The polymorphisms in Toll-like receptor genes and cancer risk

Abstract

Toll-like receptors (TLRs) are a family of pattern recognition receptors and have important role in pathogen recognition including activation of innate and acquired immune responses. They are mainly expressed in epithelium but have also been found in cancer cells, where they can have pro-tumorigenic and anti-tumorigenic effect. Single nucleotide polymorphisms (SNPs) may change protein structure and influence receptor function. Polymorphisms in TLR genes have been linked with various cancer types and reports were often contradictory. The strongest association with increased cancer risk was found for TLR2 polymorphism −196 to −174 del (Δ22) (gastric, gallbladder and cervical cancer) and TLR4 polymorphisms rs4986790 (gastrointestinal cancers and lymphoma) and rs4986791 (gastrointestinal cancers, nasopharyngeal and gallbladder cancer). Other polymorphisms associated with cancer risk include TLR10-TLR1-TLR6 gene cluster polymorphisms rs10008492 (non-Hodgkin’s lymphoma) and rs7696175 (breast cancer), TLR6 rs5743815 (non-Hodgkin’s lymphoma), TLR10 rs11466657 (meningoma), TLR2 GT microsatellite repeat number polymorphism (colorectal cancer) and rs3804100 (MALT lymphoma), TLR3 829A>C (nasopharyngeal cancer), TLR4 11350G>C (nasopharyngeal cancer), rs1927911 and rs10759931 (prostate cancer), TLR5 rs5744174 (gastric cancer) and TLR9 rs3743836 (Hodgkin’s lymphoma) and rs352140 (Hodgkin’s lymphoma and cervical cancer). Discrepancies in results of different studies regarding TLR polymorphisms and cancer risk may have arisen due to insufficient sample size, differences in ethnicity or age, undetected infections or other environmental factors.

1. INTRODUCTION

Toll-like receptors (TLRs) are a family of innate immune receptors known as pattern recognition receptors (PRRs) and they recognize molecular motifs related to pathogens or pathogen associated molecular patterns (PAMPs) (1). TLRs have a crucial role in recognition of many different pathogens, including viruses, bacteria, protozoa and fungi, and due to their important function, they are evolutionary conserved (2). They were first described in Drosophila in 1984, and were later discovered in vertebrates, including humans (1, 3). To date, 13 TLRs were discovered in mammals, and 10 are functional in humans (2). Human genes encoding TLRs reside on chromosomes 1 (TLR5), 3 (TLR9), 4 (TLR1, TLR2, TLR3, TLR6 and TLR10), 9 (TLR4) and X (TLR7 and TLR8) (1, 4). TLR signaling begins with binding of specific ligand, continues with dimerization and signal transduction into the cell followed by...
activation of three main transcription factors: interferon-
-regulatory factor (IRF3, IRF5 and IRF7), NF-kB and
AP1. They then promote the transcription of inflamma-
tion mediators: cytokines, chemokines and interferons
(2, 5). TLRs are also important in activation of adaptive
immunity: downstream signaling and expression of cyto-
kines leads to maturation of dendritic cells and activation
of B and T cells (5).

