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REVIEW

Genetic determinants of prostate cancer predisposition in Ashkenazi Jews

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Summary

Background: *Prostate cancer (PCa) is the most prevalent cancer among men in the European Union, the USA and Israel, with heritability being a key risk factor. Endogamy and kinship are known to increase the likelihood of transmitting genetic mutations associated with various cancers, as seen in populations with high levels of consanguinity, such as Ashkenazi Jews. The Ashkenazi Jewish population, with a history of genetic bottlenecks and selective migrations, has a higher prevalence of inherited mutations that predispose individuals to various diseases including cancer. This article reviews the literature examining the potential effects of founder mutations specific to Ashkenazi Jews, in enhancing the genetic risk of prostate cancer in this population.*

Methods: *We searched for English-language articles on DNA mutations in Ashkenazi Jewish patients of any age with prostate cancer of any grade, including various study types, using PubMed and other databases with relevant keywords, and confirmed the search was up-to-date as of January 31st, 2025.*

Results: *While the overall burden of PCa may not be higher than in European non-Jews, certain founder mutations in Ashkenazi Jews, especially 6174delT in BRCA2, are linked to increased risk and aggressive forms of PCa. Further research is needed to ascertain unequivocally the potential predisposing role of mutations such as 185delAG in BRCA1 or 471delAAAG in RNASEL.*

Conclusions: *Overall, genetic screening for PCa risk in Ashkenazi Jewish men, particularly within high-endogamy subgroups (Haredim), may be beneficial. Increasing awareness of familial hereditary prostate cancer among Ashkenazi men and healthcare providers is also crucial for early detection and better management of the condition. The complexity of PCa genetics in Ashkenazim, including the influence of multiple low-penetrance mutations, the possible confounding factor of phenocopies, and the need for larger, more diverse studies, underscores the challenges in identifying definitive genetic risk factors. Further studies are awaited investigating in-depth the aggressiveness and response to treatment of PC among Ashkenazi Jews.*

KEY WORDS: *Prostate cancer; Breast cancer; Ovarian cancer; DNA mutation; Jews; Ashkenazi Jews; Endogamy.*

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INTRODUCTION

Prostate cancer (PCa) is the most prevalent form of cancer among men in the European Union, the USA and Israel (1). Alongside factors such as age, diet and lifestyle, heritability has emerged as a significant determinant of PCa risk (2). Epidemiological and genetic studies indicate a hereditary predisposition in approximately 5-10% of all PCa cases (3). First-degree relatives of affected individuals have a relative risk of developing PCa ranging from 1.65 to 3.3, the risk increasing for those with an earlier diagnosis or multiple affected family members.

Specifically, having one, two, or three affected first-degree relatives progressively increases the risk ratio for PCa by 2.2, 4.9, and 10.9 times, respectively (4). Twin studies suggest that approximately 40% of PCa cases may have a hereditary component (5), while meta-analyses indicate that having an affected brother or father increases the risk of developing the disease by 2.9-fold or 2.12-fold, respectively. The risk for first- and second-degree relatives is increased by 2.2-fold and 1.8-fold, respectively (6, 7). Notably, PCa has been observed with increased frequency in families affected by the *Hereditary Breast and Ovarian Cancer* (HBOC) syndrome. Additionally, a family history of prostate cancer among first-degree relatives has been correlated with an elevated risk of breast cancer in women (8). If familial clustering is recognized as a critical risk factor for PCa, genetic bottlenecks might further enhance the likelihood of transmitting mutations within specific genes within a population. Populations with high levels of endogamy, resulting from consanguineous unions or marriages among relatives, exhibit a greater propensity for developing autosomal recessive non-cancer diseases and cancers, compared to non-endogamous populations. For example, in the Icelandic population, historically characterized by significant kinship, the 999del5 founder mutation in the BRCA2 gene, which accounts for 7-8% of female breast cancers and 40% of male breast cancers, is strongly associated with a highly aggressive form of lethal prostate cancer (hazard ratio, 3.64, 95% CI, 2.29-5.78) (9).

Ashkenazi Jews (AJ), or *Ashkenazim*, are a diaspora population that consolidated toward the end of the first mil-

lennium c.e., historically inhabiting regions of Central and Eastern Europe. Some of the founders were Jewish migrants from southern European regions, namely from southern Italy, some of whom in turn had more ancient Middle Eastern origins (10, 11). Bottlenecks were periodically generated due to selective migrations and to repeated cases of drastic Jewish population reductions following massacres of entire communities. These reductions were followed by periods of rapid expansion due to high fertility and sometimes higher-than-average life expectancies among Jewish populations (12-14). The Ashkenazi population, initially estimated to number a few tens of thousands at the end of the 12th century, grew to over 9.5 million by 1939. Following the killing of approximately 6 million *Ashkenazim* during World War II, an estimated 5-6 million *Ashkenazim* currently reside in the USA, over 3 million in Israel, and over a million in Europe, South America, and other regions worldwide (15). The high degree of endogamy historically prevalent among *Ashkenazim* has significantly contributed to elevated rates of genetically transmitted diseases, including Tay-Sachs disease, familial dysautonomia, Gaucher's disease, Bloom syndrome, cystic fibrosis and others (16, 17). With respect to neoplastic diseases, non-Hodgkin's lymphoma, as well as ovarian, pancreatic, and stomach cancers, exhibit higher incidence rates among *Ashkenazim* compared to non-Jewish populations (18, 19). In relation to breast cancer, one in ten Ashkenazi Jewish women diagnosed at any age carries BRCA1 or BRCA2 inherited mutations, which are comparatively less frequently found in the general population (approximately 1 in 50) (20). The role of inherited mutations predisposing *Ashkenazim* to PCa remains controversial. Whereas it is becoming increasingly evident that mutations that predispose AJ to various cancers (e.g., breast cancer) may also increase susceptibility to prostate cancer, it is unclear whether *Ashkenazim* have a higher burden of PCa than non-Jewish populations. Additionally, it is uncertain whether PCa-predisposing mutations demonstrate increased penetrance in this population. The objective of this article is to systematically review the existing literature on established and potential prostate cancer predisposition genes in AJ, with the goal of clarifying the genetic underpinnings and implications for risk stratification in this unique population.

Methods

Inclusion criteria for literature search

We included full-text articles published in English that reported studies evaluating the prevalence of DNA mutations in cohorts of Ashkenazi Jewish patients of any age diagnosed with prostate cancer, regardless of grade, including both lethal and nonlethal forms. Our selection encompassed a variety of study designs, including case-control studies, single-cohort studies, case series, systematic reviews and meta-analyses.

The search strategy performed in PubMed utilized a combination of keywords and MeSH terms to retrieve relevant literature. Key search terms included: "*Prostate*," "*Cancer/Carcinoma*," "*Ashkenazi*," "*Jew/Jews/Jewish*," "*Mutation*/Polymorphism*/Deletion*/Insertion**", "*Linkage*" and others. All searches were confirmed to be up to date as of January 31st, 2025. Filters were applied to limit results to human studies. Additional databases (e.g., SCOPUS, EMBASE) were searched with similar strategies. Articles written in Hebrew were also hand-searched and translated for a total of 69 records which were retrieved and are reviewed in this article.

