## Title

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*Original Article*

# Associations of immunity-related single nucleotide polymorphisms with overall survival among prostate cancer patients

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**Abstract:** The progression of prostate cancer is influenced by systemic inflammation, and may be attributed, in part, to genetic predisposition. Single nucleotide polymorphisms associated with the immune response may help mediate prostate cancer progression. We analyzed data from a hospital-based case-control study of 164 prostate cancer patients and 157 healthy male controls from the Memorial Sloan Kettering Cancer Center. We evaluated associations between six immunity-related polymorphisms (CRP rs1205 and rs1800947, FGFR2 rs1219648 and rs2981582, IFNGR1 rs11914, and IL10 rs1800871) and overall survival among prostate cancer patients, calculating adjusted hazard ratios (HR) and 95% confidence intervals (CI) using Cox proportional hazards regression. FGFR2 rs1219648 (GG vs. AA) and rs2981582 (TT vs. CC) polymorphisms were associated with more favorable overall survival (HR: 0.13, 95% CI: 0.03-0.62 and HR: 0.13, 95% CI: 0.03-0.53, respectively) in patients with primary prostate cancer. These observations highlight the need to validate and identify these and other immunity-related polymorphisms in larger studies examining survival of prostate cancer patients.

**Keywords:** Genetic predisposition, case-control, proportional hazards model, prostate cancer, immune response, polymorphisms

## Introduction

Prostate cancer is the most commonly diagnosed cancer in American men, and is the second leading cause of cancer death in the U.S. Inflammation may play a role in prostate carcinogenesis and progression, although the association is complex and not fully understood [1]. Pro-inflammatory signals are initiated by various environmental stimuli in combination with genetic factors. This is characterized by accumulation of leukocytes and production of a number of immune-related cytokines and enzymatic mediators, which may induce oxidative stress, and promote signaling leading to tumor growth and metastasis [2, 3].

Alterations in genes or proteins related to innate immunity have been observed in prostate cancer patients. Increases in gene expression or cytokine production of various members of the interleukin (IL) family such as IL-4, -6, -8 and -10, and C-reactive protein have been associated with malignant epithelium and metastasis [4, 5]. Alterations in expression of FGFR2, particularly through an isoform switch, may also correlate with prostate cancer progression [6].

Single nucleotide polymorphisms (SNPs) in immune response genes could potentially alter the susceptibility to or progression of cancer through modifications in the cancer-mediated inflammatory response, and related signaling events. Although SNPs in several inflammation-related genes such as cyclooxygenase-2 (COX-2), tumor necrosis factor-alpha (TNF-α) and various interleukins have been shown previously to be associated with increased prostate can-

**Table 1.** Demographic and clinical characteristics of prostate cancer cases in the MSKCC study

| | All, n[1] | Death, n (%) | Censored, n (%) | *P*-value[2] |
|---|---|---|---|---|
| Survival | 164 | 47 (29) | 117 (71) | |
| Age at diagnosis | | | | |
| mean, SD | | 63.0 ± 7.3 | 59.4 ± 6.0 | |
| < 65 | 103 | 24 (33) | 79 (77) | |
| > 65 | 51 | 23 (45) | 28 (55) | 0.004 |
| Ethnicity | | | | |
| Caucasian | 136 | 41 (30) | 95 (70) | |
| Other | 16 | 6 (27) | 10 (63) | 0.45 |
| Smoking | | | | |
| < 100 cigarettes | 56 | 18 (32) | 38 (68) | |
| > 100 cigarettes | 97 | 29 (30) | 68 (70) | 0.88 |
| Pack-years | | | | |
| mean, SD | | 26.8 ± 31.8 | 16.5 ± 19.2 | |
| < 20 | 96 | 26 (27) | 70 (73) | |
| 20-40 | 25 | 7 (28) | 18 (72) | |
| > 40 | 32 | 14 (44) | 18 (56) | 0.13 |
| BMI (Kg/m$^2$) | | | | |
| mean, SD | | 26.5 ± 4.3 | 27.4 ± 3.1 | |
| < 25 | 33 | 11 (33) | 22 (67) | |
| > 25 | 131 | 36 (27) | 95 (73) | 0.42 |
| Family history, No. (%) | | | | |
| Yes | 101 | 32 (32) | 69 (68) | |
| No | 51 | 15 (29) | 36 (71) | 0.83 |
| Education | | | | |
| mean, SD | | 15.8 ± 3.8 | 14.5 ± 3.6 | |
| < 12 | 56 | 16 (29) | 40 (71) | |
| 12-16 | 82 | 27 (33) | 55 (67) | |
| > 16 | 13 | 2 (15) | 11 (85) | 0.54 |
| Clinical stage | | | | |
| I | 19 | 15 (79) | 4 (21) | |
| II | 79 | 10 (13) | 69 (87) | |
| III | 41 | 12 (30) | 29 (70) | |
| IV | 13 | 4 (31) | 9 (69) | 0.0001 |
| Gleason grade | | | | |
| < 7 | 61 | 8 (13) | 53 (87) | |
| 7-10 | 22 | 10 (45) | 12 (55) | |
| Not graded[3] | 8 | 2 (25) | 6 (75) | 0.002 |

[1]All values may not sum to 164 due to missing data; [2]Calculated by performing log-rank test for homogeneity across strata; [3]Not graded because of prior hormone therapy.

cer risk [1-7], there have been very few reports of the association of immune-related SNPs with prostate cancer survival.

