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Rewiew

The Brca1 and Brca2 Proteins and Tumor Pathogenesis

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Abstract. *Germline alterations of the BRCA1 or BRCA2 genes result in susceptibility to breast and ovarian cancer. Protein-protein interaction studies, transcription activity and mouse knockout experiments have suggested that the Brca1 and Brca2 proteins are of importance in DNA repair and maintenance of genome integrity, possibly due to the transactivation function of Brca1 or Brca2. Subsequently, tumors in individuals carrying germline mutation in either BRCA1 or BRCA2 gene show instability at chromosomal and gene level. Chromosomal and gene alterations are more pronounced in tumors from BRCA1 and BRCA2 mutation carriers than in sporadic tumors. Furthermore, BRCA1 and BRCA2 mutated breast tumors differ from sporadic tumors in respect to histological phenotype. Typically, a higher grade of malignancy is observed in familial tumors. This review summarizes the putative functions of the Brca1 and Brca2 proteins and pathogenesis in tumors of BRCA1 and BRCA2 mutation carriers.*

Positive linkage of hereditary breast cancer to chromosome 17q21 and 13q12-q13 was observed in 1990 and 1994, respectively (1, 2). Later, these chromosome regions were shown to carry breast cancer susceptibility genes, termed *BRCA1* and *BRCA2* (3, 4). The large number of reported germline mutations in *BRCA1* and *BRCA2* genes increases the risk of breast, ovarian, and other cancer types (for review see reference 5). Most of the mutations are small insertions and deletions that result in a frameshift and truncated proteins. A penetrance variation is observed, probably caused by difference in genetic background, the action of modifying genes or location of the mutation within the *BRCA1* or *BRCA2* genes. Location of mutation affects the risk of ovarian cancer; there is a higher risk if mutations are located in the amino terminal or the central part of the *Brca1* protein, than in the carboxy terminal or, as in the case of *Brca2*, there is an elevated risk if mutations are located within the BRC repeats (5). Most of the present studies on the penetrance are based on high-risk families and therefore general penetrance may have been overestimated or may be relevant only to the families in question. More recent population studies have suggested lower penetrance (6). Knowledge on the *Brca1* and *Brca2* proteins has been increasing dramatically in recent months and this review will focus on their function with respect to the tumor phenotype in carriers of *BRCA1* and *BRCA2* gene mutations.

The Brca1 and Brca2 proteins. In *Brca1*, several binding domains have been identified, that interact with other proteins (Figure 1 and Table I). The cysteine-rich metal binding RING finger domain (C3HC4), located in the N-terminal of the *Brca1* protein, has been shown to be important for protein-protein interaction. The most prevalent missense germline mutations target the metal binding residues C61 and C63 in *Brca1* (27, 28). The *Bap1* protein, a ubiquitin hydrolase, and the *Bard1* protein, another RING finger protein, have been reported to bind to the wild type, but not mutated, RING finger domain of *Brca1* (7, 8). *Bap1* binding to *Brca1* suggests that deubiquitinating enzymes play a role in *Brca1* function, and *Bap1* may participate in the *Brca1* growth control pathway. In addition to a RING finger at the amino terminus, the *Bard1* protein has ankyrin-like sequences and *BRCT* domains at the carboxy terminus, homologous to those of the *Brca1* protein (8). Interestingly, germline and somatic mutations are found in the BARD1 gene in several malignancies, including breast cancer (29). The nuclear localization signals of *Brca1* interact with importin α and *Brap2*, which presumably participate in nuclear import of *Brca1* (12, 13). Experiments with *Brca1* specific antibodies support a nuclear localization of the *Brca1* protein in normal and malignant epithelial cells (30).

The most exciting feature of the *Brca1* protein is the ability to bind *Rad51* and the transactivation domain at the carboxy terminus. *Rad51* is known to be involved in DNA recombination and repair and this suggests that *Brca1* is of

