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PARP-ish: Gaps in Molecular Understanding and Clinical Trials Targeting PARP Exacerbate Racial Disparities in Prostate Cancer

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ABSTRACT

PARP is a nuclear enzyme with a major function in the DNA damage response. PARP inhibitors (PARPi) have been developed for treating tumors harboring homologous recombination repair defects that lead to a dependency on PARP. There are currently three PARPi approved for use in advanced prostate cancer, and several others are in clinical trials for this disease. Recent clinical trial results have reported differential efficacy based on the specific PARPi utilized as well as patient race. There is a racial disparity in prostate cancer, in which African American males are twice as likely to develop and die from the disease compared with European American males. Despite the disparity, there continues to be a lack of diversity in clinical trial cohorts for prostate cancer. In this review, PARP nuclear functions, inhibition, and clinical relevance are explored through the lens of racial differences. This review will touch on the biological variations that have been explored thus far between African American and European American males with prostate cancer to offer a rationale for investigating PARPi response in the context of race at both basic science and clinical development levels.

Introduction

Prostate cancer is the most frequently diagnosed and second most fatal cancer in American men (1, 2). The American Cancer Society predicts that there will be nearly 300,000 cases and approximately 35,000 deaths due to prostate cancer in the United States in 2024 (1). African American (AA) men are at the highest risk of developing prostate cancer in their lifetime as well as at the highest risk of dying from the disease (3, 4). A recent study in 2022 from the Veteran's Affairs suggested that AA men are diagnosed at a younger age, have a higher Gleason score, exhibit higher PSA expression, and are at a higher risk for prostate cancer than European American (EA) males (5). In 2007, a study from John Hopkins hypothesized that the difference in PSA in AA men may correlate with prostate size between AA and EA males (6). Their study found that elevated PSA levels in AA patients compared with EA patients were not correlated with larger prostate size in AA men. There is still no conclusive hypothesis about AA men having higher serum PSA levels compared with EA males (7). AA men also have two times higher incidence and mortality rates for prostate cancer than EA men (8). Recent data suggest that there may be biological differences between AA and EA tumors (9–12).

Primary, localized prostate cancer has a reasonable expectation of cure by either radiotherapy or surgical removal of the prostate (radical prostatectomy). Another common option is active surveillance, in which patients are monitored regularly and treated once progression occurs (13). A study from 2016 showed that AA men were more likely to receive active surveillance than EA men (12.5% vs. 7.2%; $P < 0.001$), even with more advanced disease (13). Furthermore, the same study showed that AA men were less likely to receive radical prostatectomy (27.5% AA vs. 39.8% EA; $P < 0.001$) and more likely to receive radiotherapy (37.2% AA vs. 33.1% EA; $P < 0.001$) compared with EA men. AA men may be more likely to receive radiotherapy over radical prostatectomy because they tend to be more responsive than EA men (14).

If prostate cancer is diagnosed and managed when still confined to the prostate, patients have a 10-year disease-free survival rate of 98% (15). However, there is a 20% to 40% chance of biochemical recurrence (16). If prostate cancer is left untreated, tumors can progress and metastasize, leading to advanced stage prostate cancer, for which therapy includes hormone-directed therapeutic options. The androgen receptor (AR) is a key oncogenic transcription factor (TF) in prostate cancer (17, 18). The AR is targeted in advanced stage prostate cancer most commonly by androgen deprivation therapy (ADT) in combination with AR antagonists. It has been reported that AA men are more likely to receive ADT compared with EA men (9.5% AA vs. 5.7% EA; $P < 0.001$; ref. 13). Generally, AR protein levels are higher in both benign and cancerous prostate tissue in AA men compared with those in EA men (27% higher AR immunostaining of malignant nuclei in AA men compared with EA men, $P = 0.005$; ref. 15). This may help explain not only the better response of AA men to this therapeutic option but also the more aggressive disease nature of the disease in AA men (12, 19).

Although ADT generally results in remission, relapse almost invariably occurs within 24 to 36 months and is associated with AR reactivation and subsequent resumption of the cell cycle (20). Therapeutic resistance to hormone therapy—in which AR activity is restored—results in castration-resistant prostate cancer (CRPC; bioRxiv 2023.03.23.533944; ref. 18). Increased AR activity has been

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associated with increased cell proliferation and prostate cancer progression (21, 22). Roughly 60% of CRPC tumors harbor AR mutations (23). Point mutations in the ligand-binding domain of the AR are prominent in the progression of prostate cancer to CRPC (bioRxiv 2023.03.23.533944; ref. 24). These mutations can cause the AR to lose specificity of ligand binding, therefore decreasing response to ADT (22). Of all prostate cancer cases, 10% to 20% progress to late-stage prostate cancer (CRPC), which is nearly universally fatal (25, 26). Given that the AR is a key driver of the disease, higher AR expression in AA men may correlate with worse outcomes. One standard-of-care treatment option for CRPC is taxane chemotherapy (27). In a 2019 study, AA men responded similarly to EA men to this treatment option and had a 19% lower risk of death once receiving this treatment ($P < 0.001$; ref. 28). It is important to note, however, that this study only accrued 6% AA patients compared with an accrual of 85% EA patients. It is also important to note that despite the better response of AA men compared with EA men to these treatment options, overall, there is still a higher risk of death from prostate cancer in the AA community that needs to be better understood and explored.

