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Association of Interleukin 1β Gene and Interleukin 1 Receptor Antagonist Gene Polymorphisms and Gastric Cancer Risk

Związek między polimorfizmami genu interleukiny 1β i genu antagonisty receptora interleukiny 1 i zagrożenie rozwojem raka żołądka

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Abstract

Background. Gastric cancer is the second leading cause of cancer death in both sexes worldwide and the prognosis of this malignancy remains very poor.
Objectives, Material and Methods. This study assesses the association between interleukin 1β gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms and gastric cancer susceptibility in the Romanian population. The authors investigated IL-1B –31T > C, IL-1B +3954C > T and IL1-RN +2018T > C polymorphisms in 103 subjects diagnosed with gastric cancer and 244 healthy controls. These polymorphisms were genotyped by allelic discrimination TaqMan PCR.
Results. In all gastric cancer cases, a significant association with an increased risk of gastric cancer was only observed for the IL1-RN +2018T > C polymorphism (OR 2.52, 95% CI: 1.06–6.01). A stratified analysis showed that IL1-RN +2018T > C was associated with an increased risk of gastric non-cardia adenocarcinoma (OR 2.77, 95% CI: 1.10–6.99) and intestinal type (OR 3.08, 95% CI: 1.17–8.11). The authors found no significant differences between gastric cancer cases and controls for IL1-B –31CC (OR 0.77, 95% CI: 0.32–1.84) and IL1-B +3954TT (OR 0.77, 95% CI:0.32–1.85) genotypes polymorphisms.
Conclusions. The results presented do not support the hypothesis that the IL-1B –31T > C and IL-1B +3954C > > T polymorphisms determine differences in gastric cancer risk among different individuals, but the IL1-RN +2018T > C polymorphism could contribute to gastric cancer risk in the Romanian population (**Adv Clin Exp Med 2011, 20, 4, 423–429**).

Key words: gastric cancer, interleukin, gene polymorphism, genotype, risk

Streszczenie

Wprowadzenie. Rak żołądka jest drugą pod względem częstości przyczyną zgonów z powodu nowotworów u obu płci na całym świecie, a rokowanie nadal jest bardzo złe.
Cel pracy, materiał i metody. Ocena związku między polimorfizmami genu interleukiny 1β (IL-1B) i genu antagonisty receptora interleukiny 1 (IL-1RN) a podatnością na raka w populacji Rumunii. Autorzy badali polimorfizmy IL-1B-31T > C, IL-1B +3954 C > T i IL1-RN +2018 T > C u 103 pacjentów z rozpoznanym rakiem żołądka i 244 zdrowych. Polimorfizmy genotypowano przeprowadzone metodą dyskryminacji alleli z użyciem sond TaqMan PCR.
Wyniki. We wszystkich przypadkach raka żołądka istotny związek ze zwiększonym ryzykiem tego raka obserwowano jedynie dla polimorfizmu IL1-RN +2018 T > C (OR 2,52, 95% CI: 1.06–6.01). Analiza warstwowa wykazała, że IL1-RN +2018 T > C wiązał się ze zwiększonym ryzykiem gruczolakoraka żołądka (OR 2,77, 95% CI: 1.10–6

0.99) i jelit (OR 3,08, 95% CI: 1.17–8 0.11). Autorzy nie stwierdzili istotnych różnic między przypadkami raka żołądka a grupą kontrolną dla polimorfizmów genotypów IL1-B-31CC (OR 0,77, 95% CI: 0.32-1 0.84) i IL1-B +3954 TT (OR 0,77, 95% CI: 0.32–1 0.85).
Wnioski. Przedstawione wyniki nie potwierdzają hipotezy, że polimorfizmy IL-1B-31T > C i IL-1B +3954 C > T określają różnice w ryzyku rozwoju raka żołądka wśród różnych osób, ale polimorfizm IL1-RN +2018 T > C może wpływać na zwiększone ryzyko raka żołądka w populacji Rumunii (**Adv Clin Exp Med 2011, 20, 4, 423–429**).

Słowa kluczowe: rak żołądka, interleukina, polimorfizm genu, genotyp, ryzyko.

