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Single Nucleotide Polymorphisms Associated with Prostate Cancer Progression: A Systematic Review

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ABSTRACT

Background: New biomarkers of progression in patients with prostate cancer (PCa) are needed to improve their classification and clinical management. This systematic review investigated the relationship between single nucleotide polymorphisms (SNPs) and PCa progression.

Methods: A keyword search was performed in Pubmed, EMBASE, Scopus, Web of Science, and Cochrane for publications between 2007 and 2022. We included articles with adjusted and significant associations, a median follow-up greater than or equal to 24 months, patients taken to radical prostatectomy (RP) as a first therapeutic option, and results presented based on biochemical recurrence (BCR).

Results: In the 27 articles selected, 73 SNPs were identified in 39 genes, organized in seven functional groups. Of these, 50 and 23 SNPs were significantly associated with a higher and lower risk of PCa progression, respectively. Likewise, four haplotypes were found to have a significant association with PCa progression.

Conclusion: This article highlights the importance of SNPs as potential markers of PCa progression and their possible functional relationship with some genes relevant to its development and progression. However, most variants were identified only in cohorts from two countries; no additional studies reproduce these findings.

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nucleotide; recurrence;
disease progression

Introduction

In 2020, more than 1.4 million new prostate cancer (PCa) cases were diagnosed worldwide, ranking second in cancer incidence in the male population, and It was responsible for 370,000 deaths (1). In 2023 the United States is expected to witness 288,300 new cases of prostate cancer and 34,700 related deaths (2). The implementation of prostate-specific antigen (PSA)-based PCa screening and digital rectal examination have increased the incidence of mainly indolent tumors that can lead to overtreatment. PCa progression can be detected by the presence of biochemical recurrence (BCR), defined as an increase in PSA after treatment (e.g., PSA $\geq$ 0.2 ng/ml after radical prostatectomy (RP)) (3).

There are different scales to establish the risk of progression, including Gleason score, pre-operative PSA, and clinical stratification of tumors, among other factors (4). An example is the D'Amico scale, which classifies the risk of BCR after localized PCa treatment as low, intermediate, or high, presenting a 5-year relapse-free survival rate of 94.5%, 76.6%, and 54.6%, respectively (5,6). In this sense, more than 50% of patients with localized PCa, even at high risk, will not progress, which makes it necessary to identify new elements to assess PCa progression and avoid unnecessary treatments with unwanted side effects.

Some studies have explored the molecular classification of PCa, identifying subtypes and biomarkers that may contribute to a more

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accurate prognosis (7). Single nucleotide polymorphisms (SNPs) are variations in the DNA sequence that affect a single base and occur in at least 1% of the population (8). Around 100 SNPs have been associated with the risk of developing PCa (9,10), and a significant association has been shown between the presence of these markers and disease progression. That is why the present systematic review examined the relationship between SNPs and PCa progression in patients who underwent RP as their first therapeutic option. In contrast to other studies, here we incorporate not only biologically plausible variables associated with PCa, and a schematic functional integration of the different genes involved was also carried out in prostate cells, androgen-producing cells and hepatocytes.

Methodology

Databases and search

A search was performed for scientific articles published in the last 16 years (2007-2022) in five databases: Pubmed, EMBASE, Scopus, Web of Science, and Cochrane. The search strategy included terms associated with PCa, BCR, and SNPs based on Medical Subject Headings (MeSH) terms located in the title, abstract, or keywords of the studies (Supplementary Table 1).

Inclusion and exclusion criteria

This review considered the following criteria for the inclusion of articles:

- Population: Individuals with localized PCa taken to RP without other previous treatments.
- Follow-up: Studies with a median follow-up of 24 months or longer.
- Results: Only studies presenting their results based on BCR were included.

Likewise, articles meeting any of these criteria were excluded:

- They used healthy individuals or patients with benign prostatic hyperplasia as a comparison group.
- Articles without a significant association.

- They did not evaluate associations using multivariate models, adjusted at least for age, PSA, and Gleason score.

Selection of studies

The selection of articles was made by four reviewers based on the inclusion and exclusion criteria described above: first by title, then by abstract, and finally by complete content. Likewise, articles with inconsistencies in the classification of risks and progression, the analysis of association measures, the genetic models used, and the data presented in the results were excluded.

Data extraction and synthesis

The following data were collected from each article: country of origin of the population, number of participants, type of study performed, participant selection criteria, central tendency measures, type of tissue studied, BCR percentage, and genotyping method. Subsequently, genes and SNPs with significant association with BCR, alleles, the corresponding genotype, and the type of outcome evaluated (differentiating between BCR and BCR-free time or progression) were extracted. Similarly, the gene analysis model, relationship with the outcome (risk or protection), variables included in the multivariate model, hazard ratio (HR), 95% confidence interval (CI 95%), and p-value were also collected.

Results

General characteristics of the articles

The flow chart of this study is shown in Figure 1. In the initial search, 877 articles were obtained, of which 22 (11–32) were finally selected. Other 5 (33–37) articles were identified by snowball method, reaching a total of 27 articles evaluated. Supplementary Table 2 presents all data collected from these articles. All of them were cohort studies that analyzed a median of 458 (range: 126–846) individuals and had a median follow-up of 54 (range: 24–88.8) months. In all studies, the outcome was measured in BCR or time to BCR, with a median BCR of 36.1% (range: 22.4–42.6%)