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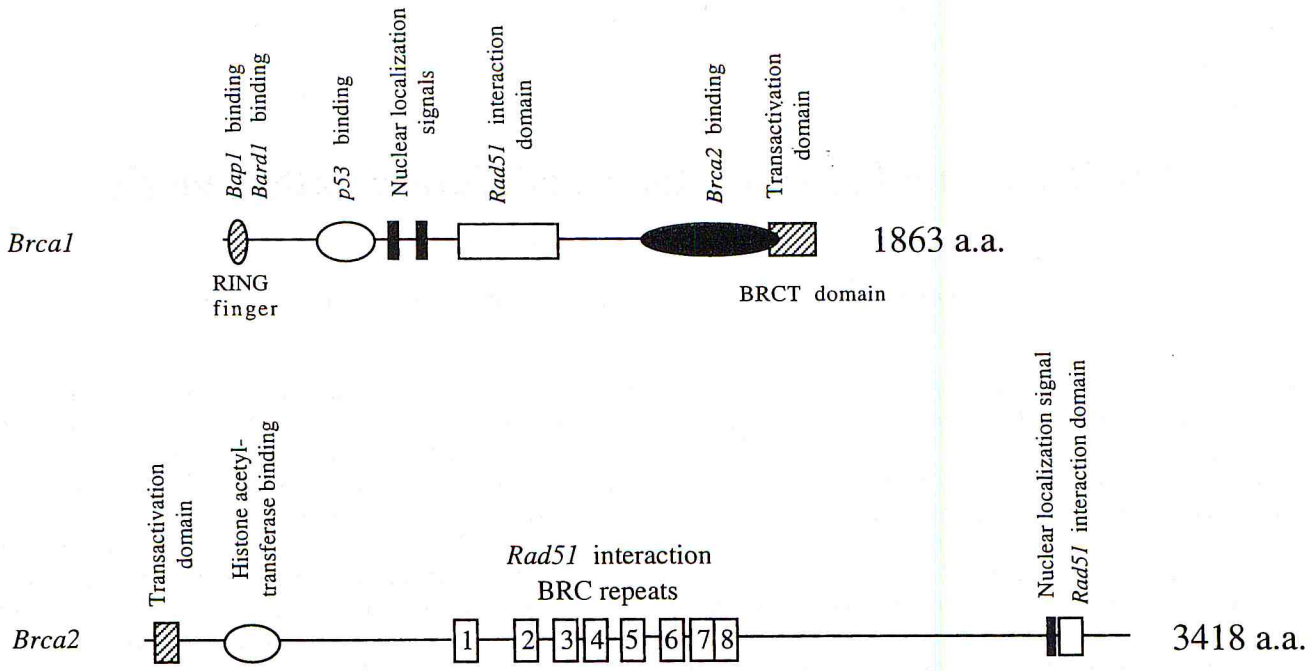

Figure 1. *Domains, motifs and repeats of the Brca1 and Brca2 proteins. See text for details and references.*

importance for this function. The role of *Brca1* in DNA repair is supported by evidence from the induction of phosphorylation in response to DNA damage (31, 32). By knockout experiments it has been shown that the *Brca1* protein is participating in transcription coupled DNA repair (33). At present it is not clear if *Brca1* has a direct role in the transcription coupled DNA repair or a role as a transcription factor, essential for the expression of genes whose products are required for this type of repair mechanism. Mapping of the transactivation function to the carboxy terminus of the *Brca1* protein and binding to the RNA polymeraseII holoenzyme strongly suggests that one of the *Brca1* function is to regulate gene expression (18, 33, 34,35). Subregions of the *BRCT* domain in *Brca1* interact with the RNA polymeraseII holoenzyme and RNA helicaseA serves as an adaptor (19). Together, these data suggest that the *Brca1* protein can function as a transcriptional coactivator. The *Brca1* protein also binds several specific transcriptional regulators like *p53*, *myc*, CtIP and E2F (9, 10, 16, 36). The exact role of the *Brca1* interaction with these transcription factors is not clear, but in some cases this results in altered expression of target genes.

In multiple fetal and adult tissue the spatial and temporal pattern of *Brca1* and *Brca2* expression is virtually indistinguishable (37, 38). Coordinated expression of *Brca1* and *Brca2* is further supported with studies on cell lines (39). The *Brca1* associated proteins *Rad51*, *Bap1* and *Bard1* have also been shown to have similar expression pattern (7, 14, 40). Ribozyme or antisense RNA studies have suggested that *Bard1* repression induces complex changes in mammary epithelial cells to a premalignant phenotype (40). These findings, together with the protein-protein interaction studies, suggest that protein complexes of *Rad51/Brca1/Brca2/Bard1*, and possibly other proteins, are of functional significance (Table I). The expression of both *BRCA1* and *BRCA2* genes is elevated in late G1 phase of the cell cycle (41-44). The *Brca1* protein undergoes serine hyperphosphorylation in the G1-S phases of the cell cycle and dephosphorylation after M phase (32, 45, 46). This suggests that both *BRCA1* and *BRCA2* proteins are regulated by expression in the cell cycle and that the *Brca1* protein is regulated by phosphorylation, in a cell cycle dependent manner. The biological activity is probably regulated by cyclin dependent kinases, since Cdk2 and other kinases associated with cyclin A and D have been shown to bind to and phosphorylate *Brca1* (36, 45).

