The Relevance of BRCA Genetics to Prostate Cancer Pathogenesis and Treatment

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Abstract: The breast cancer susceptibility genes 1 (BRCA1) and 2 (BRCA2) are cellular proteins involved in DNA repair. They are normally expressed in the breast, ovaries, prostate, and other tissues. Their germline mutation is the cause of hereditary breast-ovarian cancer syndromes. BRCA mutation carriers are also susceptible to other cancers, notably prostate cancer. In this article, we review the role of BRCA genes in the pathogenesis and clinical course of prostate cancer. We also discuss the molecular mechanisms of action and the therapeutic implications of BRCA germline mutations.

Introduction

Prostate cancer is the most commonly diagnosed non-dermatologic malignancy and is the second leading cause of cancer death among men in the United States. In 2010, there were an estimated 217,730 new cases and 32,050 deaths due to prostate cancer.[1] Although the genetics of this disease are complex, there is evidence that kindred may exhibit a highly penetrant, autosomal dominant inheritance. This is most commonly seen in men with early onset disease and those with multiple affected family members.[2] Two separate meta-analyses indicate that having a first-degree relative diagnosed with prostate cancer is associated with a 2–2.5-fold elevation in relative risk.[3,4] In a study of Swedish kindreds, it was observed that sons whose fathers survived longer than 59 months after diagnosis were 38% less likely to die of prostate cancer,[5] indicating that disease virulence is also inherited. Although the majority of prostate cancers are sporadic, a linkage between breast, ovarian, and prostate cancers based on analysis of multiple kindreds is irrefutable.[6,7] Several genome-wide association studies have mapped the common regions associated with prostate cancer risk, with 8q24 and 17q exhibiting the closest association with prostate cancer.[8] Eeles and colleagues confirmed this association and identified 3 additional loci containing susceptibility genes: MSMB, LMTK2, and KLK3.[9] Additional polymorphisms associated with prostate cancer risk have been identified in chromosome 7(JAZF1), 10 (MSMB and CTBP2), and 11.[10]

Of the known cancer susceptibility loci, heritable factors breast cancer susceptibility gene 1 (BRCA1) and breast cancer susceptibility gene 2 (BRCA2) are of particular interest in prostate cancer, as their mutation accounts for 2–3% of prostate cancers.[11] Mutations of BRCA1 and BRCA2 genes confer an increased risk for a variety of malignancies in men, including gastric cancer, breast cancer, and hematologic malignancies. The first evidence of an association between BRCA germline mutations and prostate cancer emerged from the Breast Cancer Linkage Consortium, in which the incidence of prostate cancer was noted to be increased in kindreds with a high incidence of breast and ovarian cancers. The relative risk of developing prostate cancer in BRCA1 and BRCA2 mutation carriers was 1.8 times and 7–23 times, respectively, that of the general population.[12]

Overview of DNA Repair Pathways

Ionizing radiation and oxidative agents and toxins may damage mammalian DNA. Exposure to a mutagen or a reactive oxidative species may cause spontaneous double-strand DNA breaks (DSB) during the S phase of the cell cycle. DSB are deleterious to genome integrity and hence need to be repaired. This repair occurs predominantly by either non-homologous end joining (NHEJ) or homologous recombination (HR).[13] Disruption of these DNA repair pathways leads to increased mutagenesis and genomic instability that is conducive to carcinogenesis.

Homologous recombination has been recognized to be an important DSB repair pathway in mammalian cells, accounting for 30–40% of all DSB repair events.[13,14] In homologous recombination, identical or similar DNA sequences direct the repair of damaged DNA by a gene conversion mechanism, restoring the original sequence that was present before the damage occurred.[15] Homologous repair of DSB occurs preferentially between identical sister-chromatids, with chromosome homologs or, less commonly, heterologs.[14,16] The process of NHEJ, as indicated by its name, does not require a homologous DNA sequence to act as a template, and is an inherently error-prone process. It can be a reliable form of repair if the ends are undamaged. However, if there is a base damage or nucleotides are damaged or lost, the rejoining is imprecise and results in a mutagenic sequence.[15]

BRCA Genes and DNA Repair

BRCA1 and BRCA2 genes play a critical role in DNA repair by maintaining the structural integrity of the genetic code during replication.[17] The BRCA gene products are known to coordinate HR. BRCA1 and BRCA2 colocalize with RAD51, a mammalian homolog of the bacterial protein RecA, during S phase and after DNA damage.[17,18] RAD51 plays a vital role in DSB repair and HR.[18] BRCA1 is responsible for transporting RAD51 from cytoplasm to nucleus, whereas BRCA2 is directly involved in RAD51-mediated repair.

