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COMMENTARY

Are Toll-like receptor gene polymorphisms associated with prostate cancer?

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Abstract: The suggestion that there is a connection between chronic intraprostatic inflammation and prostate cancer was declared some years ago. As Toll-like receptors (TLRs) are the key players in the processes of chronic intraprostatic inflammation, there is a hypothesis that *TLR* gene polymorphisms may be associated with prostate cancer risk. Although a number of comprehensive studies have been conducted on large samples in various countries, reliable connections between these single nucleotide polymorphisms and prostate cancer risk, stage, grade, aggressiveness, ability to metastasize, and mortality have not been detected. Results have also varied slightly in different populations. The data obtained regarding the absence of connection between the polymorphisms of the genes encoding interleukin-1 receptor-associated kinases (IRAK1 and IRAK4) and prostate cancer risk might indicate a lack of association between inherited variation in the TLR signaling pathway and prostate cancer risk. It is possible to consider that polymorphisms of genes encoding TLRs and proteins of the TLR pathway also do not play a major role in the etiology and pathogenesis of prostate cancer. Feasibly, it would be better to focus research on associations between *TLR* single nucleotide polymorphisms and cancer risk in other infection-related cancer types.

Keywords: TLRs, single nucleotide polymorphisms, genetic variation, inflammation, innate immunity

Discussion

The results of a number of studies investigating the connections between sexually transmitted infections and prostatitis, between prostatitis and prostate cancer, and between genetic and circulating markers of inflammation and response to infection all support the hypothesis that there is a connection between chronic intraprostatic inflammation and prostate cancer.[1] The list of causes of such inflammation includes exposure to various infectious agents, autoimmune disorders, damage from mechanical injuries, and chemical carcinogens (as exogenous as endogenous, for instance, certain hormones).[1]

Toll-like receptors (TLRs) constitute a family of receptors that recognize pathogen-associated and damage-associated molecular patterns, consequently playing a key role in innate and adaptive immune response, initiating the aforementioned inflammation. It has been suggested that *TLR* gene polymorphisms may affect TLR signaling, and, as a consequence, may influence TLR-mediated immune response, modulating prostate cancer risk.[2]

Since 2004, when Zheng et al[2] published the first paper devoted to the investigation of the role of *TLR* single nucleotide polymorphisms (SNPs) in cancer etiology, a

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number of other studies on this subject have been carried out. Nevertheless, results are rather discouraging: although Zheng et al[2] found the rs11536889 polymorphism is associated with increased prostate cancer risk and Chen et al[3] observed that the G allele of the rs2770150 polymorphism may be a high-risk one, Lindström et al's[7] recent meta-analysis combining the results of Zheng et al[2] and Chen et al[3] with three more large comprehensive studies[4–6] did not reveal any correlation between *TLR* gene polymorphisms and prostate cancer risk. In addition, no high-risk alleles were detected in a large study by Stevens et al,[8] not included in Lindström et al's[7] pooled analysis. The results of all four large studies[4–6,8] devoted to the association of polymorphisms of the *TLR6-1-10* gene cluster with cancer risk suggest there is no correlation and that these SNPs cannot be considered promising for the further analysis of their association with prostate cancer risk. Balistreri et al[9] obtained similar null results for *TLR2* and *TLR4* SNPs. Positive results were found only for *TLR4* gene polymorphisms by Cheng et al[10] (rs10759932, odds ratio [OR] = 4.62, 95% confidence interval [CI]: 1.55–13.78 for variant homozygous genotype), Song et al[11] (rs1927911, OR = 2.73, 95% CI: 1.54–4.87 for heterozygous genotype; OR = 6.68, 95% CI: 3.27–13.66 for variant homozygous genotype; rs11536858, OR = 2.3, 95% CI: 1.07–4.93 for heterozygous genotype), Wang et al[12] (rs10116253, OR = 3.05, 95% CI: 1.11–8.41 for variant homozygous genotype), and Kim et al[13] (rs11536889, OR = 1.81, 95% CI: 1.29–2.53 for heterozygous genotype). However, these SNPs were not detected as risk factors in Lindström et al's[7] meta-analysis and therefore it is not possible to consider them as definite risk factors overall. Additionally, Shui et al,[14] who carried out the most recent large investigation on this subject, did not detect any association between *TLR4* gene polymorphisms and prostate cancer risk. The results of all studies mentioned are summarized in Tables 1 and 2.

