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The *Aurora Kinase A* Polymorphisms are not Associated with Recurrence-free Survival in Prostate Cancer Patients

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Abstract

Background: The purpose of this study was to investigate the association between haplotype-tagging single nucleotide polymorphisms (SNPs) within the *Aurora Kinase A* (*AURKA*) gene and prostate cancer outcomes in patients with clinically localized prostate cancer.

Methods: Four intronic haplotype-tagging SNPs within the *AURKA* gene were individually selected and examined in regard to their influence on clinical outcomes in 212 patients who underwent radical prostatectomy as first-line treatment. Haplotype-tagging SNPs were selected using the ABI SNP Browser to cover SNPs with an r^2 of 0.90 or greater in the *AURKA* gene with a minor allele frequency of at least 0.25.

Results: In our study, a log-rank univariate analysis was performed to identify significant associations between probability of recurrence-free survival or disease-free survival and known prognostic indicators as well as *AURKA* genotypes. The prognostic indicators Gleason grade, surgical margin, extracapsular extension, and disease stage were associated with recurrence-free survival (all $p<0.001$). Only Gleason grade was associated with disease-free survival ($p<0.001$). No associations were found for the SNPs *rs1468055*, *rs8117896*, *rs2064863*, and *rs1468056* analyzed for either RFS ($p=0.7213$, $p=0.5140$, $p=0.0714$, $p=0.4731$, respectively) or DFS ($p=0.3282$, $p=0.1909$, $p=0.4111$, $p=0.5014$, respectively).

Conclusions: This study demonstrates no evidence for intronic *AURKA* SNPs in predicting recurrence-free survival in patients with prostate cancer.

Keywords: Aurora kinase A; Prostate cancer; Single nucleotide polymorphism; Recurrence-free survival

Abbreviations: *AURKA*: Aurora Kinase A; DFS: Disease-free Survival; ht-SNP: Haplotype-tagging Single Nucleotide Polymorphism; PSA: Prostate-specific Antigen; RFS: Recurrence-free Survival; SNP: Single Nucleotide Polymorphism

Introduction

Aurora kinase A (also known as *STK15*, *BTAK*, *AIKI*, and *AURKA*) is a well-known oncogene and serine/threonine kinase, which localizes to centrosomes in S phase to undergo phosphorylation and activation late in G2 phase. Human *AURKA* localizes to chromosome 20q13.2, a region known to be frequently amplified in multiple tumor types [1,2]. Its overexpression has been associated with centrosome amplification, chromosomal instability and malignant phenotypes of mammalian cells [3]. Overexpression of *AURKA* has been noted in prostate tumors in human and mouse models [4], and its link to tumor progression and metastasis have been demonstrated [5]. Several studies have shown that the overexpression of *AURKA* is more relevant in early tumorigenesis [6,7], whereas others have emphasized its role in tumor progression [8].

Ongoing genetic studies on *AURKA* have revealed two functional *AURKA* SNPs, *rs2273535* and *rs1047972*, that can affect *AURKA* promoter activity [9,10] and promote tumor progression in multiple cancer types, including prostate cancer [9]. Heretofore, no follow-up epidemiologic studieshave been reported describing the potential association between these functional *AURKA* SNPs and clinical outcomes in prostate cancer. Additionally, to our knowledge, no *AURKA* SNPs have been reported in any prostate cancer genome wide association studies. Further studies are necessary given the prognostic utility of SNPs in predicting cancer risk and recurrence [11,12], based on the premise that these SNP studies will enhance the accuracy of existing prognostic nomograms that incorporate clinical variables such as clinical stage, Gleason score, and prostate-specific antigen (PSA) levels [13].

Interestingly, recent studies on apoptotic and cell cycle genes have revealed a pivotal role of introns in transcriptional regulation, suggesting the potential importance of intronic SNPs in studying cancer risk-stratification. In the study herein, we analyzed the four intronic *AURKA* SNPs to determine their prognostic outcome associations in clinically localized prostate cancer after radical prostatectomy.