While several studies strongly implicate BRCA1 and BRCA2 nuclear proteins in the DNA damage response, their mutation is characterized at the cellular level by defective repair of DSB by the process of HR.[15,19-22] Thus, deficiency in this DNA repair pathway in BRCA1- and BRCA2-mutant cells directs the cells along more error-prone repair pathways, resulting in the accumulation of spontaneous and damage-induced chromosomal aberrations and contributing to tumor genesis.[20,23-25] Usually, non-repaired cell damage triggers a cell cycle checkpoint or apoptosis, thereby eliminating repair-deficient cells and preventing mutant cells from accumulating. BRCA1- and BRCA2-deficient cells have a defective S phase checkpoint response to ionizing radiation,[24,26] resulting in checkpoint evasion and persistence of mutant cells. Thus, DNA repair and checkpoint defects cooperate in BRCA-deficient cells to produce the observed chromosome abnormalities found in these cells.[15]

BRCA1 Structure and Its Role in Tumor Suppression

The BRCA1 tumor suppressor gene was localized to 17q21 by linkage analysis of cancer families, and it was identified to encode a protein of 1863 amino acids.[27,28] BRCA1 protein is a 220KDa nuclear protein, targeted to the nucleus via 2 nuclear localization signal sequences.[29] Although the BRCA1 protein has very poor sequence conservation across mammalian species, there are 2 conserved domains: a RING finger domain at the N-terminus with structural characteristics of a transcriptional regulatory protein[30] and a repeated motif of approximately 100 amino acids, termed BRCA1 C-terminal repeats (BRCT repeats). The BRCT repeats can also function as transcriptional activation domains (TAD) and are found in many other proteins involved in DNA repair and cell cycle regulation.[31,32] The recognition of this domain in BRCA1 quickly led to the identification of its widespread presence in a number of other nuclear proteins involved in DNA repair.

It has been proposed that BRCA1 works as a repair gene by multiple mechanisms. As mentioned previously, BRCA1 plays a key role in regulating the maintenance of genome integrity through the activation of DNA repair genes as well as controlling repair of DSB by HR.[33] BRCA1 is more likely to participate as a sensor or transducer rather than directly as a repair factor or effector.[34] The BRCA1 protein functions as a scaffold or platform to coordinate different activities needed for repair.[35,36]

BRCA1 is also believed to modulate checkpoints for cell cycle progression.[33] It can also induce arrest at different cell cycle check points to allow for DNA repair or apoptosis in response to DNA damage.[33] BRCA1 is phosphorylated in response to DNA damage, which in turn activates or assembles a set of proteins involved in DNA damage repair, cell proliferation, or apoptosis.[33] The BRCA1 gene product also interacts with p53, resulting in enhanced p53 transcriptional activity and growth suppression.[37] BRCA1 interacts with c-Myc and causes suppression of its transforming potential.[38] Numerous additional functions have been ascribed to the BRCA1 product, including roles in chromatin remodeling,[35,39] transcription-coupled DNA damaged repair,[33] transcriptional regulation,[40,41] mRNA polyadenylation,[42] and ubiquitination.[43]

BRCA2 Structure and its Role in Tumor Suppression

BRCA2 is a 13q12-linked gene encoding a 3418 amino acid protein that was identified in 1995 by positional cloning.[28] It has a conserved C-terminal region and a cluster of sequences (called BRC repeats) located in the central portion of the protein.[44,45] The BRC repeat regions mediate binding between BRCA2 and RAD51.[46-49] BRCA2 regulates both the intracellular localization and DNA binding ability of RAD51.[50] In BRCA2-deficient cells, RAD51 (which does not contain a consensus nuclear localization signal) is inefficiently transported into the nucleus.[51] Thus, formation of the nuclear foci that contain RAD51 after exposure to DNA damage is impaired in BRCA2-defective cell lines.[52,53] In a normal cell, RAD51 is held in an inactive state, but is readily dispatched to and activated at potential sites of repair (Figure 1) as part of the DNA damage response.[50] RAD51 and BRCA2 are known to accumulate at these defined nuclear foci in response to DNA-damaging treatments. RAD51 binds DNA to form nucleoprotein filaments and promotes strand exchange between homologous DNA molecules in a BRCA2-dependent manner, which is critical to HR. The finding that the BRCA2 C-terminal domain stimulates RAD51 strand exchange could readily account for the impaired homologous recombination found in BRCA2 mutants.

