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Chapter 8

Relationship of Breast Cancer with Ovarian Cancer

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1. Introduction

Cancer is perhaps the cruelest of deadly diseases in our era. So many factors play a role in cancer and these features were characterized in 2011 as belonging to eight categories: evasion of apoptosis, excessive growth signalling, insensitivity to anti-growth signals, maintained angiogenesis, endless replicative potential, metastasis, reprogramming of energy metabolism and avoidance of immune destruction. Types of cancer may be put in different categories (or combinations of these) according to symptoms and pathogenesis, therefore revealing many relationships.

Breast cancer is the most commonly diagnosed cancer type among women. There are similarities between breast and ovarian cancer such as similar mutations (tumor suppressors, proto-oncoges), changes in hormone regulation and microenvironment, etc. In 2014, approximately 235,030 new cases are expected, and it is estimated that 40,430 deaths from breast cancer will occur. Also, an estimated 21,980 new cases of ovarian cancer will be diagnosed in 2014, with an estimated 14,270 deaths. Statistical results and similarities raise the question of whether metastasis of breast cancer is related to the occurrence of ovarian cancer.

Several mutations in growth control genes can trigger the development of tumors in the body. The specific causes of the mutations that lead to cancer are not fully known. Recent studies have tried to uncover these unknown relationships between breast and ovarian cancer. Understanding of the correlations between different types of cancers provide knowledge to us about the disease process. Recent studies focus on common mutations, tumor microenvironment, receptor inactivation, Trastuzumab resistance, etc. Thanks to these studies, new therapeutic techniques have been developed such as using miRNA as therapeutic targets or improvement of nanodrug delivery systems. Also, mathematical modeling has been used in attempts to understand changes in metabolic pathways and metastasis.

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Briefly, understanding of the associations between breast and ovarian cancers provide opportunities for the prevention of metastasis and allow development of new ways to cure cancer.

2. Hereditary Breast and Ovarian Cancer (HBOC)

Despite intense studies about breast and ovarian cancer, these cancer types are the most significant cause of death in women in our century. Recent studies have tried to identify different types of mutations for certain genes and determine changes in copy numbers, expression profiles, etc. by using high-throughput technologies [1]. Identifying variations among breast and ovarian cancers will hopefully uncover associations between them, thus possibly revealing methods for early disease screening and allow understanding of the mechanism(s) of metastasis between these two cancer types.

Several studies have continued to find a common point for breast and ovarian cancer; all studies have defined certain mutations in BRCA1/BRCA2 for these types of cancer. The statistics show that 60-80% of BRCA1/BRCA2 gene mutation carriers will develop breast cancer and 20-40% will develop ovarian cancer. Some cases of HBOC indicate a connection with constitutive epimutations or other susceptibility genes such as several gene clusters including the Fanconi anemia (FA) cluster (FANCD2, FANCA and FANCC), mismatch repair (MMR) cluster (MLH1, MSH2, PMS1, PMS2 and MSH6), NA repair cluster (ATM, ATR and CHK1/2), and tumor suppressor cluster (TP53, SKT11 and PTEN). If a patient does not have any mutations in the BRCA genes but their cancer has a phenotype characteristic of those with BRCA mutations and a dysfunction in a DNA repair system, it is known as 'BRCAness';[1]. In conclusion,mutations that occur in some DNA repair mechanisms can increase the risk of developing breast and ovarian cancer.

