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Toll-Like Receptors Gene Polymorphism and Susceptibility to Cancer Development

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Abstract

Toll-like receptors (TLRs) play an important role in immune-surveillance and responses towards pathogenic and non-pathogenic microorganisms. They act as innate immune sensors against endogenous and exogenous danger signals by recognizing the pattern recognition molecules (DAMPs and PAMPs) and drive an adaptive immune response through their signaling pathways, which leads to NF-κB and IRF3 transactivation and induces different inflammatory cytokine genes. TLRs polymorphisms were investigated in various cancer types studies. However, precious studies have reported that the Polymorphisms on TLR1-TLR10 cluster have been associated with increased risk of prostate cancer. However, it has known that TLRs genetic variation is associated with increased the susceptibility to gastric cancer. A same synthetically meta- analysis also confirmed the association of TLRs with increased the gastrointestinal cancer but with decreased prostate cancer risk. Our previous studies have demonstrated a strong link between TLRs polymorphisms and colon cancer and breast cancer in Saudi Arabia population. Similar studies were analyzed with Korean patients with papillary thyroid cancer and their clinic-pathologic features in age matched controls by using direct sequencing. The general objective of this chapter was to investigate the role of different TLRs (i.e., TLR2, TLR4, and TLR6) polymorphisms and their association with cancer development.

Keywords: toll-like receptors, TLRs signaling pathway, polymorphism, cancer

1. Introduction

Toll-like receptors (TLRs) play an important role in immune surveillance and responses to pathogenic and nonpathogenic microorganisms. They act as innate immune sensors against

endogenous and exogenous danger signals by using pattern recognition molecules (DAMPs and PAMPs) and drive an adaptive immune response through their signaling pathways, which leads to NF-κB and IRF3 transactivation and induces different inflammatory cytokine genes. Over the past several years, different studies have indicated that TLR polymorphisms modify the cellular immune response and that some of these polymorphisms are associated with susceptibility to infectious and inflammatory diseases as well as cancer incidence and severity [1–3]. However, previous studies have reported that the polymorphisms on the TLR1-TLR10 cluster have been associated with increased risk of cancer. A meta-analysis also confirmed the association of TLRs with increased risk of cancer development. Our previous studies have demonstrated a strong link between TLR polymorphisms and colon as well as breast cancer in the Saudi Arabian population. Similar studies have been conducted with Korean patients with papillary thyroid cancer and their clinicopathologic features in age-matched controls using direct sequencing. The general objective of this chapter is to investigate the role of different TLR (i.e., TLR2, TLR4, and TLR6) polymorphisms and their association with cancer development.