Mice expressing a prostate-specific loss of BRCA2, driven by probasin-induced Cre recombinase, exhibit focal hyperplasia and low-grade prostatic intra-epithelial neoplasia (PIN).[54] Concomitant Trp53 deletion results in high-grade PIN lesions containing increased DNA damage and increased nuclear androgen receptor (AR) expression, which causes increased proliferation following castration. These data indicate that disruption of BRCA-dependent DNA repair and persistence of AR signaling act cooperatively in castrate-resistant prostate cancer (CRPC).

Influence of BRCA1 on Signal Transduction in Prostate Cancer Cells

The BRCA gene products have a number of important reactions specific to prostate cancer cell signaling (Figure 2). BRCA1 functions as an AR coregulator and plays a positive role in androgen-induced cell death. Yeh and colleagues have demonstrated that BRCA1 enhances transactivation of AR in prostate cancer cells and cooperates with AR induced-expression of P21, a cyclin dependent kinase inhibitor.[55] P21 in turn couples with cyclin-CDK2 complex, inhibiting their function and cell cycle progression. This mechanism accounts for the observation that, when expressed in high concentrations, androgen inhibits prostate cancer cell growth.

BRCA1 is also capable of suppressing insulin-like growth factors 1 (IGF-1) receptor (IGF-1R) gene transcription.[56] The IGF-1 and IGF-2 comprise a family of mitogenic polypeptides with important roles in normal cell proliferation, differentiation, and apoptosis in many tissues, including the prostate, suggesting their possible involvement in carcinogenesis.[57] Elevated IGF-1[58,59] or IGFR[60] expression is associated with elevated prostate cancer risk and advanced stage. Maor and colleagues observed that BRCA1 suppresses transactivation of the IGFR promoter, thereby inhibiting IGF-1-mediated cell growth.[56]

BRCA2 has been demonstrated to be a substrate for Skp2,[61] an E3 ubiquitin ligase that has been proposed to be a driver mutation in approximately 10% of primary prostate cancers.[62] This finding has important implications for future personalized therapeutic approaches.

BRCA Mutations and Associated Prostate Cancer Risk

Several kindred studies across a wide array of ethnic groups suggest an association between BRCA mutations and prostate cancer (Table 1). Both BRCA1 and BRCA2 mutations have been shown to confer an increased risk for prostate cancer. A large collaborative study from the Breast Cancer Linkage Consortium, based on 173 families harboring BRCA2 mutations, estimated a relative risk of 4.65 (95% confidence interval [CI], 3.48–6.22) for prostate cancer in male BRCA2 gene carriers.[63] A majority of the tumors have been traced to a single BRCA2 mutation (999del5).[64] The cumulative risk of developing prostate cancer in BRCA2 gene carriers before 80 years of age has also been estimated by the Breast Cancer Linkage Consortium to be 20% (95% CI, 15–24%). Additionally, the estimated relative risk rose to 7.33 in patients with a family history of prostate cancer diagnosed before the age of 65. In these families, 97 distinct BRCA2 mutations were observed, including 2 founder mutations identified in the Icelandic and Ashkenazi Jewish

