BRCA1 AND BRCA2 GENES: KEY GENETIC DRIVERS IN BREAST CANCER RISK AND MANAGEMENT

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Abstract

Hereditary breast cancer accounts for a small but significant percentage of breast cancer cases and is an important area of study in oncology and genetics. This literature review examines the genetic characteristics, risk factors, and biological mechanisms that affect the development of hereditary breast cancer. Alterations in the BRCA1 and BRCA2 genes are strongly linked to an elevated risk of breast cancer. Additionally, recent research highlights the role of mutations in other genes that also contribute to the hereditary nature and development of this disease. Through a review of the literature, this study aims to provide a detailed overview of the relationship between genetic and environmental factors, early diagnosis, and treatment options for individuals with a family history of breast cancer. Likewise, the importance of genetic testing and preventive strategies for individuals with a high predisposition is emphasized. To overcome limitations and ensure genuine comparability across studies, it is crucial to standardize guidelines. Publications need to include all necessary information to enable comparison among different studies and to evaluate their impacts in the results. Here we will contribute to a deeper understanding of the biological mechanisms and provide an

important basis for the development of more personalized and efficient approaches to the early diagnosis and prevention of hereditary breast cancer.

***Key words**: Genes, BRCA1, BRCA2, breast cancer, mutations, epidemiology.*

Përmbledhje

Kanceri i trashëguar i gjirit përbën një pjesë të vogël, por të rëndësishme të rasteve të përgjithshme të kësaj sëmundjeje dhe mbetet një aspekt thelbësor i kërkimeve në fushën e onkologjisë dhe gjenetikës. Ky studim literature shqyrton karakteristikat gjenetike, faktorët e rrezikut, dhe mekanizmat biologjikë që ndikojnë në zhvillimin e kancerit të trashëguar të gjirit. Mutacionet në gjenet BRCA1 dhe BRCA2 janë të lidhura ngushtë me një rrezik të shtuar për zhvillimin e këtij lloji të kancerit, por studimet e fundit kanë treguar se ekzistojnë edhe mutacione në gjene të tjera që kontribuojnë në trashëgiminë dhe shfaqjen e kancerit të gjirit. Përmes shqyrtimit të literaturës, ky studim synon të ofrojë një pasqyrë të hollësishme mbi lidhjet mes faktoreve gjenetikë dhe mjedisorë, diagnostikës së hershme dhe mundësive të trajtimit të individëve me histori familjare të kancerit të gjirit. Po ashtu, theksohet rëndësia e testimeve gjenetike dhe strategjive preventive për individët me predispozitë të lartë. Ky studim do të kontribuojë në kuptimin më të thellë të mekanizmave biologjikë dhe do të ofrojë një bazë të rëndësishme për zhvillimin e qasjeve më të personalizuara dhe efikase për trajtimin dhe parandalimin e kancerit të gjirit trashëguar.

***Fjalë kyce**: Gjene, BRCA1, BRCA2, kancer gjiri, mutacione, epidemiologji.*

Introduction

The BRCA1 and BRCA2 genes, frequently referred to as key susceptibility genes for breast and ovarian cancers, were first identified in 1990, marking a significant milestone in cancer genetics research (Varol, 2018).

An individual has two copies of each gene - one copy inherited from each parent. These genes are also named tumor suppressor genes, which play a role in some organs in the control of chromatin remodeling, transcription, regulation of the cell cycle, and the process of DNA regulation through the production of certain proteins in the normal human genome. Still, their

germline mutations predispose to an increased risk of developing breast and ovarian cancer and also increase the risk of other degenerative pathologies such as prostate and pancreatic cancer. Hereditary breast and ovarian cancer syndrome is characterized by the occurrence of breast and ovarian cancers due to a genetic predisposition. This condition arises from a hereditary germline mutation in one allele of the BRCA1 or BRCA2 genes, followed by a loss of heterozygosity in somatic cells. Clinically, the syndrome is associated with key features such as multiple family members affected by breast and/or ovarian cancers, a personal history of these malignancies, onset of cancer at a young age, and instances of male breast cancer within the family or personal history. (Clark SL, 2012) (Petrucelli N, 1998 Sep 4 [Updated 2023 Sep 21])

Over 400 distinct mutations have been identified in the BRCA1 and BRCA2 genes. Most of these mutations are unique, with individual families often carrying a specific variant. This highlights the genetic diversity and complexity associated with hereditary breast and ovarian cancer syndromes.

