Role of Cytokine Polymorphisms in the Risk of Distal Gastric Cancer Development

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Abstract

We review the current information concerning the role of cytokine polymorphisms and the risk of develop distal gastric cancer in different populations. We have included populations colonized with Helicobacter pylori as well as populations without colonization. We found that the study of polymorphisms alone seems insufficient to assess gastric cancer risk and it is necessary to examine environmental factors in different ethnic groups and geographic areas along with the study of H. pylori strains to define better the risk factors associated with distal gastric cancer. (Cancer Epidemiol Biomarkers Prev 2005;14(8):1869–73)

Introduction

Stomach cancer was the most common form of cancer in the world in the 1970s and early 1980s and is now surpassed only by lung cancer. The incidence of gastric cancer shows marked variation among countries in the world (1). Incidence rates are especially high in Japan and other Eastern Asian countries; other areas in the world, including Eastern Europe and parts of Latin America (2), have high incidence rates of gastric cancer as well.

Gastric cancer is a multifactorial disease. Mortality rates for this cancer worldwide have been declining for several decades (3). Despite the decline in distal gastric cancer in many countries of the world, it remains a major public health problem. The number of new cases in the elderly population of both developed and developing countries is rising. It is estimated that more than a million cases per year will occur in the next 10 years (1).

Since 1991, epidemiologic evidence has shown that gastric cancer is associated with H. pylori colonization (4). However, many studies have shown that even through certain regions of the world where nearly 100% of the persons are colonized with H. pylori the risk of developing gastric cancer is not as high as expected, particularly in sub-Sahara Africa and Southeast Asia (5). Bacterial virulence factors such as the cag pathogenicity island, the vacuolating cytotoxin, and others have been associated with higher risk for gastric cancer development particularly in western countries but these associations are less relevant in countries including east Asia and developing countries (6, 7).

Host genetic factors are emerging as determinants of increasing risk for many cancers (8, 9). Cytokines participate in the inflammatory response associated with innate immunity and the acquired immune response. Cytokines such as INFγ, interleukin-1β (IL-1β), and tumor necrosis factor-α (TNF-α) are up-regulated during H. pylori infection. Genes encoding cytokines and related molecules harbor polymorphic regions, which alter gene transcription and thereby influence inflammatory processes in response to infectious disease (10). Polymorphisms in human IL-10, IL-1B, TNF-A, IFN-G, and IL-1 receptor antagonist (IL-1RN) genes have been reported to influence cytokine expression. In gastric cancer, several cytokine polymorphisms, such as IL-1β, IL-10, TNF-α, and others, have been evaluated as risk factors.

IL-1B

Two diallelic polymorphisms in IL-1B have been reported (Fig. 1), each one representing C-T base transitions at positions −511 and −31. IL-1β is up-regulated in the presence of H. pylori and is important in initiating and amplifying the inflammatory response to this infection. IL-1β is also a potent inhibitor of gastric acid secretion (12). A biallelic polymorphism at positions −31 and −511 in the promoter of the IL-1B gene have been associated with the development of gastric cancer and its precursors (Table 1; refs. 13-16).

IL-1RN

The IL-1RN gene has a penta-allelic 86-bp variable number tandem repeat in intron 2, of which allele 2 (IL-1RN2) is associated with a wide range of chronic inflammatory and autoimmune conditions and enhanced IL-1β secretion (Fig. 2). The alleles 1, 2, 3, 4, and 5 in IL-1 RN gene, represent four, two, five, three, and six repeats of the 86-bp tandem repeat (see Fig. 2). As described below, the presence of allele 2 has been associated with increased risk of distal gastric cancer and its precursors (14, 15, 17, 18).

