Association among polymorphisms in the apoptosis-related NKX3-1, caspase-3, caspase-9, and BCL-2 genes and prostate cancer susceptibility from 9,706 cases and 12,567 controls

Yanyan Feng¹, Zhenting Feng², Dan Li², Jiandong Gui¹, Zhihong Song², Xiaohua Xie², Lijie Zhu²*³, and Yuanyuan Mi³

¹Jiangnan University Wuxi School of Medicine
²Shenzhen Second People’s Hospital
³Affiliated Hospital of Jiangnan University

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Abstract

Introduction While there is a growing volume of evidence suggesting that relatively prevalent functional polymorphisms present within apoptosis-related genes may influence human prostate cancer (PCa) susceptibility, the clinical relevance of these findings remains inconclusive. This meta-analysis was thus developed with the goal of generating more precise estimates of the relationships between polymorphisms in four apoptosis-associated genes (NKX3-1, Caspase-3, Caspase-9, and BCL-2) and the risk of PCa.

Material and methods The PubMed, Web of Science, Google Scholar, Embase, Cochrane Library, and SinoMed (CNKI and Wanfang) databases were searched for relevant studies published through December 20, 2023 using the following keywords: ‘polymorphism’ or ‘variant’ and ‘carcinoma’ or ‘cancer’ or ‘tumor’ and ‘NKX3-1’, ‘CASP3’ or ‘Caspase-3’, ‘CASP9’ or ‘Caspase-9’, ‘BCL-2’ or ‘B-cell lymphoma’ and ‘prostate cancer’ or ‘PCa’ or ‘prostate adenocarcinoma’.

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Keywords: Prostate cancer, Apoptosis-related genes, NKX3-1, Caspase-3, Caspase-9, BCL-2, polymorphisms, Meta-analysis

Introduction

Prostate cancer (PCa) is a leading cancer type among men, with millions of new diagnoses throughout the world each year(1). In 2023, for example, the International Agency for Research on Cancer forecasts approximately 288,300 new PCa diagnoses and 34,700 related deaths at the global level(2). PCa incidence rates rise with age such that this cancer type is most common among men over the age of 65(3). PCa incidence also varies as a function of ethnicity and geographical location, with Caribbean and African American males facing particularly high PCa rates, whereas this malignancy is less common among Asian men(4). While Japan exhibits the lowest PCa incidence among Asian nations, rates of PCa diagnoses in China continue to rise annually(5, 6). Positive family history has been increasingly established as an important factor associated with the risk of PCa(7, 8). Genetic association studies seek to elucidate the genetic risk factors associated with particular cancers or other diseases of interest. Despite the high rates of PCa diagnoses in African American populations, however, members of this community remain underrepresented in genetic association studies focused on this form of cancer(9).

PCa develops through a multi-stage process that is influenced by a diverse array of factors, with both genetic and epigenetic changes playing essential roles in facilitating oncogenesis(10). Research focused on the genetic epidemiology of PCa risk has revealed PCa to be the cancer type with the fourth highest risk of presenting in multiple members of a given family after lip melanoma, skin melanoma, and ovarian cancer(11). A family history positive for PCa is thus regarded as a major risk factor for developing this form of malignancy(12), such that genetic factors are thought to serve as particularly important regulators of PCa incidence more so than in other human cancer types(13, 14). Consistently, the variations in PCa diagnosis rates among regions and ethnic groups are thought to be partially attributable to differences in the prevalence of particular
single nucleotide polymorphisms (SNPs) associated with PCa risk(15). In particular, SNPs present within apoptosis-associated genes have been shown to be closely tied to the odds of developing PCa(16, 17).

Apoptosis is an essential mechanism of programmed cell death that shapes both pathological and physiological processes(18, 19). When apoptotic activity is dysregulated in eukaryotic cells, this can result in abnormal survival outcomes(20). Accordingly, many types of malignant cells have developed mechanisms that enable them to evade apoptotic death through the modulation of pro- and anti-apoptotic factors, thereby altering signaling pathways in the intracellular and extracellular environment to alter the expression of apoptosis-associated genes(19). The external and internal apoptotic pathways can become dysregulated in PCa, contributing to the ability of tumor cells to avoid undergoing apoptosis such that these malignant cells can instead proliferate and disseminate (18, 21).

