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# *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer

Synonym: *BRCA1*- and *BRCA2*-Associated HBOC

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## Summary

### Clinical characteristics

*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) is characterized by an increased risk for female and male breast cancer, ovarian cancer (including fallopian tube and primary peritoneal cancers), and to a lesser extent other cancers such as prostate cancer, pancreatic cancer, and melanoma primarily in individuals with a *BRCA2* pathogenic variant. The risk of developing an associated cancer varies depending on whether HBOC is caused by a *BRCA1* or *BRCA2* pathogenic variant.

### Diagnosis/testing

The diagnosis of *BRCA1*- and *BRCA2*-associated HBOC is established in a proband by identification of a heterozygous germline pathogenic variant in *BRCA1* or *BRCA2* on molecular genetic testing.

### Management

*Treatment of manifestations:* Treatment of breast cancer per oncologist with consideration of bilateral mastectomy as a primary surgical treatment of breast cancer because of elevated rate of ipsilateral and contralateral breast cancer; PARP inhibitors may be considered in *BRCA1*- and *BRCA2*-related tumors. Melanoma treatment per dermatologist and oncologist.

*Prevention of primary manifestations:* Prophylactic bilateral mastectomy, prophylactic oophorectomy, and chemoprevention (e.g., tamoxifen) have been used for breast cancer prevention, but have not been assessed by randomized trials in high-risk women. Prophylactic salpingectomy followed by delayed oophorectomy or salpingo-oophorectomy for ovarian cancer prevention.

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*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 serum 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 serum prostate-specific antigen and digital rectal exam screening should begin at age 45. Screening for melanoma should be individualized based on the family history. Screening of asymptomatic individuals for pancreatic cancer is not generally recommended.

*Evaluation of relatives at risk:* Once a cancer-predisposing *BRCA1* or *BRCA2* germline pathogenic variant has been identified in a family, testing of at-risk relatives can identify those family members who also have the familial pathogenic variant and thus need increased surveillance and specific treatments when a cancer is identified.

## Genetic counseling

*BRCA1*- and *BRCA2*-associated HBOC is inherited in an autosomal dominant manner. The vast majority of individuals with a *BRCA1* or *BRCA2* pathogenic variant inherited it from a parent. However, because the penetrance of breast, ovarian, and other cancers associated with pathogenic variants in *BRCA1* and *BRCA2* is less than 100%, not all individuals with a *BRCA1* or *BRCA2* pathogenic variant have a parent affected with cancer. The offspring of an individual with a *BRCA1* or *BRCA2* germline pathogenic variant have a 50% chance of inheriting the pathogenic variant. Once a cancer-predisposing *BRCA1* or *BRCA2* germline variant has been identified in a family, prenatal and preimplantation genetic testing are possible.

# Diagnosis

## Suggestive Findings

*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) **should be suspected** in individuals with a personal or family history (first-, second-, or third-degree relative in either lineage) of any of the following:

- Breast cancer diagnosed at or before age 50 years
- Ovarian cancer
- Multiple (i.e., >1) primary breast cancers in either one or both breasts
- Male breast cancer
- Triple-negative (estrogen receptor-negative, progesterone receptor-negative, and human epidermal growth factor receptor 2-negative) breast cancer
- The combination of pancreatic cancer and/or prostate cancer (metastatic or Gleason score ≥7) with breast cancer and/or ovarian cancer
- Breast cancer diagnosed at any age in an individual of Ashkenazi Jewish ancestry
- Two or more relatives with breast cancer, one diagnosed at or before age 50 years
- Three or more relatives with breast cancer at any age
- A family member with a known *BRCA1* or *BRCA2* pathogenic variant

Note: (1) "Breast cancer" includes both invasive cancer and ductal carcinoma in situ. (2) "Ovarian cancer" includes epithelial ovarian cancer, fallopian tube cancer, and primary peritoneal cancer.

### Probability Models for *BRCA1* and *BRCA2* Pathogenic Variants

Several models have been developed to estimate the likelihood that an individual or family has a germline pathogenic variant in *BRCA1* or *BRCA2* [Parmigiani et al 1998, Frank et al 2002, Antoniou et al 2004, Evans et al

2004, Tyrer et al 2004]. Even among experienced providers, the use of probability models has been shown to increase the ability to identify which individuals are more likely to have a *BRCA1* or *BRCA2* pathogenic variant [Euhus et al 2002, de la Hoya et al 2003]. For more information about probability models for *BRCA1* and *BRCA2* pathogenic variants, click here.

## Establishing the Diagnosis

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

Note: (1) Molecular testing is most likely to be informative in an individual with a *BRCA1*- or *BRCA2*-associated cancer (e.g., breast cancer at age <50 years, ovarian cancer; this individual 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. (2) 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. (3) Per ACMG/AMP variant interpretation guidelines, the terms "pathogenic variant" and "likely pathogenic variant" are synonymous in a clinical setting, meaning that both are considered diagnostic and can be used for clinical decision making [Richards et al 2015]. Reference to "pathogenic variants" in this section is understood to include likely pathogenic variants. (4) Identification of a heterozygous *BRCA1* or *BRCA2* variant of uncertain significance does not establish or rule out the diagnosis.

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.

  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 analysis and deletion/duplication analysis of *BRCA1* and *BRCA2* or a multigene panel.

  Note: In a family known to have a *BRCA1* or *BRCA2* germline pathogenic variant, relatives at risk may only need testing for the family-specific germline pathogenic variant, except in the following situations:

  - Individuals of Ashkenazi Jewish descent should consider testing for all three founder pathogenic variants because of the high population frequency of these variants as well as reports of the coexistence of more than one founder variant in some families. They may also consider multigene panel testing, depending on their personal and family history.
  - Individuals with a familial *BRCA1* or *BRACA2* pathogenic variant on one side of the family and characteristics of HBOC or another inherited cancer syndrome on either the same side or the other side of the family may consider sequence analysis and deletion/duplication analysis of *BRCA1* and *BRCA2* or a multigene panel, which would detect the familial germline pathogenic variant (if present) and also address whether another germline pathogenic variant may be present.