Interactions of IL-1 Polymorphisms and Gastric Cancer

The first indication of IL-1 polymorphisms and their association with increased risk for gastric cancer was reported by El-Omar et al. (11). El-Omar et al. recently reported that functional polymorphisms in the genes for IL-1β and its endogenous receptor antagonist (IL-1RN) were
IL-1B

<table>
<thead>
<tr>
<th>Locus</th>
<th>Genotype</th>
<th>Cases (n = 366)</th>
<th>Controls (n = 429)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1B –31</td>
<td>T/T</td>
<td>35.0</td>
<td>51.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>T/C</td>
<td>47.0</td>
<td>38.3</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td></td>
<td>C/C</td>
<td>18.0</td>
<td>10.7</td>
<td>2.5 (1.6-3.8)</td>
</tr>
<tr>
<td>IL-1B –511</td>
<td>C/C</td>
<td>34.7</td>
<td>50.6</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>C/T</td>
<td>46.4</td>
<td>39.7</td>
<td>1.8 (1.3-2.4)</td>
</tr>
<tr>
<td></td>
<td>T/T</td>
<td>18.9</td>
<td>10.7</td>
<td>2.6 (1.7-3.9)</td>
</tr>
</tbody>
</table>

NOTE: Modified from ref. 11.

Figure 1. Schematic illustration of polymorphisms in the IL-1B gene. Allele frequencies of the single-nucleotide polymorphisms (SNP) in the promoter region of the IL-1B gene at positions –511 and –31. SNP -511T (associated with higher IL-1β secretion) is in complete linkage disequilibrium with –31C. From an eastern European population (19).

Figure 2. IL-1RN gene has a penta-allelic 86-bp variable number tandem repeat in intron 2, of which the allele 2 (IL-1RA*2) had been associated with enhanced IL-1β production. Relative frequencies are indicated for each allele from an eastern European population (19).

Interactions of IL-1B Polymorphisms with Other Diseases

The IL-1B polymorphisms –511 and IL-1RN 2/2 have been associated with esophagitis in patients who are not colonized with H. pylori. Koivurova et al. (23) reported that the simultaneous carriage of those two polymorphisms is significantly associated with esophagitis. García-González et al. (24) confirmed that the same IL-1B and IL-1RN polymorphisms that are associated with high risk of distal gastric adenocarcinoma are associated with a reduced risk of duodenal ulcer.

Tumor Necrosis Factor-A

TNF-α is one of the proinflammatory cytokines highly expressed in H. pylori gastritis and a potent inhibitor of gastric acid secretion (25, 26). Although several polymorphisms have been reported in the TNF-A promoter, the majority of studies have been focused on the G/A polymorphism at position –307 (Fig. 3), because most of the other polymorphisms are functionally silent. Several studies found a higher concentration of TNF-α in patients with the polymorphism at position –307 with malignant tumors (27, 28).

As noted above, TNF-α is a proinflammatory cytokine, which is a mediator of the immune response in H. pylori and
Table 2. Frequencies (%) and age-, sex-, and race-adjusted ORs for the association of inflammatory polymorphisms in IL-1β, IL-1RN, IL-10, and TNF-A with non-cardia gastric cancer

<table>
<thead>
<tr>
<th>Polymorphisms</th>
<th>Cases (n = 188)</th>
<th>Controls (n = 210)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>11.7</td>
<td>35.7</td>
<td>1.0</td>
</tr>
<tr>
<td>1</td>
<td>39.4</td>
<td>40.5</td>
<td>2.8 (1.6-5.1)</td>
</tr>
<tr>
<td>2</td>
<td>33.0</td>
<td>21.9</td>
<td>5.4 (2.7-10.6)</td>
</tr>
<tr>
<td>3</td>
<td>14.9</td>
<td>1.9</td>
<td>26.3 (7.1-97.1)</td>
</tr>
<tr>
<td>4</td>
<td>1.0</td>
<td>0.0</td>
<td>∞ (undefined)</td>
</tr>
</tbody>
</table>

NOTE: Modified from ref. 12.