Results

Studies on genetic loci linked to prostate cancer

Evidence emerging from research on genetic loci linked to PCa has provided important insights into the molecular underpinnings of disease susceptibility. Genome-wide linkage studies have identified over 140 variants of susceptibility loci that may confer an increased risk of PCa in certain chromosomal regions (21, 22). A summary of the loci investigated up to year 2016 has been published by *Lynch and colleagues* (23).

HPC1 at 1q24, PCAP at 1q42, HPCX at Xq27, CAPB at 1p36, HPC20 at 20q13, and ELAC2 at 17p11 are among the most investigated genetic loci (24).

Xu et al. conducted linkage studies to investigate the genetic factors contributing to prostate cancer susceptibility in 159 AJ families with multiple affected members, focusing on the short arm of Chromosome 8 (25). They identified evidence of linkage with PCa at the 8p22-23 locus (*Logarithm of the Odds* [LOD] = 1.84, p = 0.004), which includes genes such as ZBTB7A/LRF (a transcription factor involved in cell proliferation and differentiation) and various genes with putative tumor-suppressor activity, like the N33 macrophage-scavenger receptor, the NAT1/2 N-acetyltransferases, LZTS1 (a gene frequently mutated in prostate cancer cell lines), and Deleted in Liver Cancer-1 (DLC1). Linkage analysis revealed that specific microsatellite markers were associated with prostate cancer across multiple familial lines.

A study by *Alanee and coworkers* investigated the prevalence of the rare missense variant G84E in the homeobox B13 (HOXB13) gene, a known familial PCa-predisposing gene located at the 17q21-22 region (26). In a prior study performed in the general population, the carrier frequency of the variant was found to be 1.4% in men affected by PCa, compared to 0.1% in individuals without the disease (*odds ratio* [OR] = 20.1, 95% *Confidence Interval* [CI] = 3.5-803.3) (27). The Alanee study included 889 self-reported AJ men and 920 non-AJ men. Four patients were heterozygous for the G84E variant, all of whom were of non-AJ descent. Therefore, the G84E variant does not appear to show increased prevalence in AJ.

In a genome-wide linkage analysis of Ashkenazi families, *Friedrichsen et al.* identified a prostate cancer susceptibility locus on chromosome 7q11-21, characterized by a nonparametric linkage score of 3 (LOD = 1.14; p = 0.0013) (28). Notably, they could not replicate the significant findings of *Xu et al.* regarding the 8p22 locus, as no significant linkage was observed at 8p22 (allele sharing LOD = 0.01).

In a cohort of 963 AJ cases and 613 AJ controls, *Vijai and* coworkers genotyped 29 *single nucleotide polymorphisms*

(SNPs) previously linked to PCa risk (29). They found that a number of candidate SNPs (rs7008482, rs1016343, rs13254738, rs6983267, rs7000448, rs4242382, rs7931342, rs10896449, rs4430796, and rs5945572) did not show significant differences in frequency compared to prior studies conducted on subjects of European non-Jewish ancestry (age-unadjusted analysis). It was concluded that there is no evidence of major differences between AJ individuals and non-Jewish Europeans regarding the association between these mutations and PCa.

However, in a separate investigation, the same group found that the A/A genotype of SNP rs10486567 in the 7JAZF1 gene (chromosome 7) and the rs7008482 SNP (G/G) in the 8q24 locus were significantly associated with biochemical recurrence (30). Additionally, the 7JAZF1 rs10486567 SNP (C/C) was linked to castration-resistant metastases. Notably, the 7JAZF1 gene is a transcriptional repressor of the NR2C2 nuclear receptor, which is expressed in the prostate and interacts with the androgen receptor. Two additional SNPs, rs4962416 (C/C genotype, in the 10q26 locus) and rs6465657 (C/C genotype, in the 7q21 locus), were significantly associated with metastatic disease, while rs2735839 (A/A in the 19q13 locus) was associated with PCa-specific mortality. The authors suggested that their results warrant validation in larger cohorts.

Mutations in the Y-chromosome have been linked to various cardiological and neurological diseases, as well as to male-specific neoplasia such as PCa (31). Loss of the Y chromosome is frequently observed in prostate cancer and may serve as an early marker of prostate carcinogenesis.

Wang et al. identified a significant association between specific Y chromosome haplogroups and PCa susceptibility (32). In particular, the E1b1b1c haplogroup (located in the last intron of the taxilin gamma 2 pseudogene in the Yq11.222 locus) was significant in overall PCa groups, with some evidence suggesting a protective effect. Interestingly, this haplogroup is found at a higher frequency in AJ (10-11%) compared to men of European, non-Jewish ancestry (1-2%). However, the authors cautioned that the statistical power of some analyses was insufficient, and thus refrained from making definitive conclusions.

In Jewish populations of non-Ashkenazi ancestry, a study by *Álvarez-Topete et al.* examined Y-chromosomal haplogroups prevalent in a cohort of Mexican PCa patients. Their findings revealed a significant association between haplogroups such as R1a (age-adjusted OR, 7.4, 95% CI, 1.3-42.1) and increased susceptibility to PCa.

The authors hypothesize that these lineages may reflect a founder effect associated with Converso heritage, specifically Sephardic Jews who converted to Christianity during the Spanish Inquisition (33).

Interestingly, the R1a haplogroup is also found frequently in AJ (34), suggesting that historical intermixing of Jewish populations may have contributed to the persistence of certain Y-chromosomal lineages predisposing individuals to PCa. This raises the question of whether the association reflects Sephardic ancestry or the presence of AJ in Spain. A more radical hypothesis could suggest that the mutation predates the Sephardic-Ashkenazi division; however, this theory would likely predict higher rates of PCa in contemporary Sephardic populations, which is not observed. Therefore, the hypothesis of an external genetic introduction appears more plausible.

Germline variants in HPC1 and HPCX loci

Approximately 25 years ago, susceptibility loci for *hereditary prostate cancer* (HPC) were identified at 1q24-31 (HPC1) and at Xq27-28 (HPCX) through linkage analysis of families with a high prevalence of PCa (35-37). Within the HPC1 region, the RNASEL gene (1q25), which encodes the 2'- 5'-oligoadenylate-dependent ribonuclease L, a protein involved in the interferon-regulated 2-5A pro-apoptotic pathway, was identified as a candidate for hereditary PCa due to its tumor suppressor activity (38).

In a Japanese case-control study, the Asp/Asp phenotype of the Asp541Glu RNASEL variant was associated with a 6.9-fold increased odds of PCa compared to controls (95% CI, 3.9-12.1). In contrast, the Gln/Gln phenotype of the Arg462Gln variant appeared to offer protection against PCa (OR, 0.06, 95% CI, 0.035-0.11) (39).