- A **multigene panel** that includes *BRCA1*, *BRCA2*, and other genes of interest (see Differential Diagnosis) may also be considered. Note: (1) The genes included in the panel and the diagnostic sensitivity of the testing used for each gene vary by laboratory and are likely to change over time. (2) Some multigene

panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) 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. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

**Table 1.** Molecular Genetic Testing Used in *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer

| Gene [1] | Proportion of *BRCA1*- & *BRCA2*-Associated HBOC Attributed to Pathogenic Variants in Gene | Proportion of Pathogenic Variants [2] Detected by Method | |
|---|---|---|---|
| | | Sequence analysis [3] | Gene-targeted deletion/duplication analysis [4] |
| *BRCA1* | 66% | 87%-89% [5] | 11%-13% [5] |
| *BRCA2* | 34% | 97%-98% [5] | 2%-3% [5] |

HBOC = hereditary breast and ovarian cancer

*1.* See Table A. Genes and Databases for chromosome locus and protein.

*2.* See Molecular Genetics for information on variants detected in this gene.

*3.* Sequence analysis detects variants that are benign, likely benign, of uncertain significance, likely pathogenic, or pathogenic. Variants may include small intragenic deletions/insertions and missense, nonsense, and splice site variants; typically, exon or whole-gene deletions/duplications are not detected. For issues to consider in interpretation of sequence analysis results, click here.

*4.* Gene-targeted deletion/duplication analysis detects intragenic deletions or duplications. Methods used may include a range of techniques such as quantitative PCR, long-range PCR, multiplex ligation-dependent probe amplification (MLPA), and a gene-targeted microarray designed to detect single-exon deletions or duplications.

*5.* Truty et al [2019], LaDuca et al [2020]

# Clinical Characteristics

## Clinical Description

*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) is characterized by an increased risk for male and female breast cancer, ovarian cancer (including fallopian tube and primary peritoneal cancers), and to a lesser extent other cancers such as prostate, pancreatic, and melanoma, primarily in individuals with a *BRCA2* pathogenic variant. Estimates of malignancy risk vary considerably depending on the context in which they were derived. Table 2 is a summary of the risk for malignancy in an individual with a germline *BRCA1* or *BRCA2* pathogenic variant.

**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% | 55%-72% by age 70 | 45%-69% |
| **Contralateral breast cancer** | 2% w/in 5 yrs | 20%-30% w/in 10 yrs; 40%-50% w/in 20 yrs | |
| **Ovarian** | 1%-2% | 39%-44% | 11%-17% |
| **Male breast** | 0.1% | 1%-2% | 6%-8% |
| **Prostate** | 6% by age 69 yrs | 21% by age 75 yrs;<br>29% by age 85 yrs | 27% by age 75 yrs;<br>60% by age 85 yrs |
| **Pancreatic** | 0.5% | 1%-3% | 3%-5% by age 70 yrs |

*Table 2. continued from previous page.*

| Cancer Type | General Population Risk | Risk for Malignancy [1] | |
|---|---|---|---|
| | | *BRCA1* | *BRCA2* |
| **Melanoma (cutaneous & ocular)** | 1.6% | | Elevated risk |

*1.* Verhoog et al [2000], Brose et al [2002], Satagopan et al [2002], Thompson & Easton [2002], Antoniou et al [2003], Hearle et al [2003], Kirova et al [2005], Robson et al [2005], van Asperen et al [2005], Chen et al [2006], Risch et al [2006], Chen & Parmigiani [2007], Tai et al [2007], Graeser et al [2009], Evans et al [2010], van der Kolk et al [2010], Kote-Jarai et al [2011], Iqbal et al [2012], Leongamornlert et al [2012], Moran et al [2012], Mavaddat et al [2013], Molina-Montes et al [2014], Basu et al [2015], van den Broek et al [2015], van den Broek et al [2016], Kuchenbaecker et al [2017], Nyberg et al [2020], Reiner et al [2020]

**Breast cancer.** Compared to sporadic tumors, *BRCA1*-related tumors show an excess of medullary histopathology, are of higher histologic grade, are more likely to be estrogen receptor negative and progesterone receptor negative, and are less likely to demonstrate human epidermal growth factor receptor 2 overexpression; thus, *BRCA1*-related tumors fall within the category of "triple-negative" breast cancer [Rakha et al 2008, Lee et al 2011, Mavaddat et al 2012] and overlap with basal-like breast cancers.

The histologic characteristics of *BRCA2*-related tumors have been inconsistent but appear to be more heterogeneous and are less well characterized than *BRCA1*-related tumors. They are generally estrogen and progesterone receptor positive; however, a large international series of 2,392 individuals with *BRCA2* germline pathogenic variants found that 16% had triple-negative tumors [Mavaddat et al 2012].

The evidence that a germline *BRCA1* or *BRCA2* pathogenic variant is associated with poor survival in individuals with breast cancer has been inconsistent [Verhoog et al 2000, Bordeleau et al 2010, van den Broek et al 2015, Zhong et al 2015].

**Contralateral breast cancer (CBC).** Several studies have reported higher rates of CBC [Metcalfe et al 2011a, Vichapat et al 2012, van den Broek et al 2015] in women treated conservatively. Predictors of CBC include age at first breast cancer, family history of early-onset breast cancer, and the affected *BRCA* gene [Graeser et al 2009, Malone et al 2010, Metcalfe et al 2011a, van den Broek et al 2015]. The risk of CBC is greatest among women whose initial breast cancer occurs at a young age. Most studies show an excess of CBC among individuals with a *BRCA1* pathogenic variant when compared to individuals with a *BRCA2* pathogenic variant. The risk for CBC was decreased among women who had undergone prophylactic oophorectomy [Metcalfe et al 2011a]; there was no clear association between the use of radiation therapy and an increased risk of CBC in individuals with a *BRCA1* or *BRCA2* pathogenic variant.

**Ipsilateral breast cancer.** Two case-control studies reported significantly higher rates of ipsilateral breast cancer in individuals with a germline *BRCA1* or *BRCA2* pathogenic variant compared with sporadic controls [Haffty et al 2002, Seynaeve et al 2004], however, other studies have not found an increased risk for ipsilateral breast cancer in those with a germline *BRCA1* or *BRCA2* pathogenic variant when compared with women who had sporadic breast cancer [Robson et al 2004, Graeser et al 2009] and also demonstrated a significant ipsilateral breast cancer risk reduction in individuals receiving radiation therapy compared with those who did not receive radiation therapy [Metcalfe et al 2011b].