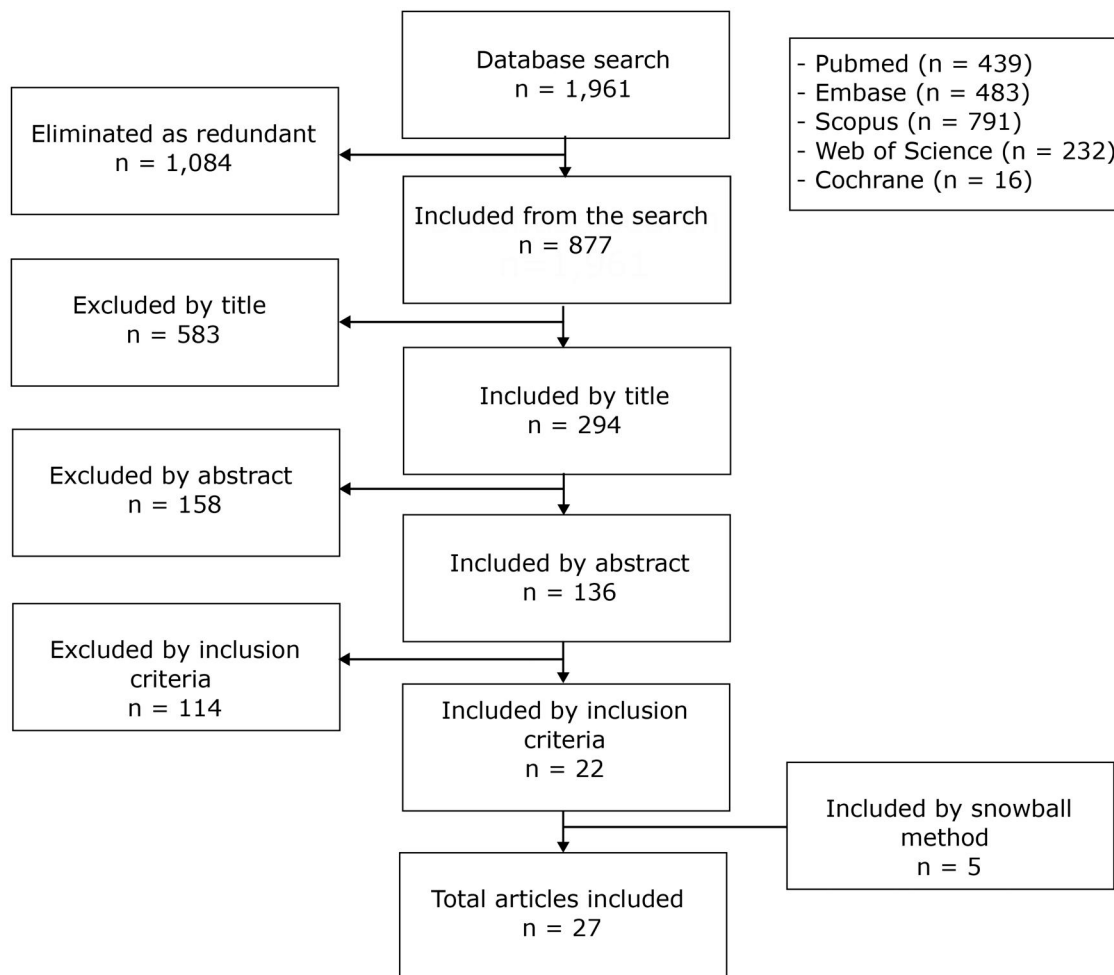


Figure 1. Flow chart of the study selection process.

in the cohorts. Most SNPs were identified in genes with biological plausibility for PCa. Genotyping was performed on blood samples from patients, and in most cases, mass spectrometry was employed; three studies used a Taqman real-time PCR method, one used genotyping arrays, and one used PCR-RFLP.

The 27 articles included in the study were conducted in Canada (n=4), Taiwan (n=20), or China (n=3). Ten cohorts were identified in these 27 articles, so there were different studies that evaluated the same cohort. All included studies performed a multivariate Cox regression model, evaluating variables such as age at diagnosis, PSA value, Gleason score, and staging; Some articles also took into account surgical margin compromise (n=18), lymph node involvement (n=12), smoking (n=4), and the use of adjuvant therapy (n=4). A single article included extraprostatic extension, vascular and perineural

invasion, and tumor multifocality ([Supplementary Table 2](#)).

SNPs associated with PCa progression

The analysis of 27 articles identified 73 SNPs in 39 genes, as presented in [Table 1](#). Of these 73 SNPs, 50 were associated with a higher and 23 with a lower risk of PCa progression. The 39 identified genes were classified into seven groups according to their primary association with the disease.

The first group involves genes related to sex steroid hormones, with 45 SNPs in 15 genes. The second one is linked to metabolism unrelated to sex steroid hormones, encompassing 6 SNPs in 5 genes. From the third to the sixth group, genes were classified according to specific cancer traits ([37,38](#)). The third group covers signaling pathways, bringing together functions like cell

Table 1. SNPs associated with PCa progression classified according to the function of the genes in which they are located.

Name and function of the product encoded by the gene	Gene / Locus	SNP	Alleles (Association model)	Hazard ratio (CI95%)	p-value	Association with progression	Country/Number of patients included (Ref.)
1. Genes related to sex steroid hormones							
Member of the hydroxysteroid 17-beta dehydrogenase family (17 β -HSD), involved in sex steroid hormone biosynthesis.	HSD17B2 / 16q23.3	rs7201637	A > T (AT/TT vs AA; Dominant)	0.45 (0.23–0.86)	0.016	Protective	Canada/n = 526 (11)
		rs1364287 ^a	C > T (TT vs CT/CC; Recessive)	2.00 (1.21–3.31)	0.007	Risk	
		rs8059915	G > C (CC vs GC/GG; Recessive)	1.92 (1.23–2.99)	0.004	Risk	
		rs2955162 ^a	G > A (AA vs GA/GG; Recessive)	2.14 (1.17–3.89)	0.013	Risk	
		rs4243229 ^a	C > T (CT vs CC; Dominant)	2.93 (1.37–6.25)	0.005	Risk	
		rs1119933 ^a	C > T (TT vs CT/CC; Recessive)	1.98 (1.09–6.25)	0.025	Risk	
	HSD17B3 / 9q22.3	rs10739847	T > A (TA/AA vs TT; Dominant)	0.65 (0.44–0.96)	0.029	Protective	
		rs2257157	A > G (GG vs GA/AA; Dominant)	0.51 (0.28–0.91)	0.024	Protective	
		rs1810711	T > G (GG vs TG/TT; Recessive)	1.54 (1.02–2.32)	0.042	Risk	
		rs11037662	C > A (CA/AA vs CC; Dominant)	0.63 (0.41–0.97)	0.036	Protective	
The cytochrome P450 protein complex catalyzes various reactions involved in the metabolism of exogenous and endogenous compounds. CYP19A1 encodes aromatase.	CYP17B12 / 11p11.2	rs10838151	A > G (AG/GG vs AA; Dominant)	0.63 (0.42–0.93)	0.020	Protective	
		rs12800235	C > A (CA/AA vs CC; Dominant)	1.65 (1.10–2.47)	0.015	Risk	
		rs1056836	C > G (GG/CG vs CC; Dominant)	0.69 (0.40–0.89)	0.002	Protective	China/n = 738 (12)
		rs1800440 ^a	A > G (GG/GA vs AA; Dominant)	1.64 (1.10–2.46)	0.016	Risk	
	CYP17A1 / 10q24.32	rs6163	G > A (AA/GA vs GG; Recessive)	1.51 (1.05–2.20)	0.028	Risk	Canada/n = 526 (13)
		rs6162	A > G (GG vs AG/AA; Recessive)	1.54 (1.07–2.24)	0.022	Risk	
		rs743572	G > A (AA vs GA/GG; Recessive)	1.56 (1.07–2.26)	0.020	Risk	
		rs2486758	T > C (TC/CC vs TT; Dominant)	1.77 (1.22–2.57)	0.003	Risk	
		rs7169770	C > T (TT vs TC/CC; Recessive)	0.43 (0.20–0.93)	0.033	Protective	
		rs17523957	A > T (TT/AT vs AA; Dominant)	3.12 (1.69–5.76)	0.0003	Risk	
The neuronal transcription factor family PAS has diverse roles, including the circadian cycle and nerve metabolism.	NPAS2 / 2q11.2	rs2446404	A > G (GG/GA vs AA; Dominant)	2.04 (1.20–3.47)	0.008	Risk	Taiwan/n = 458 (15)
		rs1870050	A > C (CC/CA vs AA; Dominant)	2.03 (1.22–3.38)	0.006	Risk	
		rs6542993	A > T (AT/TT vs AA; Additive)	1.50 (1.18–1.91)	0.001	Risk	
		rs8004379	A > C (Additive)	0.66 (0.52–0.85)	0.027	Protective	
	NQO1 / 16q22.1	rs2917670			0.039	Protective	Taiwan/n = 458 (16)