3. Identification of high penetrance of genes

The inactivation of BRCA1 and BRCA2 genes are germline mutations and trigger breast and ovarian cancer. This phenomenon was confirmed by high throughput technologies used for molecular diagnostics such as next generation sequencing (NGS). By using NGS, the DNA of 59 patients harbouring SNVs that include indels or large genomic rearrangements of BRCA1 or BRCA2 was analyzed. Also, 168 patients were used as blind study to compare NGS versus Sanger sequencing or MLPA analyses of BRCA1 and BRCA2. Then, by using three different capture methods, 708 consecutive patients were monitored. A total of 69 deleterious germline alterations within BRCA1 and BRCA2, and 4 TP53 mutations were detected in 468 patients. In addition to this, 36 variations that include either a premature codon stop or a splicing defect among other genes were found (*5/708 in CHEK2, 3/708 in RAD51C, 1/708 in RAD50, 7/708 in PALB2, 3/708 in MRE11A, 5/708 in ATM, 3/708 in NBS1, 1/708 in CDH1, 3/468 in MSH2, 2/468 in PMS2, 1/708 in BARD1, 1/468 in PMS1 and 1/468 in MLH3)*. This study shows the efficiency of NGS in performing molecular diagnosis of HBOC [2].

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In the past, full coding exon sequencing was challenging, because researchers had to analyse dozens of coding genes using the traditional method of Sanger sequencing. It is a very time consuming and labor intensive method. Thus, complicated genetic analysis was not possible. However, new techniques have made such research easy. Also, parallel sequencing allows for complicated genetic analysis in a short time. This technique is now reliable for genomic research, but applying this in the clinic is still difficult due to the requirement of complex equipment and highly trained staff [3]. In clinical applications, several library preparation methods have been used to demonstrate a novel capture method. Targeting coding sequences of genes have high coverage in every captured region. In order to streamline the number of germline mutation variants, further whole exon sequencing studies and confirmations are required in order to provide a gold standard for the investigation of germline variants.Nowadays, clinical decisions that include molecular diagnoses have a significant impact on the determination of treatments such as chemotherapy and prophylactic surgery. The association between breast and ovarian cancer try to depend on high or low penetrance of genes that are observable in both cancer types. The most common susceptibility genes in this field are BRCA1/ BRCA2. If any mutations are present in either of these genes, it translates to a 60-85% lifetime risk of developing breast or ovarian cancer [4].

Germline mutations in BRCA1 and BRCA2 can be inherited by offspring and thus are known as constitutional mutations. The mutations may have complete or partial gene deletions, large insertions, duplications, splicing, frameshifts, missense and nonsense mutations. Insertions and deletions may occur at the same position in the sequence and induce gene shuffling, which in turn leads to abnormal gene structure, function,etc. The rate of these mutations changes from population to population. According to data from the Breast Cancer Information Core website, approximately 3500 mutations have been reported for both genes. For instance, female breast cancer patients of Ashkenazi Jewish descent have a 10 – 12 % frequency of mutations in these genes. Frequency of this mutation is higher than in the rest of the Caucasian population, because the female Ashkenazi Jewish population harbors ancient BRCA1 / BRCA 2 mutant alleles. The 5266dup, BRCA2999del5 and BRCA1delexon17 mutations have been defined in some populations such as Slavic, Finnish, Icelandic and German [4].

In addition, the penetrance of mutations is important for genomic rearrangements to develop into a detectable trait. Detection of high penetrance genes is easier than lower ones, because they form symptoms and are always apparent in an individual carrying the allele. However, several variations in low penetrance alleles are more common, and these low penetrance alleles could increase risk to develop cancer and its progression [5]. Some researchers have focused on identification of new genes to explain the missing heritability in BRCA negative cancer patients, including targeted genes that may interact with BRCA pathways and proteins.

Nowadays, several studies have focused on finding these candidate genes and mutations using NGS technologies. According to these studies, additional high penetrance alleles have been found for breast/ovarian cancers; for instance, TP53, STK11,etc. Also, moderate penetrance alleles such as PALB2, BRIP1, RAD51C have a role in cancer via their alteration in pathways like Fanconi Anemia [6],[7]. In addition, ATM and CHEK2 have the same penetrance level and are involved in the homologous recombination repair pathway [8]. Detection of mutations and

penetrance within genes other than BRCA1 and BRCA2 has shed light on the genetic heterogeneity of HBOC.

