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*Advances in Brief*

# Influence of Cytokine Gene Polymorphisms on the Development of Prostate Cancer[1]

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## Abstract

**Polymorphisms in the promoter regions of cytokine genes may influence prostate cancer (PC) development via regulation of the antitumor immune response and/or pathways of tumor angiogenesis. PC patients (247) and 263 controls were genotyped for interleukin (IL)-1β-511, IL-8-251, IL-10-1082, tumor necrosis factor-α-308, and vascular endothelial growth factor (VEGF)-1154 single nucleotide polymorphisms. Patient control comparisons revealed that IL-8 TT and VEGF AA genotypes were decreased in patients compared with controls [23.9 *versus* 32.3%; $P = 0.04$, odds ratio (OR) = 0.66, 95% confidence interval (CI) 0.44–0.99 and 6.3 *versus* 12.9%; $P = 0.01$, OR = 0.45, 95% CI 0.24–0.86, respectively], whereas the IL-10 AA genotype was significantly increased in patients compared with controls (31.6 *versus* 20.6%; $P = 0.01$, OR = 1.78, 95% CI 1.14–2.77). Stratification according to prognostic indicators showed association between IL-8 genotype and log prostate-specific antigen level ($P = 0.05$). These results suggest that single nucleotide polymorphisms associated with differential production of IL-8, IL-10, and VEGF are risk factors for PC, possibly acting via their influence on angiogenesis.**

## Introduction

In Western Europe and the United States, PC[4] is the most common cancer diagnosed in men and the second most common cause of death with a continuing increase in incidence (1). The evidence that PC has a genetic component is compelling from epidemiological and genetic studies; some high-risk genes have been identified, which when present, may predispose a carrier to development of the disease (2). Examples of PC susceptibility genes include *HPC1* on chromosome 1q24-25 (3), *HPCX* on Xq27-28 (4), *BRCA1* on 17q21 and *BRCA2* on 13q12 (5), CAPB at 1p36 (6), *PCAP* on 1q42.2-43 (7), and, most recently, *ELAC2/HPC2* on chromosome 17p (8). The association between these high penetrance genes and PC susceptibility highlights the complex and multigenic mode of inheritance of PC, yet more common, lower penetrance susceptibility polymorphisms in genes may be implicated in a higher portion of the sporadic PC disease burden and so have more relevance to public health. The prostate was originally thought to be an immunologically privileged site. However, there is now good evidence that the prostate has a lymphatic system and can mount inflammatory immune responses, and these responses, as evidenced by density of tumor-infiltrating lymphocytes, may be associated with prognosis in PC (reviewed in Ref. 9). The immune system may therefore play a role in the pathogenesis of PC, via regulation of tumor growth, whereas evasion of the immune response may play a role in disease progression. Cytokines (soluble chemical messengers) play a crucial role in regulating both humoral and cell-mediated immune responses. Promoter regions of a number of key pro and anti-inflammatory cytokine genes contain polymorphisms that directly influence cytokine production (10). These promoter polymorphisms may lead to either high- or low-level production of a given cytokine, causing interindividual differences in immune responsiveness, which may influence antitumor immune responses in PC. In addition, particular cytokines (*e.g.,* IL-8, IL-10, and VEGF) may also influence tumor development via their action on pathways of tumor angiogenesis. In this study, we aimed to determine whether polymorphisms associated with differential expression of IL-1β, IL-8, IL-10, TNF-α, and VEGF are associated with susceptibility to and prognosis in PC.

## Patients and Methods

**Subjects.** Stored DNA samples from 247 Caucasian PC patients collected from one clinic were available via the Institute of Cancer Research, Royal Marsden NHS Trust, London, United Kingdom. The mean age of these patients at presentation was 68.1 years (age range 48–80 years). The method of DNA extraction used has been described previously (11).

**Controls.** The control group used in this project comprised genomic DNA samples from 263 Caucasian, cancer-free bone marrow and solid organ donors, collected via Southampton General Hospital Histocompatibility and Immunogenetics Department. The mean age of these controls (139 males and 124 females) was 39.2 years (age range 3–69 years). The DNA extraction technique used has been described previously (12).