Members of the NAD(P)H quinone dehydrogenase family, which prevent the production of reactive oxygen species and are associated with multiple estrogen-related pathways.	NQO2 / 6p25.2	rs10223369	(AA vs GA/GG; Recessive) C > T	0.53 (0.29–0.97)	Risk	Canada/n = 526 (13)
		rs1143684	(TT/CT vs CC; Dominant) T > C	1.80 (1.24–2.60)	Risk	
		rs6920900	(CC/TC vs TT; Dominant) G > C	1.51 (1.04–2.19)	Risk	
			(CC/GC vs GG; Dominant) C > T	1.89 (1.19–3.00)	Risk	
		rs1823803 ^c	(TT/CT vs CC; Dominant) A > C	0.56 (0.37–0.83)	Protective	
Uridine diphosphate glucuronosyltransferase protein generates the inactivation of sex steroid hormones via the glucuronic acid conjugation pathway.	UGT1 / 2q37.1	rs2741048 ^c	(CC/AC vs AA; Dominant) C > T	0.56 (0.38–0.82)	Protective	Canada/n = 526 (17)
		rs2602381 ^c	(TT/CT vs CC; Dominant) T > A	0.58 (0.39–0.88)	Protective	
		rs17862847 ^c	(AA/AT vs TT; Dominant) G > A	1.88 (1.26–2.80)	Risk	
		rs7608713 ^c	(AA/AG vs GG; Dominant) G > A	1.62 (1.11–2.38)	Risk	
		rs4663871 ^c	(AA/AG vs GG; Dominant) G > A	1.59 (1.09–2.32)	Risk	
	COMT / 22q11.2	rs6751673 ^c	(AA/AG vs GG; Dominant) G > A	1.68 (1.15–2.45)	Risk	Canada/n = 526 (13)
		rs11705619	(CC/CT vs TT; Dominant) A > G	0.66 (0.45–0.98)	Protective	
		rs165849	(GG vs GA/AA; Recessive) C > T	1.74 (1.01–3.01)	Risk	
		rs9332377	(TT/CT vs CC; Dominant) T > C	1.60 (1.09–2.36)	Risk	
Catechol-O-methyltransferase participates in the degradation pathways of the catecholamine transmitters and is associated with multiple estrogenic pathways.	ESR1 / 6q25.1-25.2	rs1062577	(AA/AT vs TT; Dominant) T > C	2.10 (1.38–3.22)	Risk	Canada/n = 526 (14)
		rs9341016	(CC/CT vs TT; Dominant) G > A	1.98 (1.15–3.39)	Risk	
		rs488133	(AA vs GA/GG; Recessive) G > A	1.86 (1.08–3.20)	Risk	
Estrogen receptor alpha is a member of the nuclear receptor family of transcription factors and is directly activated by estrogens.	SULT2B1 / 19q13.3	rs2665582 ^a	(AA/GA vs GG; Dominant) G > A	0.50 (0.26–0.96)	Protective	Canada/n = 526 (13)
		rs12460535 ^a	(AA vs GA/GG; Recessive) G > A	1.99 (1.13–3.49)	Risk	
Sulfotransferase family 2B member 1 participates in the inactivation of estrogens by catalyzing their conjugation with sulfate.	CES1 / 16q12.3	rs8192950	(CC vs TT/TC; Recessive) T > G	1.50 (1.24–1.90)	Risk	Taiwan/n = 643 (18)
		rs8192935	(Additive) A > G	1.43 (1.16–1.76)	Risk	
			(Additive)			
Carboxylesterase 1 plays a key role in the metabolism of endobiotics and xenobiotics and actively participates in lipid metabolism.	SLC35B4 / 1q23.1	rs4239504	(CC vs TT/TC; Recessive) T > C	1.78 (1.15–2.75)	Risk	Taiwan/n = 458 (19)
		rs1646724	(Additive) T > G	1.38 (1.09–1.74)	Risk	
Solute Carrier family 35 member B4 encodes a glycosyltransferase required in the synthesis of glycoproteins, glycolipids, and proteoglycans.	PTGS2 / 1q31.1	rs4648302	(G > T) (Additive)	0.61 (0.37–0.99)	Protective	Taiwan/n = 458 (20)

(continued)

Table 1. Continued.

Name and function of the product encoded by the gene	Gene / Locus	SNP	Alleles (Association model)	Hazard ratio (CI95%)	p-value	Association with progression	Country/Number of patients included (Ref.)
Methylenetetrahydrofolate reductase is an important enzyme in folate metabolism and is essential for DNA synthesis and methylation.	<i>MTHFR</i> / 1p36.22	rs9651118	T > C (CC vs TT/TC; Recessive)	0.51 (0.27–0.98)	0.044	Protective	Taiwan/n = 458 (21)
Adiponectin is a hormone that modulates several metabolic processes, including glucose regulation and lipid oxidation.	<i>ADIPOQ</i> / 3q27.3	rs182052	G > A (AG/AA vs. GG; Additive)	1.75 (1.20–2.57)	0.004	Risk	China/n = 738 (22)
Homeostatic iron regulator is a membrane protein involved in the regulation of iron absorption.	<i>HFE</i> / 6p22.2	rs9393682	T > C (Additive)	1.50 (1.12–2.00)	0.006	Risk	Taiwan/n = 320 (23)
MicroRNA-605 participates in the p53/Mdm2 signaling pathway, regulating cancer cell death.	<i>MIR605</i> / 10q21.1	rs2043556	3. Signaling pathways A > G (Additive)	1.33 (1.06–1.67)	0.02	Risk	Canada/Taiwan/n = 846 (24)
Cancer susceptibility 8 is a lncRNA that plays an important role in the MYC regulatory pathway.	<i>CASC8</i> / 8q24	rs1447295	C > A (AA vs. CC; NAM)	3.07 (1.36–6.96)	0.007	Risk	Taiwan/n = 320 (25)
Member of TNF superfamily receptors; it activates the nuclear factor kappa B (NFKB) signaling pathway and affects multiple events associated with immunomodulation, proliferation, anti-apoptosis, and survival.	<i>TNFRSF13B</i> / 17p11.2	rs4792800	A > G (Additive)	1.35 (1.04–1.75)	0.022	Risk	Taiwan/n = 458 (26)
Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase; it is involved in signaling pathways and control of biological processes such as protein trafficking, metabolism, cell proliferation, migration, and apoptosis.	<i>YWHAZ</i> / 8q22.3	rs2290291	G > A (Additive)	1.27 (1.02–1.59)	0.033	Risk	Taiwan/n = 643 (27)
Serine/threonine protein kinase 3; it is part of the Hippo signaling pathway that plays a central role in cell proliferation and apoptosis with growth suppressor functions.	<i>STK3</i> / 8q22.2	rs7827435	A > T (Additive)	0.72 (0.58–0.89)	0.003	Protective	Taiwan/n = 458 (28)

