COMMENT

A commentary on Helicobacter pylori and gastric cancer risk in *BRCA1/2* pathogenic germline variant carrier

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We read Dr. Sorscher's comments [1] with great interest and appreciated his valuable suggestions about our article [2]. Based on the recent paper written by Usui et al. [3], he emphasized the increased risk of developing gastric cancer due to *Helicobacter pylori* (*H. pylori*) infection in carriers of the *BRCA1/2* pathogenic germline variant (PGV), and recommended eradication of *H. pylori* if positive. Usui et al. conducted a hospital-based epidemiological study, using 1433 gastric cancer patients and 5997 controls, and demonstrated an approximately three-fold increasing risk of gastric cancer due to *H. pylori* infection in *BRCA1/2* PGV carriers in Japan (a cumulative lifetime risk at 85 years of age: 45.5% vs. 14.4%) [3].

The prevalence of *H. pylori* infection is relatively high in East Asian countries (seroprevalences: 59.6% in Korea, 58.1% in China, 57% in Thailand, 54.5% in Taiwan, and 39.3% in Japan) [4], where there are similarly high incidences of gastric cancer. Cytokine-associated gene A (CagA) is the major virulence factor associated with gastric carcinogenesis. CagA is positive in almost all *H. pylori* strains; however, the level of virulence is higher in the East Asian-type CagA strain than in the Western-type CagA strain owing to structure variants [5]. In *H. pylori* infection, CagA injected into gastric epithelial cells interacts with PAR1b and subverts the nuclear translocation of BRCA1 by inhibiting PAR1b-mediated BRCA1 phosphorylation. Oxidative stress due to *H. pylori* infection also induces BRCAness, which promotes DNA double-strand breaks while disabling error-free homologous recombination (HR)-mediated DNA repair [6]. These molecular mechanisms are thought to further reduce DNA damage-repair capacity in individuals with deleterious variants of HR-related genes [3].

According to a nationwide case-control study by Momozawa et al., the risk of esophageal cancer is also increasing in Japanese *BRCA2* PGV carriers (odds ratio: 5.6 [95% confidence interval: 2.9–11.0]) [7]. Interestingly, heterozygous *BRCA2* truncation, which lowers BRCA2 expression, sensitizes to *BRCA2* haploinsufficiency induced by transient exposure to formaldehyde or acetaldehyde [8]. In this phenomenon, the need for genetic analysis of the *ALDH2* (aldehyde dehydrogenase 2) gene is commonly emphasized, as this polymorphism is relatively common in the Asian population and is also associated with an increasing risk of esophageal cancer due to the carcinogenic accumulation by acetaldehyde. Endoscopic surveillance is recommended [9] along with the reduction of additional risks (e.g., drinking and smoking).

As mentioned above, and as shown in the comments by Dr. Sorscher, cancer risk generally consists of environmental, lifestyle, and genetic factors, in addition to aging. Modifiable risk factors should be reduced in individuals with inherited risks. The Japanese Society for Cancer of the Colon and Rectum (JSCCR) recommends *H. pylori* eradication and surveillance using upper gastrointestinal endoscopy in Lynch syndrome patients, of whom the lifetime risk of gastric cancer is 6–13% [10]. Accordingly, *H. pylori* eradication (when positive) and upper gastrointestinal surveillance in *BRCA1/2* PGV carriers are warranted. This topic should be reconsidered when the guidelines for hereditary breast and ovarian cancer (HBOC) are revised in the near future.

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COMPETING INTERESTS

All four authors are members of the HBOC guideline committee at the time of manuscript submission.

ADDITIONAL INFORMATION

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