In light of the potential roles of genetic alterations in the immune-response pathway in chronic inflammation, we examined the association of these pro-inflammatory factors on prostate cancer survival in a hospital-based case-control study.

## Materials and methods

### *Study population*

The Memorial Sloan-Kettering Cancer Center (MSKCC) study was a hospital-based study conducted from May 1, 1994 to June 30, 1997. Details of the study design have been described previously [8]. The study was approved by and in accordance with the ethical standards of the Institutional Research Board on Human Subjects of both MSKCC and UCLA.

A total of 164 cases were identified as having newly diagnosed, pathologically confirmed prostate cancer. Eligibility of cases was confirmed by review of medical records and pathology reports. Controls consisted of 157 blood donors recruited from the MSKCC blood bank free of prostate cancer and in stable medical condition, who had resided in the US for at least one year. Data was collected on demographic characteristics, family history of prostate cancer, medical history, extensive dietary history, smoking and alcohol drinking, occupational and environmental exposures, and more. Eighty percent of prostate cancer cases provided blood for genotyping. DNA was extracted from tissues and blood samples using a modified phenol-chloroform method. Patients were followed for overall survival. The social security death index (SSDI) system was employed as a follow-up method for patient survival status and related dates. The SSDI is generated from the public Death Master File of the U.S. Social Security Administration and provides death records of qualified social security recipients. These records were last retrieved on May 12, 2013. Follow-up time was calculated as the date of diagnosis to death or May 12, 2013. Patients who were not shown in the SSDI were considered alive (right-censored) on May 12, 2013. Among 164 prostate cancer patients with avail-

**Table 2.** Cox proportional hazard model results for the association between immunity-related SNPs and survival among prostate cancer patients[1]

| *CRP* rs1205 | | | *CRP* rs1800947 | | | *FGFR2* rs1219648 | | |
|---|---|---|---|---|---|---|---|---|
| Genotype | Dead/All | HR (95% CI) | Genotype | Dead/All | HR (95% CI) | Genotype | Dead/All | HR (95% CI) |
| CC | 12/48 | 1 | GG | 29/104 | 1 | AA | 15/44 | 1 |
| CT | 15/57 | 1.69 (0.70-4.07) | GC | 1/13 | 0.32 (0.04-2.46) | GA | 11/56 | 0.52 (0.23-1.15) |
| TT | 1/12 | 0.49 (0.06-3.96) | CC | 0/2 | N/A | GG | 3/18 | 0.13 (0.03-0.62) |
| Additive | | 0.98 (0.51-1.87) | Additive | | 0.30 (0.04-2.16) | Additive | | 0.43 (0.23-0.78) |
| Recessive | | 0.36 (0.05-2.70) | Recessive | | N/A | Recessive | | 0.20 (0.05-0.86) |
| Dominant | | 1.45 (0.61-3.47) | Dominant | | 0.29 (0.04-2.22) | Dominant | | 0.40 (0.18-0.89) |
| *FGFR2* rs2981582 | | | *IFNGR1* rs11914 | | | *IL10* rs1800871 | | |
| Genotype | Dead/All | HR (95% CI) | Genotype | Dead/All | HR (95% CI) | Genotype | Dead/All | HR (95% CI) |
| CC | 15/42 | 1 | TT | 19/83 | 1 | CC | 15/66 | 1 |
| CT | 10/55 | 0.50 (0.22-1.14) | TG | 10/34 | 1.42 (0.59-3.40) | CT | 11/42 | 1.35 (0.58-3.16) |
| TT | 4/21 | 0.13 (0.03-0.53) | GG | 1/2 | 10.30 (1.13-93.45) | TT | 4/10 | 2.51 (0.64-9.85) |
| Additive | | 0.41 (0.23-0.73) | Additive | | 1.77 (0.81-3.85) | Additive | | 1.49 (0.81-2.76) |
| Recessive | | 0.18 (0.05-0.71) | Recessive | | 9.48 (1.06-84.72) | Recessive | | 2.19 (0.59-8.12) |
| Dominant | | 0.36 (0.16-0.80) | Dominant | | 1.59 (0.69-3.69) | Dominant | | 1.50 (0.67-3.35) |

[1]adjusted for race, age, pack-years of smoking, family history, body mass index, and stage.

able follow-up data, 47 (29%) passed away before the date of May 12, 2013. The median follow-up time was 18.8 years.