2. Toll-like receptors signaling pathways and their activation

Toll-like receptors (TLRs) are transmembrane glycoprotein receptors that play a key role in the innate immune system. Usually, they are present on the cell surface, except for TLR3, TLR7, TLR8, and TLR9. These are located in the endosomal membranes of sentinel cells such as macrophages and dendritic cells that recognize structurally conserved molecules derived from microbes. TLRs are the first pattern recognition receptors (PRRs) identified and characterized in mammals [4]. They initiate key inflammatory responses, shape adaptive immunity against microbial infection, repair and regenerate tissues [5, 6]. Through their role in the immune system, TLRs are a possible tool for curing and preventing cancer. TLRs belong to type I transmembrane glycoproteins characterized by an extracellular leucine-rich domain and a cytoplasmic tail, which are primarily responsible for mediating ligand recognition and a single transmembrane helix. TLRs also contain a cytoplasmic tail domain that is homologous to the interleukin-1 receptor and is responsible for initiating various intracellular signaling cascades. These signaling cascades include activation of the nuclear factor-κB (NF-κB), which is considered a key transcription factor that promotes expression of genes involved in immune response such as cytokines and chemokines, as well as co-stimulatory and adhesion molecules [7, 8] (**Figure 1**). To date, 10 types of toll-like receptor families have been identified in humans, and each of them recognizes a specific PAMP [9–12]. Moreover, TLRs can form heterodimers such as TLR2/TLR1 and TR2/TLR6 to recognize the tri- or diacyl lipopeptides of bacteria, respectively [13, 14]. TLR2/6, along with CD36, has been found to have a role in recognizing the lipoteichoic acid (which is diacylated) of Gram-positive bacteria [15]. TLR2 can recognize the peptidoglycan of most bacterial species and fungi, while TLR4 along with CD14 recognizes the lipopolysaccharide (LPS) of Gram-negative bacteria. TLR3 can recognize the double-stranded RNA (dsRNA) that is found during the replication cycle of most viruses [15]. TLR5 recognizes bacterial flagellin [13, 14]. Furthermore, TLR7 and TLR8 can recognize the
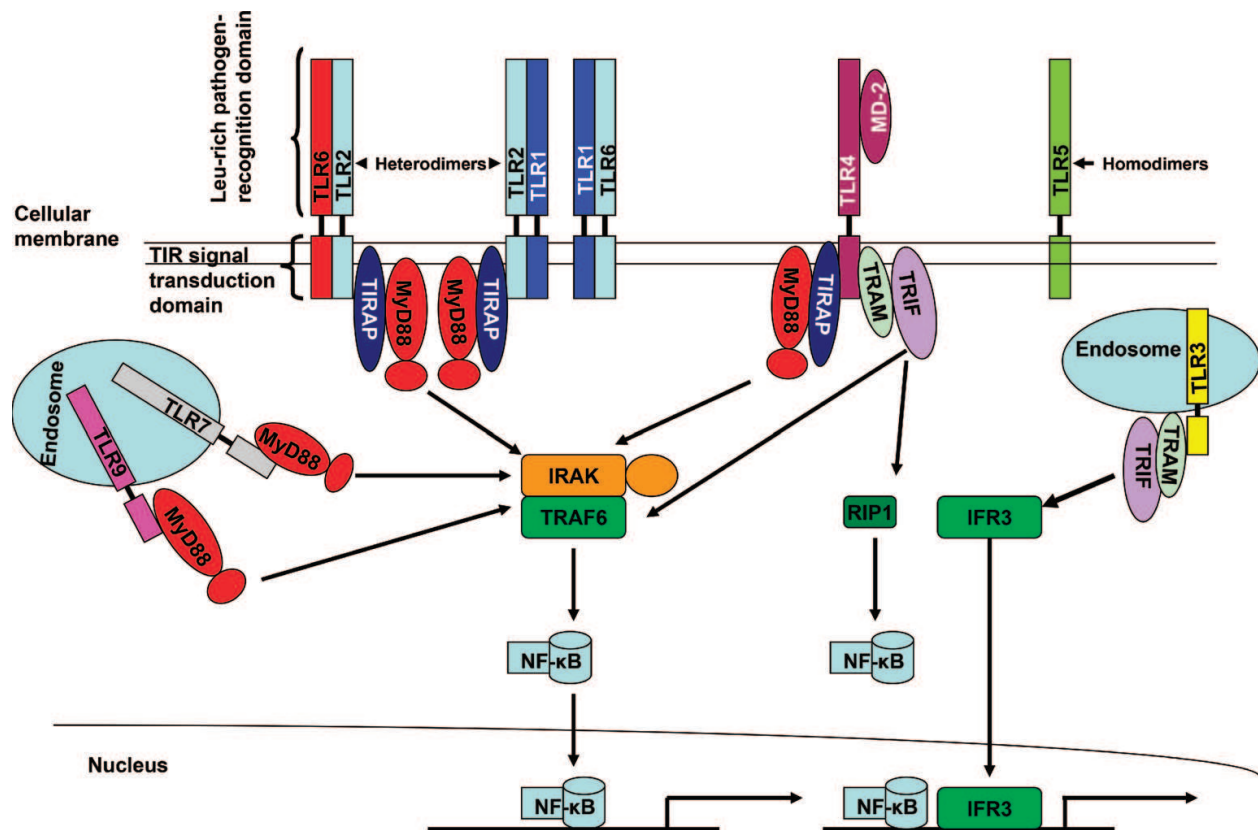
Figure 1. Toll-like receptors: localization and signaling pathways.