Additionally, the A/A genotype of the rs12757998 SNP of RNASEL was linked to a 1.63 odds ratio for PCa compared to controls (95% CI, 1.18-2.25), and a 1.9 odds ratio for high-grade disease in individuals of Northern/Western European ancestry (Gleason > 7, 95% CI, 1.25- 2.89) (40).

In addition, a Glu265X truncating variant of RNASEL was found to be expressed in PCa patients from Finland (OR, 4.56; p = 0.04) (41).

A potentially pathogenic RNASEL splice site mutation (IVS5+1delG) was identified in a study performed on Ashkenazi Jewish individuals by *Orr-Urteger et al.* (42).

Additionally, a novel Ashkenazi founder mutation was reported by *Rennert and colleagues* in two siblings affected by PCa, where *loss of heterozygosity* (LOH) of the wild-type allele occurred in the cancer cells. This mutation consists of a four-base deletion at nucleotide 471 in exon 1 (471delAAAG), resulting in premature truncation at codon 164 (43). The authors observed an increased, though not statistically significant, frequency of this deletion in PCa patients of AJ descent, compared to AJ controls (OR, 3; 95% CI, 0.6-15.3). Notably, among *Ashkenazim* mutation carriers were diagnosed at a significantly younger age compared to non-carriers (65 *vs.* 74.4 years, respectively; P < 0.001).

Subsequent studies produced inconclusive results. A single carrier of the 471delAAAG mutation was identified among 122 AJ PCa patients in Canada (44). Similarly, one deletion carrier was found among 190 Ashkenazi PCa patients in Israel, with no carriers identified among non-Ashkenazi patients (45).

In a large AJ population study (979 PCa cases and 1250 controls), *Agalliu and colleagues* could not confirm a significant effect of the 471delAAAG mutation on PCa risk, citing insufficient power to detect modest associations. In contrast to the earlier Japanese study, this research identified an inverse association between the A/A genotype (rs486907) of the Arg462Gln variant and PCa in patients diagnosed before age 65 (OR, 0.47; 95% CI, 0.23-0.96) (46). Furthermore, the study examined five microsatellite *markers* on the HPCX locus and found positive associations with low-grade PCa (Gleason score ≤ 6) for allele

135 of microsatellite STR B97 and allele 188 of the STR marker DXS1205 (OR, 1.77; 95% CI, 1.15-2.71 and OR, 1.65; 95% CI, 1.08-2.54, respectively). However, no significant associations were observed for high-grade PCa.
In conclusion, additional evidence is awaited before drawing a conclusive statement about PCa risk conferred by 471delAAAG in RNASEL.

Germline variants in BRCA1 and BRCA2 genes
The BRCA1 (Chromosome 17, 17q21.31) and BRCA2 (Chromosome 13, 13q13.1) gene products play a critical role in DNA damage detection, checkpoint arrest, double-strand break repair, and chromatin remodeling (47).
Additionally, BRCA1 regulates the androgen receptor and may be implicated in the pathogenic mechanisms of PCa associated with it (48). Germline mutations in these genes are responsible for the majority of hereditary breast and ovarian cancers. These mutations typically consist of small deletions or insertions and are inherited in an autosomal dominant fashion with incomplete penetrance. Interestingly, in certain BRCA family clusters, the inheritance pattern of PCa also resembles autosomal dominant inheritance. For example, in a Swedish family carrying the BRCA2 6051delA truncating mutation, a father and his four sons were diagnosed with early-onset PCa, while three daughters developed breast cancer (49). In the non-Jewish population, it has been demonstrated that men with a BRCA1 mutation have a lifetime 7-26% risk of developing PCa (50), while individuals with a BRCA2 mutation exhibit a 3-8- fold increased risk of PCa compared to non-carriers (51). Approximately one in 40 AJ carries a BRCA mutation, to 1 in 400 in the general population. The BRCA1 185delAG and BRCA2 6174delT founder mutations are the most common deleterious variants predisposing to breast cancer in *Ashkenazim* (52), though 185delAG has been also genotyped in a small group of Jews of confirmed Moroccan origin (53). Among Ashkenazi men diagnosed with breast cancer, about 1 in 5 carries a BRCA1/BRCA2 inherited gene mutation. In addition to their established role in breast cancer, BRCA1 and BRCA2 founder mutations have been associated with reduced life expectancy in AJ, even in the absence of cancer (54). A 1995-1996 study conducted at the *Department of Oncogenetics* at the *Israeli Sheba Ramat Gan Hospital* tested 292 women for mutations associated with breast and ovarian cancers. Among women with cancer, 45% carried a founder mutation in BRCA1/2, compared to 25% of healthy individuals. Specific mutations included 185delAG and 5385insC in BRCA1 (74.5% and 4.5%, respectively), and 6174delT in BRCA2 (13%). Notably, 80% of the tested families had first-degree relatives diagnosed with other cancers, including prostate, colon, and lung cancers. Moreover, ten close relatives of affected patients were diagnosed with prostate cancer (55).

BRCA1 and prostate cancer
A significant breakthrough in understanding the relationship between BRCA mutations and prostate cancer was provided by *Struewing and colleagues*, who studied a population of 5318 Ashkenazi Jewish women and men (56). The study identified 120 carriers of BRCA1 (185delAG, 5382insC) and BRCA2 (6174delT) founder mutations. Women with BRCA1 and BRCA2 mutations had an estimated lifetime breast cancer risk of approximately 56-87% and 45-84%, respectively. The risk of ovarian cancer for BRCA1 carriers was estimated at 16-54%, while for BRCA2 carriers it ranged between 10 and 30%. In men, carriers of any BRCA1 or BRCA2 founder mutation exhibited a significantly higher prevalence of prostate cancer (14% *vs.* 8% in non-carriers, $p < 0.01$). This study concluded that specific BRCA1 and BRCA2 mutations can significantly increase the risk of breast, ovarian, and prostate cancers in AJ.
Giusti and colleagues examined medical records of PCa patients from 23 Israeli hospitals during the early PSA era (1994-1995). By combining this Israeli dataset (n = 940) with data from the *Washington Ashkenazi Study* (n = 872), the authors calculated a significant odds ratio of 2.18 for prostate cancer in carriers of any BRCA founder mutation (95% CI, 1.09-4.43). However, the odds ratios for individual BRCA1 or BRCA2 mutations were not statistically significant (57).
In a separate study on the impact of BRCA1 5382insC on prostate cancer, *Vazina and colleagues* assessed a subset of 95 Ashkenazi patients (58). The authors found that the detection rate of 5382insC among PCa patients was significantly higher than in the general population analyzed in the study by *Struewing et al.* (3.3% *vs.* 0.37%, $p = 0.02$). Despite the limitations due to its small sample size and to the use of external controls (59), this study supports the hypothesis that BRCA1 5382insC may contribute to prostate cancer risk.
A key question is whether somatic mutations in oncogenes or tumor suppressor genes can modulate the phenotype of prostate cancer in individuals harboring BRCA mutations. *Nickerson and colleagues* examined the molecular makeup of metastatic castration-resistant prostate cancer (CRPC) in an Ashkenazi carrier of BRCA1 185delAG. Notably, all metastases analyzed (n = 11) showed somatic loss of heterozygosity. The study also reported 62 somatic non-synonymous mutations in genes implicated in cancer progression and metastasis, including TP53 (frequently altered in metastatic CRPC), PTEN (whose loss is associated with tumor aggressiveness), the androgen receptor (whose mutations and amplifications are crucial for castration resistance), KMT2C (playing a role in CRPC progression), and FAT1 (linked to the metastatic phenotype). The TET2 gene, whose loss of function is associated with epigenetic changes in cancer, was also altered (60).
These findings suggest that somatic mutations may play a crucial role in CRPC in Ashkenazi individuals with BRCA1 founder mutations. If confirmed by larger studies, these results could provide valuable insights into the molecular mechanisms driving hereditary prostate cancer and suggest potential diagnostic or therapeutic targets.

