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Role of ethnic and genetic factors in the development of prostate cancer (Review)

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Abstract. Prostate cancer (PCa) is one of the most common malignancies worldwide, particularly affecting older males. Genetic and ethnic factors play a critical role in the development, progression and mortality rate associated with PCa. The present review focuses on the influence of race and genetic predisposition, particularly the mutations in BRCA1 and BRCA2 genes, which markedly increase the risk of developing aggressive forms of PCa. African American males, in particular, are more susceptible to PCa, with a higher incidence of aggressive disease compared to other ethnic groups. These genetic disparities highlight the importance of targeted genetic screening and personalized healthcare strategies to mitigate the risk of developing PCa in vulnerable populations. The key conclusions from the present review emphasize the necessity of integrating genetic testing into routine PCa screening protocols, particularly for high-risk groups, such as males with a family history of PCa or those of African descent. Personalized treatment options, such as the use of PARP inhibitors for patients with BRCA mutations, present a promising approach to improving the outcomes of patients with PCa. The present review calls for further research into the interactions between genetic and environmental factors in PCa and the development of tailored intervention programs to reduce incidence and mortality among high-risk populations. Expanding access to genetic counselling and testing services is crucial to improving early detection and preventive care.

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Contents

1. Introduction

Prostate cancer (PCa) poses a serious global health issue, particularly among older males (1-3) and remains the second most common type of cancer diagnosed in males following skin cancer. It is also the fifth leading cause of cancer-related mortality worldwide, underscoring the critical need for effective management and prevention strategies. Understanding the complex interplay of risk factors, symptoms, treatment options and patient outcomes is essential for improving the detection and treatment of PCa. However, one of the key challenges lies in addressing racial disparities in the development and prognosis of PCa.

Several factors may increase the risk of developing PCa, including age, race, family history and genetic predispositions (4,5) (Fig. 1). Age is the most critical risk factor, with the likelihood of developing PCa sharply increasing after the age of 50 years. Genetic predisposition plays a critical role in the racial disparities observed in the incidence of and mortality associated with PCa (6). Another influential factor is race (7). The impact of race on PCa involves a multifaceted combination of genetic, socioeconomic, environmental and healthcare access factors. These variables contribute to observed racial disparities in both the incidence of and mortality associated with PCa.

African American males, for instance, have a markedly higher risk of developing PCa compared to other racial groups (8,9). Studies have identified specific genetic variants which are more prevalent among African American males, such as those affecting the androgen receptor gene, which may increase susceptibility to PCa (10,11). A study published in Nature Genetics identified 187 new genetic variants associated with an increased risk of developing PCa in males (12). Notably, several of these variants were exclusive to males of African ancestry, shedding light on the disproportionately higher risk of developing PCA in this population (12). These findings indicate that African American males are more likely to be diagnosed with aggressive forms of the disease and have higher mortality rates compared with males of other racial and ethnic groups (9,13). By contrast, Asian Americans and Hispanics have lower incidence and mortality rates than non-Hispanic Caucasian males (14,15).

Socioeconomic and healthcare access factors significantly compound racial disparities in PCa outcomes, particularly for African American males. These males are disproportionately affected by structural barriers that limit their access to timely, high-quality healthcare, which in turn exacerbates the risk of poorer outcomes. Limited access to healthcare services remains a major issue, with African American males often facing challenges, such as fewer healthcare facilities in their communities, longer waiting times for specialist consultations, and fewer opportunities for preventive care and early screening. Lower insurance coverage is another key factor. African American males are more likely to be underinsured or uninsured compared to their non-Hispanic Caucasian counterparts, leading to delayed screenings and treatments. For a disease such as PCa, where early detection is critical for an improved prognosis, these delays often result in diagnosis at more advanced stages when the cancer is more difficult to treat. Due to this lack of insurance coverage, even in the case that PCa is detected at an early stage, patients may not have access to optimal treatments, including cutting-edge therapies or personalized treatment plans based on genetic testing, which are typically costlier.

Delays in diagnosis and treatment are further aggravated by socioeconomic factors, such as lower income levels, which can make it challenging for patients to take time off work or afford the high out-of-pocket costs associated with cancer care. Additionally, the mistrust of the healthcare system, shaped by historical injustices and experiences of bias in medical treatment, can deter African American males from seeking timely care. Such a combination of delayed diagnoses, inadequate treatment options and a lack of trust in the healthcare system results in worse overall prognoses for African American males with PCa.

Moreover, disparities in healthcare access are compounded by differences in health literacy and awareness about PCa. A number of males from racial minorities groups may not receive adequate information about the importance of early screening, family history, or available treatment options, which limits their ability to make informed decisions about their healthcare. Educational campaigns and culturally sensitive healthcare initiatives are critical to improving awareness and encouraging proactive health behaviours in at-risk populations. The dual focus on genetic research and healthcare equity can help reduce the disproportionately high mortality rates from PCa in this population and may ultimately lead to more effective and equitable cancer care for all racial groups.

Family history and genetic predisposition also play a pivotal role, as males with a family history of PCa have a higher risk of developing the disease (5,16). In fact, understanding the role of family history and genetic factors involved in the risk of developing PCa is critical for the early detection of the disease, personalized screening and prevention strategies (17). A family history involves a history of PCa in close relatives, such as fathers, brothers and sons. The risk increases further if affected relatives were diagnosed at a younger age or if multiple family members are affected. This suggests a hereditary component to the risk of developing PCa, where genetic factors passed down through generations contribute to susceptibility to the disease (18,19).

Several genes have been identified that play a role in susceptibility to PCa, including BRCA1, BRCA2, HOXB13 and others (20,21). Mutations in these genes can interfere with the normal process of cell growth and division, leading to the uncontrolled growth of prostate cells and the development of cancer. In addition, changes in other genes involved in hormone regulation, DNA repair and inflammatory pathways may also contribute to the risk of developing PCa.