2. TOLL-LIKE RECEPTORS: STRUCTURE, LOCALIZATION
AND FUNCTION

TLRs are type I transmembrane glycoproteins consist-
ing of three domains: leucine rich ligand binding ectodo-
main, transmembrane region, and cytoplasmic TIR-do-
main (the Toll/interleukin-1 receptor domain). Ectodomain
contains multiple leucine rich repeats (LRRs) which
are crucial in recognition and binding of pathogen motif
and also in forming characteristic horseshoe shape
of TLRs, a structure important in ligand binding and
downstream signaling (6). TIR-domain dimerizes after
the ligand binding in the ectodomain enabling the re-
cruitment of TIR domain containing adaptor molecules
which transduce the signal downstream: MyD88 (mye-
loid differentiation factor 88), MAL (MyD88 adaptor-
like), TRIF (Toll receptor-activated-associated inter-
feron) and TRAM (Toll receptor-associated molecule) (2,
6). All TLRs except TLR3 use MyD88 for signal trans-
duction, and TLR3 depends on TRIF. TLR4 can activate
both MyD88 and TRIF. TLRs can form homodimers (like
TLR3-TLR3) or heterodimers (such as TLR1-TLR2 and
TLR2-TLR6) (2). Due to differences in ectodomain,
different TLRs bind different PAMPs, such as lipids and
lipoproteins (TLR1, TLR2, TLR4 and TLR6), proteins
(TLR5 and mouse TLR11), and microbial nucleic acids
(TLR3, TLR7, TLR8 and TLR9), while ligands of TLR10
and mouse TLR12 and TLR13 have not yet been identi-
fied (7). Nature of ligands they bind determines the
location of TLRs in the cell: TLR1, TLR2, TLR4, TLR5
and TLR6 bind components of pathogen envelope or cell
wall and are expressed on the surface of the cell (as well
as TLR10), while TLR3, TLR7, TLR8 and TLR9 bind
nucleic acids and are mainly located in the endoplasmic
reticulum membrane or endosomal membrane (2). TLRs
are mainly expressed in lymphoid tissues, innate immune
cells (dendritic cells, macrophages, monocytes, polymor-
phonuclear leukocytes, NK cells) and lymphocytes T
and B. However, they can also be expressed in different
cell types, including cancer cells and cancer cell lines (5,
8). In normal tissues, TLRs are highly expressed in many
epithelial cells (9).

3. TOLL-LIKE RECEPTORS IN CANCER

TLRs participate in many important cellular process-
es: cell proliferation, survival, apoptosis, cell migration,
metastasis and angiogenesis. Due to their important role
in inflammation, it is considered that they can have a
pro-tumorigenic and anti-tumorigenic function, an effect
known as a „double edged sword” (10, 11). In some cases
enhanced TLR activation can lead to apoptosis of cancer
cells and more efficient elimination of tumor cells by
immune system, while in others it may support tumor-
genesis by promoting chronic inflammation (8, 12, 13).
TLR signaling has been implicated in various autoim-
une and inflammatory diseases and chronic inflamma-
tion is known to create a microenvironment rich in growth
and survival factors and has been linked with develop-
ment of many types of cancer (13). TLR expression was
reported in several cancer types and cancer cell lines. It
was found that TLR4 and TLR5 are expressed in gastric
epithelium infected with Helicobacter pylori as well as in
precursor lesions and in gastric cancer cells (14). It is
considered that TLRs enable cells to interact with H.
pylori which can induce tumorigenic factors and may
promote cancer development. TLR expression has also
been found in colon cancer, hepatocellular carcinoma,
ovarian and cervical cancers, breast and prostate cancers,
lung cancer, melanoma and neuroblastoma (9). TLR
expression in cancer cells has been linked with tumor
progression, evasion of immune system surveillance,
apoptosis and survival. TLR4 expression in lung cancer
cells is linked with production of immunosuppressive
cytokines (TGFβ), angiogenic factors VEGF and IL-8,
and with increased resistance to apoptosis (15). Silencing
of TLR4 expression in breast cancer cell line MDA-
-MB-231 significantly decreased cell proliferation and
production of proinflammatory cytokines IL-6 and IL-8
(16). In ovarian cancer cells and cell lines TLR4 activa-
tion by lipopolysaccharide or Paclitaxel activated NF-kB,
promoted production of IL-8, IL-6, VEGF and MCP-1,
and inhibited Paclitaxel mediated apoptosis, while TLR4
silencing lead to loss of resistance to Paclitaxel (17).
TLR2 mRNA expression was significantly higher in spor-
dadic colorectal cancer cells than in noncancerous cells
which could implicate its role in cancerogenesis (18).