**Ovarian cancer (including fallopian tube and primary peritoneal cancers).** An excess of serous adenocarcinomas as opposed to mucinous or borderline tumors have been observed in women with germline *BRCA1* or *BRCA2* pathogenic variants [Liu et al 2012, McLaughlin et al 2013]. Serous adenocarcinomas are generally of higher grade and exhibit prominent intraepithelial lymphocytes, marked nuclear atypia, and abundant mitoses [Fujiwara et al 2012]. Most high-grade serous cancers arise from the fallopian tubes rather than the ovaries [Daly et al 2015].

Studies on ovarian cancer survival in women with a germline *BRCA1* or *BRCA2* pathogenic variant have yielded conflicting results. A pooled analysis of 26 observational studies found a more favorable survival rate among

individuals with a *BRCA1* or *BRCA2* pathogenic variant compared to individuals without a *BRCA1* or *BRCA2* pathogenic variant. These results persisted when controlling for stage, grade, histology, and age at diagnosis [Bolton et al 2012]. A large population-based case-control study found a higher response to platinum-based therapy, longer progression-free survival, and improved overall survival among individuals with a germline *BRCA1* or *BRCA2* pathogenic variant [Alsop et al 2012]. Similarly, individuals with platinum-sensitive epithelial ovarian tumors were more likely to have a germline *BRCA1* or *BRCA2* pathogenic variant than individuals with platinum-resistant tumors [Dann et al 2012]. In a large series of unselected individuals with ovarian cancer, the short-term survival of individuals with ovarian cancer with a germline *BRCA1* or *BRCA2* pathogenic variant was better than that of individuals without an identified *BRCA1* or *BRCA2* pathogenic variant; however, the survival advantage was short lived and did not lead to a long-term survival benefit [McLaughlin et al 2013].

**Male breast cancer.** The majority of *BRCA1*- and *BRCA2*-associated male breast cancers, particularly those associated with *BRCA2* pathogenic variants, are high grade, hormone receptor positive, and associated with lymph node metastases. Despite having high-grade histology, males with *BRCA1*- or *BRCA2*-associated breast cancer have demonstrated a favorable five-year survival [Ibrahim et al 2018].

**Prostate cancer.** *BRCA2*-related prostate cancer is more likely to be associated with features of aggressive disease, including a higher tumor stage and/or higher grade at diagnosis, higher Gleason scores [Gallagher et al 2010], and a higher prostate-specific antigen level at diagnosis [Ibrahim et al 2018].

**Pancreatic cancer.** *BRCA1* and *BRCA2* are among the most common of the known genetic causes of hereditary pancreatic ductal adenocarcinoma (PDAC) with a mean age at diagnosis of approximately 60.3 years (range 33-83 years) [Golan et al 2014]. There is accumulating evidence of increased sensitivity to platinum-based therapy and poly ADP ribose polymerase (PARP) inhibitors in *BRCA1*- and *BRCA2*-associated PDAC [Kowalewski et al 2018].

**Melanoma.** The risk for melanomas of both the skin and eyes is elevated in individuals with a *BRCA2* pathogenic variant [Breast Cancer Linkage Consortium 1999, Hearle et al 2003, van Asperen et al 2005, Gumaste et al 2015]. An analysis of 490 families with *BRCA1* or *BRCA2* pathogenic variants showed an increased risk for uveal melanoma in individuals with germline *BRCA2* pathogenic variants [Moran et al 2012].

**Other cancers.** Individuals with *BRCA1* and *BRCA2* pathogenic variants may be at a higher risk for additional malignancies. Furthermore, women with a *BRCA1* pathogenic variant may have an elevated risk for serous uterine cancer, but the data are not conclusive [de Jonge et al 2017].

No associated benign tumors or physical abnormalities are presently known to be associated with pathogenic variants in *BRCA1* or *BRCA2*.

## Phenotype Correlations by Gene

Ovarian cancer and primary papillary serous carcinoma of the peritoneum are considerably more common and tend to develop at an earlier age in women with a germline *BRCA1* pathogenic variant as compared to women with a germline *BRCA2* pathogenic variant [Casey et al 2005, Yates et al 2011]. Those with *BRCA2* pathogenic variants tend to be at greater risk for male breast cancer [Evans et al 2010], prostate cancer [Mersch et al 2015], pancreatic cancer [Dagan 2008], and melanoma.

## Genotype-Phenotype Correlations

*BRCA1* and *BRCA2* genotype-phenotype correlations have been identified. Such correlations are not currently used in individual risk assessment and management but may be in the future with appropriate validation.

### *BRCA1*

**p.Arg1699Gln** is a reduced-penetrance allele that was determined to be associated with intermediate risk; the estimated cumulative risk to age 70 for breast or ovarian cancer was 24% [Spurdle et al 2012].

### *BRCA2*

**p.Lys3326Ter** was associated with a lower risk of developing breast and ovarian cancer than other *BRCA2* pathogenic variants in a large case-control study based on an international consortium of individuals; for breast cancer the odds ratio ($OR_W$) was 1.28; for invasive ovarian cancer the $OR_W$ was 1.26 [Meeks et al 2015].

An ovarian cancer cluster region (OCCR) in or near exon 11 in both *BRCA1* and *BRCA2* has been identified [Rebbeck et al 2015]. Pathogenic variants within the OCCR have been associated with a higher ratio of ovarian to breast cancer than is seen in families with a pathogenic variant elsewhere in the genes.

In *BRCA1* and *BRCA2*, multiple breast cancer cluster regions have been observed and are associated with relatively elevated breast cancer risk and lower ovarian cancer risk [Rebbeck et al 2015].

## Penetrance

The penetrance of breast, ovarian, and other cancers associated with pathogenic variants in *BRCA1* and *BRCA2* is less than 100% (see Table 2).

## Prevalence

*BRCA1* and *BRCA2* pathogenic variants are the most common cause of HBOC. The prevalence of *BRCA1* and *BRCA2* pathogenic variants in the general population is estimated at 1:400 to 1:500 [Anglian Breast Cancer Study Group 2000, Whittemore et al 2004].