The *Brca2* protein has a nuclear localization signal, binds *Rad51* and has a transcriptional activation domain as *Brca1* (Figure 1 and Table I). It has also been shown that *Brca2* can bind the P/CAF protein, which is a histone acetyltransferase that can presumably release the chromatin

structure to facilitate transcription (20, 48). Experiments with knockout mice support the role of *Brca1* and *Brca2* proteins in DNA recombination and repair of double-strand DNA breaks.

Brca1 and Brca2 knockout mice. Most *Brca1* -/- and *Brca2* -/- knockout mice have a similar phenotype; they only survive early embryogenesis and show signs of a growth defect associated with activation of the *p53* pathway (Table II). The radiation sensitivity and reduced proliferation detected in *Brca1* -/- and *Brca2* -/- knockout mice is also seen in *Rad51* -/- knockout mice, suggesting a role in the same biochemical pathway (50, 53, 54). While the T*p53* -/- knockout mice develop tumors within 6 months of age, the double knockout of T*p53* -/- and *Brca1* +/- show development of tumors at younger age, and preferably mammary tumors (11, 49). This, and partial rescue of *Brca1* -/- and *Brca2* -/- lethal phenotype by T*p53* double knockout, suggest that the *Brca1* and *Brca2* proteins act in the same pathway as *p53* (52-55). One explanation could be that frequent DNA breaks due to defects in *Brca1*, *Brca2* or *Rad51* result in accumulation of the *p53* protein with consequent transcriptional upregulation of the p21 gene, resulting in reduced proliferation. By knocking out the T*p53* alleles, this checkpoint control of the cell cycle is then diminished, resulting in slightly longer survival of the mouse embryo. Indeed, an upregulation of *p53* and p21 is seen in *Brca2* -/- knockout mice and embryonic death in the double knockout p21 -/- and *Brca1* -/-, is observed at later stages than in the *Brca1* -/- knockout mice (53, 56-58). Still, the common functional pathway of *Brca1* or *Brca2* and *p53* proteins may be more complicated than this. Recent findings have shown that *p53* can interact with both *Brca1* and *Brca2* proteins (10, 11, 26). The interaction of *Brca1* with *p53* results in enhanced transcription of *p53* target genes such as the p21 and Bax genes, while it has been suggested that the *Brca2* protein specifically inhibits the *p53* transactivation (10, 11, 26).

Some *Brca2* -/- knockout mice appear to have a milder phenotype and are partly viable, presumably due to larger part of the protein expressed. These mice have DNA repair defects as a consequence of dysfunctional *Brca2* protein (56-58) (Table II). In these *Brca2* -/- knockout mice there is a high incidence of lymphomas, that may reflect defects in somatic recombination in the corresponding cell type of the immune system (57).

Table I. *Protein-protein interactions where the Brca1 and/or Brca2 proteins are involved.*

	Interacting partner	Function of the interacting protein	Domain or region*)	Reference
Brca1	Bap1	Ubiquitin hydrolase	RING finger	7
	Bard1	?	RING finger	8
	Myc	Transcriptional regulator	175-303 & 433-511	9
	p53	Transcriptional regulator	224-500 & BRCT	10, 11
	Importinα	Nuclear import	NLS	12
	Brap2	Nuclear import?	NLS	13
	Rad51	DNA recombination and repair	758-1064	14
	Brca2	Transcription and DNA repair	1314-1756	15
	CtIP	Transcriptional regulator?	1602-1863	16, 17
	RNA polII holoenzyme	Transcription	BRCT domain	18, 19
Brca2	P/CAF	Histone acetyltransferase	290-453	20
	Rad51	DNA recombination and repair	BRC repeats & 3196-3232	21-25
	p53	Transcriptional regulator	?	26
	Brca1	Transcription and DNA repair	?	15