In addition to chemotherapy, targeted therapeutics [such as PARP inhibitors (PARPi)] are an option for a subset of patients with CRPC. Patients receive this therapeutic option if they have impairments in DNA damage response (DDR) genes. Mutations in DDR genes are associated with more aggressive disease and are enriched in advanced CRPC compared with localized prostate cancer (29–32). The most common detrimental DDR alteration in prostate cancer is *BRCA2* mutation (32). Mutations in *BRCA2* have been associated with more aggressive prostate cancer (33). DDR genes, such as *BRCA2* and *PARP1*, are direct AR target genes in prostate cancer (34–36). *PARP1* has enhanced activity and contributes to CRPC disease progression and is associated with poor outcomes (37). To date and to the best of our knowledge, there are no articles assessing the difference in the response of PARPi in AA versus EA patients with prostate cancer.

Recent literature about the importance of PARP in prostate cancer progression may elucidate the ways in which the racial disparity in prostate cancer can be reduced/eliminated. It will also emphasize the need for increased diversity in both preclinical models and clinical trial participant demographics. Increased recruitment of the AA population in prostate cancer clinical trials is imperative to better understand the reasons of AA patients being more prone to developing and having more aggressive disease.

Nuclear Roles of PARP1 in Cancer Progression

PARP1 is an enzyme canonically associated with DDR (38). However, PARP1 has the capacity to impact other cancer-associated processes including DNA damage, chromatin accessibility, and TF coregulation (39–41).

DNA damage

PARP1 is the most abundant enzyme of the 17-member PARP family (42). PARP1 is a nuclear enzyme that catalyzes a posttranslational modification [poly(ADP-ribosylation), PARylation] of target proteins (43). The enzyme is canonically active in the base excision repair (BER) pathway. In the event of a single-strand break (SSB), PARP1 binds to SSB DNA nicks that are formed as intermediates during the BER process (44). NAD^+ is used as a cofactor to create PAR chains, mainly to auto-PARylate PARP1 to recruit other DDR factors (such as XRCC1; ref. 45). Accumulation of auto-PARylation causes PARP1 to dissociate from the damaged DNA due to charge repulsion as PAR chains have a highly negative charge (46). After PARP1 dissociates from the DNA, poly(ADP-ribose) glycohydrolase works to degrade the PAR chains on PARP1, rendering it inactive (47). The dissociation of PARP1 from the damaged DNA allows DDR enzymes (such as XRCC1) to repair DNA (**Fig. 1**). PARP1 is responsible for the majority (~90%) of the PARylation reactions that are associated with DDR (44). Compared with normal tissue, *PARP1* mRNA is elevated in breast, endometrial, lung, ovarian, skin, adrenal, bone, colon, prostate, and stomach cancers (37, 48, 49). PARP1 enzymatic activity (PARylation) is increased in prostate cancer (37).

Recent studies have assessed the differences between AA and EA DDR related to PARP1. In a breast cancer study, The Cancer Genome Atlas cohorts and Gene Expression Omnibus datasets with tumors derived from AA and EA communities were analyzed (50). Overall, AA-derived breast cancer tumors have 16% of their DDR enzymes mutated, whereas only 3% of EA tumors harbor DDR mutations ($P < 0.001$; **Fig. 1**). Tumors derived from AA women have an enrichment of mutations of homologous recombination genes, notably *BRCA1* ($P = 0.01$; ref. 50) and *PARP1* ($P = 0.03$; ref. 50). The AA tumors in this study also have lower *XRCC1* levels compared with tumors from EA patients in the analyzed dataset (statistics not reported). The results of a prostate cancer study showed that XRCC1 protein expression is reduced in AA tumors compared with EA tumors ($P = 0.0005$; ref. 51) and PARP1 protein expression is similar between tumors of each racial cohort ($P = 0.1562$).

Although PARP1 levels are similar in prostate cancer tumors regardless of racial background, an enzyme involved with PARP1 regulation is mutated in AA-derived prostate cancer samples. Whole-exome sequencing samples from four different AA families with a high hereditary risk for prostate cancer harbored germline mutations in ADP-ribosylhydrolase like 1 (also known as ARH2). ADP-ribosylhydrolase like 1 is a member of the ARH family. ARH3 has been associated with dePARylation of PARP1 enzymes, whereas ARH2 has been associated with binding to PAR chains but not necessarily dePARylation (52). The mutation is associated with an increase in PARP1 activation (**Fig. 1**; ref. 53). As increased PARP1 activity has been associated with prostate cancer progression and worse outcomes (37), PARP inhibition may be a suitable treatment option for AA patients with prostate cancer harboring this mutation (37).