single-stranded RNA (ssRNA) found in certain viruses and also the imidazoquinoline com-
pounds, imiquimod and resiquimod (R-848). Correspondingly, TLR9 recognizes hypometh-
ylated CpG motifs of bacterial double-stranded DNA (dsDNA) and DNA generated during
the replication process of dsDNA viruses such as the herpes simplex virus [13, 14]. On the
other hand, the PAMP recognized by TLR10 is unknown. However, TLRs can be classified
into two groups based upon cellular location [16]. TLRs 1, 2, 4, 5, and 6 are found on the cell
plasma membrane and can be activated by extracellular PAMPs. In contrast, TLRs 3, 7, 8, and
9 are principally found in membranes of intracellular compartments, such as endosomes and
lysosomes [17]. The intracellular location of TLRs 3, 7, 8, and 9 enables them to detect nucleic
acids (i.e., DNA or RNA) that have been released from viruses or bacteria and degraded within
endosomes and lysosomes inside the cell [15, 16]. Thus, the inactivation of TLRs will certainly
hamper immune function, leading to significant side effects for human health and well-being.
The TLR signaling cascade involves (or not) the activation of the adapter molecule MyD88. Both
cascades lead to the activation of NF-κB to promote transcription of pro-inflammatory cyto-
kines, chemokines, and cationic peptides. These mediators are involved in innate and adaptive
immune responses.

TLRs present in various immune cells are used to sense multiple pathogens [18, 19]. In this
sense, TLR2 activation allows the activation of NF-κB and subsequent production of IL-8 and
iNOS [19]. Also, it was demonstrated that the activation of TLR3 induced the production of IL-8,

TNFα, IL-18, and type I interferon (IFNα/β) and promoted Th-1 type immune responses [20, 21]. Furthermore, other studies have demonstrated that the activation of TLR5 in human keratino‐cytes by its ligand, flagellin, also resulted in the production of TNFα, IL-8, and the antimicrobial peptides human β-defensins 2 and 3 (hBD2 and hBD3) [22, 23]. TLR9 activation leads to the selective production of the chemokines CXCL9 and CXCL10, which promote memory T-cell responses and the production of type I interferon [20, 21]. Miller et al. showed that TLR5 and TLR9 promote the wound healing process by production of the differentiation factor TGFα [24]. Recently, Semlali et al. reported that gingival epithelial cells in engineered human oral mucosa sense *C. albicans* infection by activating TLRs and producing antimicrobial peptides, such as HBD-2 and HBD-3 [25]. Also, Rouabhia et al. demonstrated that the mutation of the *Candida* genes *IPT1* or *ECM33* prevents TLR activation and cationic peptide (beta-defensin) expression [26]. Together, these available studies demonstrated that TLRs are expressed in the immune cells, and the deregulation of TLR expression by immune cells may promote cancer initiation and development.

3. Deregulation of TLR expression may promote cancer initiation and development

The expression of TLRs, their function in cancer cells and the association with tumor pro‐gression have become a very exciting field of investigation. However, it is well reported that functionally active TLRs are expressed by multiple immune cells such as human cancer cells (lung, gastric, laryngeal, cervical, prostate, etc.) [2, 27]. The general pattern of TLR expres‐sion in tumor cells suggests that TLR-mediated signaling plays a crucial role in cancer tumor development. It is possible that tumor cells express multiple TLRs to recognize various dan‐ger-associated molecular patterns (DAMPs) in their microenvironment. This may enhance the biological process mediated by TLR activation to produce favorable conditions for growth and survival. However, the significance of the expression of several TLRs in various cancer cells is not fully understood. Semlali et al. reported that different TLRs, specifically TLR 2, 6, and 9, are expressed in normal colon epithelial tissues, and their expression has been reported to be decreased in most colorectal cancer tissues compared to normal matching tissues [8]. Conversely, TLR4 expression increases in colon and breast cancer tissues compared to nor‐mal tissues [28, 29]. To date, TLRs have been found to have the opposite effect on tumor progression. On the one hand, TLR ligands can suppress tumor growth. On the other hand, TLR agonists can promote the survival of malignant cells and increase their resistance to che‐motherapy [30]. It is possible that tumor cells express multiple TLRs to recognize various DAMPs in their microenvironment. This may enhance the biological process mediated by TLR activation to produce favorable conditions for growth and survival. Furthermore, the ligation of TLRs in tumor cells increases the production of immunosuppressive cytokines, such as interleukin (IL)-10 and transforming growth factor (TGF)-β [2], suggesting that tumor cells also utilize TLR activation to escape from tumor immune surveillance. However, several available studies support the idea that TLRs are cancer inhibitors. *Thus, further investigation is mandatory to decipher the role and the genetic variation of TLRs in cancer.*