Hereditary PCa accounts for 5-10% of all PCa cases and is characterized by the strong familial clustering of the disease. Inherited mutations in certain genes, such as BRCA1 and BRCA2, are associated with an increased risk of developing PCa, as well as other types of cancer, such as breast and ovarian cancer (22,23). Males with hereditary PCa often develop the disease at a younger age and may have more aggressive forms of the disease compared to males without a family history of the disease.

The present review aimed to address an critcal gap in the literature by examining the complex role of racial and genetic factors in PCa. While ample research has explored genetic predisposition and family history, fewer studies have comprehensively investigated the mechanisms through which race, genetics and socioeconomic factors interact to influence PCa outcomes. The present review hopes to add value by providing a deeper understanding of the mechanisms through which these factors contribute to disparities in PCa incidence, progression and mortality. Moreover, the present review offers actionable recommendations for integrating genetic screening, improving healthcare access and tailoring treatment strategies to reduce racial disparities in PCa outcomes.

By examining the intersections of race, genetics and healthcare access, the present review seeks to inform future research, policy initiatives and clinical practices aimed at reducing disparities in the diagnosis and treatment of PCa.

2. Literature search strategies

Open electronic databases, including Web of Science, PubMed, LISTA (EBSCO), Embase and the Cochrane Library, were searched using a combination of relevant keywords and Medical Subject Headings (MeSH) terms. The literature search was limited to articles published in the English language up until the date of September, 2024. The scheme representing the method of the article search is presented in Fig. 2.

The inclusion criteria for studies were as follows: Publications were included if the analyses met the following

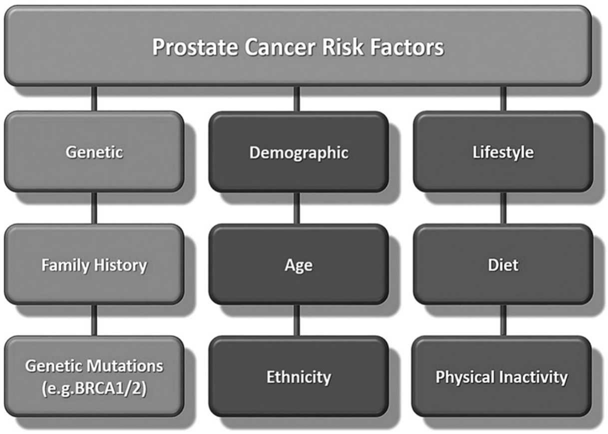

Figure 1. Factors increasing the risk of developing prostate cancer, including age, race, family history and genetic predispositions.

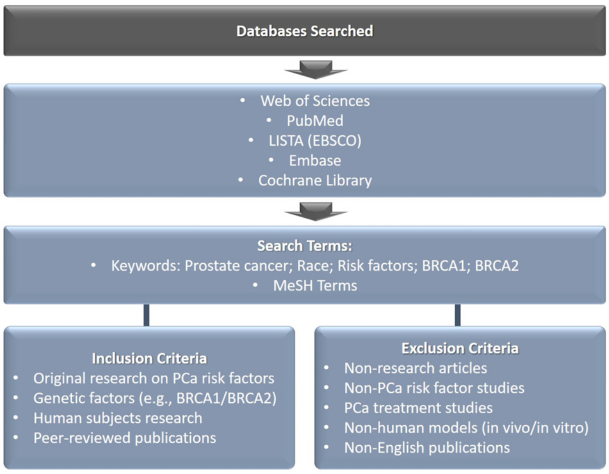

Figure 2. Schematic diagram of the literature search.

criteria: i) Original research studies that focused on the risk factors of PCa development, particularly the impact of race; ii) the studies included research on the genetic factors associated with PCa, including mutations of the BRCA1 and BRCA2 genes; iii) the studies involved human subjects; and iv) the studies were published in peer-reviewed journals.

The following exclusion criteria were used: i) Conference abstracts, case reports, editorials, letters or comments; ii) the research was not specifically related to PCa risk factors; iii) studies focused on PCa treatment; iv) PCa model studies, including *in vivo* and *in vitro* studies; v) Non-English language publications.

Quality assessment. The quality of each included study was evaluated using the National Institutes of Health's Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. This assessment was performed by two independent reviewers, with any disagreements resolved through discussion or, if necessary, third-party adjudication.

3. Influence of race on the occurrence of prostate cancer

PCa is one of the most common types of cancer among males worldwide, and its incidence and outcomes can vary significantly by race and ethnicity. Previous studies have strongly suggested that race is a key factor in the development of PCa. For example, African Americans have a higher risk of developing PCa compared to males of other racial and ethnic groups (24). Other risk factors include obesity, a diet high in red meat and processed foods and certain genetic mutations.

In fact, the role of race in the development of PCa is a complex and multifaceted issue that is still being carefully investigated (25,26). Numerous studies have consistently shown notable disparities in the incidence and mortality rates of PCa among racial and ethnic groups (27). It has been shown that African American males have the highest incidence of PCa worldwide, followed by Caribbean males of African descent (28). Moreover, African American males are more likely to be diagnosed with aggressive forms of the disease and have higher mortality rates compared with males of other racial and ethnic groups (9,13).

Ledet *et al* (25) found that, while genetic risk factors for PCa were similar across African American and Caucasian patients, African Americans had unique genetic variants and more BRCA1 mutations. Zhang and Zhang (27) observed significant dietary differences between African American and European American males, with African Americans exhibiting a higher prevalence of PCa, but limited direct dietary implications for cancer risk.