All of those who have investigated the association between *TLR* gene polymorphisms and features of prostate cancer pathogenesis (stage, aggressiveness, Gleason grade, metastases), as well as the association between *TLR* gene polymorphisms and prostate cancer mortality, obtained negative results. This suggests there is no connection between *TLR* gene polymorphisms and the pathogenetic peculiarities of prostate cancer.[2–4,6,7,11,13,14]

The active investigation of a correlation between *TLR* SNPs and prostate cancer is intriguing. Despite there being some fundamental mechanisms that indicate *TLR* gene polymorphisms may play a role in prostate cancer etiology, and despite there being a number of comprehensive studies conducted

Table 1 Association of *TLR2* and *TLR4* gene polymorphisms with prostate cancer risk

Reference	SNP	Sample size	OR (95% CI)*
TLR2			
Balistreri et al[9] (Italian population)	rs5743708 2029C/T	50 cases, 125 controls, 55 male centenarians	NA NA (with age-matched controls)
TLR4			
Zheng et al[2] (Swedish population)	rs11536889	1383 cases, 780 controls	Carriers of C allele: 1.26 (1.01–1.57) [Before 65 years: 1.39 (1.02–1.91)]
	rs5030721		NA
	rs4986790		NA
	rs2149356		NA
Chen et al[3] (US population)	rs2770150	700 cases, 700 controls	Carriers of one G allele: 1.38 (1.10–1.73)
	rs11536858		NA
	rs6478317		Carriers of GG genotype: 0.66 (0.46–0.94)
	rs10116253		Carriers of CC genotype: 0.59 (0.39–0.90)
	rs1927914		Carriers of GG genotype: 0.64 (0.45–0.93)
	rs10759932		Carriers of one C allele: 0.73 (0.57–0.93)
	rs1927911		Carriers of AA genotype: 0.63 (0.41–0.95)
	rs11536878		NA
	rs5030717		Carriers of one G allele: 0.66 (0.51–0.86)
	rs2149356		Carriers of TT genotype: 0.64 (0.45–0.91)
	rs4986790		NA
	rs11536889		NA
	rs7873784		Carriers of CC genotype: 0.51 (0.28–0.96)
	rs11536891		Carriers of CC genotype: 0.50 (0.27–0.95)
	rs11536897		NA
	rs1536898		Carriers of AA genotype: 0.38 (0.16–0.92)
Cheng et al[10] (US population)	rs10759932	506 cases, 506 controls	Carriers of CC genotype: 4.62 (1.55–13.78)
	rs2149356		NA

(*Continued*)

Table 1 (*Continued*)

Reference	SNP	Sample size	OR (95% CI)*
	rs5030728		Carriers of AA genotype: 0.91 (0.70–1.19)
	rs4986790		NA
	rs11536889		NA
	rs7873784		NA
Yeager et al[5] (European population)	rs1928298	1172 cases, 1157 controls	NA
	rs1360094		NA
	rs4837496		NA
	rs10818070		NA
	rs10759930		NA
	rs2737191		NA
	rs2770150		NA
	rs6478317		NA
	rs10116253		NA
	rs1927914		NA
	rs10759932		NA
	rs1927911		NA
	rs11536879		NA
	rs5030717		NA
	rs2149356		NA
	rs4986790		NA
	rs7873784		NA
	rs11536897		NA
	rs1927906		NA
	rs11536898		NA
	rs1554973		NA
	rs913930		NA
	rs1927905		NA
	rs7045953		NA
Song et al[11] (Korean population)	rs1927911	157 cases, 143 controls	Carriers of TC genotype: 2.73 (1.54–4.87) Carriers of CC genotype: 6.68 (3.27–13.66)
	rs11536858		Carriers of GG genotype: 2.3 (1.07–4.93)
	rs1927914		NA
	rs11536891		NA
	rs11536897		NA
Wang et al[12] (US population)	rs4986790	258 cases, 258 controls	Carriers of G allele: 0.60 (0.33–1.08) [Men younger than 65 years: 0.26 (0.08–0.87)]
	rs11536889		Carriers of C allele: 0.50 (0.28–0.89) (patients with normal cholesterol) 1.65 (0.98–2.78) (patients with elevated cholesterol)