4. THE POLYMORPHISMS OF TLR GENES

Single nucleotide polymorphisms (SNPs) may often
cause no change in protein function and pass unnoticed,
but can also lead to amino acid substitutions and changes
in protein function and stability, splicing, mRNA stabi-
licity, post-translational modifications or regulation of
expression (Figure 1A and 1B) (19). SNPs in TLR gene
domain (in LRRs) can affect binding of ligands and
SNPs in transmembrane domain may alter receptor lo-
calization and trafficking in the cell. SNPs in the cyto-
plasmic domain may lead to defects in recruitment of
adaptor proteins, receptor dimerization and internaliza-
tion after ligand binding (20, 21). TLR polymorphisms
have been linked with susceptibility or protective effect in
various diseases, mainly infective and inflammatory, but
also in cancer (Table 1) (20).

4.1. TLR1, TLR6 and TLR10 polymorphisms

Receptors TLR1, TLR6 and TLR10 have similar struc-
tures and genes TLR1, TLR6 and TLR10 form a single
gene cluster on the chromosome 4p14 (22). Receptor TLR1 recognizes triacylated lipoprotein, TLR6 binds diacylated lipoprotein and so far no specific ligand has been linked with TLR10 (7). To bind ligands TLR1 and TLR6 must form dimers with TLR2, while TLR10 homodimerizes or heterodimerizes with TLR1 or TLR2. There have been several association studies between SNPs in TLR10-TLR1-TLR6 gene cluster and prostate cancer risk, but with highly contradictory results regarding even the same investigated polymorphisms (23, 24, 25). Finally, pooled analysis on genotype data from three case control studies with more than 3,000 prostate cancer patients and more than 2,500 controls of European ancestry found no overall association between polymorphisms in TLR10-TLR1-TLR6 gene cluster or TLR4 gene with prostate cancer risk (26). However, polymorphisms in TLR10-
### Table 1
The association of polymorphisms in TLR genes with cancer risk.