4. TLR polymorphisms and their role in cancer development

Multiple single nucleotide polymorphisms (SNPs) have been identified in TLRs with potential functional consequences for infectious disease or cancers.

- TLR1 polymorphisms and cancer susceptibility

Several studies have linked TLR1 polymorphism to different types of cancer, including breast, colon, and gastric. Two SNPs related to TLR1 and breast cancer were previously investigated. Rs7696175 was found to be associated with increased risk of breast cancer in two populations: Chinese and of European ancestry (OR > 1) [31, 32]. Moreover, Chen et al. investigated the association of rs4833095 SNP and breast cancer in a Chinese population, and they found no association [33]. In colon cancer, rs5743618 (T1805G) on exon 4 results in I602S amino acid substitution in the junction of cytoplasmic and transmembrane TLR1 domain, affecting ligand binding [34]. However, several studies have demonstrated a significant decrease in cytokine response in rs5743618 as compared with wild type [34]. In patients with metastatic colorectal cancer (mCRC), TLR1 rs5743618 SNP was associated with a significant response to FOLFIRI plus bevacizumab chemotherapy. Based on these findings, TLR1 rs5743618 might be a predictive biomarker for the advantage of FOLFIRI plus bevacizumab response in mCRC patients [35]. According to Castano-Rodriguez and colleagues' review, rs5743618 polymorphism has also been associated with decreased risk of gastric cancer among the German population (OR < 1) [36]. Moreover, Ravishankar et al. investigated the association of rs4833095 polymorphism in TLR1, and they found that this SNP has conferred susceptibility of *Helicobacter pylori* patients to the development of gastroduodenal diseases, especially gastric cancer [37].

- Association between TLR2 and cancer

The link between TLR2 polymorphisms and cancer was specifically investigated in the context of chronic inflammation, which likely increases the risk of cancers. An association between TLR2–174 to −196 del polymorphism, 22 base-pair deletions in the promoter, has been found with breast, colon, gastric, and cervical cancer; therefore, the presence of this polymorphism might be used as a biomarker for these cancers. Theodoropoulos et al. demonstrated the association between −174 and − 196 del of TLR2 and breast cancer in Caucasian patients, and they found that this polymorphism may confer increased susceptibility to breast cancer [38]. Furthermore, Proença et al. found that −174 to −196 del are related to an elevated risk of colorectal cancer [39]. According to a review by Castano-Rodriguez and colleagues, TLR2–174 to −196 del have been associated with gastric cancer among different populations: Chinese, Brazilian, and Japanese (OR > 1). On the other hand, −174 to −196 del (Ins/Ins genotype) have been associated with cervical cancer as a protective factor among Tunisian women [40]. Among the Korean population, two TLR2 polymorphisms have been studied to investigate their association with papillary thyroid cancer (PTC)—rs3804099 and rs3804100—and it was found that the two SNPs are associated with PTC [41]. Additionally, rs3804100 and rs3804099 have been associated with increased gastric cancer risk in Brazilian and Chinese populations, respectively [36]. Slattery et al. have investigated some TLR2 SNPs for their impact on