(*Continued*)

Table 1 (*Continued*)

Reference	SNP	Sample size	OR (95% CI)*
	rs10116253		Carriers of CC genotype: 3.05 (1.11–8.41)
	rs1927911		NA
	rs1927914		NA
	rs2149356		NA
	rs7873784		NA
	rs11536891		NA
	rs11536898		NA
	rs2737190		NA
Balistreri et al[9] (Italian population)	rs4986790	50 cases, 125 age-matched controls, 55 centenarian controls	NA
	rs4986791		NA (with age-matched controls)
Lindström et al[7] (meta-analysis of Zheng et al,[2] Chen et al,[3] and Yeager et al[5])	rs1928298	Pooled analysis: 3101 cases, 2253 controls	NA
	rs1360094		NA
	rs4837496		NA
	rs10818070		NA
	rs10759930		NA
	rs2737191		NA
	rs2770150		NA
	rs11536858		NA
	rs6478317		NA
	rs10116253		NA
	rs1927914		NA
	rs10759932		NA
	rs1927911		NA
	rs10759933		NA
	rs11536871		NA
	rs11536879		NA
	rs5030317		NA
	rs2149356		NA
	rs4986790		NA
	rs5030721		NA
	rs11536889		NA
	rs7873784		NA
	rs11536891		NA
	rs11536897		NA
	rs1927906		NA
	rs11536898		NA
	rs1554973		NA
	rs913930		NA
	rs1927905		NA
	rs7045953		NA
Kim et al[13] (Korean population)	rs10983755	240 cases, 223 controls	NA
	rs10759932		NA

(*Continued*)

Table 1 (*Continued*)

Reference	SNP	Sample size	OR (95% CI)*
	rs1927911		NA
	rs11536879		NA
	rs12377632		NA
	rs5030717		NA
	rs2149356		NA
	rs5030718		NA
	rs7869402		NA
	rs11536889		1.81 (1.29–2.53) (for heterozygous genotype)
	rs7873784		NA
Shui et al[14] (US population)	Ten *TLR4* gene polymorphisms	1286 cases, 1267 controls	NA
			NA
			NA
			NA
			NA
			NA
			NA
			NA
			NA
			NA

Note: *Only positive or negative statistically significant results.
Abbreviations: CI, confidence interval; NA, no association; OR, odds ratio; SNP, single nucleotide polymorphism; TLR, Toll-like receptor; US, United States.

on large samples in various countries, reliable connections between these SNPs and prostate cancer risk or features of prostate cancer progression have not been detected. Results have also varied slightly in different populations. However, it is possible that some of the *TLR* gene polymorphisms may be the markers of prostate cancer risk in certain populations (eg, rs5743795, rs5743551, rs5743556, rs5743604, rs4274855, rs11096957, rs11096955, and rs4129009 in the Swedish population;[4] rs11536889 in the Swedish and the Korean populations;[2,13] rs2770150, s10759932, and rs10116253 in the US population;[3,10,12] rs1927911 and rs11536858 in the Korean population[11]). However, Lindström et al's[7] meta-analysis, in which all of the populations mentioned above were considered, revealed that *TLR* gene polymorphisms cannot be the markers of prostate cancer overall and therefore they should be considered as risk markers, even in populations where the association has been found.[7] Apparently, the lack of sample size was not the reason for negative results in either the general meta-analysis or in specific studies in particular populations, because the investigations in Swedish,[2,4,15] European,[5] and US populations[3,6,8,10,12] included a large number of case and control subjects. Although two Korean studies[11,13] had relatively small sample sizes, a recent large study in the Korean population also

Table 2 Association of polymorphisms of *TLR6-1-10* gene cluster with prostate cancer risk