Epstein *et al* (29) found higher rates of biochemical recurrence in African Americans post-prostatectomy, suggesting a need for closer monitoring in this group. Owens *et al* (13) reported similar emotional and informational support needs across racial groups among PCa survivors. In another study, Wu *et al* (14) identified factors, such as age, tumor grade and marital status as significantly affecting mortality in Asian-American patients, with surgery reducing the risk of mortality. Deuker *et al* (30) reported that Native Hawaiians or Pacific Islanders exhibited worse PCa characteristics at diagnosis than Caucasians, although the mortality rates did not differ significantly.

In a large cohort study on 4,282 patients, Würnschimmel *et al* (15) found that Asians with metastatic PCa (mPCa) had lower cancer-specific mortality rates than other groups, while Hoeh *et al* (31) reported no significant difference in mortality rates between treatment types in high-risk Hispanic patients.

Stern *et al* (32) found that South and East Asian males had lower PCa mortality rates than Caucasians, while Whittemore *et al* (33) linked family history to an increased risk of developing PCa across ethnicities. In a large study with 239,613 participants, El Khoury and Clouston (34) observed that a lower socioeconomic status increased PCa mortality rates across racial groups, indicating the importance of tailored interventions (34). Finally, Yamoah *et al* (35) found that in African American veterans, the incidence rate of PCa was almost 2-fold higher compared with that of Caucasian veterans, pointing to persistent disparities even with equal healthcare access.

It has been shown that African American males have a higher prevalence of genetic variants associated with an increased risk of developing aggressive forms of PCa, including mutations in genes such as BRCA1, BRCA2 and HOXB13 (36,37). These genetic differences may contribute to the higher morbidity and mortality rates observed in this population (38,39). In addition, differences in androgen receptor signaling pathways and tumor micro-environmental factors may also contribute to racial disparities in PCa.

A recent study by Gu *et al* (11) demonstrated that the West African ancestry-specific single nucleotide polymorphism (SNP) rs7824364 on 8q24 independently predicted positive prostate biopsy in African American males who were candidates for prostate biopsy following PCa screening.

Thakker *et al* (40) used the data from the National Cancer Database spanning 2004 to 2017, to analyze factors, such as age, race, ethnicity, geographic location, education level, income and insurance status. It was found that the percentage of patients presenting with mPCa increased after the 2012 recommendation, with Hispanics and non-Hispanic patients of African descent experiencing a higher rate of increase compared to non-Hispanic Caucasians. The insurance status significantly influenced the mPCa presentation rates, with uninsured Hispanics and non-Hispanic patients of African descent being more likely to be diagnosed with mPCa than their insured counterparts. Additionally, a lower household income, particularly among non-Hispanic subjects of African descent, was linked to a higher likelihood of presenting with mPCa (40).

Furthermore, socioeconomic and environmental factors also play a critical role in racial disparities in PCa. African American males are more likely to experience social determinants of health, such as poverty, limited access to healthcare, lower health insurance rates, and barriers to screening and early detection. These differences in access to and the utilization of health care contribute to delays in diagnoses, resulting in more advanced disease at diagnosis and poorer treatment outcomes.

Cultural and behavioral factors may also contribute to racial disparities in PCa. African American males are less likely to engage in preventive health measures, such as regular screenings and healthy lifestyle choices, which can delay detection of PCa and increase the risk of developing advanced disease at the time of diagnosis. Moreover, cultural beliefs and attitudes toward cancer and healthcare may influence treatment decisions and adherence to medical recommendations.

Asian males exhibit distinct epidemiological patterns of PCa compared with other racial and ethnic groups (32,41). Historically, PCa is less common in Asian countries, such as China, Japan and Korea compared to Western countries. However, in recent years, there has been an increase in the incidence of PCa among the Asian population, which is associated with changes in lifestyle factors, dietary habits and improvements in cancer detection methods (33,42). Genetic factors play a crucial role in the development of PCa in Asian males (14). Although specific genetic mutations associated with the risk of developing PCa have been extensively studied in other populations, such as BRCA gene mutations in Ashkenazi Jews, the genetic landscape of PCa in Asian males is less studied (43). However, recent studies have identified several genetic variants unique to the Asian population that may contribute to the susceptibility and aggressiveness of PCa (44-46).

Environmental and lifestyle factors also influence the development of PCa. In particular, African American males and males of African descent, Asian males and Hispanic males exhibit notable differences in PCa rates, suggesting that factors such as diet, physical activity, socioeconomic conditions, and access to healthcare may influence the development of the disease. However, lifestyle factors, such as diet and access to healthcare significantly affect the outcomes of African American males. Studies have demonstrated that African American males are more likely to have diets high in fat and processed foods, which have been associated with an increased risk of developing PCa (47,48). High-fat diets can lead to increased levels of testosterone, which may promote the growth of PCa cells. Environmental stressors, such as residing in communities with higher levels of pollution or lower access to fresh, healthy foods, may also exacerbate the risk of developing more aggressive forms of the disease (27). Physical inactivity and obesity, both of which are more prevalent among African American males than in other racial groups, are further environmental factors that have been linked to an increased risk of developing PCa.

By contrast, Asian males, particularly those residing in Asia, tend to exhibit lower incidence and mortality rates of PCa (49). This difference is often attributed to dietary factors and lifestyle choices common in numerous Asian cultures. Diets rich in soy products, green tea and fish, which are prevalent in countries, such as Japan and China, have been associated with a lower risk of developing PCa. Soy contains isoflavones, which are considered to have a protective effect against PCa by inhibiting the growth of cancer cells (50). However, studies have shown that Asian males who migrate to Western countries, where diets are often higher in fat and lower in plant-based foods, exhibit a significant increase in the risk of developing PCa (51,52). This suggests that lifestyle factors, particularly diet, may have a greater influence on the development of PCa than genetics alone.