*) in Brca1 or Brca2, numbers are the amino acids involved in the protein-protein interaction

BRCA1 and BRCA2 and sporadic breast cancer. The *BRCA1* and *BRCA2* genes do not appear to be somatically mutated in human breast cancer (59-62). Somatic mutations have been reported in both genes in low proportion, possibly 5-10%, of ovarian tumors (59, 63-65). LOH at chromosome regions 17q21 and 13q12-q13, harboring the *BRCA1* and *BRCA2* genes, are frequent in sporadic breast cancer but the mapping efforts so far have not revealed whether these genes are the primary targets of relevance for tumor pathogenesis (66-70). LOH at chromosome 13q12-q13 has been associated with reduced patient survival by using markers within and in the vicinity of the *BRCA2* gene (66). Markers in the vicinity of the *BRCA1* gene show also association with clinicopathology, particularly estrogen receptor negativity, suggesting that there may be some interplay between this receptor and *BRCA1* (70). Although

Table II. *Phenotypes of Tp53, Rad51, Brca1 and Brca2 knockout mice.*

Knockout mice	Viable/Embryonic death	Animal phenotype	Cell phenotype	p53 double knockout	Reference
Tp53 -/-	Viable	Various tumors		-	49
Rad51 -/-	E5-6d*		Radiation sensitive, reduced proliferation	Partial rescue (E8.5-9.5d*)	50
Brca1 +/-	Viable	Normal		Mammary tumors	51
Brca1 -/-	E5-6d*		Radiation sensitive, reduced proliferation, upregulated p21	Partial rescue (E8.5-9.5*)	52, 53
Brca2 -/-	E7.5-8.5d*		Radiation sensitive, reduced proliferation	Partial rescue (E9-10d*)	54, 55
Brca2 -/-	Partly viable	Lymphomas	Defect in DNA repair, upregulated p53, upregulated p21, reduced proliferation		56-58

*Embryonic death at the given day (d) of development

somatic mutations are rare in the *BRCA1* and *BRCA2* genes, several reports have described reduced expression of the *BRCA1* gene in human breast tumors, as a consequence of methylation in the promoter region, suggesting that absence of *Brca1* may contribute to the pathogenesis of a proportion of sporadic breast cancer (30,71-73). This reduced or absent expression of *Brca1* may be involved in the tumor progression, since it is mainly found in high-grade ductal breast tumors (30).

The instability of the genome in BRCA1 and BRCA2 associated tumors. Alterations are observed more frequently in the genome of tumors from *BRCA1* or *BRCA2* mutation carriers than in sporadic tumors, suggesting a specific or more aggressive tumor progression pathway in breast cancer in the presence of a germline mutation (Table III). Failure in DNA repair function mechanism due to dysfunctional *Brca1* and *Brca2* proteins could be responsible for this instability. Genomic alterations are observed both at chromosomal and at gene level. Several methodological strategies have been used to detect the difference in the genome of sporadic and familial breast cancer; comparative genomic hybridization (CGH), loss of heterozygosity, immunohistochemistry and DNA mutation analysis. The CGH studies that cover the complete genome in a single experiment suggest a higher number of chromosome arms affected in familial than in sporadic tumors (74). A difference with respect to affected chromosomal arms is detected in *BRCA1* and *BRCA2* associated tumors, suggesting a difference in tumor progression and maybe reflecting a specific or separate role of the corresponding genes (74). Chromosomal alterations in male breast tumors of *BRCA2* mutation carriers are almost identical to those identified in the corresponding *BRCA2* associated female breast cancers (86). These results suggest that despite hormonal differences between females and males, similar genetic changes are selected.

The wild type alleles of the *BRCA1* or *BRCA2* genes are lost at high frequency in familial tumors (77, 80, 82, 83). It is not possible from the present data to determine whether the loss of *BRCA1* and *BRCA2* wild type alleles precedes additional somatic genetic events. Such a sequence in the tumor progression fits well with the idea that the *BRCA1* and *BRCA2* genes act as tumor suppressor genes and require a double hit mechanism for malignant progression.