colon cancer risk and survival under cigarette smoking and NSAIDs usage. They found that rs7656411 (T > G) variant allele in normal colon of aspirin/NSAIDs consumers has been associated with a lower risk of colon cancer development, but not for those who did not consume aspirin/NSAIDs recently. Also, rs3804099 (T > C) and the variant allele (CC) have been linked to reduced colon cancer risk in cigarette smokers, but not for nonsmokers. While rs5743704 (C > A) CA/AA genotypes and rs5743708 (G > A) were associated with decreased survival at developed colon cancer stages III and IV, there was no effect among diagnosed stages I and II [42]. Related to hepatocellular cancer (HCC) susceptibility, Junjie et al. investigated the association of two synonymous SNPs in the coding region of TLR2 among the Chinese population. They found that rs3804099 C/T and rs3804100 C/T polymorphisms are associated with decreased risk of HCC susceptibility (OR = 0.493, 0.509, respectively) [43]. Another study was done among the Chinese population that investigated the association of rs3804099 C/T and rs7656411 G/T polymorphisms in TLR2. Huo et al. found that these two SNPs have a significant association with increased risk of HCC [44].

- Association between TLR3 polymorphisms and risk of cancer

In general, there are few reports investigating the correlation between TLR3 polymorphism and different types of cancer. Yeyeodu et al. detected that rs10025405 G allele SNP, which is located at 3'-near gene in TLR3, is associated with breast cancer. Among 100 cases of African American women, this SNP with OR < 1 was associated with a fivefold reduced risk of breast cancer [45]. Another study conducted among the Chinese population ($n = 715$) investigated the role of missense rs3775291 SNP, which is located in exon 4 of TLR3, and found that rs3775291 with A allele is associated with an increased risk of relapse in breast cancer [33]. However, the same rs3775291 polymorphism has been associated with increased survival when diagnosed at stage II among German colorectal cancer patients [46]. Furthermore, a study was done among 900 sample cases from Asian ethnic backgrounds to investigate the correlation between rs5743312 SNP and breast cancer. Rs5743312 with T allele, located in intron 3 of TLR3, was found to increase the risk of breast cancer (OR > 1) [47]. Slattery et al. investigated the association of two TLR3 polymorphisms (rs11721827 and rs3775292) and colon cancer and found that rs11721827 variant allele in the normal colon of aspirin/NSAIDs consumers is associated with a lower risk of colon cancer development, but not for those who did not consume aspirin/NSAIDs recently. The rs3775292 CG/GG genotypes in colon cancer with dietary carbohydrate intake have been associated with no significant increased risk at high intake levels and decreased risk at low intake levels. On the other hand, CG/GG genotypes have somewhat influenced survival when diagnosed at advanced colon cancer stages, with no impact among earlier stages [42]. Related to susceptibility to HCC, Li and Zheng investigated the association of two polymorphisms in TLR3: -976 T/A and + 1234C/T. They found that -976 T/A polymorphism is not associated with HCC. On the other hand, the prevalence of +1234CT and + 1234TT genotypes was found to be significantly increased in HCC cases compared to normal so +1234C/T polymorphism could be a risk factor for HCC [48]. Otherwise, investigation of TLR3 rs5743305 and rs3775291 polymorphisms has shown no significant correlation between these SNPs and the risk of cervical cancer, among a Swedish population [49]. Among North Indian population, Pandey et al. found no association between rs3775290 TLR3 polymorphism and

cervical cancer development [50], while Zidi et al. found that rs3775290 TLR3 polymorphism (+1377 C > T genotype) increased the risk of cervical cancer in advantage stages [40].

