Review

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 penetration 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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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 EZF (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 I). 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 Tp53 -/- knockout mice develop tumors within 6 months of age, the double knockout of Tp53 -/- 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 Tp53 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 Tp53 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 I). 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>
<thead>
<tr>
<th>Interacting partner</th>
<th>Function of the interacting protein</th>
<th>Domain or region</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brca1</td>
<td>Bap1</td>
<td>Ubiquitin</td>
<td>RING</td>
</tr>
<tr>
<td></td>
<td></td>
<td>hydrolase</td>
<td>finger</td>
</tr>
<tr>
<td></td>
<td>Bard1</td>
<td>?</td>
<td>RING</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>finger</td>
</tr>
<tr>
<td></td>
<td>Myc</td>
<td>Transcriptional</td>
<td>175-303 &amp;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regulator</td>
<td>433-511</td>
</tr>
<tr>
<td></td>
<td>p53</td>
<td>Transcriptional</td>
<td>224-500</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regulator</td>
<td>&amp; BRCT</td>
</tr>
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<td></td>
<td>Importina</td>
<td>Nuclear import</td>
<td>NLS</td>
</tr>
<tr>
<td></td>
<td>Brap2</td>
<td>Nuclear import?</td>
<td>NLS</td>
</tr>
<tr>
<td></td>
<td>Rad51</td>
<td>DNA recombination and repair</td>
<td>758-1064</td>
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<td></td>
<td>Brca2</td>
<td>Transcription and DNA repair</td>
<td>1314-1756</td>
</tr>
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<td></td>
<td>ChiP</td>
<td>Transcriptional</td>
<td>1602-1863</td>
</tr>
<tr>
<td></td>
<td></td>
<td>regulator?</td>
<td></td>
</tr>
<tr>
<td></td>
<td>RNA polII holoenzyme</td>
<td>Transcription</td>
<td>BRCT</td>
</tr>
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<td>P/CAF</td>
<td>Histone</td>
<td>290-453</td>
</tr>
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<td></td>
<td></td>
<td>acetyltransferase</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rad51</td>
<td>DNA recombination and repair</td>
<td>BRC repeats &amp; 3196-3232</td>
</tr>
<tr>
<td></td>
<td>p53</td>
<td>Transcriptional</td>
<td>?</td>
</tr>
<tr>
<td></td>
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<td>regulator</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Brca1</td>
<td>Transcription and DNA repair</td>
<td>?</td>
</tr>
</tbody>
</table>

*) 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 13q12-13q13, 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.

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

*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 Tp53 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).

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

<table>
<thead>
<tr>
<th>Germline mutation</th>
<th>Chromosome</th>
<th>Gene</th>
<th>Alteration</th>
<th>Method</th>
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<tr>
<td>BRCA1 +/-</td>
<td>2q</td>
<td></td>
<td>Loss</td>
<td>CGH</td>
<td>74</td>
</tr>
<tr>
<td></td>
<td>4p</td>
<td></td>
<td>Loss</td>
<td>CGH</td>
<td>74</td>
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<td>CGH</td>
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<td></td>
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</tr>
<tr>
<td></td>
<td>6p</td>
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<td>Gain</td>
<td>CGH</td>
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</tr>
<tr>
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<td>seq/IHC</td>
<td></td>
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<td>17q</td>
<td></td>
<td>Gain/LOH</td>
<td>CGH/PCR</td>
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<td>BRCA2 +/-</td>
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<tr>
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<td>3p</td>
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<td>74, 78-80</td>
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<td>LOH/</td>
<td>PCR/IHC</td>
<td>79, 81</td>
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<tr>
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<td>6q</td>
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<td>Loss/LOH</td>
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<tr>
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<td>Gain</td>
<td>CGH</td>
<td>74</td>
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Abbreviations: LOH, loss of heterozygosity; CGH, comparative genomic hybridization; IHC, immunohistochemistry; PCR, polymerase chain reaction.
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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