3.1. BRCA1 and BRCA2 genes

BRCA1 and BRCA2 genes are expressed in epithelial cells of breast and ovarian tissues. They regulate the repair of some types of DNA damage and are involved in cell fate decision; if DNA damage is too excessive and cannot be repaired efficiently, the cell will be directed to be destroyed. Briefly, BRCA1 and BRCA2 genes are tumor supressor genes that are essential in homologous recombination repair of double strand breaks [9], [10]. If any mutations or damage occurs in BRCA1/BRCA2, DNA damage cannot be properly repaired and this increases the risk of developing breast cancer [11]. However, BRCA1/2 are not oncogenes.They are normal but their mutations are abnormal and cause formation of breast cancer. Chromosomal arrangements may result from errors in the DNA damage response mechanism. It might lead to genomic instability. If genomic rearrangements are large, they may escape detection. The problem is that standard genetic testing is not capable of identifying large rearrangements and therefore next generation and whole exon sequencing technologies must be used to detect these gene modifications/changes [12].

Some studies have focused on solving the mechanisms of BRCA1 and BRCA2. According to biochemical, genetic and cytological studies, the lack of BRCA1 results in cell death because BRCA1 regulates stem/progenitor cell proliferation and differentiation. Apicobasal polarity is regulated by BRCA1 and RHAMM (hyaluronan-mediated motility receptor), AURKA (aurora kinase A) and TPX2 (microtubule-associated, homolog). This gene complex can change the miotic spindle promoting activity of RHAMM which may control tumor progression. In addition to this, BRCA1 binds and regulates AURKA which plays a role in the cell cycle as a kinase and appears to be strongly involved in centrosome regulation. Therefore, variations of the AURKA gene may contribute to breast cancer progression [13]. BRCA1 causes an accumulation of TPX2 and is required for mitotic spindle- pole assembly. Not only DNA damage response and repair, but also cell differentiation requires the BRCA core complex proteins for functional integrity.

BRCA1 interacting protein or complex	Function of interacting protein	Interacting domain(a.a. residues)	Ref.
RAD51	DSB repair	Exon 11 (758-1064)	[14]
RAD50	DSB repair	Exon 11(341- 748)	[15]
BRCA2	DSB repair	BRCT domain (1314-1863)	[14]
BASC (QTM,BLM,MSH2,MSH6,MLH1,RCF)	Mismatch repair	BRCA part of complex	[16]
p53	Transcription Factor, tumor supressor	Exon 11 and BRCT domain (224 – 500 and 1760-1863)	[17], [18]

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BRCA1 interacting protein or complex	Function of interacting protein	Interacting domain(a.a. residues)	Ref.
pRB	Cell cycle regulator	Exon 11 and BRCT domain (304-394 and 15336-1863)	[19]
c-Myc	TF,oncogene	N-terminus and exon11 (175-303 and 433-511)	[20]
ZBRK1	TF,represses GADD45	Exon 11 (341-748)	[21]
ATF	TF	RING (1-101)	[22]
STAT1	Signal transducer,TF	Exon 11(502-802)	[23]
E2F	TF, cell cycle regulator	N-terminus (1-76)	[24]
RNA Pol II holoenzyme *(RPH)	Transcription	BRCT domain (1650-1800)	[25], [26]
RNA helicase A	Component of RPH	BRCT domain (1650-1800)	[27]
Estrogen receptor	Ligand responsive TF	N-terminus (1-300)	[28, 29]
Androgen receptor	Ligand responsive TF	Exon 11;BRCT domain (758-1064 and 1314-1863)	[30]
CtIP	Transcriptional co-repressor	BRCT domain (1651-1863)	[31, 32]
p300/CBP	Transcriptional coactivator	RING and BRCT domain (1-303 and 1314-1863)	[33]
HDAC1 and 2	Histone deacetylation; chromation remodeling	BRCT domain (1563 - 1863)	[34]
Centrosome (p53,Prb,Nm23)	Chromosome segregation	*BRCA1 part of the complex	[35]
BRAP2	Cytoplasmic retention	NLS (303-701)	[36]
Vasolin- containing protein, VCP	ATPase	Exon 11 (303- 625)	[37]
BARD1	Ubiquitination	RING (1-101)	[38]
BAP1	Deubiquitinating enzyme	RING (1-100)	[39]
Importin α	Nuclear transport	NLS (303-701)	[40]
BRCA2 interacting protein or complex	-	Interacting domain (a.a. residues) on BRCA2	[41]