Reference	SNP	Sample size	OR (95% CI)*
Stevens et al[8] (US population)	TLR10: rs4129009 (MAF 18%–18.5%)	1414 cases, 1414 controls	NA
	rs11466657 (MAF 3.09%–3.38%)		NA
	rs11466655 (MAF 0.72%–0.76%)		NA
	rs11096955 (MAF 32.6%–35.8%)		A/C compared with A/A: 0.84 (0.72–0.98)
			C/C compared with A/A: 0.78 (0.61–0.99)
	rs11096956 (MAF 21.1%–23.5%)		NA
	rs11466653 (MAF 2.94%–3.93%)		NA
	rs11466651 (MAF 3.14%–3.74%)		NA
	rs11096957 (MAF 32.6%–35.8%)		A/C compared with A/A: 0.84 (0.72–0.98)
			C/C compared with A/A: 0.78 (0.61–0.99)
	rs11466649 (MAF 3.3%–3.84%)		NA
	rs10856838 (MAF 14.7%–16.4%)		NA
	rs4274855 (MAF 18%–18.5%)		NA
	rs11466640 (MAF 18.1%–18.6%)		NA
	rs11466617 (MAF 18%–18.6%)		NA
	rs7653908 (MAF 21.1%–20.6%)		NA
	rs7658893 (MAF 23.6%–25.2%)		NA
	TLR1: rs4624663 (MAF 2.46%–2.18%)		NA
	rs4833095 (MAF 23.4%–26.8%)		T/C compared with T/T: 0.90 (0.77–1.05)
			C/C compared with TT/T: 0.64 (0.47–0.86)
	rs5743611 (MAF 8.6%–8.8%)		NA
	rs5743604 (MAF 23.9%–24.2%)		NA
	rs5743596 (MAF 14.9%–18.5%)		C/T compared with C/C: 0.79 (0.66–0.93)

(*Continued*)

Table 2 (*Continued*)

Reference	SNP	Sample size	OR (95% CI)*
			T/T compared with C/C: 0.59 (0.38–0.91)
	rs5743595 (MAF 17.4%–20.6%)		T/C compared with T/T: 0.82 (0.70–0.97)
			C/C compared with T/T: 0.63 (0.42–0.93)
	rs5743594 (MAF 19.8%–17.7%)		NA
	rs5743556 (MAF 19%–19.6%)		NA
	rs5743551 (MAF 23.7%–26.7%)		A/G compared with A/A: 0.90 (0.77–1.06)
			G/G compared with A/A: 0.67 (0.50–0.91)
	TLR6: rs5743815 (MAF 1.91%–1.27%)		NA
	rs5743810 (MAF 42.1%–42.7%)		NA
	rs5743806 (MAF 30.3%–30.6%)		NA
	rs5743795 (MAF 19.9%–20.2%)		NA
Chen et al[6] (US population)	rs5743788 (MAF 50%–49%)	659 cases, 656 controls	NA
	rs5743795 (MAF 19%–21%)		NA
	rs5743806 (MAF 31%–30%)		NA
	rs1039599 (MAF 46%–46%)		NA
	rs5743810 (MAF 42%–41%)		NA
	rs3821985 (MAF 34%–33%)		NA
	rs5743815 (MAF 1%–2%)		NA
	rs5743551 (MAF 24%–26%)		NA
	rs5743556 (MAF 18%–19%)		NA
	rs5743604 (MAF 23%–26%)		NA
	rs5743611 (MAF 8%–9%)		NA
	rs4624663 (MAF 4%–4%)		NA
	rs11466617 (MAF 17%–18%)		NA
	rs11466640 (MAF 17%–19%)		NA
	rs4274855 (MAF 18%–19%)		NA
	rs11096957 (MAF 33%–36%)		NA
	rs11096955 (MAF 33%–36%)		NA
	rs11466657 MAF (4%–4%)		NA
	rs4129009 (MAF 17%–18%)		NA
Yeager et al[5] (European population)	rs10008492	1172 cases, 1157 controls	NA
	rs4331786		NA
	rs11466657		NA
	rs11096957		NA
	rs10856839		NA
	rs11466640		NA
	rs11466619		NA
	rs11466612		NA
	rs7663239		NA
	rs4543123		NA
	rs4833095		NA
	rs5743594		NA
	rs5743563		NA
	rs4833103		NA
	rs7696175		NA
	rs5743810		NA
	rs1039559		NA
	rs6833914		NA
	rs6531673		NA
Sun et al[4] (Swedish population)	TLR6: 2113 C/G (73.76%–76.35% C/G and G/G)	1383 cases, 780 controls	NA
	rs5743795 (32.8%–26.24% A/G and AA)		A/G and A/A compared with G/G: 1.38 (1.12–1.70)
	rs5743806 (89.12%–89.33% C/T and T/T)		C/T and T/T compared with C/C: 0.98 (0.73–1.31)
	rs5743810 (82.84%–82.84% C/T and C/C)		NA
	rs5743815 (3.44%–2.9% C/T and C/C)		NA
	TLR1: rs5743551 (40.16%–34.32% A/G and G/G)		A/G and G/G compared with A/A: 1.29 (1.06–1.56)
	rs5743556 (32.67%–26.65% C/T and C/C)		C/T and C/C compared with T/T: 1.33 (1.09–1.62)