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Gene (protein) region</th>
<th>Cancer type</th>
<th>Association*</th>
<th>Sample size, population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR10-TLR1-TLR6</td>
<td>In proximity of TLR1</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Negative for allele A</td>
<td>1,946 patients, 1,808 controls, Caucasian</td>
<td>(28)</td>
</tr>
<tr>
<td>rs4833103 (C&gt;A)</td>
<td>In proximity of TLR1 and TLR6</td>
<td>Breast cancer</td>
<td>Positive for allele T</td>
<td>742 patients, 658 controls, African American; 1,230 patients, 1,118 controls Caucasian</td>
<td>(30)</td>
</tr>
<tr>
<td>rs7696175 (C&gt;T)</td>
<td>In proximity of TLR10</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Positive for allele T</td>
<td>1,946 patients, 1,808 controls, Caucasian</td>
<td>(28)</td>
</tr>
<tr>
<td>rs10008492 (C&gt;T)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs743815 (c.1280 T&gt;C; Val427Ala)</td>
<td>Exon 2 (LRR)</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Positive for allele T</td>
<td>742 patients, 658 controls, African American; 1,230 patients, 1,118 controls Caucasian</td>
<td>(30)</td>
</tr>
<tr>
<td>rs10008492 (C&gt;T)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>TLR6</td>
<td>Exon 3 (LRR)</td>
<td>Meningioma</td>
<td>Negative for heterozygous genotype AG</td>
<td>101 patients, 330 controls, Caucasian (U.S.)</td>
<td>(29)</td>
</tr>
<tr>
<td>rs11466657 (Ex3-1099 T&gt;C; Val427Ala)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TLR10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rs5743815 (c.1280 T&gt;C; Val427Ala)</td>
<td>Exon 2 (LRR)</td>
<td>Non-Hodgkin’s lymphoma</td>
<td>Positive for allele C</td>
<td>458 patients, 484 controls, Caucasian</td>
<td>(27)</td>
</tr>
<tr>
<td>rs11466657 (Ex3-1099 T&gt;C; Val427Ala)</td>
<td>Exon 3 (LRR)</td>
<td>Meningioma</td>
<td>Negative for heterozygous genotype AG</td>
<td>101 patients, 330 controls, Caucasian (U.S.)</td>
<td>(29)</td>
</tr>
<tr>
<td>TLR2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>c.196 to -174 del (Δ22nt)</td>
<td>Exon 1 (5’UTR of TLR2)</td>
<td>Gastric cancer</td>
<td>Positive for ‘del’ allele</td>
<td>174 gastric cancer patients, 208 chronic gastritis patients, 225 controls, Brazilian Caucasian</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HCV associated hepatocellular carcinoma</td>
<td>Positive for ‘del’ allele</td>
<td>189 HCV associated hepatocellular carcinoma patients, 192 HCV infected patients, 347 controls, Germany</td>
<td>(35)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
<td>Positive for ‘del’ allele</td>
<td>261 patients, 480 controls, Greece</td>
<td>(36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate cancer</td>
<td>Positive for ‘del’ allele</td>
<td>195 patients, 250 controls, North India</td>
<td>(37)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gallbladder cancer</td>
<td>Positive for ‘del’ allele</td>
<td>230 patients, 230 controls, North India</td>
<td>(38)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cervical cancer</td>
<td>Positive for ‘del’ allele</td>
<td>150 patients, 150 controls, North India</td>
<td>(39)</td>
</tr>
<tr>
<td>Number of GT microsatellite repeats</td>
<td>Intron 2</td>
<td>Colorectal cancer</td>
<td>Negative for ‘M’ allele, positive for ‘S’ allele and ‘L’ allele</td>
<td>89 patients, 88 controls, Croatia</td>
<td>(40)</td>
</tr>
<tr>
<td>rs3804099 (c.597 T&gt;C; Asn199Asn)</td>
<td>Exon 3 (LRR)</td>
<td>Hepatocellular carcinoma</td>
<td>Negative for genotype CT</td>
<td>211 patients, 232 controls, China</td>
<td>(41)</td>
</tr>
<tr>
<td>rs3804100 (c.1350 T&gt;C; Ser450Ser)</td>
<td>Exon 3 (LRR)</td>
<td>MALT lymphoma</td>
<td>Positive for allele C</td>
<td>1,946 patients, 1,808 controls, Caucasian</td>
<td>(28)</td>
</tr>
<tr>
<td>TLR3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S29 A&gt;C</td>
<td>Intron 1</td>
<td>Nasopharyngeal carcinoma</td>
<td>Positive for allele C</td>
<td>434 patients, 512 controls, Southern China</td>
<td>(43)</td>
</tr>
<tr>
<td>TLR4</td>
<td>Gene Polymorphism</td>
<td>Disease</td>
<td>Risk Allele</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
