showed that levels of *miR-34b/c* methylation in noncancerous gastric mucosa from patients with multiple GCs were significantly higher than in noncancerous gastric mucosa from patients with single GCs or from healthy individuals [17].

We found that methylation of *miR-34b/c*, *SFRP2* and *DKK2* in the gastric body mucosa was strongly associated with a risk for metachronous GC, and *miR-34b/c* showed the greatest potential to serve as a predictive marker. Multivariate analysis adjusted for age, sex, *H. pylori* status and pathological findings revealed that *miR-34b/c* methylation and inflammation are independently associated with the development of metachronous GC. A number of studies have shown that chronic inflammation is strongly associated with aberrant DNA methylation, and one recent study also showed that the inflammatory response, not *H. pylori* itself, is responsible for the altered DNA methylation in the infected stomach [29, 30]. Consistent with those earlier findings, our study confirms the tight correlation between inflammation and aberrant DNA methylation, and shows that both inflammation and aberrant DNA methylation are independent risk factors of metachronous GC.

It also remains unclear why methylation in the gastric body strongly correlates with increased metachronous GC risk but methylation in the antrum does not. In gastritis patients, the antral mucosa generally exhibits more advanced histological features (e.g., metaplasia and atrophy) than the gastric body mucosa, though inflammation and activity are usually less severe in the antrum [31, 32]. In this study, we observed that methylation of a number of genes was higher in the antrum than in the body (Fig. 2a, Supplementary Figures 1 and 2). In addition, pathological findings in the gastric body mucosa are more likely to reflect the degree and extent of the inflammation and activity of the gastritis than those in the antral mucosa with severe atrophy or metaplasia. An earlier study also showed that individuals with active inflammation in the gastric body (e.g., pangastritis or corpus-predominant gastritis) are at higher risk of developing GC [8]. It is thus conceivable that aberrant methylation in the gastric body is associated an increased risk of metachronous GC.

Interestingly, we found that *miR-34b/c* methylation was also associated with metachronous GC risk in patients who underwent successful *H. pylori* eradication after treatment of their GC. Similarly, while eradication of *H. pylori* after endoscopic resection of early GC can reduce the risk of metachronous GC risk [9], eradication in patients without a precancerous lesion more effectively reduces the risk of developing GC [33, 34]. One possible reason for the development of metachronous GC, even after *H. pylori* eradication, is the presence of malignant cells that cannot be detected through endoscopic examination. In addition, our results suggest that a certain amount of aberrant DNA methylation may not be reversed by eradication, and individuals with high levels of *miR-34b/c* methylation may remain at a high risk of metachronous GC.

There are several limitations to this study. First, patient samples were collected at a single institution, and the follow-up period was relatively short (average 18 months). The cumulative incidence rate for metachronous GCs increases linearly with time [7], and we think the incidence of metachronous GCs in our study population would likely increase with a longer follow-up period. Second, the association between *miR-34b/c* methylation and GC risk in healthy individuals remains unclear because we focused on early GC patients who underwent endoscopic treatment. Thus, our findings should be validated in an independent long-term, multicenter study that includes a larger number of patients. Third, our study did not include patients who underwent *H. pylori* eradication therapy prior to their diagnosis. Earlier studies suggest that levels of aberrant methylation in *H. pylori*-infected noncancerous mucosa can be reduced by eradication therapy, but it is unclear how long the effect persists [35–38]. Further studies will be needed to define the relation between *miR-34b/c* methylation and GC risk in patients with history of *H. pylori* eradication therapy.

In summary, we observed that the level of *miR-34b/c* methylation in noncancerous gastric body mucosa is a useful biomarker that is predictive of the risk for metachronous GC risk after endoscopic resection. Thus, for early GC patients with elevated *miR-34b/c* methylation in the gastric body, more intensive and frequent follow-up endoscopy may be recommended after ESD. Our findings may greatly improve of the surveillance strategy used after ESD and contribute to the early detection of metachronous GC and a reduction in its mortality.

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Conflict of interest The authors declare that they have no conflict of interest.

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