*Laboratory analysis*

In this study we selected immunity-related SNPs that had a minor allele frequency > 5% in Caucasian populations in the National Center for Biotechnology Information SNP database, were functional or potentially functional SNPs located in the coding, 3'-, and 5'-untranslated regions, and near gene regions. SNPs were genotyped using the ABI (Applied Biosystems, Foster City, CA) TaqMan assay. Briefly, PCR was performed using fluorescently labeled sequence-specific probes. The denaturation process was performed at 92°C for 10 minutes followed by an annealing and extension phase of 60 cycles at 92°C for 15 seconds, and 62°C for 80 seconds. The genotyping call rate was ≥ 95% and reproducibility (using a 5% random sample) was > 99%. SNPs that violated Hardy Weinberg equilibrium were excluded. The final group of SNPs used in this study included C-reactive protein (CRP) rs1205 and rs1800947, fibroblast growth factor receptor-2 (FGFR2) rs1219648 and rs2981582, interleukin-10 (IL-10) rs1800871, and interferon gamma receptor-1 (IFNGR1) rs11914.

*Statistical analyses*

All statistical analyses were performed using Statistical Analysis Software (SAS) version 9.3.

Descriptive statistics were performed for characteristics of interest, using the log-rank test for homogeneity over strata to calculate *P*-values for categorical variables. In survival analysis, survival time was defined as the difference in years between diagnosis and last follow-up (May 12, 2013) or death, whichever came first. Four models were used in SNP assessment, including genotype-specific, log-additive, dominant, and recessive genetic models. In the dominant model, the hazard associated with the variant allele, including homozygous recessive and heterozygous genotypes was compared to the homozygous dominant/ancestral genotype. In the recessive model, the hazard associated with presence of two variant alleles (homozygous recessive genotype) was compared to the homozygous dominant and heterozygous genotypes. The Cox proportional hazards model was used to generate adjusted hazards ratios (HRs) and 95% confidence intervals (CIs) to determine the effect of genotype on overall survival. In the regression analysis, covariates included race (white versus non-white), pack-years of smoking (continuous), age (continuous), body mass index (BMI-continuous), family history (categorical) and stage (categorical). BMI was included because of a reported association with prostate cancer risk and mortality [9]. Missing values for BMI or smoking pack-years (< 11%) were imputed where possible using the median value among cases. Stage was defined using TNM staging criteria: stage 1-locally confined, clinically undetectable; stage 2-locally confined, palpable; stage 3-locally advanced; stage 4-advanced, metastatic prostate cancer.

## Results

Demographic and clinical characteristics of prostate cancer cases from the MSKCC study population are presented in **Table 1**. Overall survival correlated with age, as significantly shorter survival was observed among cases over the age of 65 (P = 0.004). A notable difference in survival was noted according to pathological stage (P = 0.0001) and Gleason grade (P = 0.002). However, a considerably large number of patients over the age of 65 were diagnosed with stage I prostate cancer (not shown).

Cox proportional hazards estimates for the associations of immunity-related SNPs with overall survival were calculated for individuals diagnosed with prostate cancer (**Table 2**). The homozygous GG genotype of FGFR2 rs1219648 was associated with more favorable survival (HR: 0.13, 95% CI: 0.03-0.62), as compared to the AA genotype. A linear trend associated with the G allele in hazards ratios was observed (allelic HR: 0.43, 95% CI: 0.23-0.78). The homozygous FGFR2 rs2981582 TT genotype also correlated with better overall survival (HR: 0.13, 95% CI: 0.03-0.53), and a linear trend was again associated with the variant allele (HR: 0.41, 95% CI: 0.23-0.73). No other SNPs examined were associated with significant differences in survival among prostate cancer cases.

## Discussion

Systemic inflammation promotes castration-resistance and metastasis [10]. Therefore, the role of inflammation-related SNPs in prostate

cancer survival was analyzed. In the current study, FGFR2 rs2981582 and rs1219648, two SNPs in relatively high linkage disequilibrium, were associated with more favorable overall survival among prostate cancer cases.

FGFR2 is a receptor tyrosine kinase involved in regulation of cell growth, blood vessel formation, embryogenesis, and wound healing. Altered gene expression has potential consequences in tumor cell proliferation, migration, and angiogenesis. Alterations in FGFR2 mRNA have been reported in prostate cancer patients [11], although significant associations of rs2981582 and rs1219648 SNPs with prostate cancer remain to be identified. Interestingly, FGFR2 rs2981582 and rs1219648 variants are associated with increased breast cancer risk [12-14]. rs2981582, particularly, is associated with estrogen receptor positive, low-grade tumors [15, 16], consistent with what is observed in BRCA2 mutation carriers. Although not shown to alter alternative splicing of FGFR2 isoforms [17], it is possible that FGFR2 variants rs2981582 and rs1219648 alter hormone signaling to promote conditions that are less favorable for prostate cancer metastasis. To the best of our knowledge, this is the first report of the associations of rs2981582 and rs1219648 with prostate cancer survival. However, limitations due to sample size cannot be ignored, and additional studies examining these associations are warranted.

A better understanding of prostate cancer progression will require the discovery and analysis of pro-inflammatory biomarkers. Studies of sufficient sample size may allow for the utilization of SNPs and other potential environmental pro-inflammatory agents as prognostic indicators, and may prove useful in the prevention and control of aggressive prostate cancer.

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## Disclosure of conflict of interest

None.

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