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</tr>
<tr>
<td>rs4986790 (c.896 A&gt;G, Asp299Gly)</td>
<td>Exon 4 (LRR)</td>
<td>Colorectal cancer</td>
<td>Positive for allele G</td>
<td>89 patients, 88 controls, Croatia</td>
<td>(40)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-cardia gastric cancer</td>
<td>Positive for allele G</td>
<td>45 hypochlorhydria patients, 149 controls; 312 non-cardia gastric cancer patients, 419 controls; 184 non-cardia gastric cancer patients, 123 cardia cancer patients, 211 esophageal cancer, Caucasian population</td>
<td>(45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastric cancer</td>
<td>Positive for genotype AG</td>
<td>174 gastric cancer patients, 208 chronic gastritis patients, 225 controls, Brazilian Caucasian</td>
<td>(34)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gastrointestinal cancer</td>
<td>Positive for allele G</td>
<td>9,463 patients, 10,825 controls</td>
<td>(46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prostate cancer</td>
<td>Negative for genotype GG</td>
<td>9,463 patients, 10,825 controls</td>
<td>(46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Breast cancer</td>
<td>Positive for allele Gly</td>
<td>261 patient, 480 controls, Greece</td>
<td>(36)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MALT lymphoma, Hodgkin’s lymphoma</td>
<td>Positive for allele G</td>
<td>710 patients, 710 controls, Germany</td>
<td>(47)</td>
</tr>
<tr>
<td>rs4986791 (c.1196 C&gt;T, Thr399Ile)</td>
<td>Exon 4 (LRR)</td>
<td>Gastrointestinal cancer</td>
<td>Positive for allele T</td>
<td>9,463 patients, 10,825 controls</td>
<td>(46)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nasopharyngeal carcinoma</td>
<td>Positive for allele T</td>
<td>236 patients, 287 controls, China</td>
<td>(49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gallbladder cancer</td>
<td>Positive for allele T</td>
<td>230 patients, 230 controls, North India</td>
<td>(48)</td>
</tr>
<tr>
<td>I1350 G&gt;C</td>
<td>Exon 4 (3’UTR of TLR4)</td>
<td>Nasopharyngeal carcinoma</td>
<td>Positive for genotype GC</td>
<td>486 patients, 529 controls, China</td>
<td>(50)</td>
</tr>
<tr>
<td>rs1927911 (T&gt;C)</td>
<td>Intron 1</td>
<td>Prostate cancer</td>
<td>Positive for allele C</td>
<td>157 patients, 143 controls, Korea</td>
<td>(51)</td>
</tr>
<tr>
<td>rs10759931 (G&gt;A)</td>
<td>5’UTR</td>
<td>Prostate cancer</td>
<td>Positive for genotype GG</td>
<td>157 patients, 143 controls, Korea</td>
<td>(51)</td>
</tr>
<tr>
<td>rs10759932 (T&gt;C)</td>
<td>5’UTR</td>
<td>Gastric cancer</td>
<td>Negative for allele C</td>
<td>1,053 patients, 1,100 controls, China</td>
<td>(52)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TLR5</th>
<th>Gene Polymorphism</th>
<th>Disease</th>
<th>Risk Allele</th>
<th>Cases</th>
<th>Controls</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs574174 (c.1846 T&gt;C, Phe616Leu)</td>
<td>Exon 6 (LRRCT)</td>
<td>Gastric cancer</td>
<td>Positive for allele C</td>
<td>248 gastric cancer patients, 846 gastric dysplasia and metaplasia patients, 496 controls with gastritis, China</td>
<td>(33)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TLR9</th>
<th>Gene Polymorphism</th>
<th>Disease</th>
<th>Risk Allele</th>
<th>Cases</th>
<th>Controls</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs5743836 (-1237 T&gt;C)</td>
<td>5’UTR</td>
<td>Hodgkin’s lymphoma</td>
<td>Positive for allele C</td>
<td>90 patients, 92 controls, Greece</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>rs187084 (-1486 T&gt;C)</td>
<td>5’UTR</td>
<td>Cervical cancer</td>
<td>Positive for allele C</td>
<td>426 patients, 460 controls, Poland</td>
<td>(55)</td>
<td></td>
</tr>
<tr>
<td>rs352140 (2848 A&gt;G, Pro545Pro)</td>
<td>Exon 2 (LRR)</td>
<td>Hodgkin’s lymphoma</td>
<td>Positive for allele A</td>
<td>90 patients, 92 controls, Greece</td>
<td>(54)</td>
<td></td>
</tr>
<tr>
<td>rs352140 (2848 C&gt;T, Pro545Pro)</td>
<td>Exon 2 (LRR)</td>
<td>Cervical cancer</td>
<td>Positive for genotypes CT and TT</td>
<td>426 patients, 460 controls, Poland</td>
<td>(55)</td>
<td></td>
</tr>
</tbody>
</table>