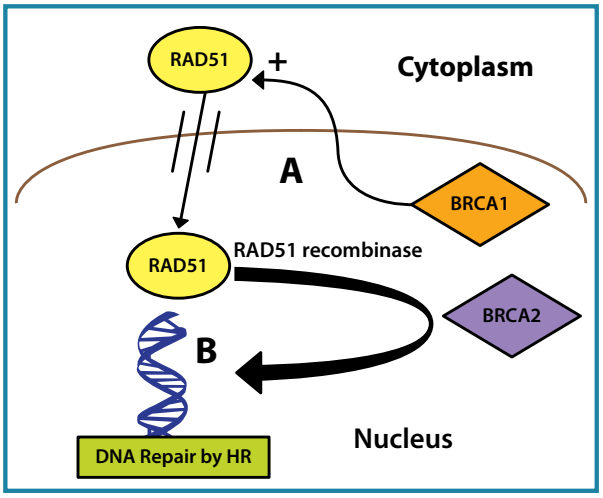

Figure 1. Interaction between RAD51 and BRCA in DNA repair. A) In response to DNA damage, BRCA1 facilitates the transport of RAD51 from cytoplasm into the nucleus. B) In the nucleus RAD51 recombinase helps Rad51 protein to colocalize with BRCA2 to ensure error-free DNA repair.

HR=homologous recombination.

populations (999del5 and 6174delT, respectively).[65] Few studies have shown the evidence for the loss of heterozygosity of the BRCA2 region in prostate cancer patients, particularly those with advanced stage disease. Willems and associates observed a significant loss of heterozygosity among BRCA2 mutation carriers (71%) and a 3.5-fold (95% CI, 1.8–12) increased risk of prostate cancer.[66]

Another study of 129 Dutch BRCA2 families also supported the observation that BRCA2 carriers are at increased risk for cancers of the prostate (RR, 2.5; CI, 1.6–3.8).[67] Johannesdottir and colleagues studied Icelandic kindreds and identified a BRCA2 mutation (999del5) in 2 of 75 (2.7%) prostate cancer cases diagnosed before the age of 65, compared with 2 of 499 (0.4%) in control subjects.[68] Additional studies of families segregating BRCA2 mutations, including families in Sweden,[69,70] Finland,[71] Iceland,[72] and Chile,[73] have supported the association between BRCA2 gene mutation and increased prostate cancer risk. Edward and colleagues screened the complete coding sequence of BRCA2 for germline mutations in 263 men diagnosed with prostate cancer who were 55 years of age or younger. They observed that protein-truncating mutations were found in 6 men (2.3%; 95% CI, 0.8–5.0%). They also reported that the relative risk of developing prostate cancer by age 56 from a deleterious germline BRCA2 mutation was 23-fold (95% CI, 9.0–57.0) as compared to developing prostate cancer without a mutation.[65] Interestingly, 4 of the patients with mutations in this study did not have a family history of breast or ovarian cancer, which raised the possibility of prostate-cancer specific mutations. Additionally, a recent study by Gallagher and associates showed that men who carried a BRCA2 mutation had a 3.18-times higher risk of prostate cancer than non-carriers (odds ratio [OR], 3.18; 95% CI, 1.52–6.66).[74]

Several studies have also suggested an increased risk of prostate cancer among male carriers of BRCA1 mutations in breast and ovarian cancer families. Ford and coauthors[75] reported a significant excess of prostate cancer cases (estimated RR to gene carriers, 3.33; 95% CI, 1.78–6.20) in breast and ovarian cancer families with evidence of linkage to BRCA1. The combined frequency of BRCA1 and BRCA2 mutations exceeds 2% among Ashkenazi Jews. Struewing and coworkers estimated the risk of prostate cancer for BRCA1 and BRCA2 mutation carriers based on 122 carriers identified from a population-based study of 5,318 Ashkenazi Jews in the Washington, DC, area to be 16% by 70 years (95% CI, 4–30%) as compared with 3.8% (95% CI, 3.3–4.4%) among non-carriers, which is roughly equal to the risk of ovarian cancer in the Ashkenazi Jewish population.[76] Similarly, based on families with a history of breast and/or ovarian cancer and with at least 1 individual known to carry a pathogenic mutation in the BRCA1 gene, Thompson and Easton[77] reported a 2-fold increased relative risk of prostate cancer in BRCA1 mutation carriers (RR, 1.82, 95% CI, 1.01–3.29; P=.05) compared with non-carriers, although the effect was restricted to men younger than 65 years at the time of diagnosis. The IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) trial, which focused on the role of targeted screening of BRCA1- and BRCA2 mutation carrier families for prostate cancer, showed a higher positive predictive value for PSA screening among carriers. However, there was not a significant difference between the incidence of prostate cancer between the 2 groups (carriers, 3.9% vs controls, 2.1%; P=.513).[78]