The prevalence of *BRCA1*- and *BRCA2*-associated HBOC is increased in certain populations due to founder variants (see Table 6):

- Individuals of Ashkenazi Jewish descent: prevalence of 1:40 [Struewing et al 1997, Gabai-Kapara et al 2014]
- Inuit from Ammassalik (Greenland): prevalence of 1:10 to 1:100 [Hansen et al 2009, Harboe et al 2009, Hansen et al 2010]

Founder variants in *BRCA1* and/or *BRCA2* have also been reported in several additional populations, including individuals of African, Amish, and Icelandic ancestry (see Table 6).

# Genetically Related (Allelic) Disorders

**Fanconi anemia.** Biallelic germline pathogenic variants in *BRCA1* and *BRCA2* are associated with Fanconi anemia. Fanconi anemia is characterized by developmental abnormalities in major organ systems, early-onset bone marrow failure with pancytopenia (often in the first decade of life), and a high predisposition to cancer, including early-onset acute leukemia and solid tumors with a cumulative probability of any malignancy of 97% by age six years.

# Differential Diagnosis

**Syndromic breast cancer.** Individuals with the following cancer susceptibility syndromes have an elevated breast cancer risk. In many instances, *BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) can be distinguished from these other disorders based on the constellation of tumors present in the family; however, in some cases, molecular genetic testing may be necessary to differentiate the disorders.

**Table 3.** Genes Associated with Cancer Susceptibility to Consider in the Differential Diagnosis of *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer

| Gene(s) | Cancer Susceptibility Syndrome | MOI | Associated Cancers / Distinctive Features |
|---|---|---|---|
| **High-penetrance (high-risk) genes for breast cancer** | | | |
| ATM | *ATM* c.7271T>G | AD | Specific *ATM* pathogenic variants (e.g., c.7271T>G) are assoc w/ high-penetrance breast cancer; heterozygosity for most other *ATM* pathogenic variants is assoc w/moderate-penetrance breast cancer (see below). [1] |
| *CDH1* | Hereditary diffuse gastric cancer | AD | Breast cancer (lobular), diffuse gastric cancer. Majority of cancers occur before age 40 yrs. |
| *PALB2* | *PALB2*-related cancer susceptibility (OMIM 620442) | AD | Breast cancer ≤58%, [2] ovarian cancer, male breast cancer, pancreatic cancer |
| *PTEN* | *PTEN* hamartoma tumor syndrome | AD | Breast cancer. Other cancers: thyroid, renal cell carcinoma, endometrial, colorectal. Multiple hamartomas, macrocephaly, trichilemmomas, papillomatous papules. Affected persons usually present by late 20s. |
| *STK11* | Peutz-Jeghers syndrome | AD | Breast cancer. Other cancers: GI, ovarian (mostly SCTAT), cervical (adenoma malignum), pancreatic, Sertoli cell testicular. GI polyposis, mucocutaneous pigmentation, hyperpigmented macules on fingers. |
| *TP53* | Li-Fraumeni syndrome | AD | Breast cancer (often premenopausal). Other cancers: soft tissue sarcoma, osteosarcoma, brain, adrenocortical carcinoma, leukemias. Early-onset & multiple primary cancers. |
| **Moderate-penetrance (moderate-risk) genes for breast &/or ovarian cancer** | | | |
| *ATM* | *ATM*-related cancer susceptibility (*ATM* heterozygotes; see Ataxia-Telangiectasia.) | AD | Specific *ATM* pathogenic variants, most notably c.7271T>G, are assoc w/high-penetrance breast cancer; heterozygosity for most other *ATM* pathogenic variants is assoc w/moderate-penetrance breast cancer. ↑ risk for other types of tumors such as pancreatic cancer & prostate cancer. |
| *BARD1* | *BARD1*-related cancer susceptibility (OMIM 114480) | AD | Breast cancer |
| *BRIP1* | *BRIP1*-related cancer susceptibility (OMIM 605882) | AD | Epithelial ovarian cancer, [3] possible ↑ risk for breast cancer |
| *CHEK2* | *CHEK2*-related cancer susceptibility (OMIM 604373) | AD | Breast cancer [4] |
| *EPCAM*<br>*MLH1*<br>*MSH2*<br>*MSH6*<br>*PMS2* | Lynch syndrome | AD | Ovarian cancer, slightly ↑ risk for breast cancer. Colorectal polyps, endometrial cancer, gastric cancer, & other cancers. [5] |
| *RAD51C* | *RAD51C*-related cancer susceptibility (OMIM 613399) | AD | Ovarian cancer, possibly breast cancer (particularly ER/PR negative breast cancer) |

*Table 3. continued from previous page.*

| Gene(s) | Cancer Susceptibility Syndrome | MOI | Associated Cancers / Distinctive Features |
|---|---|---|---|
| *RAD51D* | *RAD51D*-related cancer susceptibility (OMIM 614291) | AD | Ovarian cancer, possibly breast cancer (particularly ER/PR negative breast cancer) |

AD = autosomal dominant; ER = estrogen receptor; GI = gastrointestinal; MOI = mode of inheritance; PR = progesterone receptor; SCTAT = sex cord tumor with annular tubules

*1.* NCCN Guidelines, Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic Version 3.2023 (accessed 8-17-23)

*2.* Antoniou et al [2014], Yang et al [2020]

*3.* Ramus et al [2015]

*4.* The *CHEK2* variant c.1100delC (NM_007194.3) is associated with an estimated two- to threefold increased breast cancer risk in women and a tenfold increased risk in men [CHEK2 Consortium 2004, Bernstein et al 2006, Weischer et al 2007].

*5.* Note regarding *PMS2*: Although studies have suggested a 3% lifetime risk for ovarian cancer that is higher than the observed risk in the general population, studies that specifically examine risks among individuals with *PMS2* pathogenic variants have not demonstrated a statistically significant relative increased risk for ovarian cancer.

# Management

## Evaluations Following Initial Diagnosis

Individuals who have a germline pathogenic variant in *BRCA1* or *BRCA2* are counseled at the time of disclosure of molecular genetic test results about their options for Surveillance and Prevention of Primary Manifestations.

