

BRCA1 AND BRCA2

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Primary Disciplinary Field(s): Genetics, Oncology, Molecular Biology

1. Core Definition

The terms **BRCA1** (Breast Cancer gene 1) and **BRCA2** (Breast Cancer gene 2) refer to two critical human genes that are recognized as tumor suppressors. These genes produce proteins essential for maintaining genomic integrity by repairing damaged DNA, particularly through the highly accurate homologous recombination pathway. When these genes are functioning correctly, they act as primary safeguards against the accumulation of mutations, thereby preventing uncontrolled cellular proliferation and significantly reducing the risk of developing certain cancers, most notably breast and ovarian cancers. Their discovery marked a pivotal moment in medical genetics, enabling systematic cancer screening and personalized risk assessment.

A fundamental clinical implication of these genes lies in the inheritance of a pathogenic variant (mutation). While every individual possesses two copies of each gene, inheriting a dysfunctional copy drastically elevates an individual's lifetime susceptibility to developing cancers. The risk associated with these mutations is substantial: in women identified as carriers of a deleterious mutation in either **BRCA1** or **BRCA2**, the lifetime risk of developing breast cancer is estimated to be between 56% and 85%. Furthermore, while the primary concern is often female breast and ovarian cancer, mutations in **BRCA2** specifically also increase the rate of male breast cancer, although at a lower rate (approximately 5%), in addition to increased risks for prostate and pancreatic cancers.

2. Etymology and Historical Development

The identification of the genetic loci responsible for hereditary breast cancer was a major scientific objective in the late 20th century, driven by compelling evidence of disease clustering within families. The acronym **BRCA** simply denotes "BReast CAncer." The initial breakthrough occurred in 1994 with the successful cloning and mapping of the **BRCA1** gene, which was found situated on the long arm of chromosome 17 (17q21). This achievement, led by collaborative research efforts, validated the theory that a single, high-penetrance gene could account for a significant portion of inherited susceptibility to the disease.

The search for additional risk factors quickly led to the subsequent discovery of **BRCA2** in 1995, located on chromosome 13 (13q12). Although both genes fulfill similar roles in DNA repair, their distinct locations and slightly different molecular interactions underline the complexity of inherited cancer syndromes. The rapid identification and subsequent commercialization of diagnostic testing for these genes, particularly by Myriad Genetics, ignited intense ethical and legal controversies

concerning the patenting of human genes. This debate, which challenged the proprietary control over fundamental genetic information, ultimately culminated in a landmark 2013 U.S. Supreme Court decision that invalidated patents on naturally occurring DNA sequences, thereby expanding accessibility to testing.

3. Key Characteristics and Function

Both **BRCA1** and **BRCA2** encode large proteins that reside primarily within the cell nucleus, where they act in concert with numerous other proteins to monitor and maintain genetic stability. The proteins function predominantly within the critical DNA repair pathway known as homologous recombination (HR). The **BRCA1** protein often serves as an essential regulatory scaffold, detecting DNA double-strand breaks and coordinating the recruitment of repair machinery. It is also implicated in critical cellular processes such as checkpoint regulation, transcriptional control, and protein ubiquitination, emphasizing its multifaceted role as a central component of the cell's damage response system.

The **BRCA2** protein, conversely, plays a more direct role in the HR mechanism by managing the central recombinase protein, RAD51. Specifically, **BRCA2** is crucial for ensuring that RAD51 is properly loaded onto the single-stranded DNA overhangs created at the site of a double-strand break. This step is essential for the subsequent search for a homologous template, which guides the accurate reconstruction of the damaged DNA sequence. When either **BRCA1** or **BRCA2** is rendered defective by mutation, the cell cannot efficiently execute HR. This failure forces the cell to rely on error-prone repair pathways, leading to the rapid accumulation of genomic instability, which is the direct molecular trigger for malignant transformation and cancer development.

4. Associated Cancer Risks

Female Breast Cancer: Carriers of mutations in either gene face an average lifetime risk of developing breast cancer ranging dramatically between 56% and 85%. The penetrance, or likelihood of developing the disease, is often influenced by the specific mutation type and family history.

Ovarian Cancer: Mutations in these genes are the most common cause of hereditary ovarian cancer. **BRCA1** mutations confer a lifetime risk up to 40%, while **BRCA2** confers a risk up to 20%.

Male Cancers: Although less frequent, **BRCA2** mutations significantly elevate the risk of male breast cancer (approximately 5% lifetime risk) and are also associated with an increased risk of aggressive prostate cancer.

Other Malignancies: Both genes are linked to an elevated risk of pancreatic cancer, and **BRCA2** mutations are additionally associated with an increased incidence of melanoma.

5. Significance in Clinical Oncology

The initial discovery of **BRCA1** and **BRCA2** fundamentally transformed cancer management, establishing the framework for modern genetic risk stratification. The availability of reliable genetic testing allows clinicians to identify asymptomatic individuals who carry a pathogenic mutation, thereby enabling the transition from disease treatment to proactive prevention. Genetic counseling is now a standard component of care for individuals with strong familial histories of breast, ovarian, or related cancers, providing the necessary information to make informed decisions about personalized risk reduction.

For individuals confirmed to be carriers, risk management strategies can include intensive surveillance programs, such as combining annual magnetic resonance imaging (MRI) with mammography, starting at younger ages than the general population. Chemoprevention using hormone-modulating drugs is also an option. However, the most effective preventative measure remains prophylactic surgery, notably preventative bilateral mastectomy, which can reduce breast cancer risk by over 90%, and prophylactic salpingo-oophorectomy, which substantially reduces the risk of both ovarian and fallopian tube cancer, along with a secondary reduction in breast cancer risk.

6. Therapeutic Implications

Knowledge of a patient's **BRCA** status is not only important for prevention but also critical for directing therapeutic choices once cancer has developed. Tumors arising from **BRCA** mutations are characterized by a defect in the homologous recombination pathway, a state known as "homologous recombination deficiency" (HRD). This specific vulnerability can be exploited therapeutically using agents that induce further DNA damage or inhibit alternative repair mechanisms, a concept known as synthetic lethality.

The most prominent example of targeted therapy leveraging HRD are PARP inhibitors (Poly(ADP-ribose) polymerase inhibitors). PARP normally repairs single-strand DNA breaks. By inhibiting PARP in a tumor that is already deficient in BRCA-mediated double-strand break repair, the cancerous cells accumulate catastrophic levels of DNA damage, leading selectively to cell death. This targeted approach represents a highly successful application of precision medicine, significantly improving outcomes for patients with BRCA-associated breast, ovarian, and prostate cancers.

Further Reading

[BRCA1 and BRCA2: Cancer Risk and Genetic Testing \(National Cancer Institute\)](#)

[BRCA mutation - Wikipedia](#)

BRCA1 and BRCA2 Hereditary Breast Cancer - NCBI Bookshelf

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