BRCA2 and prostate cancer
BRCA2 harbors a PCa cluster region containing two separate domains linked to increased risk of PCa, namely the OB1 oligonucleotide-olisaccharide binding domain and the OB2 Tower DNA binding domain (61).
Kirchhoff and colleagues compared the prevalence of the three Ashkenazi founder mutations -185delAG and 5382insC in BRCA1, and 6174delT in BRCA2- among 251 unselected Ashkenazi men with PCa and 1472

healthy Ashkenazi controls. The age-adjusted odds ratio for PCa in carriers of any mutation was 3.41 (95% CI, 1.64-7.06). Statistical significance was primarily driven by carriers of the BRCA2 6174delT mutation, whose odds of developing PCa were nearly five times greater compared to controls (OR, 4.78; 95% CI, 1.87-12.25). In contrast, the odds ratio for a BRCA1 mutation did not reach statistical significance (OR, 2.2; 95% CI, 0.72-6.7) (62).

In a subsequent study by *Gallagher and colleagues*, comparing 832 AJ PCa patients with 454 healthy AJ controls, the odds ratio for PCa in carriers of BRCA2 6174delT was 3.10 (95% CI, 1.52-6.66), while the odds ratio for carriers of BRCA1 185delAG was not significant (OR, 0.38; 95% CI, 0.05-2.75) (63). Notably, a significantly higher proportion of BRCA2 6174delT carriers had high-grade PCa (Gleason score > 7) compared to non-carriers (85% *vs.* 50%, respectively; P = 0.0002), while BRCA1 185delAG carriers were evenly distributed between high- and low-grade disease (50% *vs.* 50%). Both BRCA1 185delAG and BRCA2 6174delT carriers had significantly higher hazards of biochemical recurrence (hazard ratio [HR] for 185delAG, 4.32; 95% CI, 1.31-13.62; HR for 6174delT, 2.41; 95% CI, 1.23-4.75) and prostate cancer death (HR for 185delAG, 5.16; 95% CI, 1.09-24.53; HR for 6174delT, 5.48; 95% CI, 2.03-14.79) compared to non-carriers. Additionally, carriers of BRCA2 6174delT, but not BRCA1 185delAG, exhibited a significantly higher hazard for castration-resistant metastatic disease (HR,3.01; 95% CI, 1.26-7.14).

In 2009, *Agalliu and colleagues* compared 979 Ashkenazi PCa cases with 1251 healthy AJ controls. The odds of high-grade PCa (Gleason score > 7) were significantly higher in carriers of both BRCA1 185delAG (OR, 3.54; 95% CI, 1.22-10.31) and BRCA2 6174delT (OR, 3.18; 95% CI, 1.37-7.34) compared to non-carrier patients. However, the proportion of mutation carriers in this study was lower than that reported by *Gallagher et al.* (64). Additionally, significantly higher odds ratios for PCa were observed in patients of all ages carrying 185delAG or 6174delT BRCA mutations (OR, 1.91; 95% CI, 1.05-3.48). High and significant odds ratios were also found for patients over 65 years of age carrying the 185delAG mutation (OR, 6.91; 95% CI, 1.37-34.87), or any of the 185delAG or 6174delT mutations (OR, 3.69; 95% CI, 1.47-9.29).

Consistent with these observations, in a cohort of 146 Ashkenazi men from Canada diagnosed exclusively with metastatic PCa, *Hamel and colleagues* identified two carriers of the BRCA2 6174delT mutation (65). However, this was a single-cohort study and the authors compared their data with those of other studies to attempt statistical inference.

At the *Hadassah Medical Center in Jerusalem, Israel*, *Hubert et al.* compared 87 AJ men with PCa to 87 healthy Ashkenazi controls. They identified three mutation carriers in the PCa cohort: two with BRCA1 185delAG and one with BRCA2 6174delT, while three healthy carriers were found in the control group. Despite the small sample size, the fact that all three mutation carrier patients had been diagnosed at stage B with Gleason scores of 7, 8, and > 8 -higher than the average for noncarriers at stage B and similar to the average at stage D- supports the findings of *Gallagher et al.* and *Agalliu et al.* regarding the increased likelihood of mutation carriers of being affected by high-grade PCa (66).

Kwon et al. analyzed genetic and clinical data from a cohort of 1351 men of various ethnicities diagnosed with PCa, including 150 Ashkenazi patients (11%). They found that *Ashkenazim* were more likely than Caucasian men to carry pathogenic mutations in BRCA2 or CHEK2 (6.7% *vs.* 2.8%, p = 0.01, and 5.3% *vs.* 2.8%, respectively), while pathogenic or likely pathogenic BRCA1 mutations were similar in Ashkenazi men compared to Caucasians (0.7% *vs.* 0.8%). Unexpectedly, Ashkenazi mutation carriers were diagnosed at an older age compared to Caucasians (66.6 *vs.* 60.5 years, p < 0.01) (67).

The significant findings summarized above could not be replicated in studies performed on smaller cohorts of patients. For instance, *Lehrer and colleagues* did not detect any carriers of BRCA1 or BRCA2 founder mutations in a cohort of 60 Ashkenazi PCa patients (68), and *Wilkens et al.* identified a single healthy carrier of BRCA2 6174delT in a study of 18 AJ families with at least three first-degree relatives affected by PCa (69). Other studies, such as the 1995 study by *Friedman et al.*, which examined 37 AJ families with a high prevalence of familial breast cancer, found no cases of prostate cancer among deletion carriers (70). Similarly, *Nastiuk et al.* found that BRCA1-185delAG and BRCA2-6174delT deletions were present in only 1 and 2 patients, respectively, out of 83 PCa cases. The authors concluded that the study was only powered to detect a 4-5-fold increase in prostate cancer risk associated with these mutations and recommended larger studies to investigate smaller but statistically significant increases in relative risk (71).