**Clinical Data.** A full 9-year (1993 to present day) clinical follow-up study, including family history, tumor grade (Gleason score), tumor stage classification (Tumor-Node-Metastasis), PSA level at diagnosis, and survival was available.

**Genotyping Methodology.** IL-1β-511 (CT), IL-8-251 (AT), IL-10−1082 (AG), TNF-α-308 (AG), and VEGF-1154 (AG) SNPs were genotyped by the amplification refractory mutation system-PCR technique using one reaction per allele of each SNP (13). All PCR reactions were performed in 10-μl reaction volumes, and final reagent concentrations were: AS reaction buffer (Abgene, Epsom, United Kingdom), 200 μM each deoxynucleotide triphosphate, 12% (w/v) sucrose, 200 μM cresol red, 1 μM each specific/common primer, 0.2 μM each internal control primer (see Table 1 for sequences), 0.25 units of Thermoprime$^{PLUS}$ DNA polymerase (Abgene), and 50–100 ng/μl DNA. $MgCl_2$ concentrations were optimized for each SNP (Table 1). PCR reactions were performed using a Tetrad DNA engine (MJ Research, Inc., Watertown, MA), a 9600 Thermal Cycler (PE Biosystems, Foster City, CA), or an MWG primus 96 plus Thermal Cycler (MWG Biotech United Kingdom, Ltd., Milton Keynes, United Kingdom), according to the following thermocycler conditions: 1 min at 96°C, 10 cycles of 96°C for 15 s, $T_a$ for each SNP for 50 s (Table 1), 72°C for 40 s, then 20 cycles of 96°C for 10 s, 60°C for 50 s,

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[4] The abbreviations used are: PC, prostate cancer; TNF, tumor necrosis factor; IL, interleukin; VEGF, vascular endothelial growth factor; PSA, prostate-specific antigen; CI, confidence interval; NHS, National Health Service; SNP, single nucleotide polymorphism.



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Table 1 *Cytokine SNP genotyping; primer sequences and PCR conditions*

| Primer name | Primer sequence 5′-3′ | PCR product size (bp) | Annealing temp. 10 initial cycles ($T_a$)[a] | $MgCl_2$ Conc. (mM)[b] |
|---|---|---|---|---|
| IL-1β-511 Common | AAT GGG TAC AAT GAA GGG CCA | | | |
| IL-1β-511 T (high expresser) | TGC AAT TGA CAG AGA GCT CCT | 103 | 65°C | 2.75 |
| IL-1β-511 C (low expresser) | TGC AAT TGA CAG AGA GCT CCC | | | |
| IL-8-251 Common | AAT ACG GAG TAT GAC GAA A | | | |
| IL-8-251 T (low expresser) | CTA GAA ATA AAA AAG CAT ACA T | 114 | 62.5°C | 1.75 |
| IL-8-251 A (high expresser) | CTA GAA ATA AAA AAG CAT ACA A | | | |
| IL-10-1082 Common | CTT GGA TTA AAT TGG CCT TAG A | | | |
| IL-10-1082 A (low expresser) | ACT ACT AAG GCT TCT TTG GGA A | 194 | 65°C | 4.8 |
| IL-10-1082 G (high expresser) | CTA CTA AGG CTT CTT TGG GAG | | | |
| TNF-α-308 Common | TCT CGG TTT CTT CTC CAT CG | | | |
| TNF-α-308 A (high expresser) | ATA GGT TTT GAG GGG CAT GA | 184 | 65°C | 1.65 |
| TNF-α-308 G (low expresser) | ATA GGT TTT GAG GGG CAT GG | | | |
| VEGF-1154 Common | CCC CGC TAC CAG CCG ACT T | | | |
| VEGF-1154 A (low expresser) | GCC CGA GCC GCG TGT GGA A | 130 | 61°C | 1.75 |
| VEGF-1154 G (high expresser) | GCC CGA GCC GCG TGT GGA G | | | |
| 63 CONTROL[c] | TGC CAA GTG GAG CAC CCA A | 796 | | |
| 64 CONTROL | GCA TCT TGC TCT GTG CAG AT | | | |
| HGH[d] CONTROL | GCC TTC CCA ACC ATT CCC TTA | 429 | | |
| HGH II CONTROL | TCA CGG ATT TCT GTT GTG TTT C | | | |