In addition to the variability seen in familial mutations, differences are also seen based on ethnicity and geographic location. The cumulative risk for the manifestation of the degenerative diseases mentioned above varies depending on age. Patients with BRCA1/2 gene mutations are screened with annual mammography and breast MRI along with transvaginal ultrasonography and CA15-3 and CA-125 levels every 6-12 months for breast and ovarian cancer. (Varol U, 2018). With the ongoing epidemiological shift, where infectious and transmissible diseases are increasingly under control and life expectancy continues to rise, chronic conditions—particularly degenerative diseases like cancer—have emerged as a central focus of modern medicine. Of all NCD deaths, approximately 30% will be due to cancer. (CH., 2022)

A critical challenge in managing breast cancer today is undoubtedly the persistent issue of inequality in global health care, where as a result of the inequality in the distribution of resources, poorly developed infrastructure, and minimal access to health care in low- and middle-income countries will

result in a higher mortality rate as a result of late diagnosis. Given the current global context, breast cancer must remain a primary focus of attention.

BRCA 1/2 genes and structure

The BRCA1 gene is a recessive gene cloned in 1994, located on chromosome 17q21 and is encoded by 24 exons. (Hall, 1990), (Clark SL, 2012), (Miki, 1994). It is composed of many domains that interact with molecules whose functions are different, such as tumor suppressors of the p53 type, RB, ATM, BRCA2; DNA repair protein type, RAD50, RAD51; type oncogenes, c-Myc, E2F, casein kinase; type 1 transcriptional activators and repressors, RNA polymerase II, RHA, CtIP, histone deacetylase complex; cell cycle regulators such as cyclins and their dependent kinases and others. (Deng CX, 2000)

The BRCA2 gene is located on the long arm of chromosome 13 (13q12.3), which consists of 27 exons that code for a protein with 3418 amino acids. (Fradet-Turcotte, 2016, Retrieved Oct 12, 2024), (Wooster, 1995). This gene was first discovered by Michael Stratton and his colleagues in 1995 in the United Kingdom at the Sutton Cancer Research Institute. (Fradet-Turcotte, 2016, Retrieved Oct 12, 2024)

The RING domain is situated at the N-terminus of BRCA1, facilitating interactions with the BARD1 protein and a nuclear localization sequence (NLS). (Clark SL, 2012). The NLSs are situated more centrally within BRCA1 (Chen CF, 1996), while the envelope domain is positioned toward the C-terminus, binding to the partner and localizer of BRCA2 (PALB2). A CKH2 phosphorylation site is located at S988 in the core region of this gene, while the SCD domain is phosphorylated by ATM, a crucial mechanism for the activation of BRCA1-mediated G2/M and S phase checkpoints.

At the C-terminus (terminal part) are located two BRCT domains, which bind ATM-phosphorylated abrasins, CtBP-interacting protein (CtIP), and C-terminal BRCA1-interacting protein 1 (BRIP1). The SQ/TQ cluster domain contains approximately ten potential phosphorylation sites. (Roy R, 2011), (Gorodetska I, 2019). The N-terminus of BRCA2 binds PALB2 at amino acids 21-39. (Oliver AW, 2009). More centrally located are the eight BRC repeats between amino acid residues 1009–2083 that bind RAD51. (Wong AK, 1997), (Bignell G, 1997)The DNA binding domain of BRCA2 contains

a helix (H) domain, three nucleotide-binding folds (OB), and a tower (T) domain, which enables BRCA2 to facilitate binding to both single- and double-stranded DNA (Yang H L. Q., 2005) (Yang H J. P., 2002). The C-terminus contains the NLS and a CDK-dependent phosphorylation site at S3291 that also binds RAD51, (Esashi F, 2005), also the TR2 domain. (Gorodetska I, 2019) (Roy R, 2011).