In conclusion, ensuring adequate statistical power is essential in clinical studies to reliably detect true associations between genetic variants and cancer outcomes, minimizing the risk of false negatives and ensuring that observed results reflect genuine associations rather than random variation.

Meta-analyses

As shown in the preceding section, studies conducted on small cohorts of patients have failed to provide conclusive evidence regarding the risk and frequency of prostate PCa in Ashkenazi carriers of BRCA1 or BRCA2 mutations. In such cases, meta-analyses, which combine data from smaller studies with those that have sufficient statistical power, offer a more robust understanding of statistical trends and provide clinically relevant insights. Several meta-analyses have examined the association between germline founder mutations – including 185delAG or 5382insC in BRCA1, and 6174delT in BRCA2 – and PCa risk in AJ.

A 2019 study by *Oh et al.* found that the odds ratio for PCa in carriers of BRCA1 and/or BRCA2 mutations across all populations (both Jewish and non-Jewish) was 1.90 (95% CI, 1.58-2.29). In an Ashkenazi subgroup, the unadjusted *event rate* (ER) for PCa among carriers of any BRCA founder mutation was 1.7% (95% CI, 1.5-2.1), with specific event rates of 1.4% for BRCA1 and 2.1% for BRCA2 founder mutations (95% CI, 1.0-1.8 and 1.6-2.6, respectively) (72).

A subsequent meta-analysis by *Nyberg et al.* differed from the Oh study, as it excluded the 2019 case series by *Nastiuk*

et al. (71). In men of Ashkenazi Jewish ancestry, the *risk ratio* (RR) for PCa was statistically non-significant for BRCA1 founder mutation carriers (RR, 1.12; 95% CI, 0.55-2.31), while the risk in carriers of the 6174delT mutation in BRCA2 was twofold and statistically significant (RR, 2.08; 95% CI, 1.38-3.12) (73). Risk ratios for AJ were consistently lower compared to non-Ashkenazi men of European ancestry (e.g., RR for BRCA2 6174delT in Europeans: 4.07; 95% CI, 3.45-4.80). However, the meta-analysis including non-Jewish Europeans showed substantial heterogeneity (I^2 = 66%), which was absent from the analysis including AJ (I^2 = 0).

A 2023 meta-analysis investigated the prevalence of both germline founder and non-founder mutations in BRCA1 and BRCA2 among Ashkenazi *versus* non-Ashkenazi PCa patients (74). The study found that Ashkenazi Jewish men had a higher prevalence of BRCA1 variants (0.9% *vs.* 0.5%, p = 0.09) and a lower prevalence of BRCA2 variants [1.5% *vs.* 3.5%, p = 0.08] compared to non Ashkenazi patients, though the P values do not reach statistical significance. Figure 1 presents a pooled summary of the evidence emerging from case-control studies showing similar designs. This summary specifically excludes case series, single-cohort studies, research comparing data to external population estimates, and studies utilizing controls from either (i) cohorts published by different research groups or (ii) cohorts including healthy women. Although these findings are not part of a comprehensive meta-analysis (currently in preparation), the data indicate a significantly increased odds ratio for harboring the BRCA2 6147delT mutation in prostate cancer cases (odds ratio 2.3, 95% CI 1.59-3.43) compared to controls. These findings align with those of previous meta-analyses, which reported a 2.1 risk rate (95% CI 1.6-2.6) and a 2.08 risk ratio (95% CI 1.38-3.12) for BRCA2 Ashkenazi mutation carriers (72, 73).

In conclusion, the evidence derived from case series, cohort studies, and meta-analyses suggests that the rate of BRCA mutations associated with prostate cancer in Ashkenazi Jewish men may not differ significantly from that in the general population. However, founder mutations in BRCA2, and to a lesser extent in BRCA1 are likely linked to the development of prostate cancer among AJ.

Germline APC variants

Familial Adenomatous Polyposis (FAP) is an autosomal dominant inherited disorder responsible for up to 5% of *colorectal cancer* (CRC) cases. Truncating mutations in the APC tumor suppressor gene, which encodes a protein involved in regulating β-catenin via the Wnt-CTNNB1 signaling pathway, lead to heterozygous germline loss-of-function alterations in FAP families, resulting in the onset of forms of polyposis which can ultimately progress to CRC. Two case series have reported LOH at the APC locus, detected in 3 out of 7 and 3 out of 15 metastatic prostate cancer cases, respectively (75, 76). In the late 1990s, a T-to-A transversion at nucleotide 3920 of APC, present in 10% of *Ashkenazim* and 2.7% of Sephardic Jews, causing an isoleucine-to-lysine substitution at codon 1307 was described. This alteration creates a genetically unstable and hypermutable region of the gene, and was found to be highly prevalent (28%) among AJ with a family history of CRC (77-79). Case studies indicated that relatives of CRC patients carrying the I1307K substitution had family histories of various cancers, including PCa (80). *Woodage and colleagues* investigated a cohort of 5081 *Ashkenazim* carrying either a homo- or heterozygous I1307K substitution. The odds ratio for PCa was 2.0, but the wide confidence interval (0.81-4.7) precluded statistical significance (81). A 2006 kin-cohort study comparing relatives of I1307K carriers with non-carriers observed a higher incidence of PCa in relatives of I1307K carriers over the age of 80, compared to non-carriers, although the difference was not statistically significant (82). Conclusive evidence of an association between I1307K and PCa is still to be confirmed. Conversely, a 2023 case series demonstrated that, compared to non-carrier cancer patients with somatic frameshift mutations of APC (n = 20), carriers of the germline I1307K substitution (n = 18) had a significantly increased odds of presenting with the severe and untreatable "*aggressive variant of prostate cancer*" (AVPC, odds ratio: 7.2; 95% CI: 1.3-40.7) (83), defined as an androgen receptor independent neoplasia characterized by a unique array of genetic (e.g., RB1, TP53, or PTEN mutations) and cellular characteristics (e.g., small cell histology), making the disease virtually untreatable. Among the I1307K carriers (100% AJ, personal communication from the corresponding author), five patients had somatic alterations in one or more of the RB1, TP53, or PTEN tumor suppressors, and two exhibited the AJ founder mutation S1982fs*22 (6147delT) in BRCA2. In summary, while increased odds ratios suggest a potential association between I1307K and PCa, small sample sizes and/or the limited number of mutation carriers resulted in large confidence intervals preventing the confirmation of statistical significance. Studies conducted on larger patient populations are required to provide data for a more conclusive assessment of this association.

PCa incidence in Lynch syndrome patients

Lynch syndrome (LS), also known as hereditary non-polyposis colorectal cancer, is an autosomal dominant genetic disorder caused by mutations in specific DNA mismatch repair (MMR) genes, including MLH1, MSH2, MSH6, and PMS2. Pathogenic mutations in these genes increase the risk of several cancers, notably colorectal and endometrial cancers, as well as ovarian, stomach, renal pelvis, and ureteral cancers.