Chromatin accessibility

In addition to regulating DDR, PARP1 can impact cancer cell phenotypes by altering chromatin accessibility (54, 55). PARP1 is associated with chromatin remodeling through interactions with chromatin-remodeling enzymes (56–59). Amplified in liver cancer 1 (ALC1) is a nucleosome-remodeling protein that is activated upon DNA damage to relax chromatin for repair (56). Another name for the protein is "chromodomain helicase DNA–binding protein 1-like." ALC1 is unique among chromatin remodelers in that ALC1 has a macrodomain, which is a protein domain with the capacity to bind PAR. Although ALC1 protein has not been extensively analyzed in prostate cancer, in other cancers (such as liver, breast, and colorectal cancers), it is oncogenic when amplified (57, 60–64). Upon DNA damage, the PAR-binding domain allows this chromatin remodeler to interact with the PAR chains of PARP1 and PARP2 (65, 66). This interaction releases the autoinhibitory domain on ALC1, thus increasing its activity (56, 57, 62). Increased PARylation can cause an increase in ALC1 activation, leading to an elevation of ALC1
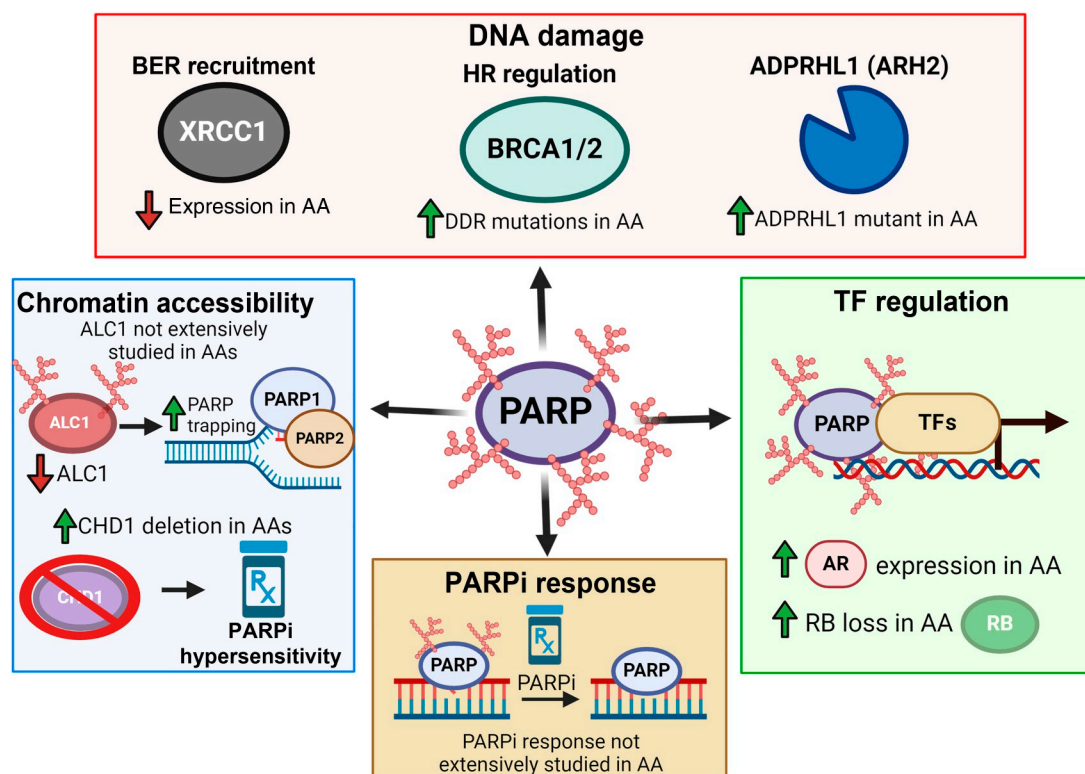
Figure 1.
PARP, prostate cancer, and racial disparity. PARP1 plays nuclear roles in DNA damage, chromatin accessibility, and TF regulation that are distinct between AA and EA men. Due to these differences, PARPi response may be distinct between AA and EA men. ADPRHL1, ADP-ribosylhydrolase like 1 (also known as ARH2). (Created with BioRender.com.)

oncogenic functions. ALC1 loss induces PARP trapping on chromatin (**Fig. 1**). Combined with PARP inhibition, ALC1 loss decreases the association between the BER enzyme XRCC1 and chromatin (57, 65). The impact of ALC1 loss as it relates to race is unclear. Studies aimed toward understanding ALC1 impact in cancer were conducted on tissue microarray samples from a hepatocellular carcinoma cohort in China (64). The studies performed to understand ALC1 expression across cell lines were done using cBioPortal data, which has a lack of diverse representation (63).

Chromatin accessibility as it relates to prostate cancer progression is an active area of research (67–69). However, differences in chromatin accessibility with respect to differing racial backgrounds have not been extensively studied. In one prostate cancer study, helicase chromodomain helicase DNA–binding protein 1 (CHD1) was found to be differentially expressed between AA and EA patient tumors (MedRxiv rs.3.rs-3995251). This study showed that CHD1 deletion is almost three times more frequent in AA men compared with EA men (29.7% vs. 12.8%, $P = 0.003$). CHD1 does not have a PAR-binding domain–like ALC1 (CHDL1). Data suggest that PARP1 and CHD1 may have an indirect impact on each other as CHD1 depletion sensitizes cells to PARPi, but no mechanisms of interaction have been proposed (**Fig. 1**; refs. 70, 71).

TF coregulation

PARP1 can coregulate the function of pro-oncogenic TFs (22). Some important TFs that PARP1 regulates in prostate cancer include AR and E2F1. In prostate cancer, the interaction between PARP1 and AR can promote tumor growth and progression (72). The AR is a key oncogenic TF in prostate cancer that can promote tumor growth through DDR gene regulation (21, 34). PARP1 can be regulated by AR (**Fig. 1**; refs. 34, 73). Upon synthetic androgen treatment, RNA sequencing data demonstrated that there is an increase in DNA repair signatures in an AR-responsive prostate cancer cell line (34). With the addition of an antiandrogen, there is a decrease in AR target genes (*PSA* and *TMPRSS2*) as well as DDR repair genes (such as *PARP1*; ref. 73). PARP1 can also affect chromatin accessibility of AR target genes and AR chromatin residence (36, 72). Somatic AR mutations are more frequent in AA than in EA communities with disease progression (74). In therapy-naïve prostate cancer, AA men have differences in AR-associated disease metabolites compared with EA men (75). After radical prostatectomy, AA men have higher AR protein expression compared with EA men ($P = 0.005$; ref. 19). It could be hypothesized that these differences in AR levels between AA and EA prostate cancer may result in differential PARP1 dysregulation, leading to more aggressive disease (76).