Association of BRCA Mutations With Clinicopathologic Determinants of Prostate Cancer

Prostate cancer can be an indolent or an aggressive disease. Indolent prostate cancer may exist for many years without causing symptoms or shortening life expectancy. Aggressive prostate cancer may cause symptoms that are difficult to palliate with conventional treatments, which may cause high cancer-specific mortality. Predicting who is at risk for which type of disease has implications in the primary and secondary prevention of prostate cancer. In addition to demonstrating a higher risk of prostate cancer, multiple studies[79-82] have also reported a more aggressive phenotype consistent with BRCA mutation–associated prostate cancer. In a series of BRCA1 and BRCA2 mutation carriers with prostate cancer, Mitra and colleagues from the United Kingdom found that the incidence of

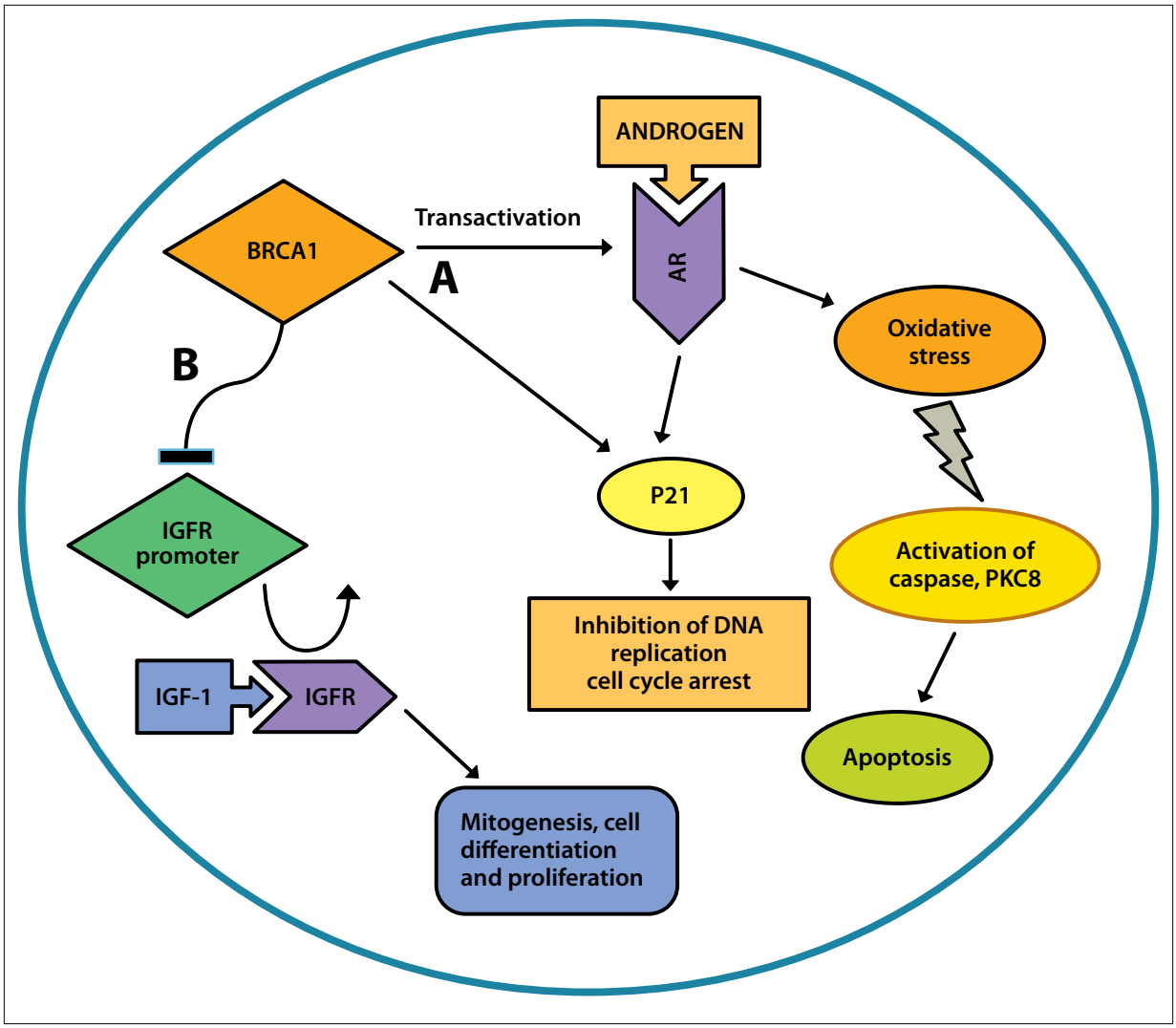

Figure 2. Role of BRCA1 in prostate cancer tumor suppression. (A) BRCA1 increases gene expression of androgen receptor (AR) and P21, which in turn decreases DNA replication and causes cell cycle arrest. (B) BRCA1 also regulates insulin-like growth factor 1 (IGF-1)-mediated cell differentiation and proliferation by decreasing IGF receptor (IGFR) promoter gene expression.

prostate cancer with a Gleason score exceeding 7 was significantly greater in the BRCA1 and BRCA2 mutation carrier group than that in the control group (*P*=.012).[81] Another study conducted among the Ashkenazi Jewish population demonstrated that BRCA2 mutation carriers had a high Gleason score (>7; OR, 3.18; 95% CI, 1.37–7.34), and the specific BRCA1 185delAG mutation was associated with high Gleason score tumors.[79]

Gallagher and associates[74] also noted that poorly differentiated prostate cancers (Gleason score 7–10) were found in 57% of non-carrier cases and in 85% of BRCA2 mutation-associated cases (*P*=.0002). After adjusting for age and stage, BRCA2 mutation carriers were more than twice as likely to have a Gleason score of 7–10 (HR, 2.63; 95% CI, 1.23–5.6; *P*=.01) than non-carriers.