Functions of BRCA1 & BRCA2

The proteins produced by *BRCA1* and *BRCA2* genes primarily function to preserve genomic stability by facilitating DNA repair through the mechanism of homologous recombination (HR) (AR., 2014). (AR., 2014), (Eeles, 1999, Retrieved Oct 13, 2024), (Gudmundsdottir, 2006). The proper dysfunction of the BRCA genes will result in genomic instability that will result in the oncogenic transformation of non-tumorigenic cells into tumor-initiating cells, also known as cancer stem cells. BRCA1 plays an important role as a protector of genome stability from oxidative stress. In specific health circumstances, under stress, during chemotherapy, exposure to UV and X radiation, and in the absence of nutrition, reactive oxygen species (ROS) levels become imbalanced, leading to an increase in their concentration and resulting in damage to cellular structures (Tudek, 2010). One study revealed that the loss of BRCA1 activity leads to an increase in cellular reactive oxygen species (ROS) and vice versa (Gorodetska, 2019; Saha, 2009; Martinez-Outschoorn UE, 2012). Both BRCA1 and BRCA2 proteins are involved in transcriptional regulation (Vidarsson H, 2002). Research has demonstrated that BRCA1 and BRCA2 are integral to cell cycle regulation (Gorodetska, 2019; Ruffner, 1997), with BRCA2 playing a significant role in this process.

Both BRCA1 and BRCA2 are essential in mitophagy, a selective autophagy pathway responsible for maintaining mitochondrial quality by eliminating defective mitochondria. Additionally, BRCA1 regulates gene expression epigenetically through chromatin remodeling.

Evidence suggests that BRCA1 and BRCA2 exhibit tissue-specific tumor suppressor functions, with mutations predominantly contributing to breast and ovarian cancer development. However, the exact mechanisms underlying

this tissue specificity are still unclear. One explanation for the observed tissue selectivity may involve estrogen dependence, as estrogen stimulates rapid proliferation in breast epithelium during puberty (Welcsh, 2001; Lee, 2014).

BRCA genes and breast cancer

Breast cancer is the most prevalent cancer among women globally and is a primary cause of female mortality. The occurrence of breast cancer differs across ethnic groups and geographic regions, emphasizing the role of environmental and lifestyle factors in its development. Epidemiological studies have identified a wide range of risk factors for breast cancer.

These include early menopause, alcohol and tobacco consumption, exposure to radiation, obesity, a sedentary lifestyle, urban living, insufficient physical activity, a diet high in fats, repeated miscarriages, lack of breastfeeding, hormone replacement therapy, aging, socioeconomic status, exogenous hormone use, breast tissue density, and a family history of breast or other cancers. While genetic factors are considered primary contributors to breast cancer risk, family history remains the most significant non-modifiable risk factor. Hereditary factors contribute to 3% to 10% of all breast cancer cases, and up to 30% of breast cancers are classified as early-onset, highlighting the role of genetics alongside environmental and lifestyle influences. (Tereschenko IV, 2002).

In his study, Armaou emphasizes that a primary genetic factor accounts for 5-10% of all cases of this type of cancer in Western countries (Armaou S, 2009). 90% of cases of hereditary breast cancer and most cases of hereditary ovarian cancer are caused by mutations in the BRCA1 and BRCA2 genes (Malone KE, 2006). According to Mehrgou, women with a BRCA1 gene mutation had a 60-80% risk of developing breast cancer. Of the 35% of families with early-onset breast cancer associated with *BRCA2* germline mutations, the risks are divided between ovarian and breast cancer in men. The risk of ovarian cancer is significantly higher for female relatives in these families, while shows a notable but relatively lower risk compared to women. Estimates indicate that men carrying *BRCA2* mutations face a breast cancer risk of approximately 6-8%, whereas *BRCA2* mutations are also strongly linked to ovarian cancer risks in women. (Mehrgou A, 2016 May).

