GENETICS: MINI-REVIEW OF THE MOLECULAR GENETICS OF BRCA1/BRCA2

Goal:
Explain the molecular basis of hereditary breast and ovarian cancer.

After completing this activity participants will be able to:

- Describe the size and location of the BRCA genes
- Discuss the normal function of the BRCA genes
- Describe how a mutation in BRCA genes results in cancer
- Locate genetic resources for patients and medical staff

Professional Practice Gaps
In an effort to define what healthcare providers need to know about medical genetics, several organizations developed core competencies (NCHPEG, 2000; ASHG, 2001). However, because clinical genetics is a relatively young and evolving field of medicine, many practitioners received insufficient formal genetics education. As a result, they express a lack of confidence in their clinical genetics knowledge and a lack of confidence in their ability to provide genetic counseling.

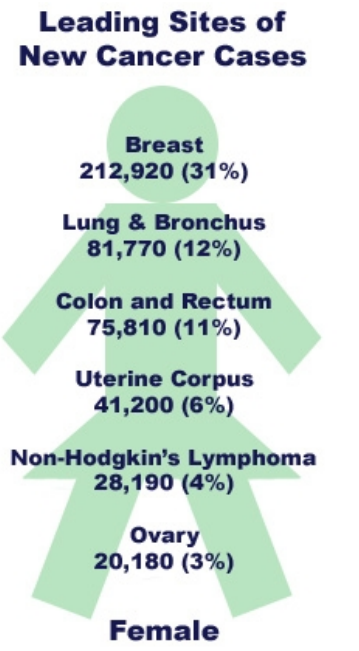
BREAST AND OVARIAN CANCER PREVALENCE – GENERAL POPULATION

One of every 8 women in the United States (or 12.5%) will develop breast cancer in her lifetime. During the year 2008, breast cancer in US women is estimated to have been

- The most commonly diagnosed new cancer (excluding skin cancer)
- The second most common cause of cancer-related death (excluding skin cancer)

Between one and two of every 100 US women (or 1%-2%) will develop ovarian cancer in her lifetime. During the year 2008, ovarian cancer in US women is estimated to have been

- The eighth most commonly diagnosed new cancer
- The fifth most common cause of cancer-related death



(Adapted from American Cancer Society, 2006)

Cancer facts and figures 2008. *American Cancer Society.* 2008. Available at: http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2008/index Accessed on: 2009-10-12.

BREAST AND OVARIAN CANCER PREVALENCE -- HEREDITARY CASES

The great majority of breast and ovarian cancer is sporadic. However, 5% to 10% of breast and ovarian cancer is inherited (CDC 2013).

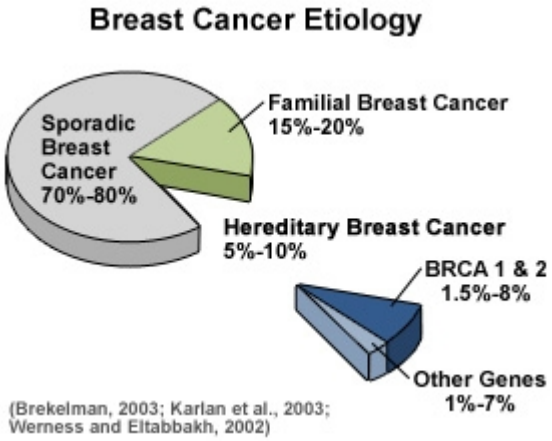
The most common cause of heritable breast and ovarian cancer is a mutation in either the BRCA1 (breast cancer 1) or BRCA2 (breast cancer 2) gene (Miki et al. 1994; Wooster et al. 1995).