[74] The investigators found that BRCA1 (HR, 4.32; 95% CI, 1.31–13.62; *P*=.016) and BRCA2 (HR, 2.41; 95% CI, 1.23–4.75; *P*=.01) mutation carriers had an increased risk of developing biochemical recurrence. The onset of castration-resistant disease following biochemical relapse is shorter in BRCA2 mutation carriers than non-carriers despite similar Gleason scores (median survival, 10.5 versus 17.2 years in carriers vs non carriers). Also, there was a trend towards a higher frequency of biochemical recurrence progressing to castrate metastasis in BRCA2 mutation carriers compared to non-carriers (HR, 2.01; 95% CI, 0.85–4.79). Thorne and associates noted a decreased overall survival in BRCA2 mutation carriers of breast cancer kindreds, with the carriers having a 4.5-fold increase in risk of

Table 1. BRCA Mutational Status as a Risk Factor for Prostate Cancer

Study	Ethnicity	Mutation	Domain	Statistical Findings
Breast Cancer Linkage Consortium[63]	Multi-ethnic	BRCA2	6174del7, 999del5, 8764delAG, 3034del4	Increased risk of PC in BRCA2 mutation carriers (RR, 4.65; CI, 3.48–6.22)
Van Asperen, et al[67]	Dutch	BRCA2	6503delTT, 6174delT, S1882X	Increased risk of PC in BRCA2 mutation carriers (RR, 2.5; CI, 1.6–3.8)
Lorenzo Bermejo, et al[69]	Swedish	NI	NI	Increased cumulative risk (1.86) for PC in families with history of breast and ovarian cancer
Eerola H, et al[71]	Finnish	BRCA2	NI	Standardized incidence ratio of 4.9 (CI, 1.8–11) compared to 1.1 in control group
Gallagher, et al[74]	Ashkenazi Jews	BRCA2	6174delT	3-fold risk of PC in BRCA2 mutation carriers (OR, 3.18; 95% CI, 1.52–6.66; *P*=.002)
Edwards, et al[65]	British	BRCA2	6710delA, CAA, 7084delA, AAAG, 8525delC, 2558insA	RR of developing PC by age 56 was 23-fold in patients with deleterious BRCA2 mutation carriers
Struewing, et al[76]	Ashkenazi Jews	BRCA1 and BRCA2	185delAG, 188del11, 5382insC	Estimated risk of PC among carriers of a BRCA1 or BRCA2 mutation was 16% (95% CI, 4–30%) at the age of 70
Ford, et al[75]	Multi-ethnic	BRCA1	NI	RR of PC of BRCA1 carriers compared to general population was 3.33 (CI, 1.78–6.20)