A 2014 study by *Haraldsottir* which involved 188 LS men from the US, demonstrated a significantly higher incidence of PCa in these individuals compared to the general population, with a standardized rate ratio of 4.87 (95% CI, 2.43-8.71) (84). Mutations were identified in all aforementioned MMR genes.

In the same year, a meta-analysis, which included both molecular studies and family/population risk studies, confirmed the findings of Haraldsdottir, despite his study being excluded from the meta-analysis. The meta-analysis revealed a 2.13-fold increased risk of prostate cancer in mutation carriers from clinic-based retrospective cohorts (95% CI, 1.45-2.80), a 2.11-fold risk (95% CI, 1.27-2.95) for male mutation carriers with a prior diagnosis of colorectal cancer, and a 2.28-fold risk (95% CI, 1.37-3.19) for men from mutation-carrying families, when compared to

the general population (85). The study also highlighted variations in prostate cancer risk, with MSH2 mutation carriers exhibiting a higher frequency of prostate cancer than carriers of other MMR genes. Despite potential recall and detection biases associated with retrospective studies, the authors concluded that prostate cancer may be considered part of the spectrum of LS associated neoplasms. To date, three founder mutations linked to LS have been identified in the Ashkenazi Jewish population. *Foulkes et al.* characterized the c.1906G>C (Ala636Pro) mutation in MSH2, which has a prevalence of 0.6% among AJ with colorectal cancer (86). Additionally, the founder truncating mutations c.3984_3987dup-GTCA (p.Leu1330ValfsX12) and c.3959_3962delCAAG in the MSH6 gene have been identified in Ashkenazi populations (87,88). Recombination analysis suggests that both mutations likely originated in the 6th and 7th centuries C.E., respectively, during the early formation of the Ashkenazi population in the Rhineland through a trickle of immigration from the south (87, 12). *Goldberg and colleagues* reported that while mutations in MSH2 and MSH6 are found in 38% and 14% of LS patients in the general population, the frequencies among *Ashkenazim* are 74% and 18%, respectively (88).

Importantly, co-inheritance of BRCA mutations and MMR gene mutations linked to Lynch syndrome has been reported in several studies (reviewed in: 88). For instance, a study by *Laish and colleagues* identified eleven double-heterozygote mutation carriers in four unrelated Israeli Ashkenazi families. All carriers had a BRCA founder mutation (BRCA2 5946delT/c.6174delT, n = 10; BRCA1 185delAG, n = 1) and an MMR AJ founder mutation (MSH2 1906G>C, MSH6 3984_3987dupGTCA, or MSH6 3956_3957dupPV). Among these carriers, one patient was diagnosed with prostate cancer (89). Further studies are required to evaluate whether the simultaneous presence of BRCA1/BRCA2 founder mutations and Lynch-linked MMR mutations exerts a deleterious effect in the Ashkenazi Jewish population.

Germline mutations in various genes

A 2008 study conducted in North America explored the role of seven newly identified SNPs in the CHEK2 gene (located on Chromosome 22q) among AJ men with prostate cancer (90). Of these SNPs, the 1270T>C variant in exon 11, which causes the missense Y242H substitution, was identified in three affected men from one family and four affected men from another. However, the mutation did not consistently segregate with the disease. It was found in 4 out of 85 families with affected probands, but in none of 136 PCa cases from Montreal, none of 221 AJ controls, and in 8 out of 740 unselected PCa cases. The authors concluded that the Y242H variant is unlikely to play a major role in PCa predisposition, though it may represent a mild predisposition allele in AJ men. At the Genetic Institute of the Tel Aviv Sourasky Medical Center, a study screened 188 AJ and 112 non-AJ PCa patients for mutations in three candidate genes implicated in prostate cancer: *phosphatase and tensin homolog* (PTEN), *Kruppel-like factor 6* (KLF6), and *macrophage scavenger receptor 1* (MSR1) (91). Controls included 200 healthy AJ women and 100 non-AJ women. Among the mutations examined, the G160X variant (478C>T) in KLF6 was found in one PCa patient but not in any of the controls. However, the premature stop codon generated by this variant did not result in reduced gene expression at the RNA level, suggesting that loss of the wild-type allele did not occur in this case. Interestingly, the intronic IVS1-27G>A mutation in KLF6, which generates a novel splice variant, was detected in a significantly larger fraction of controls (17.3%) than in PCa patients (11.9%, p = 0.043). Additionally, the IVS1-27A allele was significantly less frequent in AJ PCa patients compared to AJ controls (5.6% *vs.* 9%, respectively, p = 0.047), and was also significantly less present in all PCa patients compared to all controls (6.1% *vs.* 9.2%, respectively, p = 0.03). The authors concluded that the negative association between the IVS1-27A allele and PCa risk may be attributed to its significantly lower frequency in AJ patients.

Protection of Telomeres 1 (POT1) is a component of the six-membered shelterin complex that plays a critical role in telomere length regulation and protection. The p.(I78T) variant in POT1 has been identified as a founder pathogenic mutation in AJ. A 2024 database review detected cases of PCa among carriers and advocated for the inclusion of POT1 in germline screening panels for cancer (92). Extensive studies are required to further elucidate the pathogenic role of POT1 mutations in PCa among *Ashkenazim*.

Genetic screening, diagnosis and counseling

Genetic screening

While the role of certain genetic determinants of PCa in AJ still remains to be fully confirmed, Ashkenazi ancestry is included among the eligibility criteria for germline testing in the Framework for Prostate Cancer Genetic Evaluation and Management algorithm established at the 2019 Philadelphia Prostate Cancer Consensus Conference. Key eligibility criteria also include a strong family history (two or more male relatives diagnosed with PCa before age 60 or who died from it), specific pathological features (e.g., intraductal pathology or advanced disease), Ashkenazi ethnicity, and a family history of cancers associated with hereditary syndromes, such as HBOC or Lynch syndrome (93). The inclusion of Ashkenazi ethnicity in these criteria reflects the growing body of evidence regarding certain predisposing mutations, such as BRCA2, which informs decision-making in the Philadelphia guidelines.

Additional guidelines recommend germline testing for patients of AJ ancestry. These include the American Urological Association 2022 Advanced Prostate Cancer Guidelines, the Australian eviQ Prostate Cancer Panel testing Guides, and the US National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (94). Importantly, the National Health Service of the United Kingdom has recently initiated a special Jewish BRCA Testing Program aimed at identifying Jewish carriers of deleterious mutations at risk for breast, ovarian and prostate cancer. Testing is available to individuals over the age of 18 with Jewish ancestry documented by at least one Jewish grandparent (95). In Israel, patients with metastatic prostate cancer have access to a comprehensive sequencing panel through the Public Health Services Basket, which provides essential healthcare services to all citizens. Major hospital institutions, such as the Hadassah

Medical Center in Jerusalem, offer tests comparable to the FoundationOne® CDx test (96). These include a dedicated prostate cancer panel that assesses genetic alterations in key genes, such as BRCA1, BRCA2, ATM, BARD1, BRIP1, CDK12, CHEK1, CHEK2, FANCL, PALB2, RAD51B, RAD51C, RAD51D, and RAD54L. Sequencing for the MLH1, MSH2, MSH3, and MSH6 MMR genes is also available. Other Israeli hospitals provide tests that analyze mutation burdens and microsatellite instability across panels of approximately 400-500 genes, including BRCA1 and BRCA2. This multifaceted approach to genetic testing enhances the ability to tailor surveillance and treatment strategies for patients at increased risk of prostate cancer.