As in the human breast tumors with dysfunctional *Brca1* or *Brca2* protein, cells from *Brca1* -/- or *Brca2* -/- knockout mice show accumulation of chromosomal abnormalities (58, 87). Similarly, a human pancreatic adenocarcinoma cell line lacking functional copies of the *BRCA2* gene is defective in repairing double strand DNA breaks induced by ionizing radiation or drugs, suggesting that *Brca2* defective cancer cells are highly sensitive to agents that cause double strand breaks in DNA (88).

Elevation of T*p53* mutations in tumors of *BRCA1* germline mutation carriers has been reported (75, 76). Inconsistency is observed in this regard; Crook et al 1997 (75) reported 100% *p53* mutations in germline *BRCA1*

mutation associated breast tumors and a preferential localization of mutations in exon 5, while a lower frequency, or 20% is reported by Schlichtholz et al 1998 (89), without a preferential mutation site. Relatively high *p53* staining is detected in *BRCA1* associated tumors (76). Higher loss of heterozygosity at the *TP53* locus and overexpression of the *p53* protein has been found in tumors from *BRCA2* mutation carriers (84). The elevation of *p53* in *BRCA1* and *BRCA2* tumors may be due to accumulation of mutated forms of the *p53* protein or to cell cycle checkpoint control activation by stabilization of the wild type *p53* protein. It can be concluded that dysfunctional *Brca1* or *Brca2* proteins affect the *p53* regulation in human breast tumors. While it is tempting to conclude that somatic mutations in the *TP53* gene are necessary or give a growth advantage in tumors with *BRCA1* or *BRCA2* mutations, further evidence is needed, especially in view of the present inconsistency in the literature. These findings are consistent with the observation that *p53* and *Brca1* or *Brca2* are in the same biochemical pathway, as suggested by the knockout mice experiments.

Even though the elevated alterations in the genome of *BRCA1* or *BRCA2* mutation carriers are in line with the role of the *Brca1* and *Brca2* proteins in DNA repair, the precise mutation mechanism is poorly understood. LOH and CGH studies suggest that large regions of chromosomes are affected (74, 79, 80). Elevations of point mutations detected in the *TP53* gene, suggest that single nucleotides are affected as well. In the *BRCA2* gene carriers 2 out of 10 somatic mutations in the *TP53* gene are large deletions and a 14- nucleotide deletion is also detected (85). Crook *et al* (75, 76) also reported an unusual spectrum of *TP53* mutation in *BRCA1* associated tumors. Perhaps the mutation mechanism in tumors with dysfunctional *Brca1* or *Brca2* proteins is responsible for the unusual spectrum of *TP53* mutations.

It is possible that due to low fidelity in mitotic recombination and corresponding DNA repair as a result of dysfunctional *Brca2*, the tumors follow a more aggressive pathway of chromosomal damage, where fragile sites in the genome could be a hotspot target. The most active common fragile site FRA3B is located within the *FHIT* gene and allele-specific late replication seems to be involved in the fragility (90). *FHIT* has several characteristics of a tumor suppressor gene and abnormalities in breast tumors have been detected (91-93). LOH and expression studies of the *FHIT* gene and Fhit protein, in *BRCA2* linked and sporadic cancer, have shown its loss in a significant fraction of sporadic breast cancers and in a larger fraction of breast cancers from individuals with an inherited *BRCA2* mutation (79, 81). The numerous somatic *FHIT* gene defects detected in *BRCA2* carriers may reflect germline mutation of the *BRCA2* gene resulting in accelerated accumulation of secondary somatic genetic changes at this locus in the tumors. These genetic aberrations result in reduced expression of the putative tumor suppressor gene, *FHIT* (81).

Table III. *Chromosomes and genes with higher frequency of somatic alterations in familial breast tumors compared to sporadic breast tumors.*

Germline mutation	Chromosome	Gene	Alteration	Method	Reference
BRCA1 +/-	2q		Loss	CGH	74
	4p		Loss	CGH	74
	4q		Loss	CGH	74
	5q		Loss	CGH	74
	6p		Gain	CGH	74
	10p		Gain	CGH	74
	12q		Loss	CGH	74
	13q		Loss	CGH	74
	17p13.1	TP53	Mutation/ expression	DNA seq/IHC	75, 76
	17q		Gain/LOH	CGH/PCR	74, 77
BRCA2 +/-	1p		Loss	CGH	74
	3p		Loss/LOH	CGH/PCR	74, 78-80
	3p14.2	FHIT	LOH/ expression	PCR/IHC	79, 81
	6q		Loss/LOH	CGH/PCR	74, 80
	11p		Loss/LOH	CGH/PCR	74, 80
	11q		Loss/LOH	CGH/PCR	74, 80
	13q		Loss/LOH	CGH/PCR	74, 82, 83
	17p		LOH	PCR	84
	17p13.1	TP53	Mutation/ expression	DNA seq/IHC	84, 85
	17q		Gain	CGH	74
	20q		Gain	CGH	74