The anti-apoptotic protein B-cell lymphoma-2 (BCL-2) has been a focus of intensive research efforts(22), as changes in BCL-2 expression levels can contribute to improperly regulated apoptotic activity and aberrant cell proliferation conducive to oncogenesis and tumor progression(23). The prospective PROCAGENE study, which enrolled 702 patients with PCa, found that overall survival (OS) in patients with PCa was associated with the homozygous BCL2 -938 CC genotype(24). In line with this evidence regarding the importance of BCL2 SNPs in PCa, Hirata et al. also emphasized the association between apoptosis-related gene polymorphisms and oncogenic risk(25), while Souza et al.(26) found that the BCL2 -938 C > A polymorphism was related to an elevated risk of biochemical recurrence following radical prostatectomy, in addition to serving as an independent predictor of both OS and recurrence-free survival (RFS).

High levels of NKX3-1 protein expression are detectable within prostate epithelial cells, wherein it functions to preserve prostate specification and to support prostate ductal stem cell maintenance while inhibiting inflammation, DNA damage, and PCa incidence through its ability to shield the mitochondria from oxidative injury(27). Given its ability to tightly regulate prostate epithelial cell proliferation and differentiation(28), NKX3-1 is regarded as the most important tumor suppressor protein related to PCa incidence(29, 30). Chen et al.(31) demonstrated that a particular SNP (rs21687) within the site where NKX3-1 binds to the promoter of the gene encoding L-plastin may contribute to a lower risk of PCa incidence. Martinez et al.(32) further demonstrated that polymorphic NKX3-1 alleles can encode an abnormal version of this protein with altered DNA binding activity that can impact the risk of PCa incidence.

Caspase-3 and caspase-9 are firmly established as important enzymatic mediators of apoptotic cell death(33). Caspase-3 functions as the final executioner caspase within the apoptotic pathway following its activation in response to pro-apoptotic signals such that it can cleave substrate proteins to ensure the progression of the apoptotic cascade(34). Caspase-9, in contrast, serves as an upstream initiator of apoptotic death through its interactions with cytochrome c and apoptosis protease-activating factor 1, activating the apoptotic cascade(35). By catalyzing this signaling and the downstream activation of caspase-3 and other enzymes, caspase-9 can thus promote the clearance of abnormal cells to help maintain systemic homeostasis(36). Mittal et al.(37) reported that the CASP3 rs4647603 CT genotype and T allele were related to an elevated risk of PCa in individuals who are obese, with a positive correlation between caspase-3 and such cancer risk. Souza et al.(16) further identified an association between CASP3, NKX3-1, and BCL2 gene polymorphisms and PCa risk. These results emphasize the close association between these particular SNPs and PCa, suggesting that they may offer value as molecular biomarkers that can guide the prognostic evaluation of patients with this form of cancer.

Prior studies have explored the utility of particular SNPs as molecular markers associated with PCA patient outcomes(38, 39). The combined analysis of SNPs in the NKX3-1, CASP3, CASP9, and BCL2 genes has been tied to adverse PCa patient outcomes(16, 24), suggesting the utility of these SNPs as prognostic biomarkers in this context. However, additional studies will be essential to validate the relevance of these findings and to assess the clinical relevance of these biomarkers. The present meta-analysis was thus conducted with the goal of comprehensively screening published studies in order to facilitate pooled analyses aimed at objectively clarifying the link between apoptosis-related gene polymorphisms and PCa risk. The results of this study will provide an evidence-based foundation for early screening and clinical management strategies for PCa.
Materials and methods

Study search process

The PubMed, Web of Science, Google Scholar, Embase, Cochrane Library, and SinoMed (CNKI and Wanfang) databases were searched for relevant studies published through October 20, 2023 using the following keywords: ‘polymorphism’ or ‘variant’ and ‘carcinoma’ or ‘cancer’ or ‘tumor’ and ‘NKX3-1’, ‘CASP3’ or ‘Caspase-3’, ‘CASP9’ or ‘Caspase-9’, ‘BCL-2’ or ‘B-cell lymphoma’ and ‘prostate cancer’ or ‘PCa’ or ‘prostate adenocarcinoma’. There were no limitations placed on language or year of publication.

Study selection

Studies eligible for inclusion in the present meta-analysis were those that: (i) focused on the association between specific apoptosis-associated gene polymorphisms and PCa risk, (ii) were case-control studies, and (iii) provided sufficient genotype numbers in the case and control groups. Studies were excluded if they (i) did not include a control population, (ii) did not provide complete information on genotype frequencies, (iii) were duplicates, (iv) were meta-analyses, (v) were clinical trials, (vi) were focused on other polymorphisms, or (vii) were systematic reviews.