## Treatment of Manifestations

**Breast cancer.** National Comprehensive Cancer Network (NCCN) guidelines suggest that women with a *BRCA1* or *BRCA2* pathogenic variant could consider bilateral mastectomy as a primary surgical treatment of breast cancer because of their elevated rate of ipsilateral and contralateral breast cancer (NCCN Guidelines; no-fee registration and login required).

PARP inhibitors have emerged as a promising treatment in individuals with *BRCA1*- and *BRCA2*-associated breast cancer, given their role in DNA repair. Because *BRCA1*, *BRCA2*, and PARP participate in DNA repair, their mutual disruption could lead to "synergistic lethality" of tumor cells. PARP inhibitors were first studied in women with *BRCA1*- and *BRCA2*-associated metastatic breast cancer. Significant improvement was seen in in progression-free survival, leading to FDA approval of olaparib for women with locally advanced metastatic breast cancer in 2017 [Robson et al 2017, Litton et al 2018]. In a recent randomized, double-blind Phase III trial, olaparib also improved progression-free survival in individuals with early, high-risk, human epidermal growth factor receptor 2-negative *BRCA1*- and *BRCA2*-associated breast cancer in the adjuvant setting [Tutt et al 2021].

**Ovarian cancer.** PARP inhibitors were first found to improve response rates in the setting of ovarian cancer recurrence after failure of platinum-based therapies [Fong et al 2009]. Olaparib has subsequently shown significantly improved progression-free survival in platinum-sensitive recurrent ovarian cancer as maintenance therapy. In this study, individuals with *BRCA1* and *BRCA2* pathogenic variants showed the most benefit [Ledermann et al 2014]. Olaparib has also demonstrated significant benefit as maintenance therapy in women with newly diagnosed disease in advanced *BRCA1*- and *BRCA2*-associated ovarian cancer following primary therapy. In the SOLO-1 trial, women randomized to olaparib maintenance treatment had a 70% lower risk of disease progression or death compared to the placebo [Moore et al 2018]. Olaparib was given FDA approval for metastatic ovarian cancer in 2014, for maintenance therapy for recurrent disease in 2017, and for maintenance therapy after completion of adjuvant therapy in 2019.

**Prostate cancer.** After promising Phase I data on the use of olaparib in solid tumors, a Phase II study established its activity in men with *BRCA1*- and *BRCA2*-associated advanced prostate cancer [Kaufman et al 2015]. A subsequent Phase II trial compared olaparib to androgen targeted therapy plus prednisone in men with

progressive prostate cancer who had pathogenic variants in DNA damage repair genes, including *BRCA1* and *BRCA2*. A significant improvement in response rate and disease-free survival was seen in the olaparib treatment group. Both olaparib and rucaparib were approved by the FDA in 2020 for use in this setting [De Bono et al 2020].

**Pancreatic cancer.** The poor response of pancreatic cancer to standard systemic therapies has intensified the search for novel targeted agents. The Phase III POLO trial randomized individuals with *BRCA1*- and *BRCA2*-associated metastatic pancreatic cancer to olaparib vs placebo. Response rates were 22.1% in the olaparib group and 9.6% in the placebo group. Both progression-free survival and overall survival were doubled in the olaparib group. Toxicities, especially when a PARP inhibitor is combined with other systemic therapy, however, limit its use. The FDA has approved olaparib as maintenance therapy for *BRCA1*- and *BRCA2*-associated advanced pancreatic cancer.

**Melanoma.** Treatment is per dermatologist and/or oncologist.

## Prevention of Primary Manifestations

**Breast cancer**

- Consider prophylactic bilateral mastectomy.
- Given the conflicting data on the degree of risk reduction of breast cancer associated with prophylactic oophorectomy, consider discussing the risks and benefits of this approach with a genetics specialist.
- Chemoprevention. In a retrospective study tamoxifen reduced the risk for breast cancer by 62% among healthy women with a *BRCA2* germline variant [King et al 2001]. The sample size, however, was extremely small. There have been no prospective randomized trials of tamoxifen as a chemoprevention agent specifically in women with *BRCA1* or *BRCA2* pathogenic variants. Several studies, however, have found a significant protective effect of tamoxifen on the risk of contralateral breast cancer in women with *BRCA1* or *BRCA2* pathogenic variants. Risk reduction in these studies ranged from 50% to 69%. These studies are limited by their retrospective case-control designs [Gronwald et al 2006, Pierce et al 2006, Phillips et al 2013].

  Note: Significant adverse consequences of tamoxifen treatment included higher rates of endometrial cancer and thromboembolic episodes (including pulmonary embolism) in those individuals who took the medication than in those who did not. Women with a history of thromboembolic disease or with a coagulation disorder should avoid taking tamoxifen. Women on tamoxifen should be counseled to report any abnormal vaginal bleeding immediately to their gynecologist.
- Breast feeding for a cumulative total of more than one year reduced the risk for breast cancer [Jernström et al 2004].

**Ovarian cancer (including fallopian tube cancer)**

- Consider prophylactic salpingo-oophorectomy, recognizing that completion of childbearing may factor into this decision. A prospective cohort study of 2,482 women with *BRCA1* or *BRCA2* pathogenic variants reported a 79% reduction in ovarian cancer mortality and a 60% reduction on all-cause mortality associated with risk-reducing oophorectomy [Marchetti et al 2014].
- With the realization that the fallopian tube is frequently the site of serous ovarian cancer and its precursor lesions, a new paradigm of prophylactic salpingectomy after childbearing followed by delayed oophorectomy at the time of menopause has been suggested. While theoretically offering protection against ovarian cancer, this approach would also avoid the adverse consequences of premature

menopause. Currently studies are under way to determine its feasibility, safety, and efficacy [Swanson & Bakkum-Gamez 2016].

- Tubal ligation. A meta-analysis of 13 studies showed a reduction in risk for ovarian cancer of 34% in the general population after tubal ligation [Cibula et al 2011]. In a meta-analysis of modifiers of risk of cancer in individuals with pathogenic variants in *BRCA1* or *BRCA2,* tubal ligation was associated with a reduced risk of ovarian cancer in females with a *BRCA1* pathogenic variant, although study design issues limit the impact of these findings [Friebel et al 2014].
- A meta-analysis of 18 studies including 13,677 women with *BRCA1* or *BRCA2* pathogenic variants found a 50% reduction in risk of ovarian cancer associated with oral contraceptive use [Iodice et al 2010]. The maximum benefit of oral contraceptives is obtained with three to six years of use [Kotsopoulos et al 2015].