Fibroblast growth factor receptor 4; it is involved in the activation of signaling pathways that regulate multiple cellular functions such as cell survival, proliferation, migration, differentiation, angiogenesis, and epithelial-mesenchymal transition.	FGFR4 / 5q35.2	rs351855	A > G (AG/GG vs AA; Dominant)	1.87 (1.21–2.90)	0.005	Risk	China/n = 346 (29)
	ANO4 / 12q23.1	rs585335	4. Cell proliferation C > T (CT vs. CC; NAM)	0.63 (0.42–0.95)	0.025	Protective	Taiwan/n = 641 (30)
	ANO10 / 3p22.1-p21.3	rs11800551	T > C (TC vs. TT; NAM)	0.44 (0.26–0.75)	0.002	Protective	Taiwan/n = 641 (30)
	ANO7 / 2q37.3	rs62187431 +A61:H67	C > G (CG vs. CC; NAM)	0.67 (0.48–0.94)	0.022	Protective	Taiwan/n = 320 (30)
	ANO5 / 11p14.3	rs4622263	T > C (TC vs. TT; NAM)	1.44 (1.16–1.79)	0.001	Risk	Taiwan/n = 641 (30)
Cyclin D1 is an important cell cycle regulator involved in promoting proliferation.	CCND1 / 11q13.3	rs9344 ^d	A > G (Additive)	1.36 (1.06–1.74)	0.017	Risk	Taiwan/n = 320 (31)
	CDON / 11q24.2	rs3737336	5. Cell adhesion T > C (Additive)	1.35 (1.10–1.65)	0.005	Risk	Canada/Taiwan/ n = 846 (24)
	CDH2 / 18q12.1	rs8084948 rs643555 rs1944294	T > A (TA/AA vs TT; Dominant) C > T (TT vs CC/CT; Recessive) A > T (TT vs AA/AT; Recessive)	0.62 (0.42–0.93) 1.78 (1.19–2.67) 1.94 (1.23–3.07)	0.020 0.005 0.005	Protective Risk Risk	Taiwan/n = 643 (32)
Autophagy-related 16-like 1 acts as a coordinator of the autophagy pathway.	ATG16L1 / 2q37.1	rs78835907 rs13021297	6. Autophagy G > A (Additive) G > A (Additive)	0.70 (0.54–0.90) 1.38 (1.10–1.72)	0.006 0.005	Protective Risk	Taiwan/n = 458 (33)
	MAP1LC3B / 16q24.2	rs8044820	A > G (GG vs AG/AA; Recessive)	2.33 (1.33–4.09)	0.003	Risk	
Microtubule associated protein 1 light chain 3 gamma is an orthologue of the autophagosome protein Atg8.							
It encodes a transcription factor containing a POU homeodomain that plays a key role in embryonic development and stem cell pluripotency.	POU5F1 / 6p21.33	rs2394882	7. Others C > A (Additive)	0.68 (0.49–0.93)	0.018	Protective	Taiwan/n = 320 (34)

(continued)

Table 1. Continued.

Name and function of the product encoded by the gene	Gene / Locus	SNP	Alleles (Association model)	Hazard ratio (CI95%)	p-value	Association with progression	Country/Number of patients included (Ref.)
The X-ray repair cross-complementing group 1 protein is involved in DNA repair.	<i>XRCC1</i> / 19q13.31	Codon 399 (Arg to Gln)	G > A (AG/AA vs GG; Dominant)	4.73 (1.61–13.92)	0.005	Risk	Taiwan/n = 126 (35)
Member of the CD1 family of MHC class I transmembrane glycoproteins, which mediates the presentation of self and foreign antigens to T cells.	<i>CD1B</i> / 1q23.1	rs3181082	C > T (CT/TT vs CC; Additive)	1.42 (1.09–1.85)	0.010	Risk	Taiwan/n = 643 (36)
Microsomal protein-beta is a member of the immunoglobulin binding factor family.	<i>MSMB</i> / 10q11.22	rs10993994	T > C (CC vs. TT; NAM)	2.32 (1.25–4.30)	0.008	Risk	Taiwan/n = 320 (25)

^aThese SNPs found in different genes (*SULT2B1*, *HSD17B2*, and *CYP1B1*) are part of a haplotype associated with risk (HR 1.89; CI95% 1.19–3.00; $p = 0.007$) (13).

^bNPAS3 was included in the group of genes related to sex steroid hormones because it belongs to the NPAS family. However, NPAS3 has not been directly associated with this function.

^cThese UGT1 SNPs are part of a haplotype associated with risk (HR 1.68; CI95% 1.13–2.50; $p = 0.011$) (17).

^dThis CCND1 SNP is part of a haplotype associated with risk (HR 2.01; CI95% 1.02–3.96; $p = 0.043$) (31).

NAM: No association model.

proliferation, apoptosis, immunomodulation, migration, and survival. In this group, 6 SNPs were identified in 6 genes. The fourth group contains genes related to cell proliferation, with 5 SNPs identified in 5 genes. The fifth group corresponds to cell adhesion, with 4 SNPs in 2 genes. The sixth group reports on autophagy, in which 3 SNPs were found in 2 genes. Finally, in the seventh group 4 SNPs were identified in 4 genes, and It includes genes related to functions such as embryonic development, DNA repair, and immune response.

Discussion

Identifying new biomarkers of progression in patients with PCa is very important to improve their clinical management. Although some reviews have studied the association between SNPs and PCa progression (39,40), to our knowledge, this is the first systematic review with a search not restricted to a group of specific variants and which included patients who underwent RP. The latter is relevant since RP does not cause a direct alteration in tumor cell evolution and reduces the heterogeneity of other therapeutic regimens. We exclusively included studies in which the control group consisted of cancers that did not progress, enabling us to effectively evaluate the disease's progression. Progression was measured as BCR, given that PSA is a widely used follow-up parameter in patients with PCa. The median follow-up ranged from 24 to 88.8 months, which could imply that studies with a shorter follow-up time did not capture all individuals who were to progress. Given the origin of the cohorts, they possibly included almost exclusively Caucasian patients from Canada and Asians from China and Taiwan. There is also no reference of patients with African ancestry, who are underrepresented in these two regions. This is relevant because of differences based on ancestry in incidence, mortality, and mutational profile reported in PCa.