Another TF PARP1 can modulate is E2F1 signaling, specifically in prostate cancer (37, 77, 78). E2F1 is an oncogenic TF, and its target genes are associated with cell-cycle regulation and DNA repair (such as *BRCA1/2*; refs. 37, 77, 78). In more aggressive forms of prostate cancer, the E2F1 pathway has been reported to be dysregulated through loss or mutation of the tumor suppressor *RB1* (77, 79).

In the analysis of DNA copy number alterations from primary prostate cancer samples from publicly available datasets, deletions in *RB1* are associated with a high Gleason score (≥9; ref. 76). Detrimental RB/E2F pathway mutations are more frequently found in AA men (76, 80). Analysis of copy number alterations revealed that prostate cancer tumors in AA men harbor more *RB1* deletions than those in EA men (~70% vs. ~50%; *P* < 0.05; ref. 76). This article makes the claim that *RB1* and associated genes may have the potential to cause more aggressive disease in AAs (**Fig. 1**).

PARP activity supports E2F1 TF function. Decreased PARP activity is associated with decreased E2F1 pathway–associated genes (37, 77). In a study comparing AA men with EA and Asian American men, E2F1 target genes are upregulated in AA men with prostate cancer (80). In an *in vitro* study with PARP inhibition in a CRPC cell line (derived from an EA male), PARP inhibition decreased E2F1 target gene expression (37). Exploring the potential of PARP inhibition in AA-derived model systems may be beneficial for decreasing the expression of E2F1 target genes and thus reducing cell-cycle progression and DDR capacity.

Overall, coregulation of pro-oncogenic TFs, such as AR and E2F1, by PARP1 can potentially be harnessed therapeutically to lead to improved patient outcome. The differences discussed involving genetic mutations may impact the effectiveness of PARPi in tumors from different racial backgrounds and should be explored further.

PARPi

PARPi mechanism of action

PARPi agents are FDA-approved as anticancer therapy in breast, prostate, ovarian, and pancreatic cancer tumors that have deleterious (germline or somatic) mutations in DDR enzymes (81–84). There are several different PARPi that are used and being developed to decrease PARP enzymatic activity. These PARPi can have off-target effects that affect other PARP family members, but their primary target is PARP1 (85). The PARP1 enzyme has three major domains: a DNA-binding domain, an automodification domain, and a catalytic domain (86, 87). The DNA-binding domain encompasses a DNA recognition domain, which consists of zinc fingers I to III and a DNA-binding tryptophan–glycine–arginine–rich (WGR) domain. The WGR domain induces a conformational change in the subdomain of the automodification domain known as the helical domain (HD). The HD functions in an autoinhibitory manner by blocking the continuous binding of NAD^+. The ADP-ribosyl transferase domain is the catalytic domain of the enzyme responsible for PAR chain synthesis.

PARP2 is another member of the PARP family that is associated with recognizing DNA damage. The enzyme can similarly become trapped on the chromatin with the addition of PARPi as an off-target effect (46, 85). PARP2 has a DNA-binding domain and a catalytic domain like PARP1. The major difference between the structures of the two enzymes is the lack of a zinc finger (DNA recognition) domain in PARP2. PARP2 is able to interact with DNA through its WGR domain (88).

PARPi agents work by decreasing the ability of PARP activity to regulate SSB repair. One of the proposed mechanisms of action is through trapping of PARP1 on chromatin. PARPi can cause PARP1 to become trapped on the SSB intermediate through increased DNA retention, which is formally known as PARP trapping (46, 89). PARP becomes trapped at the replication fork, thus increasing the chance of replication stress and genome instability (90). There can be differential levels of PARP trapping depending on the PARPi

used (46, 89). Talazoparib is the most potent PARPi and is the best at PARP trapping, and veliparib is the weakest PARPi and is not as efficient in trapping PARP on the chromatin (91–93). These mechanisms can ultimately lead to cell death if the breaks in the DNA accumulate and are left unrepaired (91, 94). PARP trapping on chromatin is associated with decreased PARP activity (PARylation; ref. 95).

Tumors with DNA damage repair impairments (such as tumors with BRCA1/2 deficiencies) exhibit hypersensitivity to PARPi agents (57, 96). BRCA1 and BRCA2 are involved in the homologous repair (HR) pathway and are critical to repair double-strand DNA breaks. With HR impairments and PARP inhibition, SSB can be more rapidly converted to double-strand DNA breaks, which can ultimately lead to increased cell death (97). HR-defector tumors therefore can be hypersensitive to PARPi (98). Synthetic lethality relies on HR genes being impaired for PARPi to elicit cell death. It has been shown that PARP inhibition is a suitable treatment option in cells (and patient tissue samples) not harboring BRCA1/2 mutations because PARPi can result in the downregulation of DNA damage repair genes (37).

Different PARPi have differing capacities to trap PARP on chromatin. Based on the mechanism by which they trap PARP, PARPi have recently been classified as type I, type II, or type III PARPi (99). This is a newer classification system that is still being understood and not yet fully implemented in the field. Type I and type II PARPi have a proretention effect and trap PARP on the chromatin through allosteric or nonallosteric binding, respectively. Type I PARPi are extremely potent and increase PARP stability on DNA for extended periods of time through HD destabilization. Type II PARPi have a milder proretention effect on PARP-trapping capacity than type I PARPi. Type II PARPi induce partial HD destabilization that results in catalytic inhibition and trapping. Conversely, type III PARPi have a prorelease effect and decrease DNA retention of PARP at the DNA break. PARPi can differentially trap PARP1 and PARP2, meaning PARPi can be type III for PARP1 and type I for PARP2 (100).