Practices in screening and diagnosing PCa vary among Asian countries and may influence disease detection and outcomes. Although prostate-specific antigen (PSA) screening is widely used in Western countries for the early detection of PCa, its utility and effectiveness in Asian populations remains controversial (53-55). Cultural beliefs, healthcare infrastructure and resource availability influence the implementation of PCa screening programs in Asian countries, resulting in disparities in access to timely diagnosis and treatment (10,56). Cultural and social influences shape attitudes toward PCa prevention, screening and treatment among Asian males.

Hispanic makes exhibit intermediate PCa incidence rates compared to African American and Asian males; however, they face unique environmental and lifestyle challenges that may influence their risk. While genetic factors do play a role, Hispanic males often face socioeconomic barriers similar to African American males, such as lower access to healthcare, limited health insurance coverage and delayed diagnosis due to fewer opportunities for screening.

Dietary habits among Hispanic males may also contribute to the risk of developing PCa. Traditional diets in numerous Hispanic cultures can be high in red meat and carbohydrates, which have been linked to an increased risk of developing cancer. However, diets rich in fruits, vegetables and fiber, also common in some Hispanic communities, may offer protective effects. The variation in dietary habits within the Hispanic population underscores the complexity of identifying specific lifestyle factors that influence the risk of developing PCa.

These differences highlight the importance of considering environmental and lifestyle factors, alongside genetics, when addressing PCa disparities among racial groups. Public health initiatives should focus on improving access to healthy foods, promoting regular physical activity and increasing the awareness of PCa screening, particularly in underserved populations. Tailoring prevention strategies to the specific needs of each racial group can help reduce the burden of PCa and improve outcomes for males globally.

4. Hereditary risk factors for the development of prostate cancer

PCa is one of the most heritable cancers, and a family history of PCa is a well-known risk factor (57-59). Family history is a well-established risk factor for PCa. Studies have demonstrated that males who have a first-degree relative (father or brother) diagnosed with the disease have an ~2-fold higher risk of developing PCa themselves compared with those without a family history (60,61). This familial aggregation of PCa suggests a hereditary component, suggesting the involvement of genetic factors in the susceptibility to the disease. Several genetic variants associated with the risk of developing PCa have been identified through genome-wide association studies, with common polymorphisms in genes such as HOXB13, BRCA1 and BRCA2, and DNA repair genes contributing to the familial clustering of the disease (62,63)). A summary of the roles of BRCA1 and BRCA2 mutations in prostate cancer is presented in Table I.

PCa is known to have a strong familial component, with studies suggesting that up to 5-10% of cases are due to inherited genetic factors (62,64,65). Mutations in specific genes, such as BRCA1, BRCA2 and HOXB13, and DNA mismatch repair (MMR) genes (e.g., MutL homolog 1 (MLH1), MutS homolog (MSH)2, MSH6 and PMS2) are associated with hereditary PCa syndromes (17). These genetic alterations can interfere with normal cell growth and proliferation, increasing the risk of developing PCa.

In addition to BRCA1 and BRCA2 mutations, the HOXB13 gene has emerged as a crucial factor in hereditary PCa. The HOXB13 gene encodes a transcription factor that plays a pivotal role in the regulation of genes involved in the development and maintenance of prostate tissue (66,67). Mutations in this gene, particularly the G84E variant, have been strongly linked to a significantly increased risk of developing PCa, particularly in males with a family history of the disease.

The G84E mutation in HOXB13 is relatively rare in the general population; however, studies have found it to be more prevalent among males of European ancestry (68). In particular, research has shown that males carrying this mutation are at a 3-5-fold higher risk of developing PCa compared to non-carriers. This elevated risk renders HOXB13 G84E a key genetic marker for early detection and screening in families with a history of PCa, allowing for more personalized and proactive medical approaches (38).

The significance of the HOXB13 mutation extends beyond familial cases. Although it is rare in the broader population, its presence highlights the importance of genetic screening for hereditary PCa (69). The identification of the HOXB13 G84E mutation can help clinicians and genetic counselors stratify risk in patients with a family history of the disease, guiding decisions regarding earlier and more frequent PCa screening.

Furthermore, recent studies suggest that males with HOXB13 mutations may develop PCa at an earlier age and may be more prone to aggressive forms of the disease (38,67,70). This suggests that the gene may not only be used as a marker for an increased risk of PCa, but also as a potential indicator for more severe disease progression. Understanding the impact of HOXB13 mutations may improve both the prevention and management strategies for those at a higher genetic risk.

Furthermore, mutations in DNA MMR genes, including MLH1, MSH2, MSH6 and PMS2, are associated with Lynch syndrome, a hereditary cancer syndrome that significantly increases the risk of developing several types of cancer, including PCa. MMR genes are responsible for correcting DNA replication errors that occur during cell division. When these genes are mutated, replication errors are uncontrolled, leading to genomic instability and an increased likelihood of developing cancer. Males with Lynch syndrome not only have an elevated risk of developing colorectal cancer, but also a higher likelihood of developing PCa at an earlier age than those without the syndrome.

The presence of these genetic mutations in the BRCA1, BRCA2 and HOXB13, and MMR genes suggests that hereditary PCa syndromes involve disruptions in crucial cellular pathways, particularly those involved in DNA repair and genomic stability. This increased understanding of the genetic basis of hereditary PCa has critical implications for patient care. Males with a family history of PCa, particularly those with known genetic mutations, can benefit from genetic counselling and testing to assess their risk. Early detection strategies, such as regular PSA testing and digital rectal exams, can be tailored based on the genetic risk profile of an individual, allowing for the more proactive and personalized management of the risk of developing PCa.