Balraj's study highlights that the *BRCA1* gene is responsible for 52% of familial breast cancer cases, while *BRCA2* accounts for 32% of these cases (Balraj, 2002). It is important to note that the prevalence of *BRCA1* and *BRCA2* mutations varies among different ethnic populations. For instance, *BRCA1* mutations are more common in Jewish women, while *BRCA2* mutations are predominantly observed in Italian women. (Mehrgou, 2016).

A significant study focusing on the Western Balkans was conducted for the first time in North Macedonia, involving Albanian women from Kosovo and North Macedonia who had breast cancer. Findings revealed that 7.9% of women from Kosovo exhibited mutations in the *BRCA* genes, with 6% having mutations in *BRCA1* and 1.9% in *BRCA2*. Conversely, in North Macedonia, 3.6% of breast cancer cases demonstrated mutations in the *BRCA* genes, with 0.9% linked to *BRCA1* mutations and 2.7% linked to *BRCA2* mutations.

The study further highlighted that the *del c.3700_3704* mutation of *BRCA1* is the most prevalent in the global population, leading to the recommendation for the implementation of rapid and cost-effective genetic screening programs tailored to the Albanian population (Ivana Maleva Kostovska, 2022).

Cancer type	***General population risk***	***Risk for malignancy***	
		BRCA1	***BRCA2***
Breast	12%	55%-72% by age of 70	45%-69%
Contralateral breast cancer	2% w/in 5 years	20%-30% w/in10 yrs	40%-50% w/in 20 yrs
Ovarian	1%-2%	39%-44%	11%-17%
Breasts in men	0.1%	1%-2%	6%-8%

Prostate	6% by age 69	21% by age 75 yrs 29% by age 85 yrs	27% by age 75 yrs 60% by age 85 yrs
Pancreatic	0.5%	1%-3%	3%-5% by age 70 yrs
Melanoma	1.6%	-	Elevated risk

Table 1: Risk of malignancy in individuals with a BRCA1 or BRCA2 pathogenic variant

Technologies and genetic tests for the identification of BRCA1 and BRCA2 mutations in breast and ovarian cancer

An individual with a BRCA1- or BRCA2-associated malignancy (such as ovarian cancer or breast cancer at age <50) is most likely to benefit from molecular testing; this person is frequently referred to as the "best test candidate." In contrast to a family member who might not have a personal history of cancer or who might have an unrelated malignancy, the "best test candidate" should ideally be the first to undergo molecular genetic testing. In the event that the most suitable test candidate is unavailable, molecular testing may be conducted on a different person who has no history of cancer, with the understanding that the absence of a pathogenic variant does not rule out the possibility of a BRCA1 or BRCA2 pathogenic variant running in the family (Petrucelli N, 1998 [Updated 2023 Sep 21].).

Genetic testing to identify mutations in the BRCA1 and BRCA2 genes is a key tool in the prediction and management of breast and ovarian cancer, especially for individuals with a family history of these diseases. Mutations in these genes are closely associated with an increased risk of developing breast and ovarian cancer, making genetic testing an important tool for diagnostics and preventive strategies. These tests can help identify individuals who have a high predisposition to develop these cancers and

provide opportunities for early intervention, such as frequent screening and preventive testing such as periodic mammography, prophylactic mastectomy, or oophorectomy (removal of the ovaries). Identification of BRCA1 and BRCA2 mutations can also help determine much more personalized and convenient treatments for affected individuals, including certain therapies, such as the use of PARP inhibitors (Pujol P, 2021), that have shown efficacy in patients with these mutations. Thus, genetic testing for BRCA1 and BRCA2 offers emmense opportunities for the prevention and treatment of breast and ovarian cancer, improving patient care and chances of survival.