Clinical PARPi

PARPi created for clinical use are categorized into first-generation and next-generation PARPi. Currently, all clinically available PARPi trap PARP1 in a nonallosteric, proretention (type II) manner or in an allosteric, prorelease (type III) manner. PARPi that allosterically trap PARP and induce a proretention effect (type I) for trapping PARP1 (EB47 or BAD) are simply laboratory tools, not clinical agents, considering that more permanent trapping of PARP1 can be cytotoxic (95). Despite our understanding of the extent of extended allosteric PARP1 trapping being detrimental, all FDA-approved PARPi trap PARP2 allosterically through destabilizing the HD of the enzyme [defined by Zandarashvili and colleagues (95) as type I trapping]. A recent commentary on the structure of PARPi and their interaction with PARP enzymes is summarized in a review by Dr. Shuai Li and colleagues (101).

First-generation PARPi

First-generation PARPi trap major targets PARP1 and PARP2 on chromatin (85). The most common first-generation clinical PARPi include veliparib, olaparib, niraparib, rucaparib, and talazoparib. Currently, some first-generation PARPi are approved for ovarian, prostate, pancreatic, and breast cancers. It is important to note that for all the cancer types listed, PARPi are approved if the patients harbor inherited and/or acquired HR deficiencies. PARPi are

Table 1. Active clinical trials with PARPi in prostate cancer with race-related data.

Clinical trial identifier	Treatment	Phase	White patients, N (%)	Black patients, N (%)	First posted
PARPi					
NCT02854436	Niraparib	II	205 (71)	9 (3)	2016
NCT03148795	Talazoparib	II	110 (87)	4 (3)	2017
PARPi and AR-directed therapy					
NCT03732820 (PROpel; ref. 102)	Olaparib + abiraterone	III	557 (70)	25 (3)	2018
NCT03748641 (MAGNITUDE; ref. 102)	Niraparib + abiraterone	III	160 (74)	5 (1)	2018
NCT01972217	Olaparib + abiraterone	II	150 (95)	2 (1)	2018
PARPi and immune therapy					
NCT03338790	Rucaparib + nivolumab (arms A1 + A2)	II	136 (86)	5 (4)	2017
NCT03834519	Olaparib + pembrolizumab arm	III	419 (80)	1 (0.2)	2019

NOTE: Trials included in this table are prostate cancer clinical trials that are active and not recruiting and have results posted as well as race-associated data. No clinical trials with PARPi and DDR had race-related data as most of them are still recruiting. PARPi are underlined. Please note that for the focus of this article, other races were excluded from this table, although they make up the rest of the percentage of patients. Percentages were rounded to the nearest whole number.

actively used in clinical trials for these cancers and other cancers (**Table 1**; ref. 102).

Next-generation PARPi

First-generation PARPi interact with other PARP family members, especially PARP2 (85, 103). AZD5305, a next-generation PARPi, has a 500-fold selectivity for PARP1 over PARP2 (104). In clinical trials, this inhibitor seems to be better tolerated by patients because of the decreased affinity for PARP2 compared with first-generation PARPi and subsequently reduced hematologic toxicity. *In vitro* studies explained that binding of AZD5305 to PARP2 may be dose-dependent, as with increasing dose, there was an increased ability to bind to PARP2 (99).

Considering that all current FDA-approved PARPi have a pro-retention effect (type I) on PARP2, this may explain the reasons for issues and concerns with hematologic side effects (91, 99). It is important to note that even though AZD5305 is a next-generation PARPi selective for PARP1, it also binds with a proretention allosteric affinity (type I) to PARP2 (99). The affinity for AZD5305, however, is extremely low for PARP2, thus explaining why it may be more therapeutically tolerable, with fewer hematologic side effects.

PARP inhibition and race

Mutations in DNA repair genes have been associated with an increased risk and severity of prostate cancer disease progression (105, 106). Certain DNA damage mutations can be exploited therapeutically (i.e., *BRCA1/2*). In one study, AA men expressed differential germline mutations in important DNA repair genes with actionable therapeutic options. An eight-gene panel was used (*FANCA, MSH6, FANCL, RAD54B, BRCA1, PMS2, RAD54L,* and *RAD51*). All genes mentioned on this list are associated with increased PARPi sensitivity to at least one PARPi approved for use in prostate cancer (107–109). AA men included this study have a higher number of actionable mutations in these genes compared with EA men (11.6% AA vs. 5.8% EA; $P = 0.021$), thus potentially making PARPi a viable treatment option in AA men with prostate cancer. There is evidence in another study to suggest a trend toward higher germline mutations in DDR genes in AA patients with prostate cancer compared with those in EA patients with prostate cancer (110). An assessment of the differences in genomic profiling between Black, White, and Asian patients revealed important differences in genomic mutations. Black patients

(23%) have more actionable mutations in their DNA repair genes that can be therapeutically exploited compared with White (~15%) and Asian (~7%) patients with metastatic prostate cancer (25).