Moreover, the identification of genetic mutations in these high-risk families provides opportunities for targeted therapies. For example, males with BRCA mutations may be candidates for treatment with PARP inhibitors, a class of drugs that specifically target cancer cells with defective DNA repair mechanisms (71-73). These therapies, which have shown promise in the treatment of breast and ovarian cancers, are being explored for the treatment of PCa, particularly for patients with advanced or metastatic disease linked to genetic mutations.

Family history serves as a key component in PCa risk assessment models, helping to identify individuals who are at an increased risk and who may benefit from individualized screening and preventative interventions. Males with a family history of PCa, particularly those with multiple relatives with PCa or early-onset disease, are considered to be at a high risk and may require earlier and more frequent screening.

Current screening guidelines recommend that males with a family history of PCa initiate a discussion with their health care providers about the benefits and limitations of PSA testing and digital rectal examinations commencing at the age of 40-45 years (or earlier if considered appropriate based on individual risk factors). The recommendations can be tailored based on individual risk factors, including family history, lifestyle and genetic predisposition. Males who are at a higher

Table I. Overview of the roles of BRCA1 and BRCA2 mutations in prostate cancer.

Gene	Role in prostate cancer	Risk increase	Genetic testing	Implications for treatment	Screening recommendations
BRCA1	BRCA1 mutations are less common in prostate cancer, yet still significant. They are associated with a higher risk of developing aggressive forms of prostate cancer.	Moderate increase in risk. Individuals with BRCA1 mutations have a higher likelihood of developing prostate cancer, especially aggressive types, compared to the general population.	Recommended for individuals with a family history of BRCA1-related cancers or early-onset prostate cancer. Testing can help identify those at risk and guide decisions on preventive measures.	May influence the choice of treatment, including consideration of targeted therapies, such as PARP inhibitors. BRCA1-related prostate cancers may respond better to specific drugs.	Enhanced screening protocols may be recommended for individuals with known BRCA1 mutations. This can include starting prostate cancer antigen testing at an earlier age and conducting more frequent screenings.
BRCA2	BRCA2 mutations are more commonly associated with prostate cancer and significantly increase the risk. Males with BRCA2 mutations are more likely to develop early-onset and aggressive prostate cancer.	Substantial increase in risk. BRCA2 mutations are strongly linked to early-onset prostate cancer and more aggressive forms, making it critical for affected individuals to undergo regular and early screenings.	Strongly recommended for individuals with a family history of BRCA2-related cancers, early-onset prostate cancer, or known BRCA2 mutations in the family. Testing is crucial for early detection and prevention strategies.	Significantly influences treatment decisions, often leading to the use of PARP inhibitors and other targeted therapies. BRCA2-related cancers may also be more sensitive to certain chemotherapies.	Enhanced screening protocols are strongly recommended for individuals with known BRCA2 mutations, including earlier and more frequent prostate cancer antigen testing. MRI and other advanced imaging techniques may also be used.

risk may benefit from earlier and more frequent screening with PSA testing and digital rectal examinations to detect cancer at an earlier, more treatable stage.

5. Mutations of the BRCA1 and BRCA2 genes as a risk factor for the development of prostate cancer

According to previous studies and the Nordic Twin study, up to 57% of the risk of developing PCa is due to hereditary factors (74-76). There are two types of hereditary factors: i) Common SNPs, which themselves are associated with a slightly increased risk; and ii) rare variants or mutations in genes, which significantly increase the risk of developing PCa (for example, mutations in the BRCA1/2 genes). Mutations in tumor suppressor genes disrupt their function and lead to a significantly increased risk of developing cancer (Fig. 1). For example, mutations in the BRCA1 and BRCA2 genes increase susceptibility to the autosomal dominant mode of inheritance of PCa and ovarian syndrome (77) and manifest not only in the form of these cancers, but also in the form of PCa and rectal cancer.

BRCA1 and BRCA2 are two of the most well-known tumour suppressor genes involved in the susceptibility to inherited cancer (20,21). Mutations in these genes significantly increase the risk of developing breast, prostate, ovarian and other types of cancer (78-81).

BRCA1 and BRCA2 are large genes located on different chromosomes (17q21 and 13q12-13, respectively) and encoding proteins involved in maintaining genome stability through DNA repair mechanisms. BRCA1 plays a critical role in DNA double-strand break repair, transcriptional regulation and cell cycle control, whereas BRCA2 is primarily involved in facilitating homologous recombination, a process which is critical for DNA damage repair. Mutations in BRCA1 and BRCA2 impair these DNA repair functions, leading to genomic instability and an increased risk of developing cancer (82,83). A schematic illustration of the mutations of the BRCA1 and BRCA2 genes as a risk for developing prostate cancer and patient surveillance is presented in Fig. 3.

Inherited mutations in BRCA1 and BRCA2 have been shown to significantly increase the lifetime risk of developing PCa, as well as breast and ovarian cancer, with carriers of pathogenic variants having an up to 80% lifetime risk of developing breast cancer and an up to 40% lifetime risk of developing ovarian cancer (84,85). In addition, mutations in these genes are associated with an increased risk of developing other types of cancer, including PCa, as well as pancreatic and breast cancer in males.

Genetic testing for BRCA1 and BRCA2 mutations plays a critical role in identifying individuals who are at an increased risk of hereditary cancer and in developing personalized risk management strategies (21,86). Genetic counselling is recommended for individuals with a personal or family history suggestive of PCa (87,88).