Table 1. BRCA interacting proteins

Many biochemical studies have shed light on a multitude of proteins with defined interactions with BRCA1 and BRCA2. These proteins are involved in control mechanisms of DNA double strand breaks. Within several minutes after damage, H2AX, a member of the histone H2A family of proteins, becomes phosphorylated and foci form at the site of DNA double strand breaks [42]. BRCA1 is recruited with this area within several hours. Subsequently, RAD50 and RAD51 interact with the strand breaks. This situation shows that BRCA1 and H2AX can initiate repair mechanisms of local chromatin structure, thus DNA repair proteins can access damaged sites.

If BRCA1 and BRCA2 genes are absent from the cell, chromosomal abnormalities, breaks, aneuploidy and centrosome amplification occurs. The pathogenic tumor formation in breast and ovarian tissue may depend on chromosomal instability that is the result of deficiency of BRCA1 and BRCA2 genes. In order to reveal this relation, researchers monitored sporadic breast and ovarian tumors. 50 – 70 % of them were found to have lost an BRCA1 allele and 30 – 50 % were found to have lost an BRCA2 allele [43],[44].

Genomic instability of BRCA1 and BRCA2 genes result from the repetitive DNA elements that are of high density. 42% of BRCA1 consists of Alu sequences and 5% non-Alu repeats. The genomic region of BRCA2 consists of 47% repetitive DNA [45]. BRCA1 and BRCA2 are rare genes that include high density repetitive DNA regions. Multiple diseases are mediated by genetic rearrangements of Alu sequences. According to the given density of repeat elements in BRCA1 and BRCA2, careful analysis of these genes can reveal the risk of breast and ovarian cancer due to these susceptibility genes.

The source of the large deletions depends on repetitive regions on genes. One mechanism that manages the large deletions observed around the BRCA1 and BRCA2 that are inherited and sporadic tumors in breast and ovarian cancer (Figure1). These repeat regions may be far apart from the linear DNA but physically close in the nucleus. For instance, if a chromosome break occurs near a replication fork during replication, it might be repaired by HR to a replication fork at a nearby anchorage point.

3.2. Association between DNA damage and BRCA1-BRCA2 genes

Double strand breaks such as exposure to ionizing radiation or certain kinds of DNA-damaging agents. Genetic defects in DNA damage response genes and/or down-regulation of the DNA repair mechanisms induces genomic instability, and this can lead to carcinogenesis [46]. Among the many DNA repair pathways available in mammalian cells are homologous repair, non-homologous end-joining and single-strand annealing [47]. There are several ways that cells can repair double strand breaks. A number of signaling pathways are involved in the detection of DSBs and regulate DNA repair or apoptotic cell death. The main DNA damage recognition molecule is ATM [48], a checkpoint kinase that phosphorylates a number of proteins in response to DNA damage, including p53 and BRCA1 [Figure2].

p53 plays a critical role in preventing cancer development. Generally, p53 gene is mutated in cancer tissue, so it cannot protect the genetic integrity of cells. In physiological conditions, p53 is activated when DNA damage occurs. The failure of DNA damage response results in p53