Table 3. Estimated ORs for the association of cytokine polymorphisms in seropositive patients to H. pylori and CagA antigen preparations

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>H. pylori*</th>
<th>CagA*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1B – 511*T</td>
<td>4.2</td>
<td>9.9</td>
</tr>
<tr>
<td>IL-1RN<em>2</em>2</td>
<td>1.6</td>
<td>2.9</td>
</tr>
<tr>
<td>IL-10 ATA/ATA</td>
<td>2.9</td>
<td>5.2</td>
</tr>
<tr>
<td>TNF-A –308*A</td>
<td>2.9</td>
<td>6.2</td>
</tr>
</tbody>
</table>

IL-10

Inflammatory reactions are an essential component of host defense mechanisms, but prolonged or excessive inflammation is deleterious; therefore, the inflammatory process must be tightly regulated. The key regulators of inflammation are the cytokines, proinflammatory (IL-1β and TNF-α) and the anti-inflammatory (IL-10). The possible roles of proinflammatory cytokine in gastric cancer were noted above; anti-inflammatory cytokines also play a role. In the IL-10 gene promoter, single nucleotide polymorphisms at positions –1082 (G/A), –819 (C/T), and –592 (C/A) have been reported to produce three main haplotypes: GCC, ACC, and ATA (refs. 9, 32, Fig. 4).

Rad et al. (32) have recently shown that carriers of the IL-10 –1082G, –819C, and –592C alleles had higher mucosal IL-10 mRNA than ATA haplotype carriers. These results confirmed the relevance of IL-10 polymorphisms in the down-regulation of the inflammatory response. El-Omar et al. have recently reported that certain polymorphisms in anti-inflammatory cytokine genes, such as IL-10, were associated with more than doubling of the risk of non-cardia gastric cancer (12). Patients homozygous for the hypactive IL-10 alleles IL-10 –1082A and IL-10 –592A, as well as for the “low IL-10” haplotype ATA (IL-10 –1082A, IL-10 –819T, and IL-10 –592A) had significantly increased risks of non-cardia gastric cancer.

Garza-Gonzalez et al. (33) studied the potential role of IL-10 polymorphisms in gastric cancer patients. They found no association between IL-10 polymorphisms (–592 and –1082) and gastric cancer in a very small study (33 gastric cancer cases and 25 controls).

Association Between Multiple Polymorphisms and Gastric Cancer Risk

The combination of multiple proinflammatory polymorphisms and some anti-inflammatory polymorphisms conferred greater risk for gastric cancer as illustrated in Table 2 (12). The association of IL-10, an anti-inflammatory cytokine, with proinflammatory cytokines such as IL-1β and TNF-α may be explained by the role of IL-10 in down-regulating the proinflammatory cytokines. In addition, some reports suggest an important role for cytokine expression in the level of the inflammatory response observed in vivo (34).

In contrast, the number of inflammatory cytokine polymorphisms was not statistically significantly associated with...
Table 5. Combination of \textit{H. pylori} and \textit{IL-1B} genotype in non-atrophic gastritis and non-cardia gastric cancer patients

<table>
<thead>
<tr>
<th></th>
<th>NAG</th>
<th>NCGC</th>
<th>OR (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>\textit{vacA} S2/C homozygote</td>
<td>27</td>
<td>1</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>\textit{vacA} S2/T homozygote</td>
<td>35</td>
<td>8</td>
<td>6.2 (0.7-52)</td>
<td>0.1</td>
</tr>
<tr>
<td>\textit{vacA} S1/C homozygote</td>
<td>17</td>
<td>27</td>
<td>43 (5.3-345)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>\textit{vacA} S1/T homozygote</td>
<td>22</td>
<td>71</td>
<td>87 (11-679)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>\textit{cagA} -/C homozygote</td>
<td>35</td>
<td>4</td>
<td>1 (reference)</td>
<td></td>
</tr>
<tr>
<td>\textit{cagA} -/T homozygote</td>
<td>46</td>
<td>8</td>
<td>1.5 (0.4-5.5)</td>
<td>0.52</td>
</tr>
<tr>
<td>\textit{cagA} +/C homozygote</td>
<td>26</td>
<td>38</td>
<td>13 (4.1-40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>\textit{cagA} +/T homozygote</td>
<td>28</td>
<td>80</td>
<td>25 (98.2-77)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Other cytokine polymorphisms have been recently described, including \textit{IL-8} –251, \textit{Thr}399Ile, and \textit{TLR-4 Asp}506Gly and are currently under study for their role in cytokine level and cancer risk.