Studies have shown that mutations in the BRCA1 and BRCA2 genes not only increase the risk of developing PCa, but lead to the development of more aggressive forms of the disease, which are characterized by higher rates of disease relapse and increased mortality rates (89,90). For example, studies have found that the relative risk of PCa at an age ≤65 years is 1.8-4.5-fold higher in BRCA1 carriers and 2.5-8.6-fold higher in BRCA2 carriers (91-93). Retrospective studies have found that younger carriers of BRCA2 mutations have an aggressive disease course, with high rates of lymph node involvement and distant metastases, and higher mortality rates compared to non-carriers (94-96). The BRCA2 mutation status has now been validated as a prognostic factor for worse outcomes. BRCA2 mutations have also been associated with the early development of PCa (an age at diagnosis of ≤55 years) (97,98).

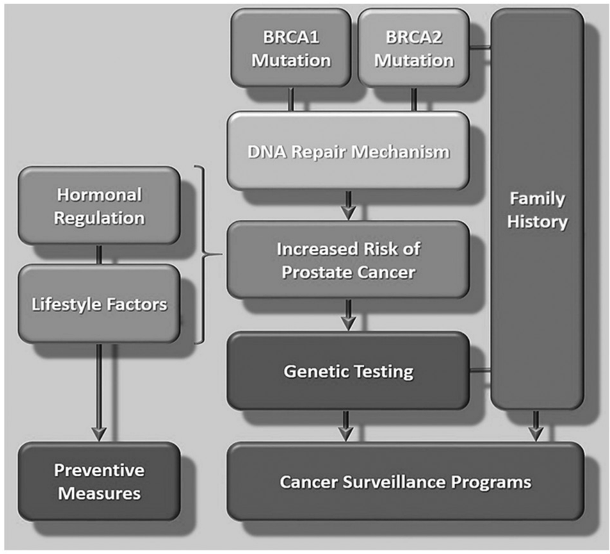

Figure 3. Schematic diagram of mutations of the BRCA1 and BRCA2 genes as a risk for developing prostate cancer.

Recent studies have highlighted the distinct impact of BRCA1 and BRCA2 mutations on the risk of developing PCa, as well as on progression and clinical outcomes, emphasizing the need for personalized genetic screening and targeted treatment strategies. Thorne *et al* (99) found that BRCA2 mutation carriers had more locoregional and digestive system involvement compared to non-carriers, suggesting distinct disease characteristics in BRCA2-associated PCa. Similarly, Paulo *et al* (100) analyzed homologous recombination repair (HRR) gene mutations in early-onset and familial PCa, identifying pathogenic variants in 3.9% of cases, most frequently in the checkpoint kinase 2, ataxia telangiectasia mutated and BRCA2 genes. This underlines the significance of HRR genes in hereditary PCa predisposition.

Kwong *et al* (101) observed an increased risk of developing breast cancer and PCa in high-risk male BRCA2 carriers, supporting a potential role for male-specific screening. Nyberg *et al* (96) further demonstrated that BRCA1 mutations increase the incidence of PCa, particularly in younger males, while BRCA2 mutations are associated with aggressive disease and higher mortality rates, particularly in those with a family history of PCa.

In the study by Fettke *et al* (102), BRCA2 alterations in DNA damage repair genes were linked to poorer clinical outcomes in metastatic castration-resistant PCa, emphasizing BRCA2 as a key prognostic marker. Additionally, Barnes *et al* (103) reported that polygenic risk scores could enhance personalized cancer risk estimation for BRCA1 and BRCA2 male carriers, aiding clinical management.

Although there is debate about whether there is an increased risk of developing PCa in BRCA1 carriers, there is increasing evidence to indicate that PCa is aggressive in these males (88,96). It has been shown that males who carry a BRCA mutation may be at risk of developing other types of cancer, such as breast cancer, pancreatic cancer and melanoma. In addition, females who carry BRCA are at an increased risk of developing breast and ovarian cancer (104,105).

The BRCA genes are known as tumor suppressor genes (106-108). Carcinogenesis occurs in carriers of germline BRCA mutations due to loss of the wild-type allele (107). BRCA1 appears to play a major role in DNA damage repair, protein transcription regulation and genomic stability (109,110). The role of BRCA2 is most likely limited to DNA damage repair (111,112). It is likely that mutations in these genes, leading to dysfunction in the DNA repair pathway, increase the risk of developing PCa; however, the mechanisms through which they affect the course of the disease are not yet fully understood. BRCA1 mutations have been identified in prostate cell lines involving the androgen receptor and insulin-like growth factor 1 receptor pathways (113,114). Additionally, the loss of the suppressive function of BRCA2 has been shown to influence focal PCa development, as well as disease progression through the regulation of matrix metalloproteinase-9 by modulating the PI3-kinase/AKT and MAP/ERK signaling pathways (115,116).

The association of BRCA mutations with aggressive characteristics of PCa was identified in the aforementioned retrospective studies (110,117). In their studies, Edwards *et al* (118,119) found a 4-year difference in the median overall survival between BRCA2 carriers and non-carriers in patients diagnosed with PCa. Gallagher *et al* (120,121) compared clinical outcomes in 26 BRCA mutation carriers and 806 non-carriers and reported a 28% increased risk of developing low-grade tumors (Gleason score ≥7) compared with non-BRCA-associated PCa. Carriers of either mutation were found to have a higher risk of relapse (hazard ratio (HR), 4.32; 95% confidence interval (CI), 1.31-13.62 for BRCA1; and relative risk (RR), 2.41; 95% CI, 1.23-4.75 for BRCA2) and mortality from PCa (RR, 5.16; 95% CI, 1.09-24.53 for BRCA1; and RR, 5.48; 95% CI, 2.03-14.79 for BRCA2) compared with non-carriers (135).