The studies included in this systematic review performed a targeted search for SNPs in genes chosen according to their biological plausibility with PCa progression, and they were conducted by a few groups of researchers. In these studies,

there is a clear interest in SNPs located in genes related to sex steroid hormones, which received the most attention and, therefore, where the majority of the associations were found. These types of studies have the limitation that they will only identify associations with pre-selected variants, eliminating the possibility of discovering other novel associations, which could happen in genome-wide association studies (GWAS) instead. Two GWAS studies were found for PCa progression, but with the established inclusion criteria they were discarded. This type of study is frequently used to estimate the susceptibility of different diseases, including PCa. The high costs of these assays and the large sample size they require might have hindered their widespread use in the studies identified in this review.

A total of 73 SNPs were identified in 39 genes, which were organized in seven groups according to their function. The functional integration of the products of the product of these genes can be seen in Figure 2.

1. Genes related to sex steroid hormones

Variants were identified in three genes of the *HSD17B* family.

- *HSD17B2*: It encodes a protein that inactivates estradiol and decreases androgen levels; it has been reported to decrease its expression as PCa progresses (41). This review found six SNPs, one protective and five risk SNPs, associated with PCa progression (11). It is not yet known how these variants are connected to PCa progression, but alterations in their function may lead to reduced androgen inactivation, potentially contributing to PCa progression.
- *HSD17B3*: It encodes a protein that increases testosterone synthesis; however, its expression was found reduced in PCa (42). Three SNPs were identified: two protective and one risk SNP for PCa progression. Risk SNP rs1810711 has been reported as part of a seven-SNP signature associated with increased susceptibility to PCa (43). One of the protective SNPs (rs2257157) has also been associated with increased susceptibility to PCa (44). On the other hand, an expression signature that included *HSD17B2* and

HSD17B3 was able to identify patients at high risk for PCa progression (45).

- *HSD17B12*: Its product converts estrone to estradiol and is involved in the elongation of fatty acids (46). Three SNPs were identified: two protective and one risk SNP for PCa progression (11). Protective SNP rs11037662 has been associated with a low response to androgen deprivation therapy (ADT) (47). The other identified variables have not been linked to PCa in other studies. Another variant not identified in this review (*HSD17B12* rs7932905) has been associated with increased tumor aggressiveness in PCa (48).

Variants were identified in three genes of the cytochrome P450 (*CYP*) family involved in steroid synthesis.

- *CYP1B1*: Its product catalyzes reactions involved in drug metabolism and the synthesis of cholesterol, steroids and other lipids. It also activates different estrogen-derived procarcinogens, and It has been reported to be overexpressed in PCa (49). Two *CYP1B1* SNPs associated with PCa progression were identified (13,28): rs1800440, which is risk SNP, and rs1056836, which is protective. They have been linked to increased susceptibility to PCa (50–52).
- *CYP17A1*: Its product promotes androgen synthesis and is expressed in about 50% of PCa cases (53). Four SNPs associated with an increased risk of PCa progression were identified: rs743572, rs6162, and rs6163 have been associated with increased tumor aggressiveness, and rs6163 with lower BCR-free survival in PCa (54); rs2486758 has been related to a worse response to ADT (55).
- *CYP19A1*: Its product codes for aromatase, which produces estrogens from androgens. Four SNPs were identified: three risk and one protective SNP (14). Risk SNP rs1870050 has been associated with an increased response to ADT (56). The other variables identified have not been linked to PCa in other studies. Another SNP not identified in this review (*CYP19A1* rs4775936) has been related to lower survival in PCa (57).