Another study compared somatic mutational differences between tumors from AA and EA men with prostate cancer. In tumors from both AA and EA men, the HR genes *BRCA1* and *BRCA2* are frequently mutated (*BRCA1*: 36% in EA and 37% in AA; *BRCA2*: 24% in EA and 17% in AA). In AA tissue samples in this same study, another member of the HR family, *RPA1*—which has been previously associated with PARP1—is differentially mutated (*RPA1*: 0% in EA and 17% in AA; refs. 74, 111). AA prostate cancer tumors harbor detrimental *BRCA2* mutations, which may lead to hypersensitivity to PARP inhibition (76, 112). Mutations in the genes discussed above may specifically validate the use of PARPi in AA patients with prostate cancer. In addition to differing mutation frequencies, AA prostate cancer tumors have lower overall expression of DDR genes compared with EA prostate cancer tumors (10–12, 113). DDR mutations have been associated with PARPi hypersensitivity. Due to the racial differences with respect to DDR gene expression and mutation frequency, it has been proposed that there may be differential PARPi response based on racial background.

To date and to the best of our knowledge, there are neither active clinical trials nor published clinical data that can be used to address the potential differences between racial responses to PARPi. A preclinical study assessed the difference in responses to several different PARPi between AA- and EA-derived cell lines (114). The IC_{50} values of 13 different PARPi were found in 12 different breast cancer cell line models. Nine cell lines were derived from EA patients, and the remaining three were derived from AA patients. Although none of the AA-derived cell lines had BRCA mutations, they were still responsive to the PARPi tested, specifically the clinical inhibitors talazoparib and rucaparib. Due to the lack of understanding of biological differences between AA and EA patients, the authors speculated that AA patients with breast cancer that may benefit from PARPi treatment may not be put on that treatment due to their lack of BRCA mutations. An ovarian cancer trial assessing the response to a PARPi, rucaparib, stated that patient demographics (including age, body mass index, and race) did not determine patient response (115). However, there was no supporting race information in supplemental figures or tables or on clinicaltrials.gov that was publicly available to support this claim. In pancreatic cancer, differences in *BRCA1* and *BRCA2* mutations have

been explored in the context of race; however, no clinical trials to date have assessed the importance of these differences (116).

Although there has been progress in understanding differences in genetic mutations in AA- and EA-derived tumors, there have not been clinical trials that can be used to make any claims to support differences (or similarities) in response to PARP inhibition (Fig. 1; refs. 74, 110, 117). It is imperative that a better understanding of the biological differences between patients with different racial backgrounds is supplemented with an understanding of their responses to actual treatment options available based on their differences.

PARPi combination therapy

PARPi have been tested in several clinical trials in combination with other therapeutics. Some combination therapies in prostate cancer may prove to be beneficial for AA men suffering from the disease. The most common combination therapeutics used with PARPi agents in prostate cancer include DNA-damaging agents (i.e., radiotherapy), AR-directed therapy (i.e., antiandrogens), and immunotherapy (i.e., PDL1 inhibitors).

PARPi and DNA-damaging therapy

PARP inhibition combined with DNA-damaging therapy has shown to have an increased antiproliferative effect (37). Ionizing radiation elicits DNA damage that results in an inhibition of cell growth. In 2018, a meta-analysis revealed that AA patients with prostate cancer are more responsive to radiotherapy than EA patients with prostate cancer ($P < 0.001$; ref. 14). These data correlate with recent genomic studies assessing differences between AA and EA prostate cancer tumors (11, 118). AA prostate cancer tumors typically have lower expression of DDR genes than EA tumors, potentially making them more sensitive to therapies such as ionizing radiation. PARP inhibition and ionizing radiation show synergism in the context of cancer therapy combination. PARPi veliparib, combined with ionizing radiation, decreases cell survival in the context of AR^+ and AR^- prostate cancer cell growth in vitro and in vivo (72, 119). Currently, there are clinical trials aiming to assess the effect of combining radiotherapy and different PARPi in prostate cancer (NCT03317392 and NCT04748042). Ascorbate (vitamin C) increases the development of reactive oxygen species involved in DDR. A study investigating the combination of PARP inhibition and ascorbate acid treatment showed synergistic effects resulting from the combination (bioRxiv 2023.03.23.533944). Although it is not yet recruiting, there is a clinical trial that aims to assess the combination of olaparib and ascorbate in patients with CRPC (NCT05501548). The combination trials mentioned herein are either not yet recruiting or are actively recruiting. Therefore, there have not yet been any published race-related data to these cohorts at the time of this review.

PARPi and androgen-directed therapy

The interaction between PARP and AR has shown promise in being exploited therapeutically for prostate cancer via the use of PARPi and hormone-based therapeutics in combination (36, 72, 120). Two phase III clinical trials used the combination of abiraterone (a hormone-directed therapy) with niraparib or olaparib [PARPi; MAGNITUDE (NCT03748641; ref. 102); PROpel (NCT03732820; ref. 121)]. More recently, a clinical trial tested the efficacy of combining talazoparib (another PARPi) and enzalutamide in TALAPRO-2 (NCT03395197).

MAGNITUDE tested abiraterone in combination with niraparib compared with abiraterone plus placebo. This trial demonstrated that the combination improved radiographic progression-free survival (rPFS) in HR-deficient tumors. There was no difference in rPFS in the HR-competent cohort of this trial. In the PROpel study, abiraterone was used in combination with a different PARPi, olaparib. In contrast to the MAGNITUDE study, the PROPEL study demonstrated improved overall rPFS with the combination treatment irrespective of HR status. The TALAPRO-2 trial also demonstrated increased rPFS irrespective of HR status.