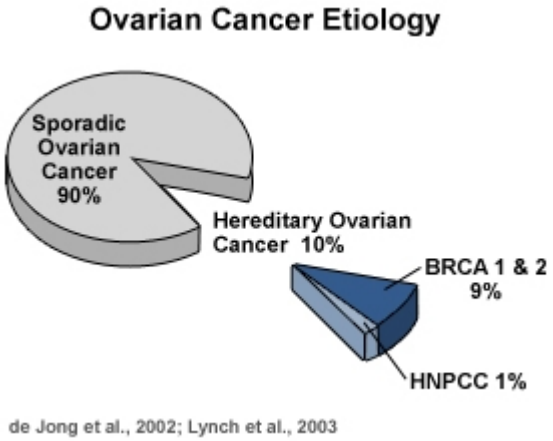
Mutations in BRCA1 are estimated to account for

- 45% to 76% of families with hereditary breast cancer only (Easton et al. 1993; Ford et al. 1998; Narod 1995)
- Approximately 75% to 81% of families with hereditary breast and ovarian cancers (Easton et al. 1993; Ford et al. 1998; Narod 1995)
- 5.7% to 7% of all ovarian cancers (Boyd 2003; Risch et al. 2001)

Mutations in BRCA2 are estimated to account for

- 32% to 35% of families with breast cancer, with or without ovarian cancer (Ford et al. 1998; Wooster et al. 1994)
- Approximately 14% of families with hereditary breast and ovarian cancers (Ford et al. 1998)
- 76% of families with male and female breast cancer (Ford et al. 1998)
- 3.8% to 4% of all ovarian cancers (Boyd 2003; Risch et al. 2001)

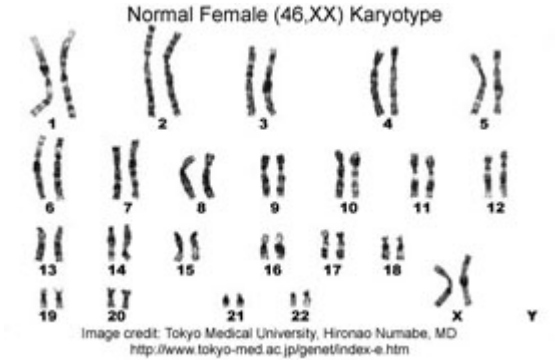


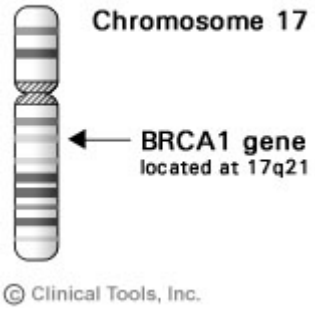


BRCA1: MOLECULAR GENETICS

BRCA1 was the first gene isolated that is known to cause hereditary breast and ovarian cancer syndrome (HBOC). BRCA1 was identified in 1994 and is located on the long arm, or q arm, of chromosome 17 (Miki et al. 1994). BRCA1 is composed of 5,592 nucleotides and codes for 1,863 amino acids (Canon-Albright and Skolnick 1996; Miki et al. 1994). This large gene has 22 coding exons and stretches over 100,000 bases of genomic DNA.

The image on the left, below, is a normal karyotype from a female. On the right is an ideogram of a single copy of chromosome 17 specifically, showing the location of the BRCA1 gene.





A mutation in BRCA1 increases a person's risk of developing specific cancers (these cancers are addressed on the next page). Hundreds of mutations have been described in BRCA1, and a central database created by the National Human Genome Research Institute houses them. The majority of documented mutations cause the BRCA1 gene product to be shorter than normal, resulting in what is called a truncated protein (Boyd and Rubin 1997; Canon-Albright and Skolnick 1996; Couch et al. 1996; Friend et al. 1995).

The BRCA1 gene is expressed in many tissues, including the testis, breast, and ovary (Coukos and Rubin 2002; Rajan et al. 1996). The normal gene product is essential to cellular function (Hakem et al. 1996; Ludwig et al. 1997). It is thought to protect the cell from genetic damage, acting as a tumor suppressor gene (Scully and Livingston 2000; Wang et al. 2000; Zhang et al. 1998). Recent studies have documented the fact that BRCA1 appears to have multiple functions in the cell, including DNA repair, cell cycle regulation, and programmed cell death (or apoptosis) (Powell and Kachnic 2003; Rosen 2003; Somasundaram 2003). When a mutation is present in BRCA1, the protective capacity of the gene product is either reduced or absent, and genetic damage accumulates in cells. If the damaged cells are able to replicate, they form abnormal or cancerous tissue.