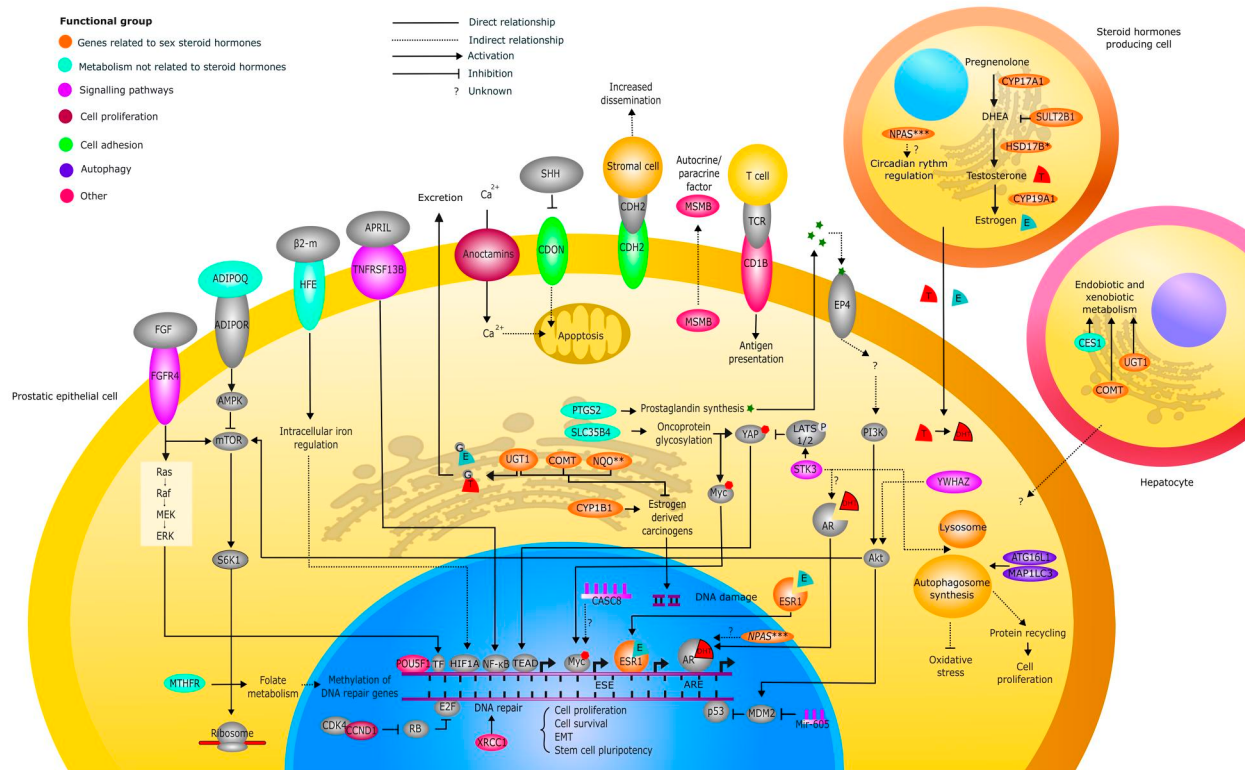


Figure 2. Functional integration of the gene products identified in the review in a prostatic epithelial cell, a steroid hormone-producing cell, and a hepatocyte. The seven groups the genes were classified into were identified with different colors, and their location in the different cell types was based on data reported in The Human Protein Atlas (<https://www.proteinatlas.org>). The group of genes related to sex steroid hormones (orange) is found in all three cell types. In the steroid hormone-producing cell, CYP17A1 and the HSD17B family are involved in testosterone synthesis, SULT2B1 decreases DHEA levels, and CYP19A1, which encodes for aromatase, facilitates the conversion of testosterone to estrogen; the NPAS family could regulate the circadian cycle of the adrenal gland or influence AR activity. In the prostatic epithelial cell, estrogen can bind to ESR1, which travels to the nucleus and activates gene transcription; in the endoplasmic reticulum, it can be metabolized into carcinogenic species by CYP1B1, which can be inactivated by UGT1, COMT, and the NQO family. UGT1 is also involved in the glucuronidation (G) of estrogen and testosterone, inactivating them and marking them for excretion. UGT1 and COMT are mostly expressed in the liver and are responsible for endobiotic and xenobiotic metabolism; however, their relationship with PCa is not entirely clear. As a consequence of the function of these genes, the transcriptional activity of these hormones is regulated in genes related to cell proliferation, growth, and survival. In the group of metabolism genes unrelated to steroid hormones (turquoise), all the products of these genes are in the prostatic epithelial cell, except for CES1, which is located in the hepatic cell and is related to endobiotic and xenobiotic metabolism. In the endoplasmic reticulum, PTGS2 participates in the synthesis of prostaglandins, which can induce an autocrine activation of the EP4 receptor activating the PI3K/Akt pathway, which, in turn, can activate mTOR and inhibit p53, among many other actions. This pathway has been related to cell proliferation and angiogenesis. Through glycosylation, SLC35B4 participates in the activation of oncoproteins such as YAP and Myc, which target the nucleus and activate the transcription of genes associated with proliferation and migration. MTHFR participates in folate metabolism, which could influence the methylation of genes associated with DNA repair and increased genomic instability. In the cell membrane, ADIPOQ binds to its receptor, activating AMPK, which is able to inhibit mTOR that normally can activate S6K1, promoting protein translation in ribosomes and cell growth. HFE regulates intracellular iron levels and may activate HIF1A, which activates EMT-related gene transcription. In the following groups, all functional integration of gene products was located only in the prostate cell. In the signaling pathway gene group (purple), FGFR4 binds to its ligand and can activate the mTOR pathway or the MAPK pathway, activating different TFs in the nucleus and promoting cell proliferation. TNFRSF13B binds to its ligand and activates NF-κB, which promotes the transcription of genes related to proliferation and EMT. LncRNA CASC8 could favor Myc expression, and Mir-605 can inactivate MDM2, favoring p53 activity, which can control cell cycle and apoptosis. STK3 prevents YAP activation through the Hippo suppressor pathway; it could promote AR activity and favors autophagosome binding to lysosomes, promoting cell proliferation. YWHAZ can also activate the Akt pathway sustaining growth signaling. In the cell proliferation group (red wine), CCND1 binds with CDK4 in the nucleus, inhibiting RB function, resulting in gene activation by E2F, which favors cell cycle progression. Anoctamins are membrane channels that help regulate intracellular calcium levels, which could regulate apoptosis. In the group of cell adhesion (green), when SHH is not present, CDON promotes apoptosis. CDH2 interacts with the membrane proteins of prostatic stromal cells and could promote tumor dissemination. In the autophagy group (blue), ATG16L1 and MAP1LC3 participate in phagosome synthesis, which, on the one hand, can reduce cellular oxidative stress and, on the other hand, can promote cell proliferation by facilitating protein recycling. In the group of other

Figure 2. (Continued)

functions (pink), POU5F1 is a transcription factor that activates genes related to stem cell pluripotency, XRCC1 is involved in DNA repair, and MSMB is secreted by prostatic epithelial cells and may have autocrine and paracrine functions related to apoptosis and cell proliferation. CDB1 can interact with the T lymphocyte receptor participating in antigen presentation. AMPK: AMP-activated protein kinase; mTOR: mammalian target of rapamycin; EMT: epithelial-mesenchymal transition; HIF-1a: hypoxia-inducible factor-1a; NF- κ B: nuclear factor kappa B; S6K1: Ribosomal protein S6 kinase beta-1; AR: androgen receptor; TCR: T cell receptor; TF: transcription factor; ADIPOR: adiponectin receptor; β 2-m: beta-2-microglobulin; APRIL: proliferation-inducing ligand; DHEA: dehydroepiandrosterone; EP4: prostaglandin E receptor 4; LATS: large tumor suppressor kinase 1; TEAD: TEA domain transcription factor 1; FGF: fibroblast growth factor; SHH: Sonic hedgehog; MDM2: murine double minute 2; PI3K: phosphatidylinositol 3'-kinase; CDK4: cyclin-dependent kinase 4. *HSD17B2, B3, B12; **NQO1, 2; ***NPAS2, 3.

The products of *NPAS2* and *NPAS3* regulate functions like neurogenesis and the circadian cycle.

- *NPAS2*: It is suggested that the product of this gene may regulate the circadian rhythm of the adrenal gland and the androgen receptor (AR) in PCa (58,59). This review found that SNP *NPAS2* rs6542993 has been associated with an increased risk of progression (15); this variant has not otherwise been related to PCa. Three other variants not identified in this review (*NPAS2* rs895521, rs23051560, and rs746924) have been linked to increased susceptibility to PCa (60–62).
- *NPAS3*: It has a low expression in castration-resistant PCa (63). *NPAS3* rs8004379 was found to increase the expression of its product and is associated with a lower risk of PCa progression (16). This is consistent with its reported tumor suppressor role in astrocytoma, regulating the cell cycle, apoptosis, and cell invasion (64). Likewise, some oncogenic pathways demonstrate increased activity when *NPAS3* expression is absent (64).

The products of *NQO1* and *NQO2* prevent DNA damage by metabolizing compounds such as quinones, which are derived from estrogens (65).

- *NQO1*: SNP rs2917670 was associated with an increased risk of PCa progression (13). Other variants not identified in this review, such as rs4986998, which reduces the activity of its product, and rs1800566 have been connected to increased susceptibility to PCa. Thus, it could be speculated that rs2917670 decreases the activity of the *NQO1* product (65,66).

- *NQO2*: Three SNPs associated with an increased risk of PCa progression were identified (13). Of these, rs1143684 decreases the activity of the *NQO2* product, so it could increase DNA damage (67). The other variants identified have not been linked to PCa in other studies.

Other genes related to estrogen metabolism and action with variants related to PCa progression were also identified.