[a] $T_a$, annealing temperature for each individual SNP.
[b] Magnesium chloride concentration for each SNP in mM per reaction.
[c] Control primers: 63 and 64 primers (amplify HLA-DRB1 intron 3 sequence) for IL-8 or HGH I and II primers (amplify HGH sequence) for IL-1β, IL-10, TNF-α, and VEGF.
[d] HGH, human growth hormone.

and 72°C for 40 s. PCR products were loaded directly onto 2% agarose gels (containing 0.5% mg/ml ethidium bromide), electrophoresed, and visualized by photography under UV transillumination.

**Statistical Analysis.** The Hardy-Weinberg equation was used to determine whether the proportion of each genotype obtained was in agreement with expected values as calculated from allele frequencies. Patient control comparisons using $X^2$ (2 × 2 contingency tables) were made, and a $P < 0.05$ was considered significant. The odds ratio with 95% CIs was calculated where a genotype showed a significantly increased or decreased incidence within the PC patient series (Statistical Solutions, Inc.). Comparisons were made between genotype with stage, Tumor-Node-Metastasis grade, and log PSA level using $X^2$ linear regression and $n \times 3$ contingency tables. Survival and disease-free survival were calculated using a Cox proportional hazards analysis generated by Stata (College Station, TX) software, version 7.0. Hazard ratios were used to estimate disease-free survival and overall survival.

## Results and Discussion

In this preliminary study, a panel of five cytokine SNPs were studied, namely IL-1β-511, IL-8-251, IL-10-1082, TNF-α-308, and VEGF-1154. These SNPs were selected, because all have been reported to influence expression of their respective cytokine *in vitro* (10, 14, 15) and represent proinflammatory (IL-1β and TNF-α) and immunosuppressive (IL-10) cytokines and cytokines which influence the process of angiogenesis (IL-8, VEGF, and IL-10). All samples were genotyped for each SNP according to DNA availability (ranging from 238 to 247 PC cases and from 220 to 263 controls genotyped, depending on SNP). Patient and control genotype distributions fitted Hardy-Weinberg equilibrium at the $P = 0.05$ level. The case control results show that the three SNPs, IL-8-251, IL-10-1082, and VEGF-1154, all with angiogenic properties, were significantly associated with PC susceptibility (Table 2). VEGF is a potent stimulator of angiogenesis, necessary for successful microvasculature development and important for metastasis, survival, and spread of the tumor. Patients (238) and 263 controls were completely genotyped in this study, and the results showed that VEGF (-1154) AA genotype (low producer of VEGF; Ref. 15) was significantly decreased in the patient group when compared with controls (6.3 *versus* 12.9%; $P = 0.01$). This result is in agreement with publications that state that many PC patients have been shown to produce VEGF at higher concentrations than in normal prostate tissue (16). Accordingly, VEGF low producers genotypes may confer protection for PC, whereas high producers may have a promoting effect on PC progression and successful survival of the tumor.