Table 6. Summary of the role of cytokine polymorphisms in the development of upper gastrointestinal pathologies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Studied population</th>
<th>Ethnicity</th>
<th>Cytokine polymorphism</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(20)</td>
<td>129 gastric cancer, 792 upper gastrointestinal pathologies</td>
<td>Caucasian (Italians)</td>
<td>\textit{IL-1B} –31</td>
<td>Failed to find association with increased risk of gastric cancer or its precursors</td>
</tr>
<tr>
<td>(21)</td>
<td>142 cases, 164 controls</td>
<td>Asian (Chinese)</td>
<td>\textit{IL-1B} –511</td>
<td>No difference between cases and controls</td>
</tr>
<tr>
<td>(31)</td>
<td>341 gastric cancer, 133 duodenal ulcer, 261 controls</td>
<td>Asian (Korean)</td>
<td>\textit{TNF-A} –386, –857, –238</td>
<td>First study to verify association with development of gastric cancer in Asian individuals.</td>
</tr>
<tr>
<td>(32)</td>
<td>207 \textit{H. pylori}+, 535 \textit{H. pylori}–</td>
<td>Caucasian (89% German)</td>
<td>\textit{IL-1B} –511+ \textit{IL-1RN} *2</td>
<td>Associated with increased mucosal \textit{IL-1B} expression and prevalence of atrophic gastritis.</td>
</tr>
</tbody>
</table>

Effect of Cytokine Polymorphisms and \textit{H. pylori} Status

An interesting finding in the El-Omar study (12) was the association between cytokine polymorphisms and \textit{H. pylori} –seropositive status. Tables 3 and 4 show clearly that the ORs are higher in \textit{H. pylori} – and CagA-positive patients than in the whole population studied in Table 2. This observation has been confirmed in patients with severe histologic changes in the gastric mucosa (20).

The study of Figueiredo et al. (15) is probably the most complete study that shows that the pattern of bacterial and host genotypes may determine risk of developing distal
It is clear that colonization with H. pylori increases the risk of developing distal gastric cancer and perhaps there are further additive effects on risk if specific host cytokine polymorphisms coincide with specific bacterial genotypes. We have presented some of the most recent evidence for these associations. Furthermore, the combination of more virulent H. pylori strains and the expression of specific cytokine polymorphisms contribute to an increased risk of developing distal gastric cancer. We have mentioned that there is a need for more studies in different geographic regions of the world and in a wide diversity of ethnic populations to explore whether colonization with virulent H. pylori strains and expression of cytokine polymorphisms contribute to an increased risk of developing distal gastric adenocarcinoma. As Furuta et al. mentioned in a recent editorial (35), the study of polymorphisms alone seems insufficient to assess gastric cancer risk and they suggest examining environmental factors in different ethnic groups and geographic areas along with the study of H. pylori strains. Studies of this type may be required to determine the most important risk factors associated with distal gastric cancer in a particular region of the world.

Conclusions

It is clear that colonization with H. pylori increases the risk of developing distal gastric cancer and perhaps there are further additive effects on risk if specific host cytokine polymorphisms coincide with specific bacterial genotypes. We have presented some of the most recent evidence for these associations. Furthermore, the combination of more virulent H. pylori strains and the expression of specific cytokine polymorphisms contribute to an increased risk of developing distal gastric cancer. We have mentioned that there is a need for more studies in different geographic regions of the world and in a wide diversity of ethnic populations to explore whether colonization with virulent H. pylori strains and expression of cytokine polymorphisms contribute to an increased risk of developing distal gastric adenocarcinoma. As Furuta et al. mentioned in a recent editorial (35), the study of polymorphisms alone seems insufficient to assess gastric cancer risk and they suggest examining environmental factors in different ethnic groups and geographic areas along with the study of H. pylori strains. Studies of this type may be required to determine the most important risk factors associated with distal gastric cancer in a particular region of the world.

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