A recent commentary following the different PARPi trials suggests that there may be differences between the pharmacologic interaction of hormone-based therapy (such as abiraterone and enzalutamide) and the differing PARPi (122). A recent commentary also provides greater insights into the details of the trials (120). For example, in the PROpel trial, although it was concluded that patients benefited irrespective of HR status, this commentary heavily focused on the trial design and not the actual HR status of the patients. The commentary clarifies that the most benefit in these trials still went to those with HR defects, specifically with *BRCA2* mutations. In the TALAPRO-2 trial, patients with HR deficiencies experienced 77% ($P = 0.0002$) lower risk of radiographic progression compared with patients without HR deficiencies who experienced 34% ($P = 0.0092$) lower radiographic progression (123). Although there are benefits in overall rPFS in patients irrespective of HR status in these trials, there is still a higher benefit seen in patients with HR deficiencies. This commentary still warrants further exploration of different PARPi and the mechanisms by which they interact with AR because no benefit (MAGNITUDE) is still different from some benefit (PROpel and TALAPRO-2).

In the MAGNITUDE study, lack of diversity was listed as a limiting factor (102); 72% of patients in the placebo arm were Caucasian and 75% in the control arm were Caucasian, whereas 0% in the placebo arm and 5% in the control arm were AA. In the supplement of the published PROpel study, a subgroup analysis of the small number of Black/AA patients enrolled in the trial ($n = 11$ in the placebo arm; $n = 14$ in the control arm) suggests that the combination of PARPi and AR-directed therapy may be differentially effective based on the racial background (hazard ratio not reported for Black/AA; hazard ratio, 0.62 for White; ref. 121). However, this study was not powered for the analysis of racial differences, and the confidence interval for the Black/AA cohort crossed 1. Unfortunately, no race-related data have been published at the time of this review for the TALAPRO-2 trial.

PARPi and immunotherapy

PARP inhibition has been associated with elevated programmed cell death protein 1 (PD1) levels through different mechanisms (124, 125). PD1 is an immune checkpoint protein that is a therapeutic target for immune therapy in cancer management. PARP inhibition combined with PD1 inhibition shows promising results as an anticancer combination therapeutic option (126, 127). In a trial combining olaparib and durvalumab (a PD1 inhibitor), an increased progression-free survival mainly in patients harboring HR mutations (NCT02484404; 12 months for all patients vs. 16.1 months for patients with HR mutations; $P = 0.031$; ref. 128) was observed. In another trial that combined olaparib with a different PD1 inhibitor, pembrolizumab, slight increased survival was observed in a specific subset of patients (NCT03834519; ref. 127). The patients were not selected based on their HR status, but it was reported that 4% of patients have HR impairments. Race data were only reported for

NCT03834519 at the time this review was written. In this trial, 84% of participants were White, and 2.9% were Black. No major conclusions based on racial differences can be deducted from this study. In Supplemental forest plots, the race category is separated by "White" and "all others" (including Black, American Indian, Alaska Native, Asian, Native, or other Pacific Islander). Given the elevated immune response gene expression levels in AA tumors, PARPi with immunotherapy (such as PDL1 inhibitors) may be a good combination strategy to target the DDR pathway, without further elevating the immune response pathways (10, 12, 118).

PARPi combination therapies and race

AA men may benefit from combination therapies with PARP inhibition because of their genetic differences. However, due to the lack of clinical trial data with an equal distribution across races, it is difficult to conclude the impact of race on the efficacy of PARPi as monotherapy or in combination therapies (129). Based on the pathways that PARP1 regulates and the increasingly expressed genetic signatures in AA men, there may be benefit in the combination therapies available for patients with prostate cancer. To make comprehensive conclusions on the differential impact race may have on available therapeutic options, clinical trials with higher/equal enrollment of AA compared with EA will be required, especially in contexts in which AA men may derive greater therapeutic benefits.

Prostate Cancer Racial Disparity and PARP

Unfortunately, racial disparities in clinical trial inclusion are common across cancer types. The GENIE database created by AACR concluded that White and Asian patients are often overrepresented in most clinical trials, whereas Black patients are significantly underrepresented (130). At the time of this review, specifically for prostate cancer, GENIE cannot be used to assess potential biological differences between AA and EA patients due to the lack of equivalent sample size. The lack of enrollment of AA patients in prostate cancer trials is multifold (131). Recent studies show a clear lack of diversity. These issues and potential solutions to these issues that have been reviewed in recent years are discussed herein (132, 133).

In 2020, a study was conducted to assess overall prostate cancer clinical trials related to treatment, prevention, and screening with race-related data (1985–2019). Roughly 30% of trials were excluded because they did not report or show any race-related data. Of the trials analyzed, 1.3% included AA participants. Screening trials (which may be the most crucial/critical for AA to have access to) had only about 0.5% AA inclusion/accrual (134). In a similar study conducted in 2023, a similar percentage (30%) of trials did not report race-associated data (1990–2020; ref. 135). In 2022, access to clinical trials as it relates to race was assessed. The study found that more densely packed AA communities had lower access to cancer facilities and had to travel outside of their neighborhoods to receive cancer care. It was determined that there was an anticorrelation between the percentage of population that was AA and that had access to prostate cancer clinical trials in that geographic area (136). Because AA men are the most affected by prostate cancer and experience the most severe outcomes, the number of AA men enrolled in these trials should be increased compared with the current deployment of clinical trial resources. Active clinical trials at the time of this review related to PARP inhibition were analyzed to better understand if there is a racial disparity in these trials. The results of

these analyses indicate that there is in fact a racial disparity in PARPi-related prostate cancer clinical trials. Of the trials that reported race-related data, AA patients represented anywhere from 0.2% to 3% of patients in the trial, whereas EA patients represented anywhere from 70% to 95% (**Table 1**). The clinical trials were all posted relatively recently, with the oldest being from 2016. Future trials can be, should be, and must be more representative of the disease disparity.