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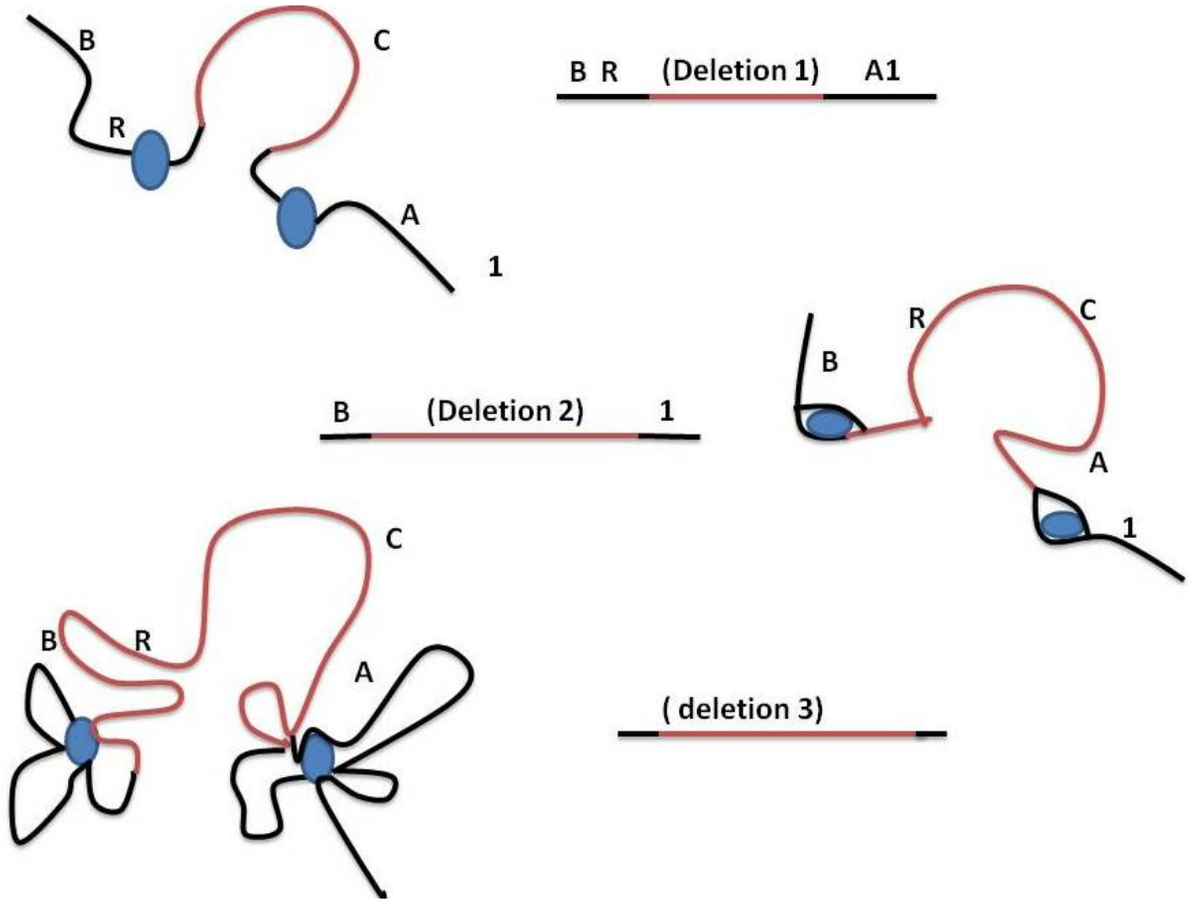


Figure 1. A mechanism for the formation of deletion by loss of a chromatin loop at different stages. Deletions of phase 1 occur in S phase, when the same repetitive sequences are physically brought together by MAR (blue ellipse). Breaks in DNA, and their repair, might lead to deletion of a chromatin loop (red). Deletions of type 2 and 3 occur by the same mechanism but occur later during DNA synthesis in the replication cycle. (Adapted from Piri et al [11])

mediated cell apoptosis [49]. Several mechanisms regulate p53 activity. p21WAF-1 has been shown to play an important role in both p53-dependent [50] and -independent pathways [51]. p21WAF-1 prevents cell cycle progression via interaction with the cyclin-dependent kinase (CDK) complex. Therefore, p53 plays a role in the most important part of providing stability to the genome by using cell cycle checkpoints, DNA repair and apoptosis.