Gastric cancer is the second leading cause of cancer death in both sexes worldwide and the prognosis of this malignancy remains very poor [1]. Gastric cancer incidence and mortality rates are different between regions and countries within the European Union but the highest incidence and mortality by gastric cancer is in Central and Eastern European countries [2]. These large geographic variations in incidence and mortality may be related to environmental and genetic factors. A multifactorial model of human gastric carcinogenesis is currently accepted; different dietary and non-dietary factors and genetic susceptibility are involved in this carcinogenesis [3]. Gastric cancer is promoted by chronic inflammation in response to the presence of *Helicobacter pylori (H. pylori)*, therefore genes influencing the immune response are logical candidates to examine for association with gastric cancer risk. Genetic variations in genes encoding cytokines and their receptors, which determine the intensity of the inflammatory response to this bacteria may contribute to individual differences in the severity of outcome of *H. pylori* infection and progression of gastric lesions [4].

Interleukin 1β (IL-1B) and interleukin 1 receptor antagonist (IL-1RN) are the cytokine genes most studied for their association with gastric cancer risk. The genes of the IL-1 family (IL-1A, IL-1B and IL1-RN) are clustered on the long arm of human chromosome 2 (2q13–14) [5]. The IL-1B gene is an important pro-inflammatory cytokine and a potent inhibitor of gastric acid secretion. IL-1RN encodes the IL-1 receptor antagonist, a regulatory cytokine that competitively binds to IL-1 receptors and thereby modulates the potentially damaging effects of IL-1 [6]. Three common single nucleotide polymorphisms (SNPs) in the IL1-B gene have been examined: –511C > T, –31T > C and +3954C > T. IL1-RN contains a variable number of tandem repeats (VNTR) polymorphism, with an 86 bp segment that varies from 2 to 6 copies [7], this polymorphism being extensively studied. However, the IL-1RN +2018T > C polymorphism was also investigated [8]. Two studies conducted by El Omar et al. were the first to report an association between genetic variations within the IL-1 gene cluster and the risk of developing gastric cancer [9,10], but association of these variants with gastric cancer remains controversial, being confirmed by some studies, but not reproduced by others.

Despite the high incidence and mortality by gastric cancer in Eastern Europe, the number of cytokine polymorphism studies in this area is still poor. The aim of our study is to investigate the IL-1B –31T > C (rs1143627), IL-1B +3954C > T (rs1143634) and IL1-RN +2018T > C (rs419598) polymorphisms and gastric cancer susceptibility in Romanian patients, an ethnic group in which the association between gastric cancer and these polymorphisms has not previously been studied.

Material and Methods

Subjects

Peripheral blood and gastric samples were collected from a total of 103 subjects diagnosed with gastric adenocarcinoma from the Clinical Hospital of Craiova, Romania. All diagnoses were pathologically confirmed. Gastric cancer was histologically grouped according to the Lauren classification as either diffuse or intestinal. *H. pylori* infection status was assessed by serology, histologic examination or the urea breath test. Clinical data and pathological characteristics of the patients were collected and confirmed from both their medical history records and questionnaires. For the control samples, peripheral blood was collected from 244 patients, without gastroduodenal lesions or cancer, who volunteered. All patients and controls enrolled in the study were from the same socioeconomic level and had similar cultural habits. Written consent for participation was obtained from all study subjects.

Taq Man Genotyping Assay

Blood (2.5 ml) was collected in an EDTA tube and stored frozen until DNA extraction. Genomic DNA was extracted from peripheral blood using a Wizard Genomic DNA Purification Kit (Promega). All three polymorphisms were genotyped using an allelic discrimination TaqMan PCR assay. Primers and SNP-specific dual fluorogenic probes labeled with Fam and Vic as a reporter and

Tamra as a quencher (Applied Biosystems Foster City, CA) were used to determine the various alleles. Assays were validated and optimized as described on the SNP500 Cancer website [11].