BRCA1: CLINICAL IMPACT

Prevalence

Between 1 in 500 and 1 in 800 people in the general population have a mutation in BRCA1 (Antoniou et al. 2008; Chen & Parmigiani 2007; National Cancer Institute 2014). However, in people of Ashkenazi Jewish decent, the prevalence of a BRCA1 mutation is 1 in 100 or greater (Roa et al. 1996; Struewing et al. 1995, 1997). Two mutations commonly detected in people of Ashkenazi Jewish ancestry are 185delAG and 5382insC. It is likely that Ashkenazi Jewish individuals have an elevated risk for BRCA1 mutations as the result of a founder effect (Levy-Lahad et al. 1997; Narod et al. 2002; Struewing et al. 1995).

Inheritance Pattern

BRCA1 mutations are inherited in an autosomal dominant fashion. The term ***autosomal*** means that BRCA1 is not located on a sex chromosome (the X and Y chromosomes). The term ***dominant*** indicates that if a person inherits a BRCA1 mutation, the mutation will be expressed. A person who has a BRCA1 mutation has a 50% chance of passing that abnormal gene onto each of his or her children.

Clinical Impact

People who are born with a mutation in BRCA1 are at increased risk for breast cancer, ovarian cancer, and prostate cancer (National Cancer Institute 2014). However, not all individuals with BRCA1 will develop cancer. Of women with BRCA1, 55% to 65% will develop breast cancer and 39% will develop ovarian cancer (Tai et al. 2007; Levy-Lahad & Friedman E 2007; National Cancer Institute 2014). Men with BRCA1 may also be at increased risk for breast cancer, and their risk for prostate cancer is approximately 8% to 16% (Levy-Lahad & Friedman E 2007). Although some data suggest that the risk of colon cancer may be fourfold higher, with an estimated cumulative risk of 6% by age 70 years (Ford et al. 1994), more recent data question the association of colon cancer with *BRCA1* and *BRCA2* mutations (Niell et al. 2004).

Estimated Risks of Developing Cancer by Age 70

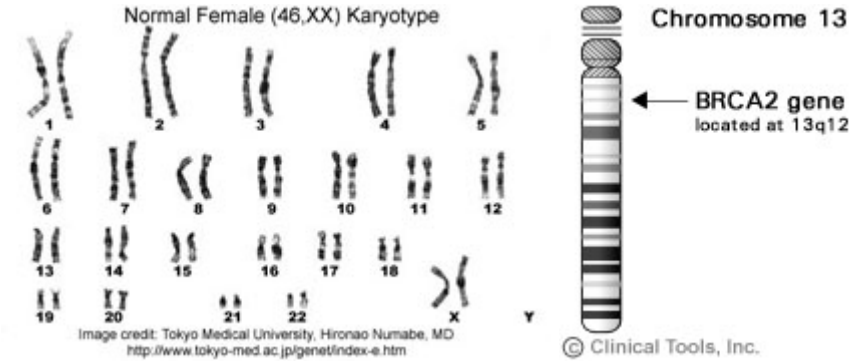
Based on BRCA1 Mutation Status

BRCA1 Mutation	No Mutation	
Breast Cancer	55%-65% (female) 1.2% (male)	12% (female) 0.1% (male)
Ovarian Cancer	39%	1.4%
Prostate Cancer	8%-16%	3.8%

BRCA2: MOLECULAR GENETICS

Shortly after BRCA1 was identified, BRCA2 was discovered. BRCA2 is located on the long arm, or q arm, of chromosome 13 (Wooster et al. 1995). BRCA2 is composed of approximately 10,000 nucleotides and codes for 3,418 amino acids (Gayther et al. 1997; Serova et al. 1997; Tavtigian et al. 1996). BRCA2 is has 27 exons and stretches over 70 kilobases of genomic DNA (Coukos and Rubin 2002; Hilton et al. 2002; Serova et al. 1997). This means that BRCA2 is almost 2 times larger than BRCA1.

The image on the left, below, is a normal karyotype from a female. On the right is an ideogram of a single copy of chromosome 13 specifically, showing the location of the BRCA2 gene.



