Letter to the Editor

Bile acids are risk factors for esophageal carcinogenesis

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I will reply to the comments on Professor Suzuki's treatise.

(I) The exposure times of bile acids in the rats are all 40 weeks. Why?

The incidence of esophageal cancer patients who have undergone distal gastrectomy has recently been increasing. Distal gastrectomy is a good model for studying the clinical effects of duodenal content reflux. Individuals with a history of gastrectomy often suffer from severe reflux esophagitis.

We retrospectively evaluated 153 patients who underwent subtotal esophagectomy for thoracic esophageal cancer (1). They were divided into two groups: group 1, comprising 14 patients who had undergone gastrectomy; and group 2, comprising 139 patients who had not undergone gastrectomy. In group 1, there 7 Billroth I procedures, 6 Billroth II procedures, and 1 total gastrectomy (R-Y); in group 2, there were 139 patients with intact stomachs. The interval between gastrectomy and esophagectomy in group 1 was significantly shorter in the patients who had undergone gastrectomy for gastric cancer (10.5±4.2 years) (n=4) than in those who had undergone gastrectomy for a peptic ulcer (28.9±3.0 years) (n=10). The histology of the esophagus in group 1 consisted exclusively of squamous cell carcinoma (SCC). In terms of cancer site, the major site in group 1 was the lower thoracic area (62%) while that in group 2 was the middle thoracic area (61%). I subsequently created a rat model: total gastrectomy followed by esophagoduodenostomy was performed to induce chronic duodenal content reflux esophagitis (2). The animals were sacrificed on the 40th week after surgery. In this model, severe dysplasia, SCC, and adenocarcinoma (ADC) occurred in 100% (27/27), 40% (10/27), and 30% (8/27) of the mice, respectively. It is unclear what factors lead to the formation of carcinoma of a specified histology. ADC is near the site of anastomosis, while SCC is distant from the site of anastomosis. In the model study, SCC developed in sites distant from the anastomosis compared to ADC. This means that histological features may depend on the volume of reflux contents; small amounts of reflux causes SCC and a large volume of reflux causes ADC. From the histological finding of COX2 and p53, overexpression of COX2 was shown in ADC and SCC. The wild-type p53 accumulation was found in ADC and not in SCC.

Regurgitation into the esophagus occurs during bed rest. Rats are bed rest, but humans are bed rest for 8 hours and remain in standing position for the remaining 16 hours. Esophageal cancer developed in the rats within 40 weeks, but it is difficult to speculate how many years this would take in humans. When a benign ulcer undergoes gastrectomy, esophageal cancer develops in about 30 years, so in humans, esophageal cancer from reflux of the duodenal fluid by distal gastrectomy may develop in about 30 years.

(II) Which fraction of the duodenal content reflux, pancreatic juice, and bile acids contributes to the development of esophageal cancer?

Reflux of duodenal contents contributes to the development of esophageal mucosal lesion. Esophageal cancer after total gastrectomy has been associated with the reflux of duodenal content (biliary and pancreatic juice) into the esophagus. We determined which fraction of the duodenum content reflux, pancreatic juice, and bile acids

contributes to the development of esophageal cancer (3). We designated a reflux of pancreatic juice and bile (TG) group, a reflux of pancreatic juice (TG + B) group, and a sham group. The TG ground only underwent end-to-end esophagoduodenostomy with total gastrectomy. Meanwhile, the TG + B group underwent end-to-end esophagoduodenostomy with total gastrectomy, and then underwent a bypass operation of the upper bile duct 25 cm below the ligament of Treitz to produce only pancreatic reflux. Choledochojejunostomy was performed. Forty weeks after, the rats were sacrificed. In the TG group, we detected severe dysplasia (100%), SCC (40%), and ADC (30%). In the TG + B group, we detected mild dysplasia (40%), but not SCC (0%) or ADC (0%). Thus, the reflux of pancreatic juice alone is probably not significant to the development of esophageal cancer after total gastrectomy compared to the reflux of bile and pancreatic juice.

(III) Does lowering the concentration of bile in the esophagus suppress esophageal carcinogenesis?

We performed an esophageal duodenal anastomosis after total gastrectomy and found prominent reflux esophagitis 3 weeks after the operation due to reflux of duodenal fluid.

We started from the 1st week after the operation for 2 weeks in the saline administration group and the rabeprazole administration group (4). Reflux esophagitis was milder in the rabeprazole group than in the saline group. The bile concentration in the esophagus was significantly lower in the rabeprazole group than in the saline group. Although there was no difference between the rabeprazole and saline group in the total bile acid in the common bile duct, bile acid concentration in the esophagus was significantly lower in the rabeprazole group due to augmentation of the duodenal motor activity.

These data suggested that administration of rabeprazole reduced bile levels in the esophageal lumen. From previous experiments (4), we know that proton-pump inhibitor (PPI) lowers bile levels in the esophagus, so long-term administration of PPI may also suppress esophageal cancer.

(IV) What is the relationship between bile concentration in the esophagus and the bile concentration in the common bile duct?

It is good to measure the bile acid concentration in the esophagus, but since it is difficult to measure the bile acid concentration in the esophagus of rats, we measured the bile acid concentration in the common bile duct. Bile acids in the common bile duct are excreted from the papilla and flow back into the esophagus, so bile acid concentrations in the esophagus appear to be similar to bile acid concentrations in the common bile duct.

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