Generally speaking, a genetic test is quite expensive even though covering all common and uncommon mutations in the BRCA1 and BRCA2 genes is desirable. Comprehensive sequencing and testing of wide genomic rearrangements are part of the usual procedure for the laboratory evaluation of BRCA genes. It is also possible to conduct a single-site targeted mutation analysis if the patient has a family who has a specific mutation. These days, multi-gene panels with wide genomic rearrangements may be used for greater affordability in risk assessment (Petrucelli N, 1998 [Updated 2023 Sep 21].) (Varol U, 2018). Several laboratories and companies specializing in genetics and diagnostics offer genetic testing to identify mutations in the BRCA1 and BRCA2 genes. The tests are based on DNA analysis from blood, tissue/biopsy samples, and saliva; they can be grouped as follows:

- Tests based on the PCR (Polymerase Amplification Reaction) technique: This technology is used to amplify specific segments of DNA and analyze specific mutations that may be present in the BRCA genes. PCR is a well-known and widely used method for detecting known mutations in these genes.

- Gene Panel Tests (Next-generation sequencing, NGS): The use of Next-Generation Sequencing (NGS) technology has increased greatly in recent years. NGS can broadly analyze many genes, including BRCA1 and BRCA2, and detect new or unknown mutations (ER., 2008). This method enables massive DNA sequencing and provides more detailed information about many genes that are associated with cancer, not only BRCA1 and BRCA2.

- Commercial tests and direct-to-consumer services: Some companies offer genetic tests to individuals without the need for a genetic counselor or

medical referral. Companies such as 23andMe, AncestryDNA, and Color Genomics offer BRCA1 and BRCA2 testing options as part of a genetic testing panel. However, these tests can be more limited and often only analyze the most common mutations of these genes.

The technology used for these tests includes:

- DNA sequencing is a method that involves reading the DNA bases to detect variations that may indicate mutations.
- Microarray (so-called "DNA chips"): This technology uses small plates equipped with DNA fragments designed to detect certain mutations, such as those in BRCA1 and BRCA2.
- Polymerase Chain Reaction (PCR): This process enables the amplification of DNA to analyze and detect possible mutations in certain genes.

(Ellison G, 2015).

In general, the technology used for BRCA1 and BRCA2 genetic tests is very advanced and continues to evolve to detect new mutations and provide faster and more accurate results.

Concluding remarks

In conclusion of this review, we emphasize that BRCA genes are essential in the maintenance of genomic integrity, protein stability, control of cellular oxidative stress, modification of transcription, promotion of cell cycle progression, and epigenetic regulation of gene expression, among other biological processes. Mutations affecting BRCA1 and BRCA2 result in the development of a series of cancerous diseases, including; breast and ovarian cancer, with lower incidence for other cancers such as prostate, pancreatic, and melanoma. Research indicates that exon 11 is the most frequently mutated exon in both BRCA1 and BRCA2 genes, accounting for more than 50% of observed mutations.

Looking ahead, advancements in genetic screening, such as next-generation sequencing, will enhance the identification of BRCA mutations, enabling broader access to early detection and preventive care. Expanding research into less understood mutations and their functional impact will further refine

risk prediction models and improve clinical interventions. Additionally, integrating genomic data with other biomarkers could pave the way for more precise and holistic treatment plans.

As personalized medicine continues to evolve, the insights gained from studying BRCA1 and BRCA2 will remain at the forefront of breast cancer research, driving innovation in prevention, early intervention, and therapeutic development, ultimately improving outcomes for patients worldwide.

The increase in breast cancer cases from year to year in Albania and the role of BRCA1/2 in this disease has prompted us to study the epidemiology of mutations in these genes for the first time in our country.

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