Diagnosis

A study by *Tamir et al.* examined age-related changes in the prostate through magnetic resonance imaging among BRCA mutation carriers. The study revealed significant quantitative alterations, including changes in prostate volume, as well as qualitative variations in tissue characteristics, such as lesions and fluctuations in signal intensity. These findings have important implications for BRCA mutation carriers, highlighting the potential benefits of tailored MRI screening for early prostate cancer detection and ongoing monitoring (97).

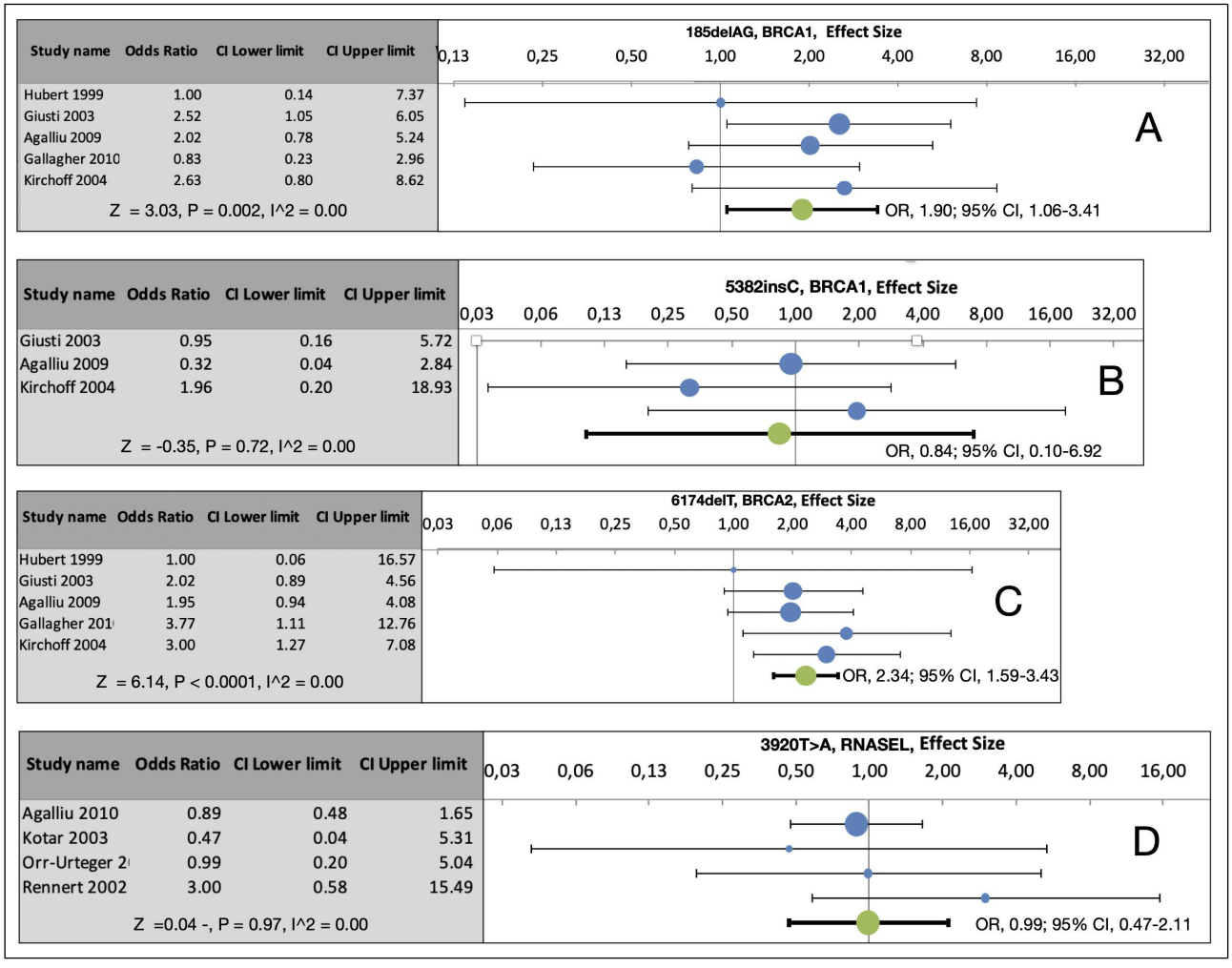
Counseling

Genetic counseling is a cornerstone in the prevention, diagnosis, and treatment of familial cancers. Counseling about the implications of specific mutations and the importance of surveillance should be routinely implemented for men with a family history of cancer. For informed decision-making in PCa, specific algorithms are used, such as the one described by Russo and coworkers (Figure 1 in: 98).

A 2008 article by *Mohamad* and *Apffelstaedt* emphasized the importance of counseling for male BRCA mutation car-

Figure 1.

Summary of studies included in this review, comparing the prevalence of accepted or putative predisposing mutations in cohorts of Ashkenazi prostate cancer cases and healthy Ashkenazi male controls. Controlled studies showing sufficient design and accrual similarities were included and pooled. Data to the right of the no-effect line represent increased odds of finding a specific mutation in BRCA1 (panels A and B), BRCA2 (panel C) or RNASEL (panel D) in prostate cancer patients compared to controls.
Overall effect sizes (odds ratios) extending to the upper and lower limits of the 95% confidence intervals, the significance of the pooled effect sizes (Z statistics) and heterogeneity data (I^2) are shown. Mantel-Haenszel weighting method, random effects model. Software: Meta-Essentials Excel workbook 1.5 (ERIM, Erasmus University, Rotterdam, The Netherlands).



riers, particularly regarding their elevated risk for prostate, pancreatic and breast cancers (99). It recommends tailored counseling for male BRCA carriers, as they are often unaware of their increased risks and may not seek genetic testing or appropriate surveillance. In the context of comprehensive counseling, discussions about lifestyle modifications may empower patients to take an active role in managing their health. For example, charred meat byproducts, particularly polycyclic aromatic hydrocarbons and heterocyclic amines such as 2-amino-1-methyl6-phenylimidazo (4,5-b) pyridine (PhIP), have been implicated in prostate cancer risk. (100, 101). This observation is significant, as high-risk dietary and lifestyle behaviors may compound the genetic predisposition, contributing to the development of neoplasia in at-risk populations.