- Potential association between TLR4 polymorphisms and cancer risk

In Saudi Arabian population, Semlali et al. investigated the association between breast cancer and four TLR4 polymorphisms: rs2770150, rs10759931, rs10759932 in the promoter region, and rs4986790 in the exon region. They found that three of them—rs2770150, rs4986790 (Asp299Gly), and rs10759932 are not associated with breast cancer, while rs10759931is strongly associated with increased susceptibility to breast cancer [28]. In Caucasian patients, Theodoropoulos et al. demonstrated an association between Asp299Gly SNP of TLR4 and breast cancer, and they found that this polymorphism may confer increased susceptibility to breast cancer [38]. Apetoh et al. also found that TLR4 rs4986790 (Asp299Gly) SNP is associated with increased risk of breast cancer [51]. Regarding lung cancer, Kurt et al. investigated two SNPs (rs4986790 and rs4986791) on the TLR4 gene, rs4986791 cytosine/thymine substitution at nucleotide 1196, and rs4986790 adenine/guanine substitution at nucleotide 896. They found no relation between rs4986790 polymorphism and lung cancer. In contrast, an rs4986791 polymorphism associated with lung cancer compared with CC genotype presences of CT genotype was 3.857 higher risk of lung cancer [52]. Additionally, Vacchelli et al. investigated the impact of TLR4 rs4986790 in response to chemotherapy in non-small-cell lung cancer. They reported that loss of function of TLR4 alleles did not affect overall survival in non-small-cell lung cancer (NSCLC) patients [53]. Another study investigated the association between the +3725 G/C polymorphism in TLR4 and breast cancer among 665 Chinese patient samples. They found that the +3725 G/C polymorphism increased the suitability to breast cancer and decreased the survival time (OR = 2.34) [54]. However, rs10759931 has been associated with colon cancer development risks among Saudi population, regardless of gender or age, while rs2770150 has been associated with colon cancer in Saudi women over 50 years old, and it was closely linked to decreased levels of female sex hormones during the postmenopausal period [55]. Another study investigated the association between rs10759932 C allele polymorphism on CRC development risks and found that there was no influence on TLR4 gene expression in CRC tumor tissue [39]. Furthermore, rs1554973 (T > C) has been associated with improved survival in colon cancer in earlier and advanced stages [42]. In exon 3, rs4986791 + 119 C/T (C > T), which has a Thr399Ile amino acid substitution, was associated with cancer development risk for Caucasians, but not for Asians [56]. A synergistic relationship has been found between rs1927911 (C/T) TT genotype and InterLukin17 (rs6973569) polymorphism with high spicy food intake, which ultimately increased the risk of CRC development [57]. Wang et al. investigated the association of TLR4 SNPs Asp299Gly (rs4986790) and Thr399Ile (rs4986791) in the Chinese population. They found that in ovarian cancer patients, rs4986790 and rs4986791 presented at a lower incidence [58]. Related to gastric cancer, a meta-analysis done by Zhou et al. demonstrated that TLR4 + 896AA/G and + 1196C/T polymorphisms may be associated with significantly increased gastric cancer risk among the Caucasian population [59]. Rs4986790, +896 (A > G) SNP causes an amino acid substitution (Asp299Gly), which leads to an altered TLR4 extracellular domain structure. Also, G allele has been reported with a diminished response to the ligands and thus reduced pro-inflammatory cytokine production

[60]. This observation led [39] to confirm the lack of association between colorectal cancer development risk and rs4986790 polymorphism. A slight frequency of rs4986790 SNP and absence of G/G homozygous have been associated with CRC in different populations, including in Croatia [61], China [62], Spain [63], Japan [64], Greece [38], Brazil [65], Saudi Arabia [55], and Kashmir [66].

- TLR5 polymorphisms and cancer risk

Recently, Shuang et al. investigated the association between the TLR5 polymorphism and breast cancer using two SNPs conducted a study among a Chinese population: the nonsense SNP rs5744168 and the missense SNP rs2072493. They found that rs5744168 T allele encodes a stop at codon 392, affecting TLR5 signaling, and it is associated with sporadic breast cancer occurrence (OR > 1). On the other hand, they found no association between rs2072493 G allele and breast cancer risk [67]. Klimosch et al. found that rs2072493 (A > G), nonsynonymous SNP coding for N592S is associated with colorectal cancer-specific and overall survival. Rs5744174 (T > C), non-synonymous SNP results in the amino acid substitution F616 L. Having a CC genotype was associated only with colorectal cancer-specific survival. These two SNPs, rs2072493 and rs5744174, were both associated exclusively with colon cancer patients [68].