BRCA1 also involves a gold standard for a tumor suppressor gene that is needed to prevent cancer development and progression. BRCA1 / BRCA2 related breast and ovarian cancers are have defects in a DNA repair pathway [52]. Studies have shed light on the functional roles of BRCA1/BRCA2 genes in DNA repair, cell cycle checkpoints and DNA damage signaling pathways [53]. BRCA1 interacts with several cyclins and CDKs, triggers the activation of the CDK inhibitor, p21WAF-1, and p53, thus it can control the cell cycle. The main function of BRCA1 depends on its phosphorylation status, so if the gene becomes hyper-phosphorylated following any damage or exposure to DNA damaging agents, it becomes non-functional[54].

Also, BRCA1 and BRCA2 genes are not only responsible for DNA damage response but also their proteins interact with the estrogen and androgen receptors [55]. These genes inhibit

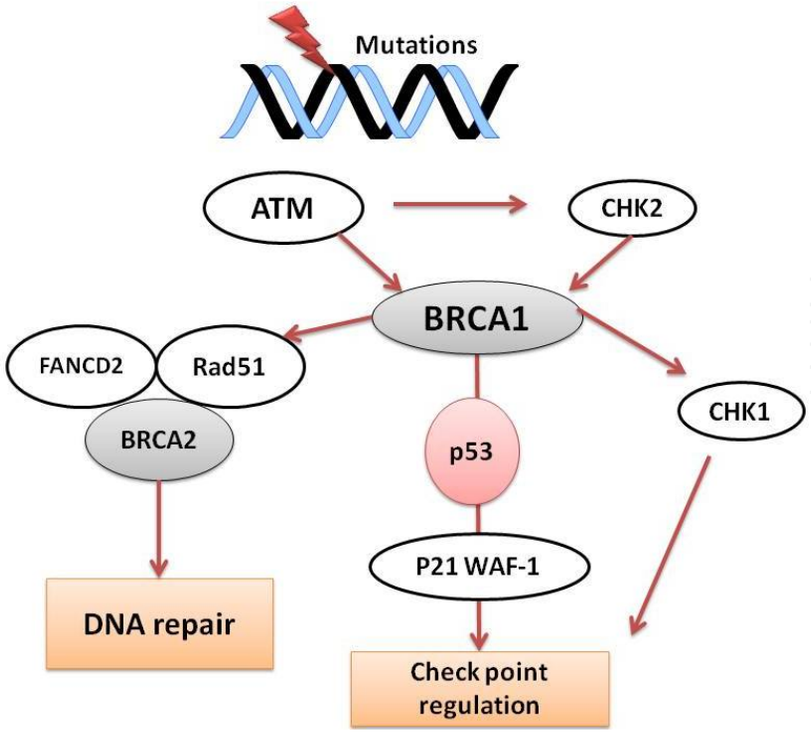


Figure 2. Schematic representation and overview of the DNA repair and checkpoint regulation of cell cycle

estrogen receptor-α activity and stimulate androgen receptors. In this way, BRCA1 mutations are associated with hormone responsive cancer. In other words, the cancer risk of BRCA1 mutation carriers will increase via hormonal factors.

3.3. Association of estrogens — Estrogen receptors with BRCA genes

Estrogen, progesterone and androgen hormones control the initiation of carcinogenesis by using special hormone receptors. Moreover, hormonal therapies frequently regulate hormone-mediated diseases such as cancer. A number of candidate genes have been identified as biomarkers for ovarian and breast cancers [56].

Frequently, damage in the DNA repair system induce growth arrest and cell death. BRCA deficient mice die in the early stages of embryogenesis. The first question that arises is why BRCA deficient breast or ovarian epithelial cells develop tumors instead of undergoing apoptosis? What is special to breast and ovarian epithelial cells that allows them to escape apoptosis or response to the DNA damage response system? Finally, how are BRCA1 and BRCA2 genes associated with estrogen levels?