The RealTime PCR reactions were carried out in a 5 µl reaction volume containing 0.5 µl of sample DNA, 2.5 µl of the Universal Master Mix (Applied Biosystems, Foster City, CA), 0.25 µl TaqMan SNP Genotyping Assays 40x (Applied Biosystems, Foster City, CA) specific for each polymorphism and 1.75 µl DNase-free, sterile-filtered water per reaction. RealTime PCR cycling conditions (RotorGene 6200 HRM-Corbett) were as follows: 95°C for 10 min, followed by 50 cycles of 92° C for 15 s and 60°C for 1 min annealing temperature.

Statistical Analysis

Genotyping frequencies were tested for compliance with Hardy-Weinberg equilibrium (HWE) using the χ^2 test. Linkage disequilibrium between SNPs was measured by calculating D´ and r^2 values. Differences of age between the two groups were assessed using the Mann-Whitney test. The effects of cytokine alleles on the risk of diseases were expressed as odds ratios (OR) with 95% confidence intervals (CI). A *P*-value less than 0.05 was considered statistically significant. The SPSS statistical software package version 19 was used for all statistical analyses.

Results

A total of 103 patients with gastric adenocarcinoma and 244 healthy controls were included. The mean age of the gastric cancer patients was 64.22 ± 5.65 and for the control group 60.69 ± 4.94. The age and gender distributions of gastric cancer cases and controls are comparable (Table 1). All gastric adenocarcinoma were Hp positive. Histologically, the majority of gastric cancers were the intestinal type (58%). The most common site of tumor was non-cardia (73%).

Genotype frequencies of the IL-1B –31T > C, IL-1B +3954C > T and IL-1RN +2018T > C polymorphisms in the gastric cancer and control groups did not deviate significantly from those expected under the Hardy-Weinberg equilibrium. No strong linkage disequilibrium was observed between polymorphisms ($r^2 < 0.33$).

The frequencies of the investigated polymorphisms are shown in Table 2. A significant association was only observed for IL-1RN +2018T > C, the subjects carrying the CC genotype were at a 2.5-fold elevated risk for gastric cancer (OR 2.52, 95% CI: 1.06–6.01) when compared with the more frequent TT genotype carriers. In addition, the frequencies of alleles were significantly different between cases (T, 67.5 and C, 32.5%) and controls (T, 76 and C, 24%) (p = 0.026).

We found no significant differences between gastric cancer cases and controls for IL-1B –31CC (OR 0.77, 95% CI: 0.32–1.84) and IL-1B +3954TT (OR 0.77, 95% CI: 0.32–1.85) genotype polymorphisms (Table 2). Also, carriers of the IL-1B –31C and IL-1B +3954T allele were not associated with an increase in the risk of gastric cancer (OR 0.99, 95% CI: 0.62–1.61, respectively OR 0.68, 95% CI: 0.41–1.13).

We examined whether the associations of these SNPs with gastric cancer risk were modified by other risk factors: tumor site, age and Lauren classification. A positive association was found for

Table 1. Patient characteristics

Tabela 1. Charakterystyka pacjentów

	Gastric adenocarcinoma (Gruczolakorak żołądka)	Control group (Grupa kontrolna)
n	103	244
Male/Female (Mężczyźni/kobiety)	65/38	152/92
Age – years, mean ± SD (Wiek – lata, średnia ± SD)	64.22 ± 5.65	60.69 ± 4.94
H. pylori positive (Wykrycie *H. pylori*)	103	
Location (Umiejscowienie) cardia non-cardia	 28 75	
Histological type (Typ histologiczny) intestinal diffuse mixed	 59 43 1	