Therapy and chemoprevention

Clinical trials have investigated the impact of various prostate cancer therapies in BRCA mutation carriers. *Gallagher and colleagues* studied whether BRCA1 or BRCA2 mutations could affect the sensitivity to taxane-based chemotherapy. Their study found that 57% of BRCA mutation carriers responded to chemotherapy, compared to 72% of non-carriers (n = 81). The difference between the groups was not statistically significant, suggesting that BRCA mutation carriers are indeed responsive to chemotherapy (102). Poly (ADP-ribose) polymerase (PARP), which plays a crucial role in DNA repair and apoptosis, is targeted by inhibitors such as Olaparib, Rucaparib, Niraparib and Talazoparib. These drugs are used in the treatment of HER2-negative, familial metastatic breast cancer in women with BRCA1 or BRCA2 mutations. Given that these inhibitors also suppress the function of the androgen receptor, their use has been explored in clinical trials for CRPC patients carrying mutations in BRCA1, BRCA2, and ATM. The PROFOUND phase III trial demonstrated that progression-free survival was significantly prolonged in patients treated with olaparib compared to untreated controls (103). Similarly, the TRITON2 and GALAHAD phase II trials, which included patients with CRPC carrying BRCA1/2 mutations as well as mutations in other PCa predisposing genes, showed that rucaparib and niraparib significantly increased both objective (TRITON2, 46% for BRCA mutation carriers *vs.* 0% for carriers of other mutations) and composite response rates in treated subjects (GALAHAD, 57.7% in BRCA mutation carriers *vs.* 14.8% in non-carriers), compared to untreated patients (104, 105). Thus, PARP inhibitors show promising clinical efficacy in treating metastatic CRPC in patients with mutations in BRCA1/2. Further investigation is needed to determine whether patient responses are associated with specific classes of mutations or if they can be generalized to all types of pathogenic BRCA variants, including Ashkenazi founder mutations. Additionally, the impact of tumor resistance to PARP inhibitors should be evaluated as the use of these agents becomes more widespread in prostate cancer treatment.

Conclusions

The genetic identity of AJ has been shaped over centuries by strict endogamy and high reproductive rates, factors which have been further potentiated by genetic bottlenecks (106). These historical phenomena have contributed to the emergence of hereditary diseases, including familial forms of cancer such as prostate cancer. This review article summarized the available evidence linking specific genetic mutations, expressed by AJ, to the heritability, onset, and progression of prostate cancer. From the evidence produced so far, it appears that the overall burden of prostate cancer may not be considerably higher in AJ compared to European non-Jewish populations (107). Furthermore, Ashkenazi founder mutations do not appear to be strongly associated with early-onset prostate cancer. However, substantial evidence supports a link between certain founder mutations and an increased risk of developing prostate cancer. Notably, the 6174delT Ashkenazi founder deletion in BRCA2 has been consistently associated with an elevated susceptibility to prostate cancer. Carriers of this mutation also face an increased risk of high-grade PCa (Gleason score > 7), as well as higher rates of castration-resistant metastatic disease, biochemical recurrence, and mortality when compared to non-carriers. Mutations in BRCA1 also appear to be linked to PCa, albeit to a lesser extent. Several findings reviewed in this article underscore the potential benefit of genetic screening for prostate cancer risk in Ashkenazi Jewish men, especially considering the high degree of endogamy observed within certain subgroups of this population, such as the "*Haredim*" (a Hebrew term for the "*fearful*", i.e. the very religious communities) (108). On the other side, contemporary Israeli society and diaspora Jewish communities have experienced growing intermarriage rates—both among *Ashkenazim* and non-AJ in Israel, and between Jews and non-Jews in the diaspora (109). This trend may serve to "*dilute*" the negative effects of endogamy over time, potentially reducing the long-term risk of hereditary diseases. However, within the highly segregated "*Haredi*" communities in Israel and in the diaspora, strict endogamy is maintained not only within the Jewish religious-cultural group at large, but more specifically within smaller Ashkenazi subgroups ("*hatzerot*") which are linked by specific extended families or geographical ancestries. In these cases, the risks of genetic disease transmission may tend to substantially increase.

Public health implications and further research

The clinical implications of identifying cancer-predisposing mutations for patient prognosis and treatment remain an open question. Further research is needed to explore the potential applications of genetic information for personalized therapeutic strategies and risk stratification. As a general caveat, we caution against over-interpreting variations in cancer rates between ethnic groups, emphasizing the need for careful consideration of public health implications. In this respect, the possible presence of diagnostic bias in populations with high rates of familial cancers should be considered, as increased preventive screening may lead to the detection of previously undiagnosed, low-risk or indolent prostate cancers. Given the indolent and often asymptomatic nature of certain forms of prostate cancer, it is essential to raise awareness among Ashkenazi men and healthcare providers, as early detection through proactive screening is crucial in contrast to other tumors, such as bladder cancer, that tend to present with more symptomatic features at earlier stages.

Unresolved issues

The role of non-BRCA mutations contributing to PCa in AJ remains unclear and demands further investigation. Additional evidence is needed before drawing definitive conclusions about the risks associated with mutations such as 471delAAAG in RNASEL or I1307K in APC. As noted by *Agalliu et al.* (46, 64), inconsistent results across studies may be attributed to factors such as small sample sizes, low statistical power, false-positive findings, genetic heterogeneity in prostate cancer, or errors in distinguishing hereditary, familial, and sporadic forms of the disease. The identification of highly penetrant genetic markers for prostate cancer is more complex than for other common cancers due to a variety of factors. Prostate cancer is often diagnosed at an older age, compared – for instance – to early-onset, BRCA-linked breast cancer, making it difficult to obtain multi-generational DNA samples from affected individuals. Furthermore, the diversity of mutations observed in Ashkenazi populations also complicates our understanding of how these genetic variants influence prostate cancer biology and patient outcomes. Variability in mutations and their functional consequences underscores the complexity of prostate cancer in this population. In addition, high-risk pedigrees may include phenocopies, i.e., sporadic PCa cases that may act as confounders and complicate the distinction between familial and non-hereditary forms. It should also be taken into consideration that certain mutations may act as risk modifiers, contributing to disease susceptibility in combination with other genetic factors rather than as dominant determinants. In families with a strong history of prostate cancer, the disease may result from a combination of multiple mutations with moderate/low penetrance rather than a single high penetrance mutation. The presence of a combination of multiple risk alleles may thus increase the likelihood of developing prostate cancer more than any individual mutation. *Seibert and colleagues* demonstrated that when the penetrance of mutations is plotted against their frequency in a given population, low-penetrance prostate cancer risk variants -when combined into polygenic risk scores- can have a net effect comparable to that of rare pathogenic mutations with modest-to-intermediate penetrance (110). Moreover, many linkage analyses in studies examining prostate cancer among AJ are limited by small sample sizes and lack of cohort diversity. *Simard and colleagues* suggested that association studies should ideally be based on at least one thousand blood samples from prostate cancer cases, compared to ethnically matched controls (24). Therefore, adequately powered studies are necessary to provide more definitive insights into prostate cancer susceptibility conferred by low-penetrance genes.

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