- *UGT1*: Its product regulates estrogen excretion and metabolism, inactivating derived carcinogenic metabolites; its inhibition contributes to androgen receptor (AR) activation in PCa (68). This study found seven associated SNPs (3 protective and 4 risk SNPs) (17), which have not been linked to cancer in other studies. Another variant not identified in our study (*UGT1* rs3064744) has been associated with increased susceptibility to PCa (69).
- *COMT*: Its product inactivates estrogen-derived reactive compounds, which can induce the neoplastic transformation of prostate cells (70). Its inhibition may increase cell proliferation in PCa (71). This review found three SNPs: one protective and two risk SNPs (13). The two risk SNPs (rs9332377 and rs165849) have been linked to increased susceptibility to stomach and thyroid cancer (72). The other identified variant has not been linked to cancer in other studies. Another variant not found in this review (*COMT* rs4680) has been associated with lower susceptibility to PCa (73).
- *ESR1*: Encodes for estrogen receptor 1, which regulates the expression of genes related to cell proliferation and contributes to the development of PCa. Its high expression has been linked to metastases refractory to ADT, which has been

connected to worse prognosis (74–76). This review found three *ESR1* SNPs associated with an increased risk of PCa progression (14). Of these, rs1062577 increases *ESR1* expression; it has been related to more aggressive PCa, and it results in the loss of *miR-186* binding site, an inhibitor of cell proliferation in PCa (54,77). SNP rs9341016 has been associated with serum estrone levels, and rs488133 has been linked to an increased number of chromosomal aberrations in patients exposed to occupational radiation (78,79). Another variant not identified in this review (rs9340799) has been associated with increased susceptibility to PCa (80).

Variants in other genes related to androgen and other lipid metabolism.

- *SULT2B1*: Its product decreases the levels of androgenic precursor dehydroepiandrosterone (DHEA). *SULT2B1* expression is reduced in PCa, and its inhibition promotes cell proliferation in this type of cancer (81,82). This review found two *SULT2B1* SNPs associated with PCa progression: one risk and one protective SNP. These variants have not been linked to PCa in other studies.

2. Metabolism unrelated to steroid hormones

Variants were identified in genes related to the metabolism of carbohydrates, lipids, vitamins, and iron.

- *CES1*: Its product is involved in endobiotic and xenobiotic metabolism, including toxins and drugs. *CES1* is also a transcription factor target gene whose activity has been associated with lipid metabolism, lower androgen levels, and decreased cell proliferation in PCa (83). Likewise, *CES1* expression has been associated with decreased lipid accumulation and the induction of apoptosis in PCa (84). In this review, two SNPs were found that decrease their expression and are associated with an increased risk of PCa progression: rs8192950 and rs8192935 (18).
- *SLC35B4*: Through its product, it transports nucleotide sugars from the cytoplasm to the

Golgi apparatus. Studies have linked its function to changes in glycosylation of oncoproteins such as YAP1 and c-Myc, and its expression is elevated in different cancer types (85,86). *SLC35B4* is overexpressed in PCa, where it is linked to greater aggressiveness and worse prognosis (19). This review found two SNPs associated with an increased risk of progression (19). Of these, rs1646724 increases the expression of *SLC35B4* (19). The other variant identified has not been connected to PCa in other studies.

- *PTGS2*: Its product participates in prostaglandin biosynthesis and is overexpressed in PCa, which is associated with an increased risk of BCR (87). Likewise, *PTGS2* inhibition suppresses cell proliferation in PCa by decreasing angiogenesis and increasing apoptosis (88). Prostaglandins could also activate the PI3K/AKT pathway resulting in increased cell proliferation in CaP. The present review identified the protective rs4648302 variant, which decreases the expression of this gene (20).
- *MTHFR*: Through its product, it participates in folate metabolism and DNA synthesis, methylation, and repair. *MTHFR* is overexpressed in PCa, which has been linked to lower BCR-free survival (21). Likewise, low *MTHFR* expression has been associated with lower levels of hypermethylation in genes involved in DNA repair (89). This review identified the rs9651118 variant, which decreases the expression of this gene and is associated with a lower risk of PCa progression (21).
- *ADIPOQ*: It encodes for adiponectin, which has pleiotropic functions in the metabolism of lipids and glucose. Adiponectin reduces cell proliferation and epithelial-mesenchymal transition in PCa, where low *ADIPOQ* expression has been seen in metastatic lesions (90). Binding of *ADIPOQ* to its receptor can activate AMPK, which can inactivate mTOR. This review observed that rs182052 is associated with an increased risk of PCa progression (22), and it correlates with lower serum adiponectin levels and increased susceptibility to PCa (91).
- *HFE*: Its product can form a complex with β 2-microglobulin, which promotes cell activation and metastasis in PCa by regulating the intracellular iron level, which can activate the

transcription factor 1- α inducible by hypoxia (HIF1A) (92,93). Likewise, *HFE* inhibition has been shown to increase sensitivity to radiotherapy in PCa (94). This review found that rs9393682 was a risk factor, which has been reported to increase the expression of this gene (23).

3. Signaling pathways

Variants were identified in genes related to the regulation of signaling pathways controlling functions like cell proliferation and survival.

- *MIR605*: It encodes a miRNA that suppresses a p53 inhibitor and may reduce tumor proliferation and invasion in PCa, where its expression is decreased (95). This review found a risk SNP (rs2043556) (24), which has been reported to decrease the expression of this gene and which could explain this association (96). This SNP has also been linked to increased susceptibility to different cancer types (97).
- *CASC8*: It encodes a long non-coding RNA located at 8q24.1, where other non-coding RNAs promote the interaction between the *MYC* promoter and its enhancers (98). *MYC* is a proto-oncogene that regulates cell cycle progression, apoptosis, and cell transformation (99). This review found a risk SNP for PCa progression (rs1447295) (25), which has also been linked to increased susceptibility to PCa (100).
- *TNFRSF13B*: Through its product, it activates the signaling pathway of nuclear factor kappa B (NF- κ B), promoting cell proliferation (101). In PCa, NF- κ B plays a key role in the development of castration resistance (102). This review found that *TNFRSF13B* rs4792800 increases its expression and is associated with an increased risk of PCa progression (26).
- *YWHAZ*: Its product activates the phosphatidylinositol 3-kinase (PI3K)/AKT pathway, promoting cell survival (103). *YWHAZ* is overexpressed in PCa cell lines associated with high Gleason score and BCR (104). This review found that rs2290291 increases the expression of this gene and the risk of PCa progression (27).
- *STK3*: Although its product is part of the Hippo tumor suppressor pathway, it also has a non-canonical protumor function in PCa (105). Likewise, its product has proven to be important for the binding of the autophagosome to the lysosome. *STK3* is amplified, its expression has been associated with AR activity, and it promotes cell proliferation under conditions similar to castration in PCa (105). This review found that *STK3* rs7827435 decreases its expression and is linked to a lower risk of PCa progression (28).
- *FGFR4*: The binding of its product to a growth factor activates the MAPK/ERK pathway, which is involved in the regulation of cell proliferation and differentiation. This review found that *FGFR4* rs351855 increases the risk of PCa progression (29), and it has been associated with increased PCa invasiveness, increased stability, sustained AR activation, and increased susceptibility to PCa (106–108).

4. Cell proliferation

Products of the ANO family can activate cell proliferation pathways by increasing intracellular calcium levels (109).