CI=confidence interval; NI=no information; OR=odds ratio; PC=prostate cancer; RR=relative risk.

prostate cancer-related death (*P*<.001) versus non-carriers.[83]

Recent data suggest that DSB, acting through the AR, produce the TMPRSS2-ERG gene fusion that is found in 50% of prostate cancer cases. The TMPRSS2-ERG gene fusion has been associated with aggressive disease, and it is possible that, in the absence of BRCA, accumulating DSB facilitate this translocation.[84,85]

Fiorentini and associates[86] demonstrated a direct correlation between BRCA1 expression and the Ki67 proliferation index in prostate cancer. Ki67 is a well-known predictor of adverse prognosis and resistance to therapy in prostate cancer.[87,88] The investigators found that BRCA1-positive tumors were marked by a substantially increased tumor proliferation index when compared with BRCA1-negative tumors (47.0 Ki67-positive nuclei vs 10.3; *P*=.0016).[86] They also found that cases that stained positively for BRCA1 had a significantly higher Gleason score (35.0% vs 15.7%), higher PSA levels at diagnosis (27.0 [95% CI, 15.9–38.1 vs 10.2 [95% CI, 6.0–14.4]), a more advanced stage, and worse prognosis (HR, 4.6; 95% CI, 2.4–8.7) compared to those with tumors that did not stain for BRCA1.[86] Burga and coworkers proposed that even non-malignant mammary epithelial cells in BRCA1 mutation carriers had increased clonal and proliferative properties, predisposing them to aggressive cancerous transformation.[89] Collectively, these data imply that BRCA mutation–associated prostate cancer has the potential to behave more aggressively than its wild-type counterpart and emphasize the importance of genetic counseling in kindreds at risk (ie, those harboring multiple individuals with BRCA-associated cancers).

Implications for Prostate Cancer Treatment

Besides influencing tumorigenesis, BRCA mutations have important therapeutic implications. Cancers with BRCA mutations are more sensitive to DNA damaging treatments. Unlike their normal counterparts, cancer cells with BRCA1 and BRCA2 mutations have defective DNA repair. Researchers have made attempts to develop newer drugs that can exploit this defect and target these cancer cells. One such class of agents is poly (adenosine diphosphate [ADP]–ribose) polymerase (PARP) inhibitors. PARPs are a family of enzymes involved in the repair of DNA single-strand breaks through the repair of base excisions. In DNA repair–defec-

tive BRCA1- and BRCA2- mutant cells, PARP inhibitors—acting as a second hit—cause accumulation of DNA lesions and selectively kill them.[90] PARP inhibitors, by virtue of inhibiting DNA repair, are postulated to sensitize tumors to other DNA damaging therapies, thereby preventing treatment resistance.[91] PARP inhibitors are now being extensively evaluated in cancers associated with BRCA mutations. In a phase II study by Tutt and colleagues in advanced breast cancer patients, olaparib administered at either 100 mg or 400 mg twice daily was associated with overall response rates of 22% and 41%, respectively, with minimal, predominantly low grade toxicity that was most commonly in the form of fatigue and nausea.[92] In their phase I study of olaparib, Fong and associates observed a greater than 50% reduction in PSA and objective responses in metastatic, castration-resistant, prostate cancer patients.[93]

Conclusion

BRCA genes are tumor suppressors in prostate cancer that play a pivotal role in cellular damage response. They regulate cell proliferation, cell cycle progression, transcription, and induction of apoptosis. Their mutation results in defective DNA repair by HR, which fosters an ideal environment for carcinogenesis. BRCA mutations confer an increased risk of multiple cancers including breast, ovary, prostate, and other visceral tumors. A BRCA mutation is the only known genetic factor to be associated with prostate cancer. Studies across multiple ethnicities consistently demonstrate that BRCA1 and BRCA2 mutations not only increase the risk of prostate cancer, but also predispose patients to early onset and aggressive, potentially lethal disease. BRCA mutational status may be an important consideration in exploring newer therapeutics such as PARP inhibitors and DNA-damaging agents in prostate cancer.[84]

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