  Note: There is no evidence that use of current (after 1975) oral contraceptive formulations increases the risk for early-onset breast cancer for women with a germline *BRCA1* or *BRCA2* pathogenic variant.

## Surveillance

**Table 4.** Recommended Surveillance for Women with *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Breast cancer** | Breast self-exam | Monthly |
| | Clinical breast exam | Every 6-12 mos beginning at age 25 yrs |
| | Mammogram | Annually beginning at age 30 yrs |
| | Breast MRI | Annually beginning at age 25 yrs or earlier if breast cancer was diagnosed in family member < age 30 yrs |
| **Ovarian cancer** | Screening not recommended [1] | |
| **Melanoma** | Skin exam w/dermatologist | Individualized based on family history |
| **Pancreatic cancer** | In asymptomatic persons who meet criteria based on mutation status & family history, contrast-enhanced MRI/MRCP &/or EUS may be considered in a research setting to better delineate the risks & benefits of pancreatic cancer screening. | |

EUS = endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography
*1.* For women who have not elected to undergo prophylactic bilateral salpingo-oophorectomy: while some clinicians conduct annual transvaginal ultrasound and/or CA-125 concentration, these modalities have not been effective in detecting early-stage ovarian cancer, either in high-risk or in average-risk women.

**Table 5.** Recommended Surveillance for Men with *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Breast cancer** | Breast self-exam training | At the time of identification of a *BRCA1* or *BRCA2* pathogenic variant |
| | Breast self-exam | Monthly beginning at age 35 yrs |
| | Clinical breast exam | Annually beginning at age 35 yrs |
| **Prostate cancer** | Serum PSA; digital rectal exam | Annually beginning at age 40 yrs |
| **Melanoma** | Skin exam w/dermatologist | Individualized based on family history |

*Table 5. continued from previous page.*

| System/Concern | Evaluation | Frequency |
|---|---|---|
| **Pancreatic cancer** | In asymptomatic persons who meet criteria based on mutation status & family history, contrast-enhanced MRI/MRCP &/or EUS may be considered in a research setting to better delineate the risks & benefits of pancreatic cancer screening. | |

EUS = endoscopic ultrasound; MRCP = magnetic resonance cholangiopancreatography

## Agents/Circumstances to Avoid

No data specific to individuals with *BRCA1* or *BRCA2* pathogenic variants are available.

## Evaluation of Relatives at Risk

Once a cancer-predisposing *BRCA1* or *BRCA2* germline variant has been identified in a family, testing of at-risk relatives can identify those family members who also have the familial variant and thus need increased surveillance and specific treatments when a cancer is identified.

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

## Therapies Under Investigation

Several ongoing studies are investigating novel approaches to the treatment of *BRCA1*- and *BRCA2*-associated breast and ovarian cancer. The majority of these studies involve PARP inhibitors.

Several prospective and randomized clinical trials are investigating PARP inhibitor treatment of metastatic pancreatic cancer [Chi et al 2021, Macchini et al 2021].

Studies to identify biomarkers of disease resistance and expected treatment toxicity are also under way [Jeong & Park 2021].

Additional clinical trials are exploring the use of other PARP inhibitors alone or in combination with other systemic treatments.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for information on clinical studies.

## Other

**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-controlled trial of HRT [Chlebowski et al 2003].

Three observational studies on the impact of HRT on breast cancer risk in *BRCA 1* and *BRCA2* heterozygotes have been published. Rebbeck et al [2005] 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. 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 1,299 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 [Domchek et al 2011]. 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 [Eisen et al 2008]. 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 [Kotsopoulos et al 2016]. Taken together, these studies support the short-term use of HRT among *BRCA1* and *BRCA2* heterozygotes who have undergone surgical menopause.

# Genetic Counseling

*Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional.* —ED.

## Mode of Inheritance

*BRCA1*- and *BRCA2*-associated hereditary breast and ovarian cancer (HBOC) is inherited in an autosomal dominant manner.

## Risk to Family Members

**Parents of a proband with a *BRCA1* or *BRCA2* pathogenic variant**

- The vast majority of individuals with a germline pathogenic variant in *BRCA1* or *BRCA2* inherited it from a parent. The parent with the pathogenic variant may or may not have had a cancer diagnosis depending on the following variables:
  - Penetrance of the variant
  - Sex of the parent
  - Age of the parent
  - Cancer risk reduction in the parent as a result of screening or prophylactic surgeries
  - Early death of the parent
- It is appropriate to offer molecular genetic testing to both parents of an individual with a *BRCA1* or *BRCA2* germline pathogenic variant to determine which side of the family is at risk. Generally, the pattern of cancers seen in the family guides which parent is tested first.
- If the pathogenic variant identified in the proband is not identified in either parent and parental identity testing has confirmed biological maternity and paternity, the following possibilities should be considered:
  - The proband has a *de novo* pathogenic variant. *De novo* variants have been rarely reported (≤5%) [Golmard et al 2016, Antonucci et al 2017].
  - The proband inherited a pathogenic variant from a parent with germline (or somatic and germline) mosaicism [Alhopuro et al 2020]. Note: Testing of parental leukocyte DNA may not detect all instances of somatic mosaicism and will not detect a pathogenic variant that is present in the germ cells only.
- An apparently negative family history cannot be confirmed unless molecular genetic testing has demonstrated that neither parent is heterozygous for the *BRCA1* or *BRCA2* pathogenic variant identified in the proband.

**Sibs of a proband with a *BRCA1* or *BRCA2* pathogenic variant.** The risk to full sibs of the proband depends on the genetic status of the proband's parents:

- If one parent has the *BRCA1* or *BRCA2* germline pathogenic variant identified in the proband, the risk that a sib will inherit the pathogenic variant is 50%.

- The risk of developing cancer in a sib who inherits the familial *BRCA1* or *BRCA2* pathogenic variant depends on numerous variables including the penetrance of the pathogenic variant and the sex and age of the heterozygous sib.