A mutation in BRCA2 increases a person's risk of developing specific cancers (these cancers are addressed on the next page). Hundreds of mutations have been described in BRCA2, and a central

database created by the National Human Genome Research Institute houses them. The majority of documented mutations cause the BRCA2 gene product to be shorter than normal, resulting in what is called a truncated protein (Friend et al. 1995; Serova et al. 1997; Shih et al. 2002). Although the majority of mutations in BRCA2 result in a truncated protein product, the position of the mutation in the BRCA2 gene may impart different cancer risks. Several studies have demonstrated that individuals with a mutation in a specific region of exon 11 of BRCA2 have a higher risk for ovarian cancer and a lower risk for breast cancer than persons with a mutation elsewhere in the gene (Gayther et al. 1997; Risch et al. 2001; Thompson et al. 2001). Thus, this region of exon 11 has been named ovarian cancer cluster region (OCCR). In individuals with mutations in this OCCR, a 19.5% chance of developing ovarian cancer by age 70 years was documented, compared to individuals with mutations elsewhere in the gene who had a 10.9% chance of developing ovarian cancer by age 70 (Thompson et al. 2001).

Like the BRCA1 gene, BRCA2 is expressed in many tissues, including the testis, breast, and ovary (Coukos and Rubin 2002; Rajan et al. 1996). The normal gene product is essential to cellular function (Ludwig et al. 1997). It is thought to protect the cell from genetic damage, acting as a tumor suppressor gene (Bertwistle et al. 1997; Coukos and Rubin 2002; Scully and Livingston 2000; Zhang et al. 1998). Recent studies suggest that a single function for BRCA2 exists. BRCA2 is thought to play a role in DNA repair (Powell and Kachnic 2003; Venkitaraman 2004). When a mutation is present in BRCA2, the protective capacity of the gene product is either reduced or absent, and genetic damage accumulates in cells. If the damaged cells are able to replicate, they form abnormal or cancerous tissue.

BRCA2: CLINICAL IMPACT

Prevalence

The prevalence of BRCA2 in the general population has not been studied as well as the prevalence of BRCA1, so accurate figures are unavailable. People of Ashkenazi Jewish descent, however, have a 1 in 100 or greater chance of having a mutation in BRCA2 (Roa et al. 1996; Oddoux et al. 1996). One common mutation found in individuals of Ashkenazi Jewish descent is the 6174delT mutation (Oddoux et al. 1996). It is likely that Ashkenazi Jewish individuals have an elevated risk for a BRCA2 mutation as the result of a founder effect (United States Preventive Services Task Force 2004; Fackenthal & Olopade 2007; Narod et al. 2002).

In addition to individuals of Ashkenazi Jewish descent, people in Iceland also have an increased chance of having a mutation in BRCA2. In fact, in contrast to other populations, individuals in Iceland are more likely to have a mutation in BRCA2 than in BRCA1. The 999del5 mutation is especially common (Szabo and King 1997; Thorlacius et al. 1996). The mutation can be found in 1 of every 167 Icelanders (0.6%) (Thorlacius et al. 1997).

Inheritance Pattern

BRCA2 mutations causing hereditary breast and ovarian cancer are inherited in an autosomal dominant fashion. The term ***autosomal*** means that BRCA2 is not located on a sex chromosome (the X and Y chromosomes). The term ***dominant*** indicates that if a person inherits a BRCA2 mutation, the

mutation will be expressed. A person who has a BRCA2 mutation has a 50% chance of passing the gene onto each of his or her children.

An Exception to the Rule

Recently, a rare exception to the autosomal dominant pattern of inheritance was discovered by a group of researchers studying another genetic condition, Fanconi anemia (Howlett et al. 2002). Individuals born with Fanconi anemia have congenital physical anomalies, bone marrow failure, and an increased risk of numerous cancer types. Howlett et al. discovered that a small group of Fanconi anemia patients were born with deleterious mutations in **both** of their BRCA2 genes. In other words, the BRCA2 mutations were inherited in an autosomal recessive manner. Apparently, inheriting 2 abnormal BRCA2 genes results in a clinical presentation distinct from the hereditary breast and ovarian cancer syndrome associated with inheritance of a single BRCA2 mutation.

Clinical Impact

People with a mutation in *BRCA2* are at increased risk for breast cancer and ovarian cancer. An increased risk of prostate cancer and pancreatic cancer may also occur in individuals with *BRCA2* cancer-predisposing mutations (van Asperen et al. 2005; Friedenson 2005, Gayther et al. 1997, Naderi & Couch 2002, Hahn et al. 2003). Similar to those with a *BRCA1* mutation, not all people with a *BRCA2* mutation will develop cancer. Women with *BRCA2* mutations have approximately a 45% chance of developing breast cancer and an 11% to 17% chance of developing ovarian cancer by age 70 (Easton et al. 1997; Tai et al. 2007; National Cancer Institute 2014).