*Negative association: polymorphism is linked with decreased cancer risk (odds ratio (OR) < 1)
*Positive association: polymorphism is linked with increased cancer risk (OR > 1)
5’UTR: 5’ untranslated region
5’UTR: 5’ untranslated region
LRR: leucine rich repeats
LRRCT: leucine rich repeats C-terminal domain
HCV: hepatitis C virus
MALT: mucosa associated lymphoid tissue
’L’ allele: 26 – 43 GT repeats in intron 2 of TLR2 (40)
’M’ allele: 19 – 25 GT repeats (40)
’S’ allele: < 18 GT repeats (40)
TLR2 gene polymorphisms

4.2.1. TLR2 -196 to -174 del polymorphism

TLR2 gene maps to 4q32 and TLR2 receptor binds lipoproteins, peptidoglycans and glycoproteins (22). Special attention has been focused on TLR2 -196 to -174 del (Δ22) functional polymorphism in 5’ untranslated region known to reduce TLR2 transcriptional activity. There have been several studies regarding impact of Δ22 polymorphism on gastric cancer development, but with contradictory results, especially in Japanese and Chinese populations (31, 32, 33). Recently, Δ22 polymorphism was associated with increased gastric cancer risk in Brazilian population (34) and with higher hepatitis C viral load and was more frequent in hepatitis C associated hepatocellular carcinoma patients than controls in Germany (35). Also, Δ22 polymorphism was found to be more frequent in breast cancer patients than in healthy controls in Greece (36). It was also associated with increased prostate (37), gallbladder (38) and cervical cancer risk (39) in India.

4.2.2. Other TLR2 polymorphisms

Microsatellite GT number repeat polymorphism is located in intron 2 of TLR2 gene. Middle (M) size ‘allele’ with 20 and 21 GT repeats is found to be associated with decreased colorectal cancer risk in Croatian population when compared with shorter (S) and larger (L) number of repeats (40), suggesting possible impact of polymorphism on receptor transcriptional activity. Also, TLR2 polymorphism rs3804100 (c.1350T>C, Ser450Ser) was associated with increased mucosa associated lymphoid tissue (MALT) lymphoma risk (28), and together with rs3804099 (c.597T>C, Asn199Asn) with decreased hepatocellular carcinoma risk (41), but not with breast cancer risk (42).

4.3. TLR3 gene polymorphisms

TLR3 maps to 4q35 and binds double stranded RNA (22). There have been few reports of TLR3 polymorphisms in cancer and mainly with no cancer risk association. Those which were proven to be associated include: (1) TLR3 polymorphism 829A>C, associated with increased nasopharyngeal carcinoma risk in Chinese population (43), and (2) TLR3 polymorphism rs3775291 (c.1234 C>T, Leu412Phe) which was implicated as a negative prognostic factor for survival of stage II colorectal cancer patients (44).

4.4. TLR4 gene polymorphisms

TLR4 gene maps to 9q32-33 and TLR4 receptor binds lipopolysaccharide (22). TLR4 polymorphisms have been investigated in numerous studies and in various cancer types, with main focus on polymorphisms rs4986790 (c.896A>G, Asp299Gly) and rs4986791 (c.1196 C>T, Thr399Ile). Both polymorphisms lead to amino acid substitution in extracellular domain of the TLR4 receptor and are known to diminish response to lipopolysaccharide. Polymorphism Asp299Gly was found to be more frequent in colorectal cancer patients than healthy controls (40). It was also later associated with increased non-cardiac gastric cancer risk, but not with gastric carcinoma or esophageal cancer (45). Recently, association with increased gastric cancer risk was confirmed in Brazilian population (34) and meta analysis based on data from 22 studies confirmed association with increased gastrointestinal cancer risk, but with decreased prostate cancer risk (46). Also, Asp299Gly was more frequent in breast cancer patients than healthy controls in Greece (36). On the contrary, no such association was found in breast cancer patients from Croatian population (42). Therefore it is still under the question whether this polymorphism could be used as a marker for breast cancer susceptibility. Polymorphism Asp299Gly was also associated with increased MALT lymphoma and Hodgkin’s lymphoma risk (47), but not with non-Hodgkin’s lymphoma risk (28). Interestingly, Asp299Gly was associated with improved survival in melanoma patients (48). Polymorphism Thr399Ile was found to be associated with increased gastrointestinal cancer risk and increased overall cancer risk in recent meta analysis (46), but there have also been reports of no association with gastric cancer (34), possibly due to small sample size. Also, polymorphism Thr399Ile was associated with increased nasopharyngeal carcinoma risk in China (49) and increased gallbladder cancer risk in India (38).