**Offspring of a proband with a *BRCA1* or *BRCA2* pathogenic variant**

- The offspring of an individual identified as having a *BRCA1* or *BRCA2* germline pathogenic variant have a 50% chance of inheriting the pathogenic variant.
- The risk of developing cancer in offspring who inherit the *BRCA1* or *BRCA2* pathogenic variant depends on numerous variables including the penetrance of the pathogenic variant and the sex and age of the heterozygous individual.

**Other family members of a proband with a *BRCA1* or *BRCA2* pathogenic variant.** The risk to other family members depends on the genetic status of the proband's parents. If a parent has a *BRCA1* or *BRCA2* germline pathogenic variant, the parent's family members are at risk. Their exact risk depends on their biological relationship with the proband.

## Related Genetic Counseling Issues

See Management, Evaluation of Relatives at Risk for information on evaluating at-risk relatives for the purpose of early diagnosis and treatment.

**Family planning**

- The optimal time for the determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected or at risk.

**Genetic cancer risk assessment and counseling.** For a comprehensive description of the medical, psychosocial, and ethical ramifications of identifying at-risk individuals through cancer risk assessment with or without molecular genetic testing, see Cancer Genetics Risk Assessment and Counseling – for health professionals (part of PDQ®, National Cancer Institute).

**At-risk asymptomatic adult relatives.** In general, relatives of an individual who has a *BRCA1* or *BRCA2* germline pathogenic variant should be counseled regarding their risk of having inherited the same variant, their options for molecular genetic testing, their cancer risk, and recommendations for cancer screening (see Surveillance) and prophylactic surgery (see Prevention of Primary Manifestations).

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.

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 pathogenic 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.

**Testing of asymptomatic individuals younger than age 18 years.** In general, genetic testing for *BRCA1*- and *BRCA2*-associated HBOC is not recommended for at-risk individuals younger than age 18 years. Guidelines

established jointly by the American College of Medical Genetics and the American Society of Human Genetics state that predictive genetic testing should only be performed in individuals younger than age 18 years when it will affect their medical management. Surveillance for *BRCA1*- and *BRCA2*-associated HBOC is typically recommended to begin at approximately age 25, which is why it is recommended that the decision to test be postponed until an individual reaches adulthood and can make an independent decision. It is important to note, however, that since there are rare reports of individuals with *BRCA1*- and *BRCA2*-associated HBOC diagnosed with cancer at very young ages, it is recommended that screening be individualized based on the earliest diagnosis in the family.

For more information, see the National Society of Genetic Counselors position statement on genetic testing of minors for adult-onset conditions and the American Academy of Pediatrics and American College of Medical Genetics and Genomics policy statement: ethical and policy issues in genetic testing and screening of children.

### Prenatal Testing and Preimplantation Genetic Testing

Once the *BRCA1* or *BRCA2* germline pathogenic variant has been identified in the family, prenatal and preimplantation genetic testing for *BRCA1*- and *BRCA2*-associated HBOC are possible.

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful. For more information, see the National Society of Genetic Counselors Position Statement on prenatal testing in adult-onset conditions.

## Resources

*GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.*

- **Breast Cancer Information Core**

  *Breast cancer resources*

  National Human Genome Research Institute (NHGRI)

  research.nhgri.nih.gov/bic/resources.shtml

- **Bright Pink**

  670 North Clark Street

  Suite 2

  Chicago IL 60654

  www.brightpink.org

- **FORCE: Facing Our Risk of Cancer Empowered**

  *A discussion forum specifically for women who are at a high risk of developing ovarian cancer or breast cancer*

  16057 Tampa Palms Boulevard West

  PMB #373

  Tampa FL 33647

  **Phone:** 866-288-7475 (toll-free)

  **Fax:** 954-827-2200

**Email:** info@facingourrisk.org
www.facingourrisk.org

- **Gilda's Club Worldwide**
  48 Wall Street
  11th Floor
  New York NY 10005
  **Phone:** 888-445-3248 (toll-free)
  **Fax:** 917-305-0549
  **Email:** info@gildasclub.org
  www.cancersupportcommunity.org
- **National Breast Cancer Coalition (NBCC)**
  **Phone:** 800-622-2838
  **Fax:** 202-314-3458
  **Email:** info@stopbreastcancer.org
  www.stopbreastcancer.org
- **National Cancer Institute (NCI)**
  6116 Executive Boulevard
  Suite 300
  Bethesda MD 20892-8322
  **Phone:** 800-422-6237 (toll-free)
  **Email:** cancergovstaff@mail.nih.gov
  Breast Cancer
- **National Cancer Institute (NCI)**
  **Phone:** 800-4-CANCER
  **Email:** NCIinfo@nih.gov
  Genetics of Breast and Ovarian Cancer (PDQ)
- **National Ovarian Cancer Coalition (NOCC)**
  2501 Oak Lawn Avenue
  Suite 435
  Dallas TX 75219
  **Phone:** 888-682-7426 (Toll-free Helpline); 214-273-4200
  **Fax:** 214-273-4201
  **Email:** nocc@ovarian.org
  www.ovarian.org
- **NCBI Genes and Disease**
  Breast and ovarian cancer

- **Probability of Breast Cancer in American Women**
  National Cancer Institute Public Inquiries Office
  6116 Executive Boulevard
  Suite 300
  Bethesda MD 20892-8322
  **Phone:** 800-422-6237 (toll-free)
  **Email:** cancergovstaff@mail.nih.gov
  Probability of Breast Cancer in American Women
- **Sharsheret**
  **Phone:** 866-474-2774
  **Email:** info@sharsheret.org
  www.sharsheret.org
- **Susan G. Komen Breast Cancer Foundation**
  **Phone:** 877 GO KOMEN
  **Email:** helpline@komen.org
  www.komen.org
- **American Cancer Society**
  **Phone:** 800-227-2345
  www.cancer.org
- **CancerCare**
  **Phone:** 800-813-4673
  **Email:** info@cancercare.org
  www.cancercare.org
- **National Cancer Institute (NCI)**
  **Phone:** 800-422-6237
  **Email:** NCIinfo@nih.gov
  www.cancer.gov
- **National Coalition for Cancer Survivorship (NCCS)**
  **Phone:** 877-NCCS-YES
  **Email:** info@canceradvocacy.org
  www.canceradvocacy.org
- **Familial Ovarian Cancer Registry**
  Roswell Park Cancer Institute
  Elm and Carlton Streets
  Buffalo NY 14263
  **Phone:** 716-845-4503

www.ovariancancer.com

# Molecular Genetics

*Information in the Molecular Genetics and OMIM tables may differ from that elsewhere in the GeneReview: tables may contain more recent information.* —ED.