- TLR6 polymorphisms and risk to cancer development

The same SNP in TLR1 (rs7696175) that was found to be associated with breast cancer was also found in TLR6, and it was found to be associated with increased risk of breast cancer in two populations: Chinese and of European ancestry (OR > 1) [31, 32].

- TLR7 and TLR8 polymorphisms and their association with cancer

Generally, TLR7 and TLR8 polymorphisms have not been associated with cancer, except rs3853839 (G/C) polymorphism in TLR7, which might be a biomarker for the benefit of cetuximab-based chemotherapy for *KRAS*-wild type metastatic colon cancer patients. They found that having the GG genotype is related to a longer progression-free survival benefit than having the CC genotype [69].

- Association between TLR9 polymorphisms and cancer risk

Resler et al. have examined two single nucleotide polymorphisms (SNP, rs352140 and rs187084) in TLR9 and their association with breast cancer. In over 800 Caucasian case samples, they found that rs352140 does not alter the protein amino acid sequence but might alter protein function or stability. In addition, this SNP was found to be associated with breast cancer risk (OR = 0.85, protective effect) while rs187084 has not been found to have an association with breast cancer [70]. In a comparison study of African American (AA) and European American (EA) breast cancer patients, the association of rs352140 was investigated. It was found that rs352140 SNP, located at the CpG site, has a protective effect that is 1.6X more common in EA compared to AA [71]. In contrast, Etokebe et al. found no association of rs352140 with breast cancer among 130 case samples of Croatian patients [72]. Rs187084 (C/T) was found to be significantly associated with colon cancer development risk in female patients, which might be linked to sex hormones, including estrogen and progesterone. It has been suggested by previous studies that female sex hormones might have a role in protecting against colon cancer [73, 74]. Additionally, reduced TLR-9 expression was observed in colon

cancer tissues compared with normal tissues. Previous studies demonstrated that reduced TLR-9 transcription activity is relatively associated with C genotype frequencies as compared to T genotype. However, female T allele frequency is lower than controls. The authors suggest that some introns might have some regulatory functions including alternative splice influence, which finally affects both mRNA and protein products [8]. Moreover, rs352139 (A/G) and rs352144 (A/C), in the promoter region, were found to be significantly associated with colorectal cancer development and localization. Reduced TLR-9 expression has been observed in colon cancer, and that might be linked to the fact that promoter mutations seem to affect the stability of regulation processes [8]. On the other hand, Lee et al. investigated the rs5743845 polymorphism in the TLR9 gene. They found that the 2588 G/A SNP in TLR9 did not correlate with increased lung disease in the European population [75]. The relation between cervical cancer susceptibility and TLR3 (rs3775290) and TLR9 (rs352140) polymorphisms has been studied by Pandey et al. in a North Indian population. They found no association between rs3775290 and rs352140 polymorphisms and cervical cancer development. In terms of the effect, TLR 3 (c.1377C/T) and TLR 9 (G2848A) SNPs with clinical stages of cervical cancer, the AA genotype of TLR 9 presents a marginally increased risk for advanced cancer stages (OR = 2.63). In contrast, the TLR3 SNP did not present any significant correlation with cervical cancer clinical stages [50]. Another study investigated the polymorphisms -1486 T/C (rs187084) [76] in TLR9 and cervical cancer susceptibility in the Chinese population and found that rs187084 is associated with cervical cancer development. Moreover, genotype TC was significantly correlated with increased cervical cancer risk in the Polish population [76]. In a meta-analysis, Mu et al. investigated whether (TLR9) -1486 T/C and 2848G/A polymorphisms have a role in cervical carcinogenesis. They demonstrated that rs187084 was associated with an increased risk of cervical cancer while rs352140 did not affect cervical cancer risk [77]. Among a Swedish population, TLR-9 (rs5743836, rs352139, and rs352140) polymorphisms showed no significant correlation with the development of cervical cancer risks [49].

5. Conclusion

TLRs SNPs could serve as a predictive biomarker for different cancer patient treatment. These available studies demonstrate that TLR polymorphism and its functional consequences could be a significant step forward in preventing and curing colon cancer.

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