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Editorial

Controversy in polymorphisms of interleukin-1β in gastric cancer risks

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Novel interleukin 1β polymorphism increased the risk of gastric cancer in a Korean population
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Host genetic factors have recently been focused on as the reasons for the divergent clinical outcomes by *Helicobacter pylori* (*H. pylori*) infection. Interleukin-1 beta (IL-1β) is one of the representative pro-inflammatory cytokines induced by *H. pylori* infection.[1] IL-1β induces inflammation as well as inhibits gastric acid secretion.[2] It also promotes the development of gastric cancer induced by MNNG in rodents.[3] Therefore, IL-1β is now thought to have an important part in the development of *H. pylori*-related gastric cancer.[4] The *IL-1B* gene encoding IL-1β is highly polymorphic, and several diallelic polymorphisms have been reported in the promoter region (C/T transition at −511 and T/C transition at −31), and exon 5 (C/T transition at +3954).[5–7] Carriers of the *IL-1B*-511 T allele or *IL-1RN**2 allele are known to be high producers of IL-1β.[7,8] El-Omar et al.[9,10] reported that proinflammatory genotypes of the IL-1 gene cluster (*IL-1B*-511 T/-31 C and *IL-1RN**2/*2) were associated with increased risk of gastric cancer and its presumptive precursors, gastric atrophy and hypochlorhydria, in Caucasian populations from Poland and Scotland. Following their reports, several independent reports on the effect of polymorphisms of genes coding IL-1β on the gastric cancer risk in Caucasians have been published.[11–13] For Asians, Hwang et al.[14] reported that the *IL-1B*-511 T and *IL-1RN**2 alleles were associated with increased IL-1β production in *H. pylori*-infected gastric mucosa in Japanese subjects. Furuta et al.[15,16] reported that *IL-1B*-511 T was associated with gastric atrophy and hypochlorhydria in the same population. However, there have recently been some opposing or differing reports.

Zeng et al.[17] recently reported that the *IL-1B*-511 T/T genotype increased the risk of gastric cancer in Chinese people, whereas He et al.[18] reported that carrying the *IL-1B*-31T allele increased the risk of gastric cancer in the same population, which seemed to contradict the report by Zeng et al.,[17] although both reports came from China. However, Zeng et al.[17] found no linkage-disequilibrium between the T/C transition at *IL-1B*-31 and the C/T transition at *IL-1B*-511, results that are different from those of previous reports.[9,12–15] Matsukura et al.[19] reported an ethnic difference in the effect of the *IL-1B* polymorphism on gastric atrophy. In their report, the *IL-1B*-511 T allele increased the risk of gastric atrophy in Chinese, but decreased that risk in Japanese, and was not associated with the risk of gastric atrophy in Thai and Vietnamese peoples. Kato et al.[20] reported that the *IL-1B*-511 T allele was not associated with increased risk of development of gastric cancer but was associated with decreased risk of intestinal metaplasia, although intestinal metaplasia is known to be one of the presumptive precursors of intestinal type of gastric cancer.

The effects of *IL-1B* polymorphisms have been studied in fields other than that of upper gastrointestinal disorders. The *IL-1B*-511 T/T genotype has been reported to increase the risk of HCV-related hepatocellular carcinoma,[21] alcoholic liver cirrhosis,[22] and multiple system atrophy[8] in Japanese subjects. The *IL-1B*-31 C (≈ *IL-1B*-511 T) allele is reported to increase the risk of breast cancer.[23] There are, indeed, some reports demonstrating that there was no association between *IL-1B* polymorphisms and such disorders. However, there have been no reports that the IL-1β high producer genotypes (i.e., *IL-1B*-511 T or *IL-1RN**2) are associated with decreased risk of several disorders, as noted above. Therefore, controversies on *IL-1B* genotypes appear to be specific to the field of gastric disorders.

Lee et al.[24] reported a new *IL-1B* polymorphism in this month's issue of *Journal of Gastroenterology*. They tested the C/G transition at *IL-1B*-1473 as well as C/T transition at -511 and T/C transition at -31 of *IL-1B* in gastric cancer cases and controls and found that there were no significant differences in genotype frequencies

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for the three polymorphisms between gastric cancer cases and controls. When cases were divided according to the histological types of the tumors, however, a significant difference in genotype frequencies for *IL-1B*-1473 was observed only between intestinal-type cases and controls. They reported that carriers of *IL-1B*-1473G had an increased risk of development of the intestinal type of gastric cancer. *IL-1B*-1473 C/G transition seemed weakly linked with *IL-1B*-31C/T/-511T/C; therefore, this study appeared to contradict the results of several previous reports.[9,11–13,17,25] The curious point in their report is that carriers of *IL-1B*-1473G tended to have a decreased risk of diffuse type of gastric cancer (OR 0.7, CI 0.4–1.1), which is the opposite in cases of the intestinal type of gastric cancer, although both intestinal and diffuse types of gastric cancer are related to *H. pylori*-induced gastritis. The odd ratio for the diffuse type of gastric cancer should be higher than 1, if severe inflammation underlies the development of the diffuse type of gastric cancer related to *H. pylori* infection. As described above, functional roles of *IL-1B* genotypes in gastric cancer risks differed among the different studies. In any case, whether this new *IL-1B* polymorphism (*IL-1B*-1473 C/G transition) could resolve the recent IL-1β polymorphism-related controversies should be tested in different ethnic groups, with an appropriate study design.

Interestingly, Zeng et al.[17] demonstrated that this *IL-1B* genotype-dependent risk was limited in the specific area where the prevalence of gastric cancer was low. In their study, the *IL-1B* genotype-related risk of gastric cancer seemed obscure in the area where the prevalence of gastric cancer was high, indicating that there must exist some more dominant risk factor superior to *IL-1B* polymorphism in each study area. As is well known, gastric cancer risk is associated with many genetic factors other than IL-1β (e.g., IL-6, IL-10, TNF-α, GST, NAT, Cytochrome P450 isoenzymes, MUC1, hOGG1, XRCC1, and HLA) as well as a variety of environmental factors (e.g., salt intake and smoking). Strains of *H. pylori* also differ among different geographic areas. The magnitude of each factor might differ among the different study groups. Therefore, the study of only two single nucleotide polymorphisms appears insufficient, and examinations of a variety of factors including host genetic factors as well as environmental factors in different ethnic groups and geographic areas may be required in order to elucidate what the most important risk factor is in each study area.

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