Men born with a *BRCA2* mutation have a 6% to 16% increased risk for prostate cancer, similar to men with a BRCA1 mutation (Levy-Lahed & Friedman 2007; Tai et al. 2007; National Cancer Institution 2014). In addition, for men with a *BRCA2* mutation, the risk of breast cancer by age 80 years has been estimated at 6.9% (Thompson & Easton 2001).

Estimated Risks of Developing Cancer by Age 70 Based on BRCA2 Mutation Status

BRCA2 Mutation	No Mutation	
Breast Cancer	45% (female) 6% (male)	12% (female) 0.1% (male)
Ovarian Cancer	16%-27%	1.4%
Prostate Cancer	6%-16%	3.8%

GENETIC TESTING FOR BRCA1 AND BRCA2

Genetic testing for BRCA1 and BRCA2 mutations is commercially available. For a specific group of individuals either at risk for or diagnosed with breast or ovarian cancer, genetic testing can be extremely helpful for medical management and in making important life decisions.

However, genetic testing is not appropriate for everyone. The testing is time-consuming, expensive, and has limitations. In addition, genetic testing has the potential to raise many psychological issues for patients as well as the families of patients undergoing testing. Because of the complexity of testing, several organizations have published guidelines for healthcare providers to follow when

testing patients for a genetic predisposition to developing breast and ovarian cancers (American Society of Clinical Oncology 2014; American College of Medical Genetics Foundation 2007; Smith, Cokkinides, & Brawley 2009). These guidelines recommend that extensive genetic counseling be provided to patients throughout the testing process.

TEST METHODS

General Population

The analysis technique used for the majority of people undergoing genetic testing for BRCA is called sequencing. Sequence analysis allows the laboratory to review a person's genetic information at the most basic level, nucleotide by nucleotide. However, sequencing cannot detect all genomic rearrangements, some RNA transcript processing errors, and may not detect mutations in regions studied due to rare technical limitations (such as polymorphisms underlying primer sites).

The reduced detection rate for the 2 BRCA genes makes it difficult to interpret test results. A negative result does not always mean that a patient is without a clinically significant mutation. Conversely, not all mutations detected during analysis cause disease. Mutations that do not cause disease are called polymorphisms. Some polymorphisms in the BRCA genes are well documented; however, rarer polymorphisms have yet to be studied. When a mutation is found for the first time in a patient, it is not always possible to predict its clinical impact. In such a situation, it can be helpful to study the genetic status of family members who do and do not have cancer.

Ashkenazi Jewish Heritage

People of Ashkenazi Jewish descent are at a higher risk to have BRCA mutations than non-Ashkenazi Jewish people. Unlike the general population, which harbors hundreds of different types of gene changes, there are 3 specific mutations commonly found in Ashkenazi Jewish individuals (185delAG, 5382insC, and 6174delT) (Antoniou et al. 2005). It is estimated that in the Ashkenazi Jewish population, 20% to 35% of women with early-onset breast cancer and approximately 60% of women with ovarian cancer have one of the 3 common mutations (Rubinstein 2004; Abeliovich et al., 1997; King et al., 2003). These 3 mutations can be easily tested for without sequencing the BRCA genes in entirety. Multiple laboratories in the United States offer this 3-mutation panel, and cost generally is under $500. If such an analysis is performed and is negative (no mutation detected), it may be appropriate to proceed to full sequencing in a patient with a significant family history of breast and/or ovarian cancer.

COST AND REIMBURSEMENT FOR TESTING

Myriad Genetics created a special division to help patients and doctors obtain insurance coverage for genetic testing, the Myriad Reimbursement Assistance Program. Most health insurance plans pay for BRACAnalysis®. More than 90% of tests receive coverage, and the average reimbursement is more than 90% (Myriad Genetics 2009). Testing coverage depends on the insurance company and the indication for testing. Even when insurance companies agree to cover the majority of testing expenses, patients will still be required to pay an average of several hundred dollars out of pocket.

For those choosing not to file an insurance claim, out-of-pocket expenses can be as high as $3,000.00.