(*Continued*)

Table 2 (*Continued*)

Reference	SNP	Sample size	OR (95% CI)*
	rs5743604 (42.1%–35.69% C/T and C/C)		C/T and C/C compared with T/T: 1.30 (1.08–1.60)
	rs5743611 (98.35%–98.21% G/C and G/G)		NA
	rs4624663 (7.79%–7.16% G/A and G/G)		NA
	TLR10: 3260C/T (29.79%–26.06% T/C and C/C)		T/C and C/C compared with T/T: 1.20 (0.99–1.46)
	1692C/T (30.34%–26.04% C/T and T/T)		C/T and T/T compared with C/C: 1.23 (1.01–1.50)
	rs4274855 (32.04%–26.93% A/G and A/A)		A/G and A/A compared with G/G: 1.27 (1.04–1.56)
	rs11096957 (60.18%–55.85% A/C and C/C)		A/C and C/C compared with A/A: 1.20 (1.00–1.43)
	rs11096955 (57.19%–51.70% A/C and C/C)		A/C and C/C compared with A/A: 1.25 (1.04–1.50)
	rs11466657 (4.39%–4.08% T/C)		NA
	rs4129009 (31.20%–26.31% G/A and G/G)		G/A and G/G compared with A/A: 1.26 (1.03–1.54)
Lindström et al[7] (meta-analysis of Sun et al,[4] Chen et al,[6] and Yeager et al[5])	rs10008492	3101 cases, 2523 controls	NA
	rs4331786		NA
	rs4129009		NA
	rs11466657		NA
	rs11096955		NA
	rs11096957		NA
	rs10856839		NA
	rs4274855		NA
	rs11466640		NA
	rs11466619		NA
	rs11466617		NA
	rs11466612		NA
	rs7663239		NA
	rs4543123		NA
	rs4624663		NA
	rs4833095		NA
	rs5743611		NA
	rs5743604		NA
	rs5743594		NA
	rs5743563		NA
	rs5743556		NA
	rs5743551		NA
	rs4833103		NA
	rs7696175		NA
	rs5743815		NA
	rs3821985		NA
	rs5743810		NA
	rs1039559		NA
	rs5743806		NA
	rs5743795		NA
	rs5743788		NA
	rs6833914		NA
	rs6531673		NA

Note: *Only positive or negative statistically significant results.
Abbreviations: CI, confidence interval; MAF, minor allele frequency; OR, odds ratio; SNP, single nucleotide polymorphism; TLR, Toll-like receptor.

obtained negative results.[14] Therefore, the statistical power of almost all of the studies was sufficient. Population stratification in various studies revealed no subcategorical differences when compared with general results, although a dependence of association on age was found in one study in the Swedish population,[2] and cholesterol level was found to influence the association in one study in the US population.[12] However, alone these results cannot provide sufficient information on the subcategorical modification of association of *TLR* gene polymorphisms with prostate cancer. In addition, there are no studies considering the gene-gene and gene-environment interactions in relation to prostate cancer.

Sun et al[15] did not observe any correlation between polymorphisms of the genes encoding the interleukin-1 receptor-associated kinases (IRAK1 and IRAK4) and prostate cancer. The data obtained by Sun et al[15] might also reflect a lack of association between inherited variation in genes encoding proteins of the TLR signaling pathway and prostate cancer risk, since IRAK1 and IRAK4 are key proteins of this pathway.

Conclusion

In conclusion, it is possible to suggest that TLR and TLR pathway gene polymorphisms do not play a major role in the etiology of prostate cancer, although in certain populations their minor role can be established. Feasibly, it would be better to focus research on associations between *TLR* SNPs and cancer risk in other infection-related cancer types.

Disclosure

The authors report no conflicts of interest in this work.

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