Table 2. Risk of gastric cancer by genotype

Tabela 2. Ryzyko raka żołądka w zależności od genotypu

Polymorphism (Polimorfizm)	Gastric cancer (Rak żołądka) n = 103 (%)	Control group (Grupa kontrolna) n = 244 (%)	OR (95% CI)	p value (Istotność statystyczna)
IL-1B –31T > C				
TT	48 (46.60)	111 (45.49)	Ref	–
TC	47 (45.63)	109 (44.67)	0.99 (0.62–1.61)	0.99
CC	8 (7.77)	24 (9.84)	0.77 (0.32–1.84)	0.60
T : C	69.42 : 30.58%	67.83 : 32.17%	1.08 (0.76–1.53)	0.73
IL-1B +3954C > T				
CC	63 (61.17)	128 (52.46)	Ref	–
CT	32 (31.07)	95 (38.93)	0.68 (0.41–1.13)	0.18
TT	8 (7.77)	21 (8.61)	0.77 (0.32–1.85)	0.60
T : C	76.70% : 23.30	71.93% : 28.07%	1.28 (0.88–1.88)	0.26
IL-1RN +2018T > C				
TT	47 (45.63)	140 (57.38)	Ref	–
TC	45 (43.69)	91 (37.30)	1.47 (0.90–2.39)	0.17
CC	11 (10.68)	13 (5.33)	2.52 (1.06–6.01)	0.046
T : C	67.48 : 32.52	76.02 : 23.98%	1.52 (1.07–2.18)	0.026

Table 3. Risk of cardia and non-cardia adenocarcinoma by genotype

Tabela 3. Ryzyko gruczolakoraka wpustu i innych w zależności od genotypu

Polymorphism (Polimorfizm)	Cardia (Wpust) n = 28		Non-cardia (Inne) n = 75	
	n (%)	OR (95% CI); p value	n (%)	OR (95% CI); p value
IL1B –31 T > C				
TT	13 (46.43)	Ref	35 (46.67)	Ref
TC	12 (42.86)	0.94 (0.41–2.15); 0.93	35 (46.67)	1.02 (0.59–1.74); 0.95
CC	3 (10.71)	1.07 (0.28–4.04); 0.96	5 (6.67)	0.66 (0.23–1.86); 0.47
IL1B +3954C > T				
CC	17 (60.71)	Ref	46 (61.33)	–
CT	9 (32.14)	0.71 (0.31–1.67); 0.48	23 (30.67)	0.67 (0.38–1.18); 0.22
TT	2 (7.14)	0.72 (0.15–3.33); 0.71	6 (8.00)	0.79 (0.30–2.09); 0.69
IL1RN +2018T > C				
TT	12 (42.86)	Ref	35 (46.67)	Ref
TC	14 (50.00)	1.80 (0.79–4.06); 0.21	31 (41.33)	1.36 (0.78–2.36); 0.32
CC	2 (7.14)	1.79 (0.36–8.90); 0.54	9 (12.00)	2.77 (1.10–6.99); 0.042

the IL-1RN+2018C allele, limited to an increased risk of non-cardia adenocarcinoma (OR 2.77, 95% CI: 1.10–6.99) (Table 3). The sub-classification of gastric cancer histology into intestinal and non-intestinal showed a significant risk only in the intestinal type of gastric cancer for carriers of the IL-1RN +2018CC genotype (OR 3.08, 95% CI: 0.1.17–8.11) (Table 4). For both polymorphisms of IL-1B, the sub-classification of gastric cancer site (non-cardia and cardia) or gastric cancer histology (intestinal and non-intestinal) did not show any association with gastric cancer risk for any of the genotypes studied.

Discussion

Previous studies on the association between IL-1 genetic polymorphisms and the risk of gastric cancer have produced controversial results.

We found no evidence of increased gastric cancer risk among IL-1B –31T > C or IL-1B +3954C

Table 4. Risk of intestinal and diffuse adenocarcinoma by genotype

Tabela 4. Ryzyko gruczolakoraka jelit i rozlanego w zależności od genotypu

Polymorphism (Polimorfizm)	Intestinal (Gruczolakorak jelit) n = 59		Diffuse (Gruczolakorak rozlany) n = 43	
	n (%)	OR (95% CI); p value	n (%)	OR (95% CI); p value
IL1B –31 T > C				
TT	29 (49.15)	Ref	18 (41.86)	Ref
TC	27 (45.76)	0.95 (0.53–1.71) 0.91	20 (46.51)	1.13 (0.56–2.26) 0.78
CC	3 (5.08)	0.48 (0.13–1.70) 0.27	5 (11.63)	1.28 (0.43–3.80) 0.71
IL1B +3954C > T				
CC	38 (64.61)	Ref	24 (55.81)	Ref
CT	18 (30.51)	0.64 (0.34–1.19); 0.20	14 (32.56)	0.79 (0.38–1.60); 0.55
TT	3 (5.08)	0.60 (0.14–1.70); 0.27	5 (11.63)	1.27 (0.44–3.69); 0.72
IL1RN +2018T > C				
TT	28 (47.46)	Ref	18 (41.86)	Ref
TC	23 (38.98)	1.26 (0.69–2.33);0.50	22 (51.16)	1.88 (0.96–3.70); 0.12
CC	8 (13.56)	3.08 (1.17–8.11); 0.034	3 (6.98)	1.80 (0.47–6.91); 0.47

