.
			Soft tissue sarcoma	
			Osteosarcoma	
			Brain tumors	
			Adrenocortical carcinoma	
			Leukemias	

Cowden syndrome	*PTEN*	AD	Breast cancer 25%-50%, may be ≤85% 2	Multiple hamartomas, macrocephaly, trichilemmomas, papillomatous papules
			Thyroid cancer	Affected individuals usually present by late 20s
			Renal cell carcinoma	
			Endometrial carcinoma	
			Colorectal cancer	
Hereditary diffuse gastric cancer	*CDH1*	AD	Breast cancer 39%-52% 3	Majority of cancers occur before age 40 years
			(lobular breast cancer)	
			Diffuse gastric cancer	
CHEK2	*CHEK2*	AD	Breast cancer 25%-39% 4	
			Prostate cancer 5	
			Stomach cancer 5	
			Sarcoma 5	
			Kidney cancer 5	
ATM heterozygotes	*ATM*	AD	Breast cancer 17%-52% 6	
			Other cancers	
PALB2	*PALB2*	AD	Breast cancer ≤58% 7	
			Male breast cancer 8	
			Pancreatic cancer 9	
Peutz-Jeghers syndrome	*STK11* 1	AD	Breast cancer 32%-54%	Gastrointestinal polyposis, mucocutaneous pigmentation, hyperpigmented macules on the fingers
			Gastrointestinal malignancies	
			Ovarian (mostly SCTAT)	
			Cervical cancer (adenoma malignum)	
			Uterine cancer	
			Pancreatic cancer	
			Sertoli cell testicular cancer	
			Lung cancer	
Bloom's syndrome	*BLM*	AR	Breast cancer risk increased 10	Severe pre- & postnatal growth deficiency, sparse subcutaneous fat tissue, short stature, sun-sensitive, erythematous skin lesion of the face
			Epithelial carcinoma	
			Lymphoma	
			Leukemia	
			Other cancers	
Werner syndrome	*WRN*	AR	Breast cancer risk increased 11	Characterized by the appearance, usually in the 20s, of features associated w/normal aging
			Sarcomas	
			Melanoma	
			Thyroid cancer	
			Hematologic malignancies	
Lynch syndrome	*MLH1*	AD	Ovarian cancer 12	It is currently unknown whether Lynch syndrome is associated w/increased risk for breast cancer.
	MSH2		Nonpolyposis colorectal cancer	
	MSH6		Endometrial cancer	
	PMS2		Other cancers	
	EPCAM			

Hormone replacement therapy (HRT).

General population studies suggest that long-term estrogen replacement therapy in postmenopausal women may increase breast cancer risk, but that short-term use to treat menopausal symptoms does not. However, even relatively short-term combined estrogen plus progestin use was shown to increase the incidence of breast cancers in a randomized, placebo control trial of HRT.

Three observational studies on the impact of HRT on breast cancer risk in *BRCA 1/2* heterozygotes have been published evaluated breast cancer risk associated with HRT after bilateral prophylactic oophorectomy in a cohort of 462 women with a *BRCA1* or *BRCA2* germline pathogenic variant and found that HRT of any type after bilateral prophylactic oophorectomy did not significantly alter the reduction in breast cancer risk associated with the surgery[13]. The postoperative follow up was 3.6 years. It was concluded that short-term HRT does not substantially increase the risk for breast cancer in women with a *BRCA1* or *BRCA2* germline pathogenic variant. A subsequent study of expanded data from this cohort included 1299 women with a mean follow-up of 5.4 years. There was no increase in breast cancer risk, and a significant decrease in breast cancer risk was found among *BRCA1*heterozygotes. In another matched case-control study of 472 postmenopausal women with a *BRCA1* pathogenic variant, the use of HRT was associated with a reduction in breast cancer risk. Finally, a case-control study of 432 matched pairs with a mean follow up of 4.3 years also found a decrease in the risk for breast cancer in *BRCA1* heterozygotes . Taken together, these studies support the short-term use of HRT among *BRCA1/2* heterozygotes who have undergone surgical menopause[14].

Poly(ADP-Ribose) Polymerase (PARP)

Poly(ADP-ribose) polymerase (PARP) is an enzyme involved in the recovery of cells from DNA damage and the regulation of the molecular events such as BER, a key pathway in the repair of DNA single-strand breaks (SSB). The inhibition of PARP leads to the induction of synthetic lethality and cell death by targeting HR-mediated DNA repair deficient tumors.[15] Tumors that lack functional BRCA1, BRCA2, or TP53 are hypersensitive to inhibition of PARP. Several proteins involved in HR on sensitivity to PARP inhibition may include BRCA cluster (RAD51C, RAD51D and RAD54), FA cluster (FANCD2, FANCA and FANCC), Cdk cluster, nucleotide excision repair (NER) cluster (RPA1 and NBN), DNA repair checkpoint cluster (ATR, ATM, CHK1 and CHK2) and TP53 cluster. Therefore, therapeutic approach using PARP inhibitors may be feasible for BRCA dysregulated tumors and appear promising in a variety of cancer types, including breast and ovarian cancers. The presence of these germline mutations and epimutations types might be a hallmark of BRCAness and a potential biomarker for sensitivity to PARP inhibition[16].

CONCLUSION:

A significant percentage of high-risk families with hereditary breast cancer are negative for mutations in BRCA1/2 genes. The genetic etiology of BC in these subjects may be attributable to variations in other moderate- or low-penetrance susceptibility alleles and/or variations in specific chromosomal regions. HBOC syndrome is the inherited tendency to develop breast, ovarian and other cancers and believed to be transmitted by mutations in the specific genes. Clinical characteristics, including the type of tumor and age at occurrence as well as family history, predict the prevalence of BRCA germline mutations. A number of clinicians usually take into account the age of the youngest breast cancer patient and the number of ovarian cancer cases in a family as well as pathological diagnosis. Up to 80% of the HBOC cases are due to mutations in BRCA1 or BRCA2 genes. Both BRCA1 and BRCA2 mutations are scattered throughout the whole coding exons. The genetic or epigenetic loss-of-function mutations of genes that are

known to be involved in the repair of DNA damage might lead to increased risk of developing a broad spectrum of breast and ovarian cancers.

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