Data extraction

Two investigators (YF and ZF) independently selected relevant studies and used a standardized approach to extract the following information from each study: first author, publication year, country, study population ethnicity, control population source, total case and control numbers, apoptosis-related genes of interest, polymorphisms that were analyzed, numbers of genotypes and alleles, Hardy-Weinberg equilibrium (HWE) results for control subjects, and the genotyping methods employed.

Statistical analyses

Initially, data related to SNPs in apoptosis-related genes including NKX3-1 (rs2228013, rs2228013, rs11781886, rs1512268), Caspase-3 (rs4647603), BCL-2 (rs2279115), and Caspase-9 (rs1052571, rs4645978, rs4645982) were extracted, with data for each SNP being extracted from two or more studies. The ethnicity of participants in these studies was classified using two different classification patterns (Asian, Caucasian, African, and South American) based on source analyses of control subgroups, including hospital-based (HB) and population-based (PB) classifications. Genotypic distributions in cases and controls were used to compute odds ratio (OR) values with 95% confidence intervals (CIs) as a means of clarifying the association between these apoptosis-related gene polymorphisms and PCa incidence. These ORs were analyzed with Z-tests, and heterogeneity was evaluated with the Q-test, with P < 0.05 as the threshold used to define significant heterogeneity. Fixed-effects models were used unless significant heterogeneity was observed, in which case a random-effects model was instead employed. Allelic contrast (M-allele vs. W-allele), heterozygous (MW vs. WW), homozygous (MM vs. WW), dominant (MM+MW vs. WW), and recessive (MM vs. MW+WW) genetic models were then employed to examine the associations between particular SNPs and susceptibility to PCa. Pearson’s chi-square test was used to assess the HWE status of control subjects, with P < 0.05 as the threshold used to define significance. Publication bias was assessed based on Egger’s regression test and Begg’s funnel plots. Stata 11.0 (StataCorp LP, TX, USA) was used to perform all statistical analyses.

Bioinformatics analyses

GEPIA (http://gepia.cancer-pku.cn/) was used to evaluate NKX3-1 expression in PCa tumors and adjacent tissues, and to evaluate patient OS and disease-free survival (DFS). Similarly, the Cancer Genome Atlas (TCGA) database (https://www.cancer.gov/ccg/research/genome-sequencing/tcga) was used to compare CL-2 expression levels in tumors and normal tissues. The STRING database (http://string-db.org/) was also used to construct gene-gene interaction networks for each of these four apoptosis-associated genes in order to better understand how they may contribute to PCa risk.
Results

Study characteristics

An initial literature search revealed 2,240 potentially relevant articles of which 2,099 were included following title or abstract review. Of the remaining articles, 141 were excluded because they were duplicates (n=6), meta-analyses (n=23), clinical trials (n=25), systematic reviews (n=12), or focused on other polymorphisms (n=57). The remaining articles included 20 reports focused on associations between SNPs in these four apoptosis-related genes of interest (NKX3-1, CASP3, CASP9, BCL2) and PCA. These included 3 articles related to BCL2 polymorphisms focused on rs2279115 were analysed, as well as 3 focused on the CASP3 rs4647603 SNP, 7 focused on CASP9SNPs (including 2 focused on rs1052571 and 3 focused on rs4645978 and 2 focused on rs4645982 that were retained for analysis), and 7 focused on NKX3-1 SNPs (including 3 focused on rs2228013, 2 focused on rs1178188, 2 focused on and studies focused on rs1512268). The basic characteristics of these studies are summarized in Table 1, including the first author, publication year, country, ethnicity, control population source, numbers of cases and controls, apoptosis-related genes of interest, polymorphisms of interest, numbers of genotypes and alleles, HWE results, and genotyping methodology. In total, these case-control studies included 9,706 cases and 12,567 controls (Figure 1), with control subjects primarily being derived from healthy populations. Overall these analyses included 3 Caucasian, 9 Asian, 4 South American, and 4 American case-control studies, of which 11 and 9 were respectively based on HB and PB populations. Next, the 1000 Genomes Browser was used to assess the minor allele frequency (MAF) values for rs2228013 (PB populations. Next, the 1000 Genomes Browser was used to assess the minor allele frequency (MAF) values for rs2228013 (n=57). The remaining articles included 20 reports focused on associations between SNPs in these four apoptosis-related genes of interest (NKX3-1, CASP3, CASP9, BCL2) and PCA. These included 3 articles related to BCL2 polymorphisms focused on rs2279115 were analysed, as well as 3 focused on the CASP3 rs4647603 SNP, 7 focused on CASP9SNPs (including 2 focused on rs1052571 and 3 focused on rs4645978 and 2 focused on rs4645982 that were retained for analysis), and 7 focused on NKX3-1 SNPs (including 3 focused on rs2228013, 2 focused on rs1178188, 2 focused on and studies focused on rs1512268). The basic characteristics of these studies are summarized in Table 1, including the first author, publication year, country, ethnicity, control population source, numbers of cases and controls, apoptosis-related genes of interest, polymorphisms of interest, numbers of genotypes and alleles, HWE results, and genotyping methodology.

Meta-analysis

In pooled analyses, NKX3-1 rs2228013 (GA vs. AA, OR = 1.18, 95%CI = 1.00-1.38, P heterogeneity = 0.565, P = 0.047, Figure 4), CASP9 rs1052571 (GG+GA vs. AA, OR = 1.19, 95%CI = 1.01-1.40, P heterogeneity = 0.850, P = 0.037, Figure 5), and CASP9 rs4645982 (GG vs. GA+AA, OR = 1.41, 95%CI = 1.03-1.93, P heterogeneity = 0.431, P = 0.032, Figure 6) were associated with an elevated risk of PCA when evaluated using different genetic models. Conversely, CASP3 rs4647603 was associated with a significant reduction in PCA risk (GG vs. AA, OR = 0.44, 95%CI = 0.26-0.75, P heterogeneity = 0.647, P = 0.002; GG vs. GA+AA, OR = 0.61, 95%CI = 0.43-0.87, P heterogeneity = 0.594, P = 0.006; G-allele vs. A-allele, OR = 0.82, 95%CI = 0.68-0.99, P heterogeneity = 0.113, P = 0.041, Figure 7) (Table 2).

Gene-gene interaction network analyses

In order to better understand the role of apoptotic genes in prostate cancer, the STRING database was next used to characterize the interactions between NKX3-1, caspase-3, BCL-2, caspase-9, and a variety of other genes (Figure 8). The genes that were most closely associated with NKX3-1 included SAM pointed domain-containing Ets transcription factor (SPDEF), androgen receptor (AR), RAC-alpha serine/threonine-protein kinase (AKT1), transmembrane protease serine 2 (TMPRSS2), and RAC-beta serine/threonine-protein kinase (AKT2). The genes most closely associated with caspase-3 included the E3 ubiquitin ligase XIAP, Poly [ADP-ribose] polymerase 1 (PARP1), and baculoviral IAP repeat-containing protein 2 (BIRC2). The genes most closely associated with BCL-2 included beclin-1, the apoptosis regulator BAX, and the antitumor protein p53 (TP53). The genes most closely associated with caspase-9 included CYS(Cytochrome c, somatic) / Cytochrome c (Electron carrier protein), XIAP, and apoptotic protease-activating factor 1 (APAF1).

Discussion
PCa is among the most common cancers in the world, but many affected patients experience progressive
disease and fail to attain persistent benefits from therapeutic interventions(40). Apoptosis is an important
target of cancer treatment efforts given the important role that this process plays in restraining the pro-
liferation of malignant or injured cells(41). Members of the BCL-2 gene family function as key regulators
of apoptotic activity with the potential to be leveraged to enable the more effective treatment of PCa and
other forms of cancer(42). Many prior reports have also documented key roles for caspase-3, caspase-9, and
NKX3-1 as regulators of apoptotic death, particularly in the context of treating PCa(43, 44).

Several prior reports have focused on polymorphisms in the genes encoding BCL-2, caspase-3, caspase-9
and NKX3-1, and their relevance to cancer treatment. Javid et al(45)., for example, pointed that BCL-
2 (-938 CC ) genotype was an independent poor prognostic factor in patients with non-small-cell lung
cancer. The CASP3 rs4647601 TT genotype has also been linked to head and neck squamous cell carcinoma
risk(46), while CASP9rs4645981C is related to lung cancer incidence(47). Gelmann et al.(41) highlighted
the association between particular NKX3-1 allelic mutations and PCa risk. These data emphasize the
relevance of apoptosis-associated gene polymorphisms and cancer risk. Systematic studies focused on such
polymorphisms in PCa and other cancer types, however, are lacking.

Through pooled analyses of prior case-control studies, the present data highlight the clinical relevance of
specific SNPs in apoptosis-related genes to PCa risk. Stratified analyses revealed that the NKX3-1 rs2228013,
CASP9rs1052571, CASP9 rs4645982, and CASP3 rs4647603 SNPs were all closely tied to the risk of this
cancer type. Specifically, the former three of these polymorphisms were identified as risk factors for PCa,
whereas CASP3 rs4647603 was a protective factor associated with a lower risk of disease.

Dysregulated apoptotic activity is a key factor that contributes to the inability of malignant cells to undergo
appropriate programmed cell death in PCa tumors(48). The present data highlight the close relationship
between multiple apoptosis-associated genes and cancer-related outcomes, in line with the ability of SNPs
in these genes to alter apoptotic signaling activity and to thereby influence PCa incidence and progression.
Members of the BCL-2 gene family, for example, are well-established as important regulators of apoptotic
death(23), with BCL-2 overexpression contributing to the development of this cancer type. Particular SNPs
in these genes can contribute to altered signaling that enables transformed cells to more readily grow and
metastasize. Efforts focused on studying SNPs in apoptosis-associated genes thus have the potential to inform
research focused on the mechanistic drivers of PCa incidence while also allowing for better predictions of
disease susceptibility on an individualized basis and facilitating personalized treatment planning. Research
analyzing SNP distributions in various populations can also help clarify the genetic heterogeneity of PCa
risk, thereby uncovering new therapeutic targets and approaches to preventing or treating this devastating
disease.

There are certain limitations to this meta-analysis. First, 2 of the included studies failed to conform to
the HWE. Gene-environment interactions and a range of other covariates have the potential to influence the
findings of these pooled analyses, emphasizing a need for future comprehensive research efforts aimed at fully
clarifying the association between particular genes and PCa-related risk. Even so, the present results offer
greater statistical power than that afforded by any individual analysis, and the employed selection criteria
were strict such that high-quality case-control studies were used as a basis for these analyses, ensuring that
the results are more robust and reliable.

Conclusion
In summary, the results of the present meta-analysis suggest that certain SNPs in the genes encoding the
apoptosis-related proteins NKX3-1, caspase-3, caspase-9, and BCL-2 are associated with the risk of PCa.
Future large-scale research efforts, however, will be vital to fully confirm the role of these and other apoptosis-
related gene polymorphisms in shaping PCa onset and progression.

Data Availability Statement
The original contributions presented in the study are included in the article material. Further inquiries can
be directed to the corresponding authors.

**Ethics Statement**

None

**Author Contributions**

YF, ZF, and DL were major contributors in writing the manuscript. YF and ZF created all the figures. DL and JG performed the literature search. ZH, HX, LZ and YM made substantial contributions to the design of the manuscript and revised it critically for important intellectual content. All authors have read and approved the final version of this manuscript.

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**Figure Legends**

**Figure 1** The flowchart illustrating the search strategy used effectively to identify association apoptosis-related genes and prostate cancer risk.

**Figure 2** 1000 Genomes database results corresponding to the frequencies of signal site alleles in the NKX3-1 (rs2228013, rs11781886, rs1512268), CASP3 (rs4647603), BCL2 (rs2279115), and CASP9 (rs1052571, rs4645978) genes.

**Figure 3** (A) The expression of the CASP3 gene in PCa. (B) Analyses of overall survival (OS) for patients with PCa, revealing a positive correlation between NKX3-1 expression and patient OS. (C) BCL2expression in PCa cases in the TCGA database with different sample types. PCa: Prostate Adenocarcinoma. TCGA: The Cancer Genome Atlas.

**Figure 4** A forest plot representing the relationship between the NKX3-1 rs2228013 polymorphism and PCa risk (G-allele vs. A-allele model).

**Figure 5** A forest plot representing the relationship between the CASP9 rs1052571 polymorphism in PCa (G-allele vs. A-allele model).

**Figure 6** A forest plot representing the relationship between the CASP9 rs4645978 polymorphism in PCa (G-allele vs. A-allele model).

**Figure 7** A forest plot representing the relationship between the CASP3 rs4647603 polymorphism in PCa (G-allele vs. A-allele model).

**Figure 8** (A-D) Networks documenting interactions between NKX3-1 (A), Caspase-3 (B), BCL-2 (C), and Caspase-9 (D) and other genes as retrieved using the STRING database, with details provided for 10 core genes in each case.

**References**


34. Eskandari E, Eaves CJ. Paradoxical roles of caspase-3 in regulating cell survival, proliferation, and tumorigenesis. J Cell Biol. 2022;221(6).


A

Disease Free Survival

C

B

Expression of BCL2 in PRAD based on Sample types

TCGA samples

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