- *ANO4*: Low *ANO4* expression may predict increased BCR-free survival (110). This review identified a protective variant in *ANO4* (30); however, no other studies were found to link this SNP to cancer.
- *ANO5*: This review found that *ANO5* rs4622263 increases the risk of progression in PCa (30); rs4622263 can regulate a transcription factor associated with cell regeneration in cancer (30,111).
- *ANO7*: Its expression is reduced in PCa, which has been associated with early BCR (112). This review identified a protective variant in *ANO7* (30); however, no other studies were found to link this SNP to cancer.
- *ANO10*: This gene plays an important role in apoptosis (113). This review identified a protective variant in *ANO10* (30); however, no other studies were found to link this SNP to cancer.

Likewise, a variant was identified in another gene involved in the regulation of cell proliferation.

- *CCND1*: It encodes cyclin D1, which induces cell cycle transition from G1 phase to S phase promoting cell proliferation. Its high expression has been related to perineural invasion in PCa (114). This review found that *CCND1* rs9344 increases the risk of PCa progression (31); it regulates the alternative splicing of *CCND1* mRNA, resulting in a longer half-life of its product (115). Likewise, rs9344 has been linked to higher *CCND1* expression and a worse prognosis in esophageal cancer (116). Interestingly, in the included article, association with progression was found in the G allele, which, unlike the A allele, has not been frequently linked to cancer.

5. Cell adhesion

Variants were identified in two genes associated with cell adhesion.

- *CDON*: It encodes a membrane protein that regulates cellular interactions during myogenic differentiation. Likewise, when sonic hedgehog (SHH) is present, the proapoptotic activity of the product of *CDON* is inhibited, which promotes cell proliferation in PCa (117). It has been evidenced that *CDON* is overexpressed in PCa, and its silencing reduces invasive capacity (118). This review found that *CDON* rs3737336 increases the expression of this gene and is associated with an increased risk of PCa progression (24). In contrast to these findings, rs3737336 has also been linked to a lower risk of PCa progression in patients with ADT (119).
- *CDH2*: Its product participates in tumor cell migration and invasion, and its expression has been linked to increased tumor aggressiveness (120). In PCa, its expression has been associated with metastasis and resistance to castration (121). This review identified three *CDH2* SNPs associated with PCa progression: two risk and one protective SNPs (32). Risk SNP rs643555 increases *CDH2* expression, which has been associated with reduced BCR-free survival (32).

The other identified variants have not been linked to PCa in other studies.

6. Autophagy

Autophagy can decrease oxidative stress and DNA damage, but It also can promote cell proliferation through protein recycling (122).

- *ATG16L1*: Its product is involved in autophagosome synthesis and its loss increases the production of inflammatory cytokines (123). Reduced *ATG16L1* expression has been associated with lower relapse-free survival in PCa (33). This review identified two variants in *ATG16L1* associated with PCa progression (33). Protective rs78835907 is associated with increased *ATG16L1* expression in PCa (33). The other identified variant has not been linked to PCa in other studies.
- *MAP1LC3*: Its product also participates in autophagosome synthesis. To supply the nutrients needed for their growth, cancer cells increase autophagy to recycle damaged proteins and organelles (124). In PCa, *MAP1LC3* is overexpressed and is associated with a higher Gleason score (125). This review found that *MAP1LC3* rs8044820 increases the risk of PCa progression (33). This variant has not been linked to PCa in other studies.

7. Other functions

Variants were identified in genes associated with cell differentiation, DNA repair, the immune system, and prostatic secretions.

- *POU5F1*: Its product is a transcription factor that maintains the pluripotency of embryonic stem cells. *POU5F1* expression is associated with the self-renewal capacity of cancer stem cells (126). In PCa, these cells have a high level of self-renewal, can differentiate into heterogeneous tumor cells, and can be resistant to chemotherapy (127). *POU5F1* is overexpressed in 25% of castration-resistant tumors and in less than 11% of primary PCa tumors (128). This review found that *POU5F1* rs2394882 decreases the expression of this gene and reduces the risk of PCa progression (34).

- *XRCC1*: It participates through its product in cancer control by acting as a scaffolding protein for DNA repair enzymes (129). This review found that *XRCC1* Arg399Gln increases the risk of PCa progression (35). Arg399Gln has been associated with increased DNA damage, possibly due to the decreased function of the *XRCC1* product (130). Likewise, it has been related to increased susceptibility to PCa (131).
- *CB1B*: Through its product, it participates in the presentation of antigens to T lymphocytes. It has been demonstrated that *CBD1* is important for the immune system to recognize tumor neoantigens, and its low expression is associated with lower BCR-free survival in PCa (36,132). This review found that *CBD1* rs3181082 decreases the expression of this gene while increasing the risk of PCa progression (36).
- *MSMB*: It has been expressed mostly in benign rather than malignant prostate tissue (133). Its expression has been associated with a favorable prognosis in PCa, and the T allele of rs10993994, which reduces *MSMB* expression, has been linked to increased susceptibility to PCa (134,135). However, this review found that the C allele of rs10993994, which increases *MSMB* activity and expression, increases the risk of PCa progression (25). Some studies support this finding as the T allele of rs10993994 is not always associated with more aggressive PCa; *MSMB* expression has also been linked to a shorter time to BCR (136,137).

Finally, four haplotypes were found to be associated with an increased risk of PCa progression (Supplementary Table 3). One haplotype with seven variants in *UGT1A* (17); one haplotype with eight variants in *CYP1B1*, *SULT2B1*, and *HSD17B2* (13); one haplotype with four variants in *CCND1* (30); and one haplotype with three variants in *TCF7L2* (138). The *TCF7L2* product promotes cell proliferation and regulates the expression of AR by being an effector of the Wnt pathway (139). The variants in *TCF7L2* (rs7094463, rs10749127, and rs11196224) are located close to enhancers of this gene, so they could have an effect on its activity (138).

Conclusions

This systematic review examines the relationship of SNPs with PCa progression. The organization of genes in subgroups stands out as a strength since it allows for a functional perspective of the identified variants. As evidenced, some of these SNPs have been linked to changes in the activity or expression of genes with a significant role in PCa development and progression. Despite this, the conclusions of our study also have limitations. The mechanism by which some of these variants are associated with PCa is not entirely clear. Likewise, the data focused on specific polymorphisms; thus, it is possible that other variants with a significant association were not identified. On the other hand, SNPs were mainly described in two cohorts from Taiwan and Canada, so these findings have not been confirmed in patients from other populations. Similarly, as they are retrospective studies, factors like information quality and selection bias may have influenced the results. Lastly, excluding articles that used patients under PCa medications may have limited the amount of SNPs that were found in our revision. It is important to continue exploring the relevance of SNPs in PCa progression and prognosis to expand the molecular understanding of the disease and find a repertoire of potential biomarkers with a clinical impact on different populations. Also, incorporating additional variables like PSA levels and Gleason scores could enhance clinicians' decision-making and potentially pave the way for future research studies, however, because of the lack of data from individual patients in these publications we couldn't perform this analysis.

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