4.4.1. Other TLR4 polymorphisms

There have been reports regarding several TLR4 polymorphisms and cancer risk in China. TLR4 polymorphism 11350G>C was associated with increased nasopharyngeal carcinoma risk (50). rs1927911 (T>C) and rs10759931 (G>A) were associated with increased prostate cancer risk (51) and rs10759932 (T>C) with reduced gastric cancer risk (52).

4.5. TLR5 gene polymorphisms

TLR5 gene maps to 1q33.3 and TLR5 receptor binds flagellin (22). TLR5 polymorphisms have mainly not been associated with cancer risk. However, TLR5 polymorphism rs5744174 (c.1846T>C, Phe616Leu), which
Toll-like receptor gene polymorphisms

A. Gomaz

Toll-like receptors have numerous important roles in innate and acquired immunity. Wide spectrum of their signaling pathways and downstream effectors makes them crucial in development of infective diseases, chronic inflammation and cancer. Polymorphisms in TLR genes can reduce receptor function, cause over excessive signaling or change the level of transcription, and therefore influence disease development and progression. Although there have been numerous studies regarding impact of polymorphisms on TLR function and disease development, there is a lot of controversial and yet uncertain data. Contradictory results in different studies may reflect insufficient sample size, ethnicity or age differences, infection with undetected pathogens or other environmental factors. The role of TLR10- TLR1- TLR6 polymorphisms in prostate cancer is controversial and so far those polymorphisms cannot be firmly associated with prostate cancer risk.

Epstein-Bar virus (EBV) infection plays important role in development of non-Hodgkin’s lymphoma as well as nasopharyngeal carcinoma. The association of polymorphisms in TLR genes with increased cancer risk has been shown in lymphoma (TLR6 rs5743815) and nasopharyngeal carcinoma (TLR3 829A>C and TLR4 rs4986791). This may affect virus recognition and immune response to pathogens leading to increased disease susceptibility.

Discrepancies regarding TLR2 -196 to -174 del polymorphism and gastric cancer risk are similar to those in TLR4 (rs4986790 and rs4986791). Both receptors are important in H. pylori infection, which has been implicated in gastric cancer development, and it is possible that they influence cancer development only in presence of H. pylori infection. Conflicting outcome may also result from different types of cancer investigated, only noncardia gastric cancer or all gastric cancer types. Despite somewhat contradictory results, TLR2 -196 to -174 del polymorphism and TLR4 rs4986790 and rs4986791 have been linked with various cancer types (gastric, hepatocellular, breast and prostate cancer) in various populations (Japanese, European, Indian) and their role in carcinogenesis and modulation of immune response to pathogens should be further investigated.

Little and less is known about effects of polymorphisms in TLR3, TLR5, TLR7 and TLR8 genes on cancer risk and development. TLR3 polymorphism 829A>C has been implicated in nasopharyngeal carcinoma risk and TLR3 polymorphism rs5744174 in gastric cancer risk, but possible impact of TLR7 and TLR8 polymorphisms on cancer risk still remains a mystery.

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