> T carriers of any genotype. Our results are in accordance with 2 meta-analyses that showed no significant association between IL-1B –31T > C and gastric cancer risk in Caucasians [12, 13]. IL-1B –31CC and +3954TT genotypes were not associated with an increased risk of developing gastric cancer [14] and no statistically significant association was found between IL-1B –31T > C and IL-1B +3954C > T polymorphisms and histological types or locations of gastric cancer in a Japanese and other Korean studies [15, 16]. Another report from Spain also showed no association between variable cytokine gene polymorphisms including IL-1B and IL1-RN with gastric cancer [17].

In the largest prospective study on healthy volunteers from Western countries, EPIC-EURGAST, IL-1B –31T > C and IL-1B +3954C > T polymorphisms were not associated with gastric cancer risk [8]. No correlation with gastric cancer risk was observed for IL-1B –31C carriers in two Italian studies: one included *H. pylori* negative gastric cancer cases [18] and other *H. pylori* non-cardia adenocarcinoma patients [19]. Hurme and Santilla, by examining the IL-1B polymorphisms 511T/C and +3954T/C, concluded that the IL-1B SNPs did not have a direct effect on plasma IL-1Ra levels, but that the enhancing effect of allele 2 on IL-1Ra levels required the presence of IL-1B –511T or the absence of IL-1B +3954T. IL-1RN allele 2 carriers had higher plasma IL-1Ra than non-carriers [20].

Other previous studies have reported that polymorphisms of the IL-1B and IL-1RN are associated with an increased risk of both hypochlorhydria and gastric carcinoma. The first investigation on IL-1B and IL-1RN and gastric cancer susceptibility was reported in 2000. El Omar et al. showed an increased gastric cancer risk for carriers of the homozygous IL1B –31CC genotype and IL-1RN 2 genotype, the frequency of the ILB –31CC genotype was 65% from patients and 49% in controls enrolled in Scotland and Poland [9, 10]. Contrarily, for both IL-1B polymorphisms, we found a higher frequency of IL-1B –31CC and IL-1B +3954TT genotypes in the control versus gastric cancer group (9.84 versus 7.77% and 8.61 versus 7.77 %, respectively). The frequencies of IL-1B –31T > C genotypes from our study are similar to the frequencies from other Western studies [8, 18, 19].

In a study on Mexican people, Garza-Gonzalez et al. showed that among IL-1B, IL-1RN, TNF-α gene polymorphisms, only IL-1B –31T > C is associated with an increased risk of distal gastric cancer [21]. A positive association between IL-1B +3945T and an increased risk of gastric cancer was found by Alpinzar et al. in the population of Costa Rica [22].

Crusius et al. found that the IL1-RN +2018 T > C polymorphism was associated with a significantly increased risk of gastric cancer. They observed that the association was restricted to non-cardia neoplasm. Only those carrying the C allele of IL1-RN +2018T/C were found to have an increased risk of non-cardia adenocarcinoma [8]. Similarly, we found that carriers of the IL-1RN +2018CC genotype were significantly associated with an increased risk of non-cardia adenocarcinoma (OR 2.77, 95% CI: 1.10–6.99). The strongest positive association was observed in a stratified analysis for the intestinal type (OR 3.08, 95% CI: 1.17–8.11).

In conclusion, polymorphism IL1-RN +2018T > C may contribute to gastric cancer risk, mainly

for non-cardia and intestinal types of gastric cancer. Our results do not support the hypothesis that IL-1B –31T > C and IL-1B +3954C > T polymorphisms determine differences in the risk of gastric cancer among different individuals. Further, larger studies are required in order to clarify the role of these polymorphisms in the pathogenesis of gastric cancer.

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