PARPi trials

NCT02854436 and NCT03148795 both accrued only 3% known AA patients compared with 70% to 90% EA patients. The trials had patient molecular data attached focusing on DDR mutations given the hypersensitivity of DDR-defective tumors to PARPi. Tumors in the AA patients in both trials harbored BRCA mutations (137, 138). NCT02854436 classified patients into a BRCA cohort (patients with mutations in *BRCA1* and/or *BRCA2*) and an "other homologous recombination repair (HRR)" cohort (patients with mutations in *BRIP1*, *CHEK2*, *FANCA*, *HDAC2*, and *PALB2*). Five AA patients in NCT02854436 harbored tumors with BRCA mutations, whereas no AA patients harbored "other HRR mutations." In NCT03148795, patients were classified by impairments in *BRCA1*, *BRCA2*, *PALB2*, ATM, or others (*ATM*, *CHEK2*, *FANCA*, *MLH1*, *MRE11A*, *NBN*, and *RAD51C*). Tumors may have had mutations in other genes on the list, but they were classified based on the genes that were most mutated. *BRCA2* mutations are most common across the board (48% of patients), and all three AA patients enrolled harbored *BRCA2* mutations (137). There were no AA patients in any of the other cohorts analyzed.

PARPi and AR-directed therapy trials

NCT03732820 stratified patients by HRR mutation (HRRm) status (121). Patients with HRRm were classified as having mutations in any of the following genes: *ATM*, *BRCA1*, *BRCA2*, *BARD1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51B*, *RAD51C*, *RAD51D*, or *RAD54L*. Other classifications included non-HRRm (patients without HRRm) and HRRm unknown (patients with unknown status of HRRm). Although participants' race was reported, data to support percentages of those patients of differing racial backgrounds harboring HRRm mutations were not reported. Overall, in the study, only 3% of patients enrolled were AA compared with 70% of EA men. In the NCT03748641 trial, patients were separated by HRR mutations. HRR+ patients had mutations in at least one of the following HRR genes: *ATM*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK2*, *FANCA*, *HDAC2* or *PALB2*. HRR− patients did not harbor detectable HRR mutations in the gene list created. Results of HRR+ patients revealed that all five of the AA patients enrolled had some form of HRR mutation (139). The mutations in specific genes broken down by race were not reported. For NCT01972217, there was one AA patient in each arm of the study (olaparib plus abiraterone and abiraterone plus placebo) for a total of two AA patients in the entire trial compared with 150 EA patients (139). In this trial, patients with mutations in HRR genes (*ATM*, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDK12*, *CHEK1*, *CHEK2*, *FANCL*, *PALB2*, *RAD51C*, *RAD51D*, and *RAD54L*) were analyzed separately from patients without HRR mutations. No publicly available information on HRR status as it relates to race has been published.

PARPi and immune therapy trials

In NCT03338790, patients' HRR status was documented as either positive or negative (66). Although the specific HRR genes analyzed were not reported, the trial concluded that the differences in HRR

status did not affect the response of the patients to PARPi. No data on HRR status as it related to race were reported. Overall accrual to the trial was 9.5% AA, but for the arm focused on assessing the treatment combination of rucaparib plus nivolumab, overall accrual was only 1% AA. In NCT03834519, the HRR status of patients was classified as having *BRCA1* or *BRCA2* mutations (or lack thereof). There was only one AA patient (which made up 0.2% of the study) in the olaparib plus pembrolizumab combination treatment arm. Four AA patients were enrolled in the arm assessing the impact of next-generation hormonal agent monotherapy. Overall accrual to the study was only 0.6% AA.

Some studies suggest that socioeconomic status is the main contributor to the differences in prostate cancer survival and outcomes between AA and EA patients (140, 141). Even if socioeconomic factors are the driving cause of the difference between outcomes, as a field, we should not neglect the biological impact of those differences. It has been suggested that socioeconomic status is not solely to blame and that there are biological differences between EA and AA prostate cancer tumors (140, 142). There have also been several recent studies analyzing the differences between EA and AA tumor biology cited in this review (12, 74, 118, 143). The major limitation of most studies is inadequate access to data that are properly powered to ask race-related questions, as suggested in the Surveillance, Epidemiology, and End Results study (140).

The proximity of hospitals may be a barrier, as suggested earlier (136), which may allow for detrimental biological differences to progress at a more aggressive rate. When these types of cases are presented in the clinic, the excuse should not be that they are from a lower economic status. Science should be able to help provide solutions to the more aggressive form of disease. Medicine is moving toward providing more personalized care for patients, which is even more of a reason to pursue and elucidate mechanistic differences in tumor progression between AA and EA patients.

Conclusions

Although there has been progress in recent years to better understand racial differences and their impact on prostate cancer progression, and cancer progression in general, more needs to be done. The field has just begun to scratch the surface of understanding the underlying impacts of biological differences that may influence racial differences in treatment response. In addition to having better clinical representation, there needs to be better representation at a preclinical level. There are several established prostate cancer cell lines derived from EA tumors. More recently, Black American cell lines are being created (144, 145), but they (currently) are not widely used. There are still many questions to explore in the context of PARP inhibition and the benefit it may pose specifically to the AA community.

Authors' Disclosures

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