The transition of the hormone independence induces the progression of breast and ovarian cancer because of DNA repair defects. The estrogen-bound receptor dimerizes and associates with chromatin. The estrogen response elements that are present on a DNA sequence motif bind directly to the receptor dimers. There are two kind of estrogen receptors:estrogen receptor-α and estrogen receptor-β. Estrogen receptor-α plays a role in proliferation, and the activation of estrogen receptor-β controls apoptosis [57]. An increase in estrogen receptor-β

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levels might be related with a reduction in breast cancer risk [58]. Estrogen receptor-β may prevent cellular proliferation by action opposite to that of estrogen receptor-α.

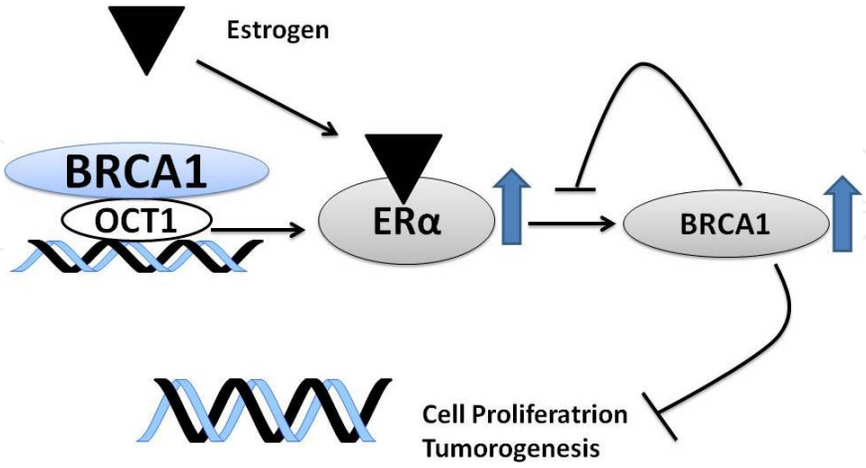


Figure 3. Schematic representation of interaction between BRCA1 and estrogen receptor (ER)-α

A woman exposed to estrogen either endogenously or exogenously, has an increased risk of developing breast or ovarian cancer. BRCA1 and BRCA2 expression levels are highest during pregnancy and puberty, when estrogen levels are increased [59].

If estrogens triggers cell proliferation [60], increased estrogens promotes the probability of developing random genetic rearrangements and errors. Metabolic processes produce reactive oxygen species (ROS) that cause oxidative damage to genomic DNA. In addition, some hormone oxidative metabolites catalyzed by cytochrome p450 enzymes can form unstable adducts in DNA which then leads to mutations [61].

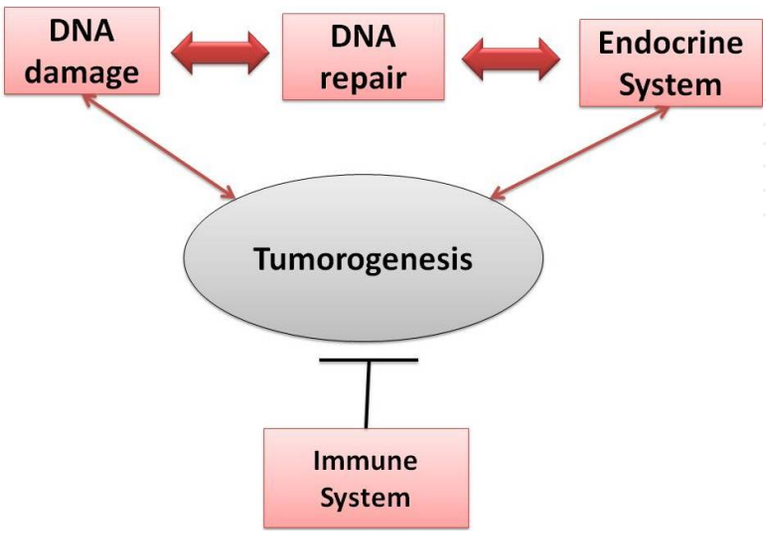


Figure 4. Connection of the hormone endocrine, immune, DNA damage and DNA repair systems in cancer

A long period of exposure to estrogen is strongly associated with an increased risk of developing breast and ovarian cancer. However, activation of DNA damage response mechanisms may be triggered via androgen signaling [62]. The estrogen receptor-mediated pathways are inhibited by BRCA1 and BRCA2 proteins which function as a suppressor in mammary epithelial cell proliferation. Also, the estrogen receptor complex regulates the transcription of BRCA1 and BRCA2 under the condition of estrogen stimulation. In addition, estrogens are not only essential for mammary growth and differentiation, but also enhance the activity of the p53 tumor suppressor protein [63].