Thorne *et al* (122) found that BRCA2 mutation carriers had a worse PCa survival (HR, 4.97; 95% CI, 2.19-11.25), although this may be due to a higher incidence of undifferentiated (Gleason ≥8) tumors (65.8 vs. 33.0%) and stage T3-T4 tumors (39.5 vs. 22.6%) in carrier vs. non-carrier cohorts. In another study, Tryggvadottir *et al* (123) identified 596 patients with PCa among 29,603 male relatives of unselected probands with breast cancer. They staged and evaluated a subgroup of 89 patients that included carriers of all mutations. Each carrier was matched to two non-carriers according to year of diagnosis and birth. Compared with non-carriers, BRCA2 999del5 mutation carriers had a younger mean age at diagnosis (69.0 vs. 74.0 years, P=0.002), a more advanced disease stage (79.3% with stages 3 and 4 vs. 38.6%, P<0.001), a lower tumor grade (84.0% grade 3-4 vs. 52.7%, P=0.007) and a shorter median survival time (2.1 years; 95% CI, 1.4-3.6 years, vs. 12.4 years; 95%, CI 9.9-19.7 years). The BRCA2 999del5 mutation was also associated with an increased risk of mortality from PCa (adjusted for year of diagnosis and birth (HR, 3.42; 95% CI, 2.12-5.51); the association remained following adjustment for stage and grade (RR, 2.351 95% CI, 1.08-5.11) (135). Narod *et al* (124) noted that the 5-year overall survival rate was shorter for BRCA2 than BRCA1 carriers (42 vs. 64%, respectively), with a median overall survival of 15 years for BRCA1 mutation carriers and 5 years for BRCA2 mutation carriers.

Castro *et al* (125,126) examined the clinical characteristics and outcomes of 2,181 patients with PCa, of whom 5 patients were BRCA1 carriers and 31 patients were BRCA2 mutation carriers. They reported a spectrum of pathogenic mutations causing a more aggressive PCa phenotype (Gleason score ≥8: 50% BRCA2 carriers, 20% BRCA1 carriers, 21% non-carriers; P=0.017), a higher incidence of lymph node involvement (N1: 35% BRCA2 carriers, 50% BRCA1 carriers, and 11% non-carriers, P<0.001) and a higher likelihood of distant metastasis at diagnosis (M1: 21% BRCA2 carriers, 20% BRCA1 carriers, 9% non-carriers, P=0.034) (127). Additionally, compared with non-carriers, patients with BRCA2 mutations had a significantly shorter overall survival (10.8 vs. 13.3 years, respectively; HR, 2.5; P<0.001) and cancer-specific survival (8.6 vs. 16.3 years; odds ratio, 2.8; P<0.001) (127).

According to the American National Comprehensive Cancer Network (NCCN) guidelines, genetic counselling is recommended for males (128-130). In addition, genetic testing may be performed if the individual has a Gleason score ≥7 and has one of the following criteria: i) One close blood relative with ovarian cancer or breast cancer aged ≤50 years; or ii) two relatives with breast cancer, ovarian or prostate (Gleason score ≥7 or higher) at any age.

Despite the studies and results obtained on the association of BRCA 1/2 gene mutations and the risks of developing certain types of cancer, the importance of genetic counselling and testing in males remains underestimated (131-133). Due to the autosomal dominant pattern of inheritance, transmission of BRCA mutations through fathers or mothers occurs equally.

6. Synopsis

Genetic screening and testing are becoming increasingly vital in oncology, providing insight into individuals who are at risk of developing various types of cancers, including PCa. Among the genetic factors associated with the risk of developing PCa, mutations in the BRCA1 and BRCA2 genes have been identified as key contributors. These mutations underscore the need for integrating genetic testing into diagnostic processes, enabling early detection and personalized care (20,21).

Mutations in the BRCA1 and BRCA2 genes, initially identified as drivers of hereditary breast and ovarian cancer, are increasingly implicated in PCa susceptibility (22,134). Males with inherited mutations in these genes are known to have a significantly increased risk of developing PCa compared to the general population. Research has shown that males with BRCA2 mutations in particular have a 4-8-fold higher risk of developing PCa, often at a younger age and with more aggressive disease characteristics (61,86). Given the clinical implications, genetic screening holds significant promise for identifying at-risk individuals, facilitating early detection and improving treatment outcomes.

The findings discussed in the present review suggest clear public health implications. Integrating genetic testing for

BRCA mutations into routine PCa screening protocols, particularly for high-risk groups, such as those with a family history of PCa or belonging to certain racial groups, is a critical next step. The early identification of mutation carriers could lead to the adoption of tailored screening protocols that enable timely intervention and more personalized treatment plans. For example, evidence suggests that BRCA-mutated PCa may better respond to PARP inhibitors, which opens the door to precision medicine approaches that could markedly improve patient outcomes (135).

Ethnicity plays a critical role in the incidence and mortality rates of PCa. African American males have the highest incidence of PCa worldwide, followed by Caribbean males of African descent (136,137). They also tend to be diagnosed with more aggressive forms of the disease and have higher mortality rates compared to men of other racial and ethnic groups (36,138,139). The disparities are partly due to the higher prevalence of certain genetic variants, including BRCA1, BRCA2 and HOXB13, which are more common in African American males. The demonstrated racial disparities in PCa outcomes, particularly the elevated risk faced by African American males, highlight the need for targeted public health initiatives. Policymakers need to prioritize expanding genetic testing and counseling services for at-risk populations. Outreach programs should focus on increasing awareness of genetic risk factors and providing accessible screening options, particularly in underserved communities. For example, expanding genetic screening programs in healthcare settings that primarily serve African American populations could help address the higher PCa mortality rates in this group.

By contrast, Asian Americans and Hispanics generally exhibit lower incidence and mortality rates for PCa compared to non-Hispanic Caucasian males (140-143). These differences highlight the importance of considering ethnic background in the risk assessment and management of prostate cancer.