Abbreviations: LOH, loss of heterozygosity; CGH, comparative genomic hybridization; ICH, immunohistochemistry; PCR, polymerase chain reaction.

The histology of BRCA1 and BRCA2 tumors. A difference in the tumor spectrum of *BRCA1* and *BRCA2* mutation carriers is observed, mainly based on elevated frequency of

ovarian cancer in *BRCA1* mutation carriers and male breast cancer, ovarian cancer, prostate cancer and pancreatic cancer in *BRCA2* mutation carriers, in addition to female breast cancer (5). Studies that are mainly based on high-risk families have suggested a phenotypic difference in the histology between breast carcinomas occurring in patients carrying a germline mutation in *BRCA1* or *BRCA2* and those occurring in non-carriers. Furthermore, carriers with *BRCA1* and *BRCA2* mutations differ from each other with respect to histological phenotype (94). The breast carcinomas of *BRCA1* carriers are more frequently of medullary or atypical medullary type and more likely to be high grade (94-101). Tumors from *BRCA1* mutation carriers have been shown to express lower levels of receptors for estrogen and progesterone than sporadic cases (95, 96, 100-102). *BRCA2* associated breast carcinomas are high grade tumors with a rapid proliferation rate and show histological differences from *BRCA1* tumors or sporadic tumors, of which most striking, is the absence of tubular carcinoma (94, 97, 103). This, and the difference in the chromosomal alteration spectrum in *BRCA1* and *BRCA2* mutated tumors, suggests that even though *Brca1* and *Brca2* share a common function, the two proteins have a specific role.

In a population-based study of the histological phenotypes it is reported that breast tumors occurring in carriers of a *BRCA1* mutation have more frequently a high mitotic count and are more likely to contain areas of confluent necrosis, than those occurring either in age-matched controls or in carriers of a *BRCA2* mutation (104). These findings are consistent with previous studies on high risk families, although breast tumors of *BRCA2* mutation carriers had no histological features that occurred significantly more frequently than in control tumors, except for an excess of pleomorphic lobular carcinoma (104).

The difference in histological phenotype of *BRCA1* and *BRCA2* mutated tumors compared to sporadic tumors could reflect an aggressive phenotype of the genome alterations and this is in line with the proposed role of the *Brca1* and *Brca2* multidomain proteins in transcription, DNA recombination and DNA repair. From these combined data the conclusion which may be drawn is that tumor pathogenesis and progression differ in sporadic and familial breast cancer, and that probably there is also a difference between tumors from *BRCA1* and *BRCA2* mutation carriers. Although the *BRCA1* and *BRCA2* mutated tumors seem to be of a phenotype of higher malignancy, studies on patient survival have not shown a significant reduction when compared to sporadic cancer (101).

Conclusion. Knowledge on the *Brca1* and *Brca2* protein function has been growing dramatically during the last year. The *Brca1* and *Brca2* are large multifunctional proteins and have been characterized by studies on protein-protein interaction, transactivation, knockout mice, tumor phenotypes in mutation carriers, genomic instability and tumor pathology. These studies direct our idea of *Brca1* and *Brca2* protein functions towards DNA repair, which may or may not be dependent on their transcriptional activation function. There can be little doubt that additional studies on the proteins will yield new information with respect to tumor pathogenesis. At present it is not possible to establish a complete model of multistep carcinogenesis in the breast, but several findings suggest a difference of the pathogenesis in tumors from individuals carrying either *BRCA1* or *BRCA2* germline mutations and sporadic tumors. This probably reflects the role of *Brca1* and *Brca2* proteins in DNA repair and maintaining the integrity of the genome. The pathogenesis of *BRCA1* and *BRCA2* tumors, like sporadic tumors, is probably subject to regulation by multiple factors, genetic, epigenetic and hormonal.

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