4. Biomarkers in breast and ovarian cancer

4.1. The KRAS-variant (A germline microRNA binding site-disrupting variant)

Cancer susceptibility genes increase the risk of malignancy as a result of mutations in tumor suppressor or oncogenes that control different pathways. The KRAS variants are active at the site of the 3'-untranslated region of the complementary site of let-7 miRNA. miRNAs are 22-nucleotide long noncoding RNAs that are conserved regions. They are a novel class of oncogenes and tumor supressors that are upregulated in cancers [64]. Recent studies showed that SNPs that are present in miRNA binding sites can be powerful markers of cancer risk [65]. Ratner et al. reported that KRAS is associated with 61% of cases of breast and ovarian cancer syndrome. In another study, KRAS variants were observed to be increased within women with triple-negative breast cancer [66]. A study at Yale University, involving 58 hereditary breast and ovarian syndrome patients tested for the presence of the KRAS variant. The KRAS-variant was identified in 60% of HBOC patients who lacked BRCA1 or BRCA2 mutations. These findings strongly support the hypothesis that the KRAS-variant is a genetic marker of an increased risk of developing ovarian cancer[67].

The KRAS variant might be a new biomarker for breast and ovarian cancer. Therefore, preventing or identifying cancer in early steps may be possible by using this biomarker.

4.2. Flap Endonuclease 1 (FEN1) as a biomarker in breast and ovarian cancer

FEN1 is a kind of flap structure endonuclease that is critical for DNA repair processing. It is involved in long patch base excision repair (LP-BER) and Okazaki fragment maturation during replication. In addition, it plays a role in rescue delayed in replication forks, managing of telomere stability and apoptotic formation of DNA [68] [69]. Fen1 is also a main actor in posttranslational modifications such as acetylation, phosphorylation, sumoylation, methylation and ubiquitylation which control nuclease activities [68] [69].

FEN1 has a role in tumor formation. A FEN1 E160D mutant mouse model shows alteration in DNA repair [70] [71]. These changes trigger an increased frequency of cancer development. Polymorphic variations of FEN1 in humans may be associated with high frequency cancer susceptibility [72, 73].

FEN1 has an impact on breast tumors. It affects BRCA1, PARP1, XRCC1 and TOP2A genes. There is an association between high FEN1 and ATM expression. FEN1 may regulate the ER-induced transcriptional response with interaction of estrogen response elements [74]. There is a complex network between ER, FEN1 and ATM in breast cancer cells. Similarly, in ovarian cancer, FEN1 expression is linked to an aggressive phenotype and poor survival [75]. Abdel-Fatah et al. demonstrated that FEN1 overexpression is associated with an aggressive phenotype and poor survival in breast and ovarian cancer.

5. Conclusion

Despite the more intense studies about breast and ovarian cancer, these cancer types are the most significant cause of death in women in our century. Recent studies have tried to streamline the number of mutations for specific genes and identify changes in copy number, expression profiles, etc. by using high-throughput technologies for identification of variations. Identification of all kinds of variations will uncover associations between breast and ovarian cancer, and thus reveal potential disease screening methods and provide an understanding of the mechanism of metastasis between these two cancer types. In this chapter, we aimed to gather the current knowledge about susceptibility genes BRCA1 and BRCA2 which are highly connected with breast and ovarian cancer. Also, mechanisms and hormones (estrogen) that induce cancer associated with BRCA1/BRCA2 have been discussed. Finally, new biomarkers including FEN1 and KRAS for breast and ovarian cancer have been discussed.

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