BRAC Analysis Technical Specifications. *Salt Lake City, Utah: Myriad Genetics, Inc.* February, 2009.

SUMMARY AND KEY POINTS

- Between 5% and 10% of all breast and ovarian cancer cases are hereditary. The majority of hereditary cancers are caused by mutations in either the BRCA1 or BRCA2 gene.
- BRCA1 is located on chromosome 17, and BRCA2 is located on chromosome 13. Both genes are quite large. BRCA2 is about twice as large as BRCA1.
- Hereditary breast and ovarian cancer syndrome associated with BRCA mutations is inherited in an autosomal dominant pattern. Each individual born with a BRCA mutation has a 50% chance of passing that mutation onto his or her children.
- The BRCA genes are classified as tumor suppressors. Mutations in either BRCA1 or BRCA2 prevent the respective gene product from protecting cells from genetic damage. The genetic damage results in an increased risk of breast, ovarian, prostate, colon, and possibly other cancers.
- Commercial genetic testing for BRCA is available. For the general population, testing is done by direct sequencing of the genes. For Ashkenazi Jewish individuals, sequencing the genes in entirety often can be avoided.
- Many genetic resources for healthcare professionals and patients are available online.

RESOURCES AVAILABLE THROUGH THIS MODULE:

- American Cancer Society
  The American Cancer Society has many resources for both patients and physicians.
- Autosomal Dominant Inheritance 
  Diagrams of classic autosomal dominant inheritance and pedigree.
- Autosomal Recessive Inheritance 
  Images and descriptions of autosomal recessive inheritance.
- BRACAnalysis® Large Rearrangement Test (BART) Criteria
  In August 2002, Myriad launched an enhancement to the BRACAnalysis test to detect five common large rearrangements. The BRACAnalysis Rearrangement Test, or BART, launched in August 2006, is designed to detect large rearrangements beyond these five. For patients who meet the defined clinical criteria, BART will automatically be performed concurrently with the sequence analysis of Comprehensive BRACAnalysis®.
- Fact Sheet on Genetic Testing for Breast and Ovarian Cancer Susceptibility
  This article discusses how Genomics and Health are tied with Breast and Ovarian Cancer and Family Health History.
- Fanconi Anemia
  Fanconi anemia (FA) is characterized by physical abnormalities, bone marrow failure, and increased risk of malignancy.
- Fanconi Anemia from OMIM

Fanconi anemia is an autosomal recessive disorder affecting all bone marrow elements and associated with cardiac, renal, and limb malformations as well as dermal pigmentary changes.

- Jewish Virtual Library
  The Jewish Virtual Library is the most comprehensive online Jewish encyclopedia in the world, covering everything from anti-Semitism to Zionism. So far, more than 13,000 articles and 6,000 photographs and maps have been integrated into the site.
- Myriad Genetics Laboratory
  Myriad Genetics Laboratory performs a blood test that can let you know your risk for hereditary breast and ovarian cancer
- Myriad Introduces Enhanced BRACAnalysis Test for Exceptionally High-Risk Breast Cancer Patients
  This added test detects rare, large rearrangements of the DNA in the BRCA1 and BRCA2 genes and will be performed for women with exceptionally high risk who have tested negative for sequence mutations and the common large rearrangements already included in Myriad's test.
- National Human Genome Research Institute
  This website contains information about the Human Genome Project and also provides free online educational materials.
- Online Mendelian Inheritance In Man (OMIM)
  OMIM is a comprehensive, authoritative, and timely compendium of human genes and genetic phenotypes. The full-text, referenced overviews in OMIM contain information on all known mendelian disorders and over 12,000 genes. OMIM focuses on the relationship between phenotype and genotype. It is updated daily, and the entries contain copious links to other genetics resources. OMIM is intended for use primarily by physicians and other professionals concerned with genetic disorders, by genetics researchers, and by advanced students in science and medicine. While the OMIM database is open to the public, users seeking information about a personal medical or genetic condition are urged to consult with a qualified physician for diagnosis and for answers to personal questions (From their Website).
- Online Mendelian Inheritance in Man (OMIM) BRCA2
  A journal article about the BRCA 2 Gene. The article details cloning, gene structure, mapping, gene function, role in DNA repair, and molecular genetics.

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