**Table A.** BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer: Genes and Databases

| Gene | Chromosome Locus | Protein | Locus-Specific Databases | HGMD | ClinVar |
|---|---|---|---|---|---|
| *BRCA1* | 17q21.31 | Breast cancer type 1 susceptibility protein | BRCA1 homepage - LOVD<br>Database of BRCA1 and BRCA2 sequence variants that have been clinically reclassified by a quantitative integrated evaluation<br>Breast Cancer Information Core (BRCA1)<br>BRCA1 @ ZAC-GGM | BRCA1 | BRCA1 |
| *BRCA2* | 13q13.1 | Breast cancer type 2 susceptibility protein | BRCA2 homepage - LOVD<br>Database of BRCA1 and BRCA2 sequence variants that have been clinically reclassified using a quantitative integrated evaluation<br>Breast Cancer Information Core (BRCA2)<br>Fanconi Anaemia Mutation Database (FANCD1 - BRCA2)<br>BRCA2 @ ZAC-GGM | BRCA2 | BRCA2 |

Data are compiled from the following standard references: gene from HGNC; chromosome locus from OMIM; protein from UniProt. For a description of databases (Locus Specific, HGMD, ClinVar) to which links are provided, click here.

**Table B.** OMIM Entries for BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer (View All in OMIM)

| | |
|---|---|
| 113705 | BRCA1 DNA REPAIR-ASSOCIATED PROTEIN; BRCA1 |
| 114480 | BREAST CANCER |
| 600185 | BRCA2 DNA REPAIR-ASSOCIATED PROTEIN; BRCA2 |
| 604370 | BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 1; BROVCA1 |
| 612555 | BREAST-OVARIAN CANCER, FAMILIAL, SUSCEPTIBILITY TO, 2; BROVCA2 |
| 613347 | PANCREATIC CANCER, SUSCEPTIBILITY TO, 2 |
| 614320 | PANCREATIC CANCER, SUSCEPTIBILITY TO, 4; PNCA4 |

## Molecular Pathogenesis

*BRCA1* encodes breast cancer type 1 susceptibility protein (BRCA1), a phosphoprotein normally located in the nucleus [Chen et al 1996]. BRCA1 interacts with several proteins involved in cellular pathways, including cell-cycle progression, gene transcription regulation, DNA damage response, and ubiquitination [Deng 2006, Rosen et al 2006].

The BRCA1/BARD1 protein complex enhances ubiquitin ligase activity, which is associated with the regulation of centrosome function and involved in DNA repair and cell cycle regulation [Bork et al 1997, Callebaut & Mornon 1997, Sankaran et al 2006].

BRCA1 colocalizes with BRCA2 and RAD51 at sites of DNA damage and activates RAD51-mediated homologous recombination repair of DNA double-strand breaks [Cousineau et al 2005]. BRCA2 regulates the availability and activity of RAD51, which coats single-strand DNA to form a nucleoprotein filament that invades and pairs with a homologous DNA duplex to initiate strand exchange [Venkitaraman 2002].

**Mechanism of disease causation.** Loss of function

**Table 6.** *BRCA1*- and *BRCA2*-Associated Hereditary Breast and Ovarian Cancer: Notable Pathogenic Variants by Gene

| Gene | Reference Sequences | DNA Nucleotide Change (Alias [1]) | Predicted Protein Change | Comment [Reference] |
|---|---|---|---|---|
| *BRCA1* | NM_007294.4 NP_009225.1 | c.68_69delAG (185delAG or 187delAG) | p.Glu23ValfsTer17 | Founder variant in Ashkenazi Jews; accounts for 72% of pathogenic variants in this population [2] |
| | | c.115T>G | p.Cys39Gly | Founder variant in Inuit from Ammassalik; accounts for >95% of pathogenic variants in this population [3] |
| | | c.815_824dupAGCCATGTGG (943ins10) | p.Thr276AlafsTer14 | Founder variant in those of West African ancestry [4] |
| | | c.5096G>A | p.Arg1699Gln | Intermediate risk variant [5] |
| | | c.5266dupC (5385insC or 5382insC) | p.Gln1756ProfsTer74 | Founder variant in Ashkenazi Jews; accounts for 26% of pathogenic variants in this population [2] |
| *BRCA2* | NM_000059.4 NP_000050.3 | c.771_775delTCAAA (999del5) | p.Asn257LysfsTer17 | Founder variant in Icelanders [6] |
| | | c.5073dupA | p.Trp1692MetfsTer3 | Founder variant in Amish of Somerset County, Pennsylvania [7] |
| | | c.5946delT (6174delT) | p.Ser1982ArgfsTer22 | Founder variant in Ashkenazi Jews; accounts for 95% of pathogenic variants in this population [2] |

Variants listed in the table have been provided by the authors. *GeneReviews* staff have not independently verified the classification of variants.

*GeneReviews* follows the standard naming conventions of the Human Genome Variation Society (varnomen.hgvs.org). See Quick Reference for an explanation of nomenclature.

*1.* Variant designation that does not conform to current naming conventions

*2.* Bahar et al [2001], Frank et al [2002], Phelan et al [2002], Ferla et al [2007], Cox et al [2018]

*3.* Hansen et al [2009], Harboe et al [2009], Hansen et al [2010]

*4.* Mefford et al [1999]

*5.* Moghadasi et al [2018]

*6.* Rafnar et al [2004]

*7.* See Resources for Genetics Professionals — Genetic Disorders Associated with Founder Variants Common in the Amish Population.

# Chapter Notes

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- 20 January 2011 (me) Comprehensive update posted live
- 19 June 2007 (me) Comprehensive update posted live
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- 29 March 2004 (ca) Comprehensive update posted live
- 4 March 2000 (me) Comprehensive update posted live
- 4 September 1998 (pb) Review posted live
- January 1998 (jbc) Original submission

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