Table 2 *Cytokine genotype case control comparisons*

| Genotype | | PC cases n (%) | Controls n (%) | P | OR[a] (95% CI) |
|---|---|---|---|---|---|
| IL-1β-511 | CC | 105 (43.2) | 87 (33.3) | ns[b] | |
| | CT | 110 (45.3) | 135 (51.7) | ns | |
| | TT | 28 (11.5) | 39 (13.5) | ns | |
| IL-8-251 | AA | 59 (24.8) | 54 (23) | ns | |
| | AT | 122 (51.3) | 105 (44.7) | ns | |
| | TT | 57 (23.9) | 76 (32.3) | 0.04 | 0.66 (0.44–0.99) |
| IL-10-1082 | GG | 56 (22.7) | 57 (25.6) | ns | |
| | AG | 113 (45.7) | 120 (53.8) | ns | |
| | AA | 78 (31.6) | 46 (20.6) | 0.01 | 1.78 (1.14–2.77) |
| TNFα-308 | GG | 167 (69.9) | 150 (68.2) | ns | |
| | AG | 66 (27.6) | 57 (25.9) | ns | |
| | AA | 6 (2.5) | 13 (5.9) | ns | |
| VEGF-1154 | GG | 114 (47.9) | 120 (45.6) | ns | |
| | AG | 109 (45.8) | 109 (41.4) | ns | |
| | AA | 15 (6.3) | 34 (12.9) | 0.01 | 0.45 (0.24–0.86) |

[a] OR, odds ratio.
[b] ns, not significant.

Table 3 *Log PSA level at diagnosis using multinomial regression and tumor stage and grade using linear $X^{-2}$*

| Cytokine | Log PSA $X^{-2}$ (2df)[a] | P > $X^{-2}$ | Grade $X^{-2}$ (2df) | P | Stage $X^{-2}$ (2df) | P |
|---|---|---|---|---|---|---|
| IL-1β | 2.38 | 0.31 | 0.06 | 0.99–0.95 | 3.69 | 0.2–0.1 |
| IL-8 | 5.95 | 0.05[b] | 1.58 | 0.50–0.2 | 1.71 | 0.5–0.2 |
| IL-10 | 3.32 | 0.18 | 0.17 | 0.95–0.5 | 1.65 | 0.5–0.2 |
| TNF-α | 0.41 | 0.81 | 0.67 | 0.95–0.5 | 0.71 | 0.95–0.5 |
| VEGF | 1.60 | 0.45 | 1.82 | 0.5–0.2 | 0.40 | 0.95–0.5 |

[a] 2df, two degrees of freedom.
[b] Borderline significance in the data.

IL-10 (-1082) AA genotype (low producer of IL-10; Ref. 17) was significantly increased in the patient group when compared with controls. Patients (247) and 223 controls were completely genotyped, and the results showed that the AA genotype was increased significantly in frequency in the patient group compared with the controls (31.6 *versus* 20.6%; $P = 0.01$). This result is in agreement with a recent publication from this laboratory that showed IL-10 low expression genotype was increased significantly among patients with cutaneous malignant melanoma compared with controls (18). Therefore, IL-10 genotype may influence predisposition to a number of solid tumors. The mechanism for this may be via the ability of IL-10 to down-regulate synthesis of VEGF (19). IL-10 has also been shown to inhibit angiogenesis of immortalized human PC cell lines *in vitro* (20). An alternative explanation for the action of IL-10 is via down-



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Table 4 *Disease-free (relapse-free) and overall survival analysis*

| Cytokine genotype | | Disease-free survival (95% CI) hazard ratio | Disease-free *P* | Relapse-free survival (95% CI) hazard ratio | Relapse-free *P* |
|---|---|---|---|---|---|
| IL-1$\beta$ | TT[a] | | | | |
| IL-1$\beta$ | CT | 0.88 (0.39–1.97) | 0.75 | 0.76 (0.29–1.99) | 0.58 |
| IL-1$\beta$ | CC | 0.77 (0.33–1.76) | 0.53 | 0.93 (0.36–2.43) | 0.88 |
| IL-8 | TT[a] | | | | |
| IL-8 | AT | 1.58 (0.84–2.99) | 0.16 | 0.81 (0.43–1.53) | 0.51 |
| IL-8 | AA | 1.26 (0.59–2.67) | 0.55 | 1.13 (0.55–2.30) | 0.74 |
| IL-10 | AA[a] | | | | |
| IL-10 | AG | 1.31 (0.78–2.22) | 0.31 | 1.59 (0.89–2.81) | 0.11 |
| IL-10 | GG | 1.44 (0.78–2.66) | 0.24 | 1.09 (0.52–2.30) | 0.81 |
| TNF-$\alpha$ | AA[a] | | | | |
| TNF-$\alpha$ | AG | 1.34 (0.18–10.04) | 0.77 | 1.15 (0.15–8.63) | 0.90 |
| TNF-$\alpha$ | GG | 1.51 (0.21–10.98) | 0.68 | 1.12 (0.15–8.15) | 0.91 |
| VEGF | AA[a] | | | | |
| VEGF | AG | 0.71 (0.28–1.82) | 0.48 | 2.90 (0.40–21.34) | 0.29 |
| VEGF | GG | 0.49 (0.19–1.26) | 0.14 | 2.62 (0.36–19.35) | 0.34 |