The findings underscore the necessity of integrating genetic testing into routine PCa screening protocols, particularly for high-risk groups identified through family history and ethnic background. The early identification of BRCA mutation carriers can facilitate more personalized and effective treatment plans, potentially improving patient outcomes. Public health initiatives should focus on raising awareness about the importance of genetic testing for males, particularly those with a family history of BRCA-related cancers. Efforts should also be made to expand access to genetic testing and counselling services, ensuring that at-risk populations receive appropriate screening and preventive care.

While the present review underscores the importance of BRCA mutations in PCa, further research is required to explore the mechanisms through which these mutations interact with other genetic and environmental factors to influence PCa development. For instance, studies are required to investigate how mutations in BRCA genes may combine with other risk factors such as lifestyle, diet and exposure to environmental carcinogens to impact disease progression. Additionally, the role of epigenetic modifications in PCa among different racial groups is an emerging area of research that warrants further exploration. Understanding these complex interactions could lead to more effective prevention strategies and better-targeted therapies.

Additionally, policymakers should consider revisiting current clinical guidelines for PCa screening. While current guidelines often recommend PSA testing, incorporating genetic screening into standard protocols, particularly for males with a family history of BRCA-related cancers or those from high-risk racial groups, could significantly improve early detection efforts. Given the rapidly evolving landscape of genomic medicine, existing guidelines may need to be updated to reflect the growing role of genetic testing in PCa management.

Despite the clear benefits, there are challenges to implementing genetic screening at a population level. Cost and accessibility remain major barriers, particularly for individuals residing in low-resource settings. Policymakers will need to address how to fund and implement widespread genetic testing without exacerbating existing healthcare disparities. Additionally, ethical considerations surrounding genetic testing such as patients' privacy and the potential for discrimination based on genetic risk need to be carefully managed.

Expanding genetic testing would require a coordinated effort between healthcare providers, insurance companies and government bodies to ensure that the benefits of this technology are equitably distributed. Ultimately, integrating genetic screening into PCa prevention strategies could help shift the focus from reactive to proactive healthcare, reducing the overall burden of this disease on individuals, families and healthcare systems. Continued efforts to promote genetic screening and integration of genetic information into clinical practice are essential to advancing prostate cancer treatment and ensuring optimal outcomes for patients with cancer.

7. Conclusions and future perspectives

The present review underscores the significance of ethnic and genetic factors in the development, progression and clinical outcomes of PCa, particularly in the context of BRCA1 and BRCA2 gene mutations. The impact of race on PCa risk and prognosis is profound, with African American males displaying the highest susceptibility and mortality rates among racial groups. Contributing factors include genetic predispositions, socioeconomic disparities and environmental influences that collectively worsen the outcomes of patients with PCa. This is also evident in Asian and Hispanic males, who experience intermediate risk levels, but are affected by unique genetic profiles and lifestyle-related factors, such as dietary patterns and access to healthcare.

Genetic predispositions, particularly BRCA1 and BRCA2 mutations, significantly increase the riks of developing PCa and are associated with aggressive forms of the disease. Given the high mortality rates associated with BRCA-mutated PCa, the integration of genetic screening into PCa prevention and management is essential. The advent of genetic counselling and testing enables the early identification of high-risk individuals, facilitating personalized and proactive medical strategies. However, genetic testing faces several obstacles, including costs, accessibility and the need for supportive healthcare infrastructure. To address these challenges, policy initiatives need to prioritize equitable access to genetic counselling and testing, particularly for underserved populations. Expanding public awareness campaigns, reducing healthcare disparities, and advocating for culturally sensitive healthcare practices will help bridge the gap in PCa diagnosis and treatment. Additionally, the ethical considerations of genetic testing such as patient privacy, potential discrimination and the psychological impact of genetic risk knowledge must be carefully managed to ensure that genetic testing is implemented responsibly and equitably.

While the role of BRCA mutations in PCa is increasingly recognized, further research is essential in order to understand the interactions between genetic and environmental risk factors. Studies focusing on how lifestyle, diet and environmental carcinogens influence PCa progression in genetically predisposed populations could provide insight into more effective prevention strategies. Emerging research into the role of epigenetic alterations in PCa among different racial groups also holds promise for understanding the mechanisms driving these disparities.

To truly reduce the burden of PCa, healthcare guidelines need to evolve. Current protocols predominantly emphasize PSA testing, which, while beneficial, is less effective in addressing the underlying genetic and ethnic complexities of PCa risk. Integrating genetic testing and counselling into standard screening practices, particularly for males with a family history of BRCA-related cancers or those from high-risk racial groups would enhance early detection and ultimately improve survival rates.

In conclusion, addressing the complex interplay of ethnic, genetic and environmental factors in PCa requires a multifaceted approach that combines scientific advancement with social responsibility. Policymakers, healthcare providers and researchers need to work collaboratively to promote personalized medicine, expand genetic screening access and advocate for targeted public health interventions. These efforts will help shift PCa management from a reactive to a proactive model, improving outcomes for all males, particularly those in high-risk groups. Continued research, resource allocation and public health focus are essential to transforming the landscape of PCa care and reducing the global disparities that persist in this disease.

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TS was involved in the writing, reviewing and editing of the manuscript, as well as in study supervision, in the writing of the original draft of the manuscript, and in project administration. NA was involved in the data collection and analysis of the literature. SA was involved in the in the writing of the original draft of the manuscript, and preparing the figures. MN was involved in in the collection and analysis of data from the literature. AT was involved in the preparation of the figures and in the analysis of the literature. ZD was involved in the writing of the original draft of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

The authors declare that they have no competing interests.

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