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Methods

Study population and clinical data

Patient population consisted of 212 predominantly Caucasian prostate cancer patients status-post radical prostatectomy at Vanderbilt University Hospital between 1997 and 1999. Patient consent and approval by the Vanderbilt University Institutional Review Board preceded the collection of prostate tissues for research. Histologic confirmation of all prostate samples revealed adenocarcinoma. Clinical data on patient follow-up at Vanderbilt University Medical Center were retrospectively gathered via electronic medical records. The mean follow-up for disease-free survival and assessment of prostate cancer progression were 8.3 ± 2.4-y and 4.4 ± 3.9-y, respectively. The endpoints analyzed were recurrence-free survival (RFS) and disease-free survival (DFS). Recurrence post-prostatectomy was classified as biochemical (which has been shown to be a poor predictor of overall survival in patients with localized prostate cancer treated with radical prostatectomy) [14], local or distant, and the most advanced recurrence type documented was assigned to each patient. Biochemical recurrence was defined as a prostate-specific antigen (PSA) detection of > 0.1 ng/ml in at least two consecutive tests. DFS was defined as the length of time between the date of prostatectomy to the date of death or last follow-up.

Genotyping of Aurora Kinase A polymorphisms in prostate cancer samples

Prostatectomy specimens were processed and genomic DNA extracted from deparaffinizedspecimens as described previously [15]. Purified genomic DNA was genotyped for the following haplotype-tagging SNPs in the *AURKA* gene: *rs1468055*, *rs8117896*, *rs2064863*, and *rs1468056*. Haplotype-tagging SNPs (htSNPs) were selected using the ABI SNP Browser to cover SNPs with an r^2 of 0.90 or greater in the *AURKA* gene with a minor allele frequency (MAF) of at least 0.25. A total of 4 SNPs were selected and genotyped in our patient cohort. Allelic discrimination of these *AURKA* polymorphisms was performed using Taqman SNP genotyping assays (Applied Biosystems: C_31520284_10 [rs8117896], C_26713921_10 [rs2064863], and C_8947664_10 [rs1468056]). The final volume for each reaction was 5µl, consisting of 2.5µl TaqMan Universal PCR Master Mix (Applied Biosystems), 900 nM of each primer, 200 nM of each TaqMan probe, and 5ng genomic DNA. The PCR profile consisted of an initial denaturation step at 95°C for 10 min and 50 cycles with 95°C for 15 sec and 60°C for 1 min. The fluorescence level was measured with the ABI PRISM 7900HT sequence detector. Genotypes were determined utilizing ABI SDS software. Quality control samples were included in genotyping assays.

Statistical analysis

Statistical analyses were executed to detect associations between the four *AURKA* htSNPs and RFS/DFS. SNPs associated with survival outcomes were evaluated based on log-rank tests. DFS was defined as the length of time between the date of prostatectomy to the date of death or last follow-up, where death events were defined as patients who died of prostate cancer only. RFS was defined as the interval between the date of surgery and the date of recurrence or last follow-up. Data were censored for live (or recurrence-free) patients as of their last follow-up visits. Kaplan-Meier survival curves were calculated for the subgroups of potential risk factors and were compared using the log-rank test. For multivariable analysis, Cox proportional hazards model was applied to investigate the association between SNPs and RFS with adjusting for PSA, surgical margin, and grade. Descriptive statistics, including mean and standard deviation for continuous variables, as well as percentages and frequencies for categorical variables, were calculated (Table 1). All *P* values are based on two-sided tests, and differences were considered statistically significant when p value < 0.05. Analyses were performed using SAS system version 9.1 and R version 2.8.

Bioinformatics tools

Web-based databases used in the present study include NCBI Database of Single Nucleotide Polymorphisms (dbSNP) [Build 129, http://www.ncbi.nlm.nih.gov/SNP] and the International HapMap Project [16], for its allele frequency data in the CEU population (i.e., Utah residents with ancestry from Northern and Western Europe) and for its genome browser and Haploview software to measure the extent of linkage disequilibrium (LD) between SNPs and generate an LOD

Characteristic	Number (N=212)
Race, n(%)	
White	208 (98.11)
Black	4 (1.89)
Age at diagnosis, n(%), years	
Mean (SD)	61.2 (7.08)
<60	86 (40.57)
60-70	104 (49.06)
>70	22 (10.38)
Pre-prostatectomy PSA, n(%), ng/ml	
Mean (SD)	8.4 (6.21)
<4	22 (10.38)
4-10	113 (53.30)
>10	43 (20.28)
Missing	34 (16.04)
Gleason score, n(%)	
2-6	130 (61.32)
7	70 (33.02)
8-10	12 (5.66)
Surgical margin, n(%)	
Negative	133 (62.74)
Positive	78 (36.79)
Missing	1 (0.47)
Extracapsular extension, n(%)	
Negative	125 (58.96)
Positive	67 (31.60)
Missing	20 (9.43)
Disease classification[1], n(%)	
Clinically inapparent (T1)	8 (3.77)
Confined within prostate (T2)	134 (63.21)
Regional (T3)	5 (26.89)
Missing	13 (6.13)
Recurrence, n(%)	
No	168 (79.25)
Yes	44 (20.75)
Disease-free survival, n(%)	
No	5 (2.36)
Yes	207 (97.64)

Abbreviations: PSA: Prostate-specific Antigen

[1]Based on the American Joint Committee on Cancer classification.

Table 1: Patient Demographics.

score plot [http://www.hapmap.org]. The HapMap datasource used was HapMap Data Rel 23a/Phase II Mar 08, on NCBI B36 Assembly, dbSNPb126.

Results

Patient characteristics

Demographic, clinicopathologic, and outcomes information are summarized in Table 1. The mean age of study subjects at the time of prostate cancer diagnosis and definitive treatment with prostatectomy was 61.2 ± 7-y. After a median follow-up time of 9.1-y, 83% of the patients were alive. The median follow-up time for prostate cancer progression was 3.4-y. The recurrence rate was 21%, with the majority classified as biochemical and a lower incidence for local or distant recurrence (80%, 5% and 16% of recurrences, respectively). Based on the risk stratification scheme suggested by the National Comprehensive Cancer Network® guidelines [17], which incorporates Gleason grade, PSA levels and staging parameters to predict probability of biochemical failure after definitive local therapy, the majority of our patient population (64%) could be classified as having an intermediate risk for biochemical failure.

Lack of association between intronic *AURKA* SNPs and recurrence and survival outcomes in prostate cancer

Four intronic *AURKA* SNPs *rs1468055*, *rs8117896*, *rs2064863*, and *rs1468056* were genotyped to examine their association with prognostic outcomes in prostate cancer treated with radical prostatectomy (Table 2). For the majority of SNPs, allelic discrimination assays were informative for at least 86% of genomic DNA samples. The genotype frequency distribution for the SNPs in our study population closely matched the one previously reported in the HapMap database for the CEU population [16], adding confidence to the accuracy of our genotyping reaction.

A log-rank univariate analysis was performed to identify significant associations between RFS or DFS and known prognostic factors as well as *AURKA* genotypes, which is shown in Table 3. Prognostic factors analyzed, including pre-prostatectomy PSA levels ($p<0.001$), Gleason score ($p<0.001$), surgical margin ($p<0.001$), and AJCC tumor category ($p<0.001$) [17] showed statistically significant associations with RFS. In the present study, only Gleason score was significantly associated with differential probability of DFS ($p<0.001$). No statistically significant associations were found for the SNPs *rs1468055*, *rs8117896*, *rs2064863*, and *rs1468056* analyzed for either RFS (p=0.7213, p=0.5140, p=0.0714, p=0.4731, respectively) or DFS (p=0.3282, p=0.1909, p=0.4111, p=0.5014, respectively). The Kaplan-Meier method was used to estimate the probability distribution of RFS as a function of genotype for each SNP, and the log-rank test was used to determine the significance of RFS differences across the different genotypes (Figure 1). No statistically significant genotypes were demonstrated.

Additionally, a Cox proportional hazards model was used to identify associations between *AURKA* SNPS and RFS. Due to a limitation of only 5 events for DFS, a multivariable model could not be obtained for DFS. Hazards ratios for SNPs *rs1468055*, *rs8117896*, *rs2064863*, and *rs1468056* ranged from 0.489 to 1.004 and are shown in Table 4.

Discussion

Aurora Kinase A (*AURKA*) is a serine/threonine kinase that functions to ensure a proper G2-M transition in cell cycle. *AURKA* has been accepted as an oncogene [reviewed in 18], with its overexpression leading to centrosomal and chromosomal instability with subsequent accretion of invasive and malignant phenotypes in many human cancer types [1,2]. Some studies have associated *AURKA* overexpression with early prostate tumorigenesis due to a higher *AURKA* expression level in high-grade prostate intraepithelial neoplasia (PIN) than in advanced tumors [19]. In other studies, upregulation of *AURKA* has shown to promote prostate cancer metastasis [20]. At present, the mechanistic details on how *AURKA* overexpression contributes to cancer progression remains largely unknown.

Over the years, the list of biomarkers with potential prognostic implication in prostate cancer has grown [21]. With *AURKA* in particular, several single-nucleotide polymorphisms (SNPs) have been identified to contribute to adverse outcomes in cancer. One most studied functional *AURKA* SNP is *rs2273535* resulting in a T91A change at codon 31 and displaying an independent risk-enhancing effect in multiple tumors including colon, breast, prostate, skin, lung and esophagus [22]. Another functional *AURKA* SNP is *rs1047972* with

					Population Diversity						
dbSNP ID[1]	Chromosomal Position[2]	Location (relative to *AURKA*)[3]	Alleles[1]	Amino Acid Change	Genotype Frequency in Study Population				HapMap-CEU Genotype Frequency[1]		
					Patient No.[4]	Genotypes			Genotypes		
rs1468055	Chr20:54,399,308	Intron	*C/A*	N/A	194	*C/C* 0.585	*C/A* 0.250	*A/A* 0.080	*C/C* 0.567	*C/A* 0.367	*A/A* 0.067
rs1468056	Chr20:54,399,395	Intron	*C/G*	N/A	156	*C/C* 0.137	*C/G* 0.349	*G/G* 0.349	*C/C* 0.133	*C/G* 0.533	*G/G* 0.333
rs8117896	Chr20:54,389,471	Intron	*C/T*	N/A	146	*C/C* 0.330	*C/C* 0.198	*T/T* 0.160	*C/C* 0.417	*C/T* 0.433	*T/T* 0.150
rs2064863	Chr20:54,396,179	Intron	*A/C*	N/A	200	*A/A* 0.202	*A/C* 0.392	*C/C* 0.349	*A/A* 0.150	*A/C* 0.500	*C/C* 0.350

Abbreviations: *AURKA*: Aurora Kinase A; dbSNP: Database Single Nucleotide Polymorphism; chr: Chromosome; HapMap: International HapMap Project; CEU: Population Consisting of Utah Residents with Ancestry from Northern and Western Europe

[1]Data obtained from NCBI Database of Single Nucleotide Polymorphisms (dbSNP) Build ID: 129, http://www.ncbi.nlm.nih.gov/SNP/, accessed December 2008. Ancestral allele is written first.

[2]Based on alignment with the NCBI Build 36.1 human reference sequence using the BLAT software, http://genome.ucsc.edu/, accessed December 2008.

[3]Relative to annotated genomic sequence for human *AURKA*, chr20: 20q13.2-q13.3.

[4]Indicates number of patients (n=212) for which the genotyping sequence yielded informative results.

Table 2: *AURKA* SNP Frequencies among Prostate Cancer Patients.

Factor	Number of Patients[1](n=212)	3-Yrs Recurrence-Free		5-Yrs Disease-Free Survival	
		% (95% CI)	P Value[2]	% (95% CI)	P Value
Race			0.8354		0.7082
Black	4	NA[3]		NA[3]	
White	208	88 (83- 92)		98 (96- 100)	
Age at diagnosis (years)			0.8123		0.1935
60-70	104	85 (78- 92)		NA[3]	
<=60	86	89 (83- 96)		97 (93-100)	
>70	22	81 (65- 98)		NA[3]	
Pre-prostatectomy PSA (ng/ml)			0.0434		0.6713
4-10	113	88 (82- 94)		97 (93- 100)	
<4	22	NA[3]		NA[3]	
>10	43	84 (72- 95)		96 (87- 100)	
Gleason score			<0.001		<0.001
2-6	130	94 (89- 98)		NA[3]	
7	70	77 (67- 87)		98 (93- 100)	
8-10	12	67 (40- 93)		71 (43- 100)	
Surgical margin			<0.001		0.3690
Negative	133	95 (91- 98)		99 (96- 100)	
Positive	78	74 (64- 84)		95 (90- 100)	
Extracapsular extension			<0.001		0.2664
Negative	125	93 (88- 97)		99 (96- 100)	
Positive	67	76 (65- 86)		94 (88- 100)	
Disease Stage			<0.001		0.1248
Localized (T1)	8	71 (38-100)		NA[3]	
Localized (T2)	134	94 (90- 98)		99 (96- 100)	
Localized (T3)	57	71 (59- 83)		95 (89- 100)	
AURKA SNP *rs1468055*			0.7213		0.3282
A/A	17	76 (57- 100)		NA[3]	
A/C	53	84 (74- 94)		97 (91- 100)	
C/C	124	88 (83- 94)		98 (95- 100)	
AURKA SNP *rs8117896*			0.5140		0.1909
C/C	70	87 (79- 85)		96 (91- 100)	
C/T	42	82 (70- 94)		NA[3]	
T/T	34	88 (77- 99)		NA[3]	
AURKA SNP *rs2064863*			0.0714		0.4111
G/G	74	83 (75- 92)		97 (92- 100)	
G/T	83	89 (82- 96)		97 (92- 100)	
T/T	43	88 (78- 98)		NA[3]	
AURKA SNP *rs1468056*			0.4731		0.5014
C/C	29	73 (55- 90)		NA[3]	
C/G	53	89 (80- 97)		97 (92- 100)	
G/G	74	90 (83- 97)		NA[3]	

[1]Analysis were limited to patients for whom data were available.
[2]P values for each factor were calculated by the log-rank test.
[3]Unable to calculate because all recurrence or death events occurred before 3-y or 5-y, respectively.

Table 3: Effect of Patient Factors on Post-prostatectomy Outcomes, Univariate Analysis.

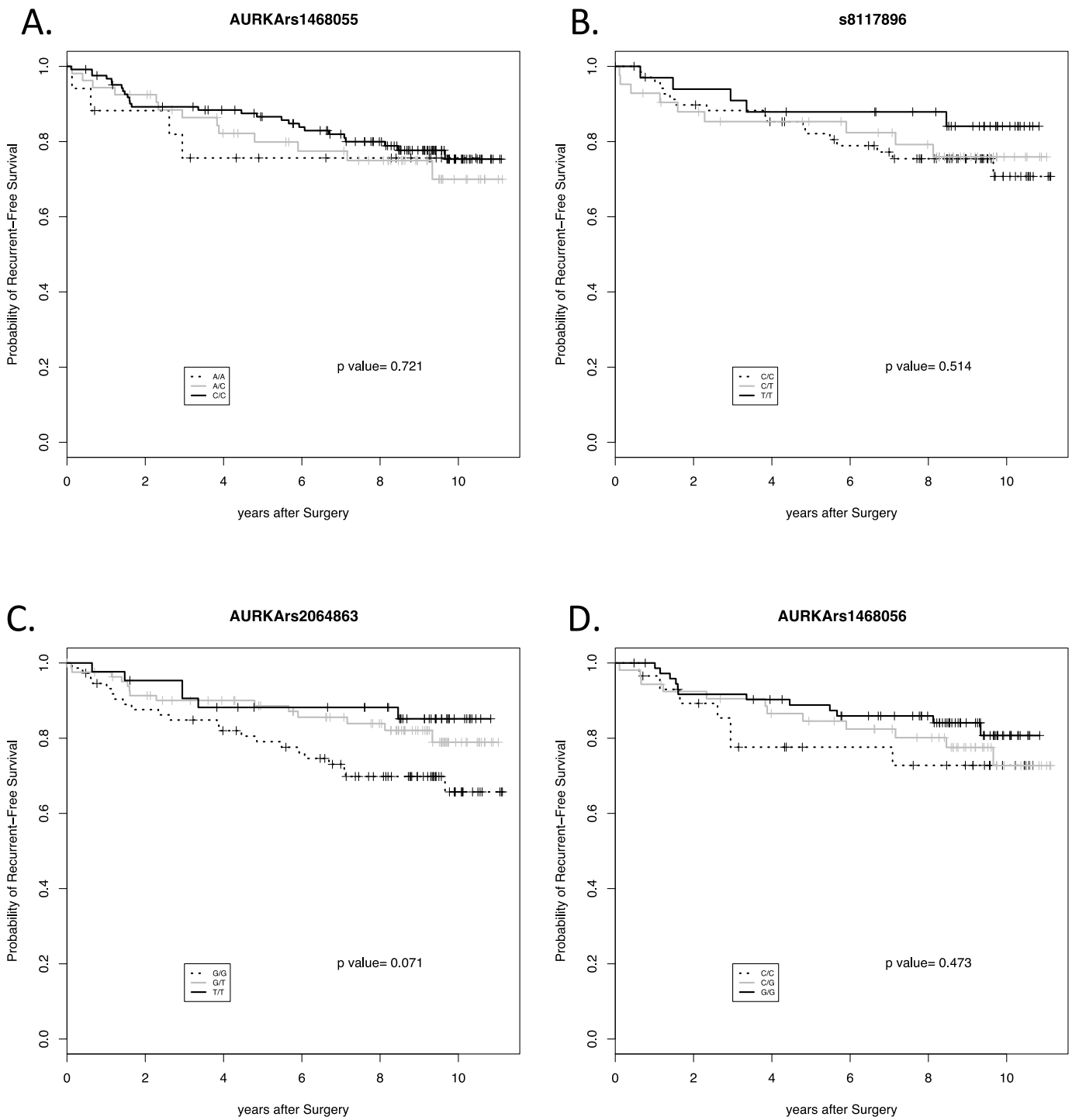

Figure 1: Kaplan-Meier estimates of recurrence-free survival following radical prostatectomy treatment for localized prostate cancer. Recurrence-free survival curves were plotted for the individual genotypes for each *AURKA* SNP: (A) SNP *rs1468055* (B) SNP *rs8117896* (C) SNP *rs2064863* (D) SNP *rs1468056*.

a *A169G* change shown to occur more frequently in advanced than in early gastric cancers [9]. The same study also noted that its effects on gastric cancer progression are related to the enhancement of relative kinase activities of *AURKA* variants. Such SNP studies will not only provide the starting point for unraveling the molecular mechanisms behind tumor aggression, but also equip us with accurate biomarkers for patient-tailored risk assessment and treatment.

This retrospective study demonstrated no evidence for intronic *AURKA* SNPs *rs1468055, rs8117896*, *rs2064863*, or *rs1468056* in predicting recurrence-free survival or disease-free survival in patients with prostate cancer. There are several limitations in our study. First, tumor registry data examining the causes of death yielded

	P Value[1]	Hazards Ratio (95% CI)[2]	
AURKA SNP *rs1468055*	0.7018	A/C	0.613 (0.189 – 1.991)
		C/C	0.657 (0.225 – 1.921)
AURKA SNP *rs8117896*	0.9786	C/T	1.004 (0.398 – 2.530)
		T/T	0.902 (0.319-2.551)
AURKA SNP *rs2064863*	0.1585	G/T	0.533 (0.253 – 1.212)
		T/T	0.489 (0.178 – 1.347)
AURKA SNP *rs1468056*	0.5365	C/G	0.681 (0.247 – 1.877)
		G/G	0.555 (0.197 – 1.564)

[1]P values were calculated by Chi-square anaylysis.
[2]Hazards ratio calculated by Cox proportional hazards model. CI = confidence interval.

Table 4: Recurrence-Free Survival, Multivariable Analysis.

only 5 confirmed prostate cancer deaths out of the 40 reported deaths in the reviewed patient population. This could especially have an impact on calculation of disease-free survival. In addition, 20 patients had unknown causes of death. A multivariate analysis of only the known deaths with independent prognosticators of prostate cancer did not achieve statistical significance (data not shown). Various confounders contributing to the death of prostate cancer patients need to be taken into account before any statement about the SNP significance on survival outcome is made. Secondly, the population size may have limited the power to detect existing associations between the SNPs studied and the prostate cancer outcomes, contributing to a possible false negative result. The study population was also primarily Caucasian (98%) which may limit the application of this genetic marker across different races. Future validation studies are warranted.

Despite these limitations, our study examined the potential clinical significance of intronic *AURKA* SNPs in prostate cancer outcome for the first time. Additional patient numbers and longer follow-up may allow detection of a statistical difference in RFS or DFS with *AURKA* SNP genotype in the event that our results yielded a false negative due to these limitations. In addition, future studies with a complete compilation of the causes of death will allow a more accurate assessment of the role of these SNPs in prostate cancer progression and outcome.

Conclusions

Our study examined the potential clinical significance of intronic *AURKA* SNPs in prostate cancer outcome for the first time. These findings have implications to the state of the field with the demonstration for the lack of association between intronic *AURKA* SNPs as biomarkers for predicting recurrence and survival outcomes in patients with prostate cancer.

Authors' Contributions

JJJ extracted the DNA, participated in the updating of the database, participated in the design of the study, and generated the list of haplotype-tagging SNPs. NLA assisted in interpretation of the data analysis and writing of the manuscript. MH assisted with stastistcal analysis and writing the intital draft of the paper. HC provided statistical analysis. KJN participated in the design of the study and its coordination and helped draft the manuscript. NJG assisted in the analysis of the data and preparation of the manuscript. RC and QC carried out the genotyping. BCT revised the manuscript. BL participated in study design, discussed analyses, interpretation, and presentation. All authors read and approved the final manuscript.

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