[a] Genotype taken as a hazard ratio of unity, and all data for the other genotypes were calculated against this.

regulation of class I expression, causing enhanced natural killer cell lysis of tumor cells and resulting in control of tumor metastasis (21).

Conversely, other studies have suggested that high IL-10 levels are tumor promoting and that elevated serum IL-10 levels have been observed in patients with various solid tumors (22). These imply that IL-10 may influence tumor escape from the immune response based on its immunosuppressive functions, through suppression of Th1 type cytokine production, especially IL-2. However, the present immunogenetic study does not support an immunosuppressive role of IL-10 in tumor development in PC.

The IL-8 (-251) TT genotype (low producer of IL-8; Ref. 14) was decreased significantly in PC patients when compared with controls. Patients (238) and 235 controls were fully genotyped, and the results showed that the TT genotype, associated with low IL-8 production, was decreased significantly among the PC patients (23.9 *versus* 32.3%) compared with controls ($P = 0.04$). IL-8 has a known function in the regulation of angiogenesis and tumor growth in PC. A recent report showed that neutralizing antibodies to IL-8 inhibited angiogenic activity in a human PC cell line/murine model and reduced tumorigenicity *in vivo,* implicating IL-8 as an important modulator of PC growth (23). In support of this, results from this study suggest that genetically determined low levels of IL-8 product may be protective in PC. IL-1$\beta$-511 and TNF-$\alpha$-308 genotypes showed no significant associations with PC in this case control study (Table 2), suggesting that these genotypes may not play a role in PC susceptibility and progression.

The cytokine SNP genotypes were compared within the PC patient series and stratified according to the three key prognostic indicators (Table 3) and overall and disease-free survival (Table 4) to determine whether cytokine genotypes influence prognosis in PC. The data in Table 3 show a significant correlation and also a possible influence of IL-8 (AA, high producer) genotype on increased log PSA level measured before removal of tumor ($P = 0.05$). No significant associations between cytokine genotype and tumor stage, grade, disease-free survival, or overall survival were seen, although a number of nonsignificant trends were observed (Tables 3 and 4). These results suggest that a more definitive investigation is required in a larger subject group.

In summary, this preliminary investigation has demonstrated a number of novel findings, most notably, that three of the five cytokine SNPs genotyped showed significant associations in the patient control comparisons. Association was also observed between IL-8 genotype and level of log PSA at presentation. Survival and disease-free survival showed no significant results, but trends were observed with some of the other cytokine SNPs. This may be attributable to the low resolving powers of the survival data because the number of events (deaths) was small, and patient numbers were further decreased by subdivision into genotype.

In conclusion, the most significant findings from this exploratory study (the first study of cytokine SNPs in PC) indicate that although the influence of cytokine SNPs on PC is likely to be complex, and influences on antitumor immune responses cannot be ruled out by this study, cytokine genotypes associated with the angiogenic pathway (IL-10, VEGF, and IL-8) may have a significant effect on disease development. A definitive study of SNPs influencing this pathway is indicated by these preliminary results to confirm their association with PC susceptibility and investigate possible associations with prognosis.

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## Influence of Cytokine Gene Polymorphisms on the Development of Prostate Cancer

Sarah L. McCarron, Stephen Edwards, Philip R. Evans, et